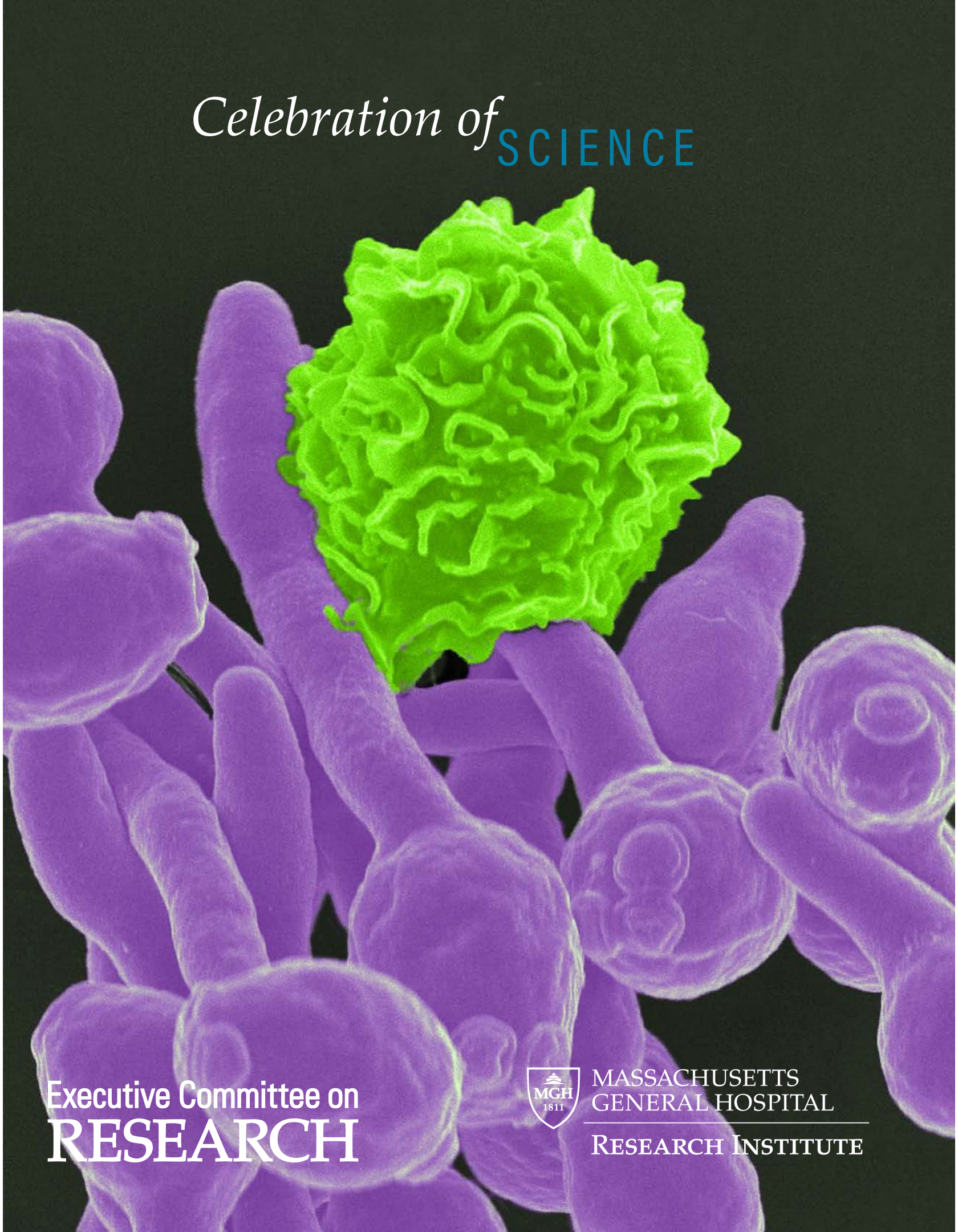
Celebration of SCIENCE



Executive Committee on RESEARCH

MASSACHUSETTS GENERAL HOSPITAL

RESEARCH INSTITUTE

Agenda

Monday, September 21, 2020

Celebration of SCIENCE

2:00 - 2:30 pm

Welcome
Peter L. Slavin, MD
President, Massachusetts General Hospital

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

Introduction of the 2020 Claflin Distinguished Scholar Awards & MGH Physician Scientist Development Awards
David E. Fisher, MD, PhD, Chair, Executive Committee on Research (ECOR)

Introduction of the Anne Klibanski Visiting Scholar Awards
Miriam A. Bredella, MD, Director, Center for Faculty Development

2:30 - 2:45 pm

Introduction of the Class of 2020 MGH Research Scholars and new MGRI Chairs
Susan A. Slaugenhaupt, PhD, Scientific Director, MassGeneral Research Institute

2:45 - 3:10 pm

2020 Howard M. Goodman Fellowship
Immunity to Commensal Papillomaviruses for Cancer Prevention
Shawn Demehri, MD, PhD
Assistant Professor of Dermatology, Harvard Medical School
Investigator, Center for Cancer Immunology & Cutaneous Biology Research Center, Massachusetts General Hospital

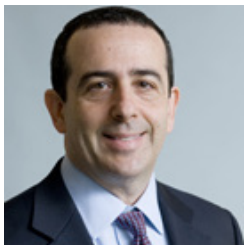
3:10 - 3:35 pm

2020 Martin Prize for Fundamental Research
Targeting the CBM Complex Causes Treg Cells to Prime Tumours for Immune Checkpoint Therapy
Thorsten Mempel, MD, PhD
Bob and Laura Reynolds MGH Research Scholar 2014-2019
Associate Professor of Medicine, Harvard Medical School
Associate Investigator, Center for Immunology and Inflammatory Diseases & Rheumatology, Allergy & Immunology, Massachusetts General Hospital

3:35 -4:00 pm

2020 Martin Prize for Clinical Research
Exercise Reduces Inflammatory Cell Production and Cardiovascular Inflammation via Instruction of Hematopoietic Progenitor Cells
Matthias Nahrendorf, MD, PhD
Richard Moerschner Endowed MGH Research Institute Chair in Men's Health
Weissman Family MGH Research Scholar 2014-2019
Professor of Radiology, Harvard Medical School
Investigator, Center for Systems Biology, Massachusetts General Hospital

Executive Committee on Research
Officers and Members 2020



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

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

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

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

*Chair Appointment, ‡ Chiefs Council

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

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

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

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

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

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

Facundo D. Batista, PhD
Co-Chair, Subcommittee on Animal Resources (SAR)
Ex-officio

Joseph R. Betancourt, MD
Vice President and Chief Equity and Inclusion Officer
Ex-officio

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

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

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

James A. Brink, MD*
Chief, Radiology
April 2018 - March 2024

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

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

Beth A. Costine-Bartell, PhD
Co-Chair, Subcommittee on Animal Resources (SAR)
Ex-officio

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

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

Georges El Fakhri, PhD
Radiology
Co-Chair, Subcommittee on Review of Research Proposals (SRRP)
Ex-officio

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

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

Andrea Foulkes, ScD*
Biostatistics Center
April 2018 - March 2024

Executive Committee on Research

Officers and Members 2020

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

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

Bob Kingston, PhD*
Chief, Molecular Biology
April 2018 - March 2024

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

Elizabeth A. Lawson, MS, MMSc
Medicine / Endocrinology
Elected Representative
January 2020 - December 2022

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

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

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

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

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

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

Yakeel T. Quiroz, PhD
Psychiatry / Neurology
Elected Representative
January 2020 - December 2022

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*
Psychiatry
April 2018 - March 2024

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

Paul S. Russell, MD
Honorary Member

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

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

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

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

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

Ravi Thadhani, MD, MPH
Chief Academic Officer, Partners Healthcare
Ex-officio

Maria J. Troulis, DDS, MSc‡
Chief, Oral and Maxillofacial Surgery
April 2017 - March 2023

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

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

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

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

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

*Chair Appointment, ‡ Chiefs Council

Scientific Advisory Committee

David Altshuler, MD, PhD
Executive Vice President, Global Research
Chief Scientific Officer
Vertex Pharmaceuticals

Mark C. Fishman, MD
Professor, Stem Cell and Regenerative Biology
Harvard University
Chief, Pathways Clinical Service
Massachusetts General Hospital

Constance L. Cepko, PhD
Professor, Genetics and Ophthalmology
Investigator, Howard Hughes Medical Institute
Harvard Medical School

Elaine Fuchs, PhD
Rebecca C. Lancefield Professor of Mammalian Cell Biology and Development
Investigator, Howard Hughes Medical Institute
The Rockefeller University

Elazer R. Edelman, MD, PhD
Professor, Medical Engineering and Science
Director, Institute for Medical Engineering and Science (IMES)
Massachusetts Institute of Technology

Richard O. Hynes, PhD
Daniel K. Ludwig Professor for Cancer Research
Investigator, Howard Hughes Medical Institute
Massachusetts Institute of Technology

Scientific Advisory Committee

Talmadge E. King, Jr., MD
Dean, School of Medicine
Vice Chancellor, Medical Affairs
University of California, San Francisco

Daniel Podolsky, MD
President
University of Texas Southwestern Medical Center

Vivian S. Lee, MD, PhD, MBA
President, Health Platforms
Verily Life Sciences

Selwyn M. Vickers, MD, FACS
Senior Vice President, Medicine
Dean, School of Medicine
University of Alabama at Birmingham

Douglas A. Melton, PhD
Xander University Professor
Co-Director, Harvard Stem Cell Institute
Investigator, Howard Hughes Medical Institute
Harvard University

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

B-lieve It! Annual Research Revenue Tops $1B (In Spite of Continued Space Challenges)

Continued progress in strategic initiatives underway within the Mass General Research Institute (RI) has yielded another year of exceptional growth in our research portfolio, with revenues in 2019 surpassing $1 billion for the first time. Revenue jumped to $1,013M, increasing $85M over FY18, another all-time high. New NIH awards also continued to increase in FY19, jumping $34M to break the $500M mark. This growth was fueled by an impressive increase in application success rates to 30%, ten percent higher than the national average. Early award rate returns in FY20 show the trend continuing, with projections that FY20 will exceed the $1,013M record achieved this year. Unfortunately, the paucity of available research space mentioned in last year's report continues to pose a major challenge to sustaining the growth projected by the influx of new awards. While we continue to explore nearby locations to expand our research footprint and to refine metrics to improve the efficiency of current space use, overcrowding has now become the rate-limiting factor to sustaining our leading role in biomedical innovation. I will devote a major portion of the "Looking at the Year Ahead" section of my report to discussing this challenge, but, first, let's look at the progress and developments across the research enterprise this past year.

Highlights of RI accomplishments/milestones in 2019 include:

- The appointment of the 60th MGH Research Scholar (five new ones in 2019).
- An increase of 20 industry-sponsored clinical trials in the Translational and Clinical Research Centers, bringing the total number of studies in 2019 to 69.
- Continued expansion of our RI external communication and marketing efforts. The Research Institute Blog this past year nearly tripled its traffic (198% growth). It was recognized in the industry with two awards and a distinction; Gold Award for Best Blog by the NESHCo Lamplighter Awards, Gold Award for Best Healthcare Content and a Distinction for Best Blog by the Healthcare Leadership Awards.
- Steady growth in the Partners Biobank at MGH, with consented patient recruitment now over 113,000 and genotyped samples exceeding 36,000. To date, the Biobank has supported over 240 studies with specimens and data.
- While MGH patents filed in FY19 remained steady at around 1600, patents issued increased from 467 last year to 629 in FY19. Royalty and licensing income also increased from $95M to $298M, due in part to a $142M buyout. Even without the buyout, income grew 50% from $95M to $142M.
- To partially offset the overcrowding in our research spaces, leadership approved over $20M of capital renovation projects to improve use and efficiency of current research space, more than doubling the amount approved in the four previous fiscal years.

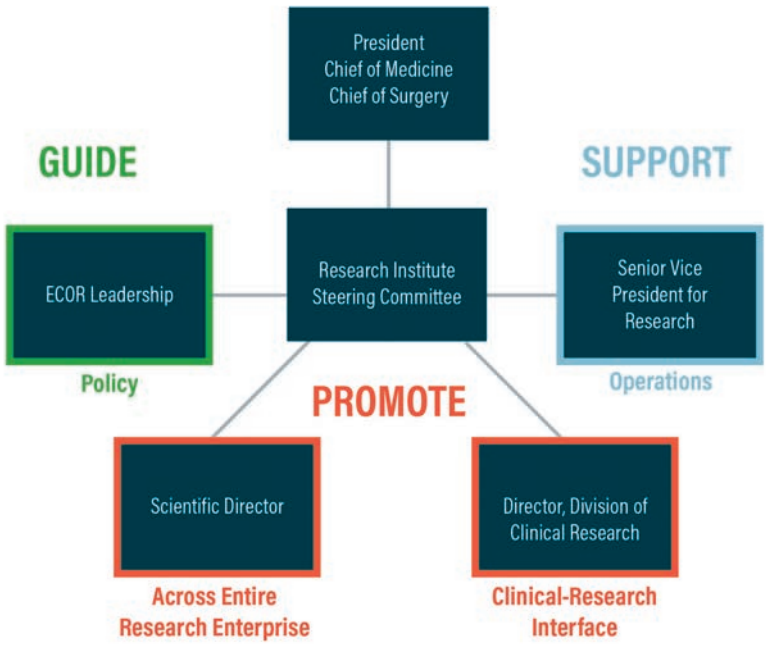
- Continued researcher participation in the Isuggest program, with the number of suggestions to improve research services at the end of 2019 exceeding 1,400 and the number implemented exceeding 750. Suggestions continue to come in at a rate of five per week.
- With a continued increase in the number of research misconduct cases related to the inability to produce original experimental data, MGH (and all of Partners) mandated use of approved electronic lab notebooks (ELN's). An enterprise-wise license for Lab Archives was procured and made available at no cost to all researchers. Most labs are now using Lab Archives, with a few being granted exceptions to use other systems that have been vetted and approved by Partners IS Security.
- Implementation last year of an entirely new IACUC protocol submission process that dramatically simplified and reduced the amount of work required by PIs is having a very positive impact on protocol turnaround times (TAT's). Median turn-around-times for new applications decreased 7 days (Full Board) and 19 days (Designated Review), triennial review applications decreased 11 days (Full Board) and 17 days (Designated Review), while Amendments decreased 24 days (Full Board) and 14 days (Designated Review).
- Major programmatic and staffing changes to the Center for Faculty Development (CFD) signal a new era for the Center. A new Director, Dr. Miriam Bredella from Radiology was named to replace Dr. Anne Klibanski, who has gone on to become the CEO of Partners Healthcare. Donna Lawton, long-time CFD Executive Director, retired this past year and a search will begin soon for her replacement. Director positions for the Office of Research Careers and the Graduate Student Division will also soon be filled by Dr. Bredella. Finally, the entire CFD staff will relocate from their isolated location in Bulfinch to 125 Nashua Street, adjacent to the ECOR and Research Institute administrative offices, allowing for better support from and integration into the Research Institute support staff.

These and other important developments from the past year are reported below, in a sectional format that aligns with the organizational components (Guide, Promote, Support) of the RI governance structure. I conclude the report by "Looking at the Year Ahead", where I discuss the most notable opportunities and challenges facing the research enterprise in 2020.

The Research Institute Steering Committee (RISC)

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

Leadership Structure of Research at MGH



GUIDE

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

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

Leadership of ECOR

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

ECOR Membership

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

There is a total of 6 elected representatives to ECOR, two from each faculty rank. Elected representatives serve a 3-year term and represent faculty concerns and issues. To ensure a balance of continuity and renewal, terms are staggered so that two seats are up for election every year. Please see pages 4 & 5 to view the entire committee membership.

ECOR's broad areas of focus include:

Meetings and Events

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

Research Council

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

Scientific Advisory Committee

The MGH Scientific Advisory Committee (SAC) is a group of distinguished scientists who advise the hospital's leadership on issues related to its research mission. For over 70 years the committee members have served as a sounding board for the hospital's leadership, helping us evaluate our research mission and address challenges we are facing. SAC membership has included Nobel laureates and leaders in science and medicine from academia, industry and government. Current membership is listed on pages 6 & 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,

A medallion of Dr. Warren, presented to recipients

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 2018, the Warren Prize has been awarded on 43 occasions to 73 recipients. Twenty-four of these individuals have also received the Nobel Prize, which was first presented in 1901. Each Prize recipient presents his or her scientific work in a symposium at MGH and receives a $50,000 cash award.

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

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

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

The Subcommittee on Animal Resources (SAR), which meets quarterly, makes recommendations on the allocation and management of animal research space and provides guidance to the Center for Comparative Medicine (CCM) and Institutional Animal Care and Use Committee (IACUC). Additionally, this committee is charged with ensuring that the Animal Space Policy is working smoothly. For more information on our animal program, see page 31.

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

Charlestown Navy Yard (CNY) Quality of Life Committee
The CNY Quality of Life Committee was founded in mid-2018 with the goal of enhancing the research community located in the Navy Yard in Charlestown. The committee has identified four key areas for improvement:

1. Better transportation between campuses
2. Increased food options
3. Community building and need to enhance scientific interactions
4. Improving facilities and technology

The committee has made a significant impact and has been able to:

- Obtain funding and successfully petitioned research leadership for financial support to enhance community building
- Improve transportation between campuses by:
    - Working with the city and Partners Transportation to implement changes to the shuttle route to reduce travel time from Charlestown to the main campus

    - Update and amend parking policies across the hospital
    - Modify egress from buildings 24-7 from bridges and at the West End of 149
    - Provide bike and walking routes between campuses
- Add and improve meal options by:
    - Inviting food trucks to offer lunch options on Thursdays and Fridays in the summer and fall
    - Sponsoring Pop-up food options 5 days a week, 3 days in Building 149 and two days a week in Building 114
    - Implemented a 20% discount on food purchased by MGH employees at the Spaulding
- Build community and enhance interactions by:
    - Holding Town Hall meetings to allow open discussions and feedback
    - Holding a monthly Lunch Scientific Seminar Series
    - Offering Cookies, Coffee and Classical Music events several times throughout the year
    - Offering Ice Cream Socials in the summer (Over 600 people attended each one!)
    - Working with MGH retail to have pop-up shops at CNY
    - Hosting the Science as Art Event and installing permanent art exhibit at CNY
    - Hosting the CNY Science Grand Slam with the MGRI

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

- Renovate the building including Coffee Central and the First-Floor space
- Upgrade video conferencing and AV in conference rooms
- Host the CNY Trainees Retreat to showcase 20 top trainee talks followed by dinner reception – planned for summer 2020
- Increase MGRI branding at CNY

Taskforce on Equity and Respect in the Research Workplace

The theme of the 2019 SAC meeting was the Research Faculty. In preparation for the meeting ECOR wanted to understand the work experiences and quality of life of MGH Investigators – so we surveyed the research PIs for the first time.

Key outcomes:

- Overall positives: collaboration, colleagues, mentoring, excitement about the science and technology in this environment
- Overall negatives: bureaucracy, soft money, stress
- Gaps in perceived respectful treatment by gender, race and ethnicity
- Lack of awareness of many research management structures and supports

Results from our first survey of the research faculty revealed some harsh realities in our research workforce. At the recommendation of our Scientific Advisory Members, ECOR established a taskforce to gather input and advice on how best to address these challenges. Robert Kingston, PhD, Chief of Molecular Biology and Marcia Goldberg, MD, Director of Research Program Development, Department of Medicine, are co-chairing this task force.

The issues facing this task force are of significant concern not only to the hospital but also to the Trustees and therefore the recommendations emanating from this committee will be paid attention to by leadership at the highest levels.

The taskforce has been meeting monthly and expects to present recommendations to hospital leadership by the end of the summer.

Communication

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

Awards and Grants

ECOR manages a multi-million-dollar grant program, virtually a mini-foundation, which annually reviews over 800 applications from MGH investigators and fellows, and awards approximately 120 internal grants. Over the past several years, ECOR has experienced a significant increase in the number of grant mechanisms administered by ECOR, along with an increase in applications to these opportunities. To meet

the needs of an increasing application pool, we established an online grant management system where we manage the entire lifecycle of an ECOR application from the start of an application, through the review process, and to the notification of funding.

In FY19, we awarded $10.3M to 110 investigators.

Grant	$	PIs	Target Group
Interim Support Funds (ISF) Formulaic/Deliberative)	$4.3M	55	All faculty
FMD & Tosteson Fellowships (Postdoctoral Awards)	$1.7M	22	Research fellows/trainees
MGH Research Scholars	$2.5M	5	Mid-career faculty
Claflin Distinguished Scholar Awards	$690,000	6	Female junior faculty
CDI Physician-Scientist Development Award	$483,000	5	Underrepresented minorities who are junior faculty
Howard M. Goodman Fellowship	$345,000	1	Junior faculty
Martin Prize	$200,000	2	All faculty
Shared Instrumentation Grants Institutional Commitment	$75,000	2	All faculty
SAC Abstracts	$13,800	12	Grad students, research fellows, and junior faculty

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: 82% of investigators who received funding from the Interim Support Program between 2006-2019 are still working within the institution. Since the program's inception in 2006, ECOR has awarded over $58.9M of interim support funding. Our investigators have gone on to leverage these funds ten-fold, bringing in nearly $633M of federal funding to the institution. Within this program are two grant mechanisms, Formulaic Bridge Support and Deliberative Interim Support Funding, which provide similar funding under different guidelines.

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

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

In order to help as many people as possible, we ask investigators who receive their NIH funding during the ISF award to return the remaining funds to ECOR. This helps ECOR support more awards in the future. Since the beginning of the program, ECOR has recovered a total of $9.1M to date.

Tosteson & Fund for Medical Discovery Fellowship Awards
The Tosteson & Fund for Medical Discovery (FMD) Fellowship Awards are intended to support junior investigators (MD and PhD fellows/postdocs) at MGH pursuing clinical or fundamental research. The award is offered three times per year, with one cycle dedicated solely to clinical research. Each award includes a salary stipend of $50,000. In FY19, 22 fellows received fellowship awards through this program.

Claflin Distinguished Scholar Awards
Although women scientists are recruited to MGH programs, their advancement to senior faculty positions is still far less frequent than that of their male counterparts. In 1993, The Women in Academic Medicine Committee, originally chaired by Mrs. R. Morton Claflin, Honorary

Trustee, was established to facilitate the academic careers of women in science at MGH. Recognizing that a significant obstacle to career advancement is the difficulty of maintaining research productivity during the child-rearing years, this committee, with the sponsorship of ECOR, established the Claflin Distinguished Scholar Awards. It is intended that this funding will increase opportunities for women to advance to senior positions in academic medicine. In FY19, six women received the Claflin Award.

Andrea Edlow, MD, MSc
Assistant Professor
OB/GYN

Kelly Irwin, MD
Assistant Professor
Psychiatry

Jacqueline Lane, PhD
Instructor
Anesthesia

Deborah Mitchell, MD
Assistant Professor
Pediatrics

Randi Schuster, PhD
Assistant Professor
Psychiatry

Christiane Wrann, DVM, PhD
Assistant Professor
Medicine/Cardiology

MGH Physician-Scientist Development Award

The MGH Physician/Scientist Development Award (PSDA), which is managed by ECOR in collaboration with the Center for Diversity Inclusion (CDI), is designed for MD and/or PhD investigators at MGH to support the development of research investigators who are considered underrepresented in medicine (URiM), and thereby increase opportunities for URM researchers to advance to senior positions in academic medicine at MGH. To better address the needs of underrepresented faculty at MGH, the CDI and ECOR agreed to fund an additional three awards. In FY19, five investigators received this award:

George Alba, MD
Instructor
Medicine/Pulmonary

Sophia Kamran, MD
Instructor
Radiation Oncology

Patricia Musolino, MD, PhD
Assistant Professor
Neurology/Center for
Genomic Medicine

Erica Warner, ScD, MPH
Assistant Professor
Medicine
Clinical & Translational
Epidemiology Unit

Oladapo Yeku, MD, PhD
Instructor
Medicine
Hematology & Oncology
Cancer Center

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 2019, 60 Scholars have been appointed, each receiving research funding of $100,000 a year for five years.

The 2019 Class of Mass General Research Scholars

Jodie Babitt, MD
Associate Professor
Medicine/Nephrology

Dara Manoach, PhD
Professor
Psychiatry/Martinos Center

Miguel Rivera, MD
Assistant Professor
Pathology/
Molecular Pathology Unit

Natalia Rost MD, MPH
Associate Professor
Neurology

Amar Sahay, PhD
Associate Professor
Psychiatry/Center for
Regenerative Medicine

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 $165,000 per year.

2020 Howard M. Goodman Fellowship
Shadmehr Demehri, MD, PhD
Assistant Professor of Dermatology
Cancer Center

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.

2020 Martin Research Prize for Clinical Research
Matthias Nahrendorf, MD, PhD
Professor of Radiology
Center for Systems Biology

Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. *Nature Medicine*, November 2019; 25: 1761-1771.

2020 Martin Research Prize for Fundamental Research
Thorsten Mempel, MD, PhD
Associate Professor of Medicine
Rheumatology, Allergy, and Immunology

Targeting the CBM complex causes Treg cells to prime tumours for immune checkpoint therapy. *Nature.* June 2019; 570: 112-116.

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. After leading the Committee for over 5 years, the baton was passed to Dr. Jerry Rosenbaum, Psychiatrist-in-Chief emeritus and Director of the Center for Anxiety and Traumatic Stress Disorders, who now chairs the committee. The committee ensures that there is an MGH nominee for over 40 major national and international scientific awards and prizes and provides hospital endorsements for faculty member admission to distinguished honorific societies. The committee is comprised of 17 esteemed leaders from throughout our institution who meet regularly. In 2019, the committee championed the nominations of more than 25 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 2019 include the following:

National Academy of Medicine (NAM)
Peter Slavin, MD (MGH President)
Mehmet Toner, PhD (Surgery)
Scott Rauch, MD (Psychiatry)

National Academy of Inventors
Larry Wald, PhD (Martinos Center)
Ebru Oral, PhD (Orthopaedics)

Fellows of the American Association for the Advancement of Science (AAAA)
Samuel Thier, MD (Medicine)

8-Spoked Salute
Harry W. Orf, PhD (Senior Vice President for Research)

A. Clifford Barger Award for Excellence in Mentoring from Harvard Medical School (HMS)
Lee S. Cohen, MD (Center for Women's Mental Health)
Vicki A. Jackson, MD, MPH (Palliative Care and Geriatrics)

Academy of Emergency Ultrasound Society (AEUS) of Academic Emergency Medicine Award for Academic Excellence
Hamid Shokoohi, MD (Emergency)

Academy of Emergency Ultrasound Society (AEUS) of Academic Emergency Medicine SAEMMY Award for Best Research on Medical Education
Andrew Liteplo, MD (Emergency)

Academy for Radiology & Biomedical Imaging Research 2019 Distinguished Investigator Award
Ken Arai, PhD (Radiology)
Rajiv Gupta, MD, PhD (Radiology)
Matti Hamalainen, PhD (Radiology)
Vitaly Napadow, PhD (Radiology)
Pari Pandharipande, MD, MPH (Radiology)
Ona Wu, PhD (Radiology)
Hiroyuki Yoshida, PhD (Radiology)

Alzheimer's Drug Discovery Foundation 2019 Young Investigator Award and Scholarship
Yulong Xu, PhD (Radiology)

American Association for Cancer Research (AACR) Waun Ki Hong Award for Outstanding Achievement in Translational and Clinical Cancer Research
Andrew T. Chan, MD, MPH (Clinical & Translational Epidemiology Gastroenterology/Cancer Center)

American Academy of Microbiology
Deborah Hung, MD, PhD (Molecular Biology)
Galit Alter, PhD (Ragon Institute)

American Academy of Neurology Clinical Research Training Scholarship
Jennifer Ahjin Kim, MD, PhD (Neurology)

American Academy of Neurology Michael S. Pessin Stroke Leadership Prize
Alessandro Biffi, MD (Neurology)

American Association for the Study of Liver Disease (AASLD) Leonard B. Seeff Award
Tracey Simon, MD, MPH (Gastroenterology)

American Clinical and Climatological Association (ACCA)
M. Amin Arnaout, MD, FASN (Nephrology)

American College of Cardiology 2019 Douglas P. Zipes Distinguished Young Scientist Award
Amit Khera, MD (Center for Genomic Medicine/Cardiology)

American College of Cardiology/William F. Keating Esq. Endowment Career Development Award
Mazen Albaghdadi, MD, FACC (Cardiology)

American College of Gastroenterology Young Physician Leadership Scholars Program
Yasmin Genevieve Hernandez-Barco, MD (Gastroenterology)

American College of Psychiatrists Second Vice President
Gene Beresin, MD, MA (Psychiatry)

American Glaucoma Society Mentoring for Advancement of Physicians-Scientists Award
Nazlee Zebardast, MD, MSc

American Heart Association Harold Amos Medical Faculty Development Award
James Sawalla Guseh, MD (Cardiology)

American Institute for Medical and Biological Engineering (AIMBE) College of Fellows
Matti Hamalainen, PhD (Martinos Center)
Ebru Oral, PhD (Orthopaedics)
Timothy Padera, PhD (Radiation Oncology)
Guillermo Tearney, MD, PhD (Wellman Center)

American Medical Association Vice President of the Minority Affairs Section
Fatima Cody Stanford, MD, MPH, MPA

American Neurological Association 2019 Raymond D. Adams Lectureship Award
Merit Cudkowicz, MD (Neurology)

American Neurological Association (ANA) Derek Denny - Brown Young Neurological Scholar Award
M. Brandon Westover, MD, PhD (Neurology)

American Pediatric Surgical Association President
Joseph P. Vacanti, MD (Pediatric Surgery)

American Psychiatric Association (APA) Hartford-Jeste Award for Future Leaders in Geriatric Psychiatry
Jennifer Gatchel, MD, PhD (Psychiatry)

American Society for Dermatologic Surgery Vice President
Mathew Avram, MD, JD (Dermatology)

American Society of Addiction Medicine (ASAM) 2019 Ruth Fox Scholarship
Benjamin Bearnot, MD (Internal Medicine)

American Society of Anesthesiologists 2019 James E. Cottrell, M.D., Presidential Scholar Award
Oluwaseun Johnson-Akeju, MD, MMSc (Anesthesia)

American Society of Interventional Pain Physicians (ASIPP) 2019 Academic Achievement Award
Joshua A. Hirsch, MD (Radiology)

American Society of Transplantation 2019 Lifetime Achievement Award
Jay Fishman, MD (Infectious Disease)

American Stroke Association Advisory Committee Chair
Lee H. Schwamm, MD, FAHA, FANA (Neurology)

American Thoracic Society Clinical Problems Assembly Early Career Achievement Award
Lida P. Hariri, MD, PhD (Pathology)

American Urological Association (AUA) Research Council New England Representative
Siam Oottamasathien, MD (Pediatric)

Andrew L. Warshaw, M.D., Institute for Pancreatic Cancer Research Award
Yasmin Genevieve Hernandez-Barco, MD (Gastroenterology)

Banting Postdoctoral Fellowship
Marc-André Tétrault, PhD (Radiology)

Behavior Research Foundation NARSAD Young Investigator Award
Annie Kathuria, PhD (Psychiatry, Center for Genomic Medicine)

Beirut Golden Award (Neurology)
Bakhos Tannous, PhD

Brain Research Foundation 2019 Dr. Frederic A. Gibbs Discovery Award for Scientific Achievement
Rudolph Tanzi, PhD (Neurology)

Brain Tumour Charity Expanding Theories Award
Jan Schuemann, PhD (Radiation Oncology)

Burroughs Wellcome Fund Career Award for Medical Scientists
Gaurav Gaiha, MD, DPhil (Ragon Institute)

College of the Holy Cross Sanctae Crucis Award
Arthur Weyman, MD (Cardiology)

Commission of Sciences de la Vie et de la Sante-4
Jeanine Wiener-Kronish, MD, MGH (Anesthesiology)

Damon Runyon-Dale F. Frey Award for Breakthrough Scientists
Liron Bar-Peled, PhD (Cancer Center)

Damon Runyon-Rachleff Innovation Award
Marcela V. Maus, MD, PhD (Cancer Center)
Jan Schuemann, PhD (Radiation Oncology)
Alexandra-Chloé Villani, PhD (Cancer Center)

Department of Defense Peer-Reviewed Cancer Research Program Impact Award
Dan G. Duda, DMD, PhD (GI Radiation Oncology)

2020 Dietary Guidelines Advisory Committee
Ronald Kleinman, MD (Pediatrics)
Elsie Taveras, MD, MPH (Pediatrics)

Doris Duke Physician Scientist Fellowship
Jacob E. Lemieux, MD, DPhil, (Infectious Disease)

Ellis Island Medal of Honor
Reza Dana, MD, MSc, MPH (Ophthalmology)

European Association of Cardiovascular Keynote Lecturer
Michael Picard, MD (Cardiology)

Executive Leadership in Academic Medicine (ELAM) Program for Women
Maryam Asgari, MD (Dermatology)

Gilead Sciences Research Scholar Award
Suman Srinivasa, MD, MS (Neuroendocrinology)

2019 Harold Amos Faculty Diversity Award from Harvard Medical School
Mayra Lorenzo, MD, PhD (Dermatology)

Harvard Chan School of Public Health Program in Cardiovascular Epidemiology 2019 Outstanding Fellow/Trainee Award
Andrew Synn, MD (Pulmonary and Critical Care)

Harvard Medical School Young Mentor Award
Arunava Bandyopadhaya, PhD (Surgery)
Adeline A. Boatin, MD, MPH, (Obstetrics and Gynecology)
Alex S. Keuroghlian, MD, MPH (Psychiatry)

International Society of Experimental Hematology Donald Metcalf Award
David Scadden, MD (Center for Regenerative Medicine)

Italian Bilateral Scientific Cooperation Award
Alessio Fasano, MD (Pediatrics)

John T. Potts, Jr., MD, Faculty Mentoring Award
Rochelle P. Walensky, MD, MPH (Infectious Diseases)

Manfred S. Guttmacher Award
Jake Holzer, MD (Psychiatry)

Morton M. Ziskind Clinical Research Scholar Award
Andrew Synn, MD (Pulmonary and Critical Care)

2019 O'Keanos-CAPA Young Investigator Award from the Chinese-American Chemistry and Chemical Biology Professors Association
Steven H. Liang, PhD (Radiology)

National Academies of Science, Engineering and Medicine Committee
Phyllis Carr, MD (Women's Health Associates)

National Gold Medal for Achievement in Medicine and Science in Belgrade, Serbia
Branko Bojovic, MD (Surgery)

NEJM Journal Watch Emergency Medicine Editor-in-Chief
Ali Raja, MD, MBA, MPH (Emergency Medicine)

The Ophthalmologist's 2019 Power List
Demetrios G. Vavvas, MD, PhD (Ophthalmology)

Partners Healthcare Innovator Award
Marc Succi, MD (Radiology)

Partners Innovation Discovery Grant 2019: Artificial Intelligence (AI) Meets Clinical Care Award
Charles Bormann, PhD (Obstetrics and Gynecology)

Respiratory Disease Young Investigators' Forum Basic Science Research Award
Jehan Alladina, MD (Pulmonary and Critical Care)

Robert Wood Johnson Foundation American Heart Association-Harold Amos Medical Faculty Development Program Award
Mabel Toribio, MD (Endocrinology)

Sleep Research Society 2019 Outstanding Early Investigator Award
Jacqueline M. Lane, PhD (Center for Genomic Medicine)

Society of Behavioral Medicine Distinguished Scientist in Complementary and Integrative Medicine Award
Ana-Maria Vranceanu, PhD (Psychiatry)

Society of Behavioral Medicine Fellow
Ana-Maria Vranceanu, PhD (Psychiatry)

Society of Nuclear Medicine & Molecular Imaging 2019 Technologist Section Travel Award
Ping Bai, PhD (Martinos Center)

Society of Thoracic Surgeons and the Thoracic Surgery Foundation Nina Starr Braunwald Research Fellowship Award
Philicia Moonsamy, MD (Surgery)

2019 SPIE-Franz Hillenkamp Postdoctoral Fellowship
Andreas Wartak, PhD (Wellman)

Research to Prevent Blindness 2019 Stein Innovation Award
Eric Pierce, MD, PhD (Ophthalmology)

Triple Negative Breast Cancer Foundation 2019 Hero Award
Steven Isakoff, MD, PhD (Cancer Center)

University of Virginia Medical Alumni Association and Medical School Foundation Early Achievement Award
Scott Beach, MD (Psychiatry)

Vehbi Koc Award
Mehmet Toner, PhD (Surgery)

Von Hippel-Lindau (VHL) Alliance Grant
Othon Iliopoulos, MD, PhD (Cancer Center)

2019 William B. Coley Award for Distinguished Research in Basic Immunology
Brian Seed, PhD (Center for Computational and Integrative Biology)

Women's Dermatologic Society (WDS) Legacy Award
Lynn A. Drake, MD (Dermatology)

PROMOTE

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

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

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

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

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

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

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

External Communications: We publish a quarterly newsletter designed for our donor audience called the MGH Research Scholars Notebook. We have published seven volumes to date and these newsletters include information about our MGH Research Scholar awardees and their accomplishments. This publication is available on the Mass General website and it is emailed directly to our donor community.

The Research Institute Blog: Our Blog is in its third year and has become a major vehicle for sharing research news and updates both within the Mass General community and to the world at large. The blog typically features three new postings each week and includes original content, recaps of news articles, awards and honors announcements, infographics, tips for communicating science and much more. This past year blog traffic nearly tripled (198% growth) and our blog was recognized in the industry with two awards and a distinction: Gold Award for Best Blog by the NESHCo Lamplighter Awards, Gold Award for Best Healthcare Content and a Distinction for Best Blog by the Healthcare Leadership Awards. Since launching the blog, we've had 608 published blog posts, 112,132-page views, and over 88,000 visitors.

Social Media: In 2019, we used promoted posts to reach 10 million people on Facebook (@MassGeneral_RI), and those posts generated approximately 1 million engagements (likes, shares, comments, reactions, link clicks, etc.). In addition, we more than tripled our number of Facebook followers from 1,559 to 5,110 in 2019.

The MGRI Twitter (@MGH_RI) account is used primarily as a tool to engage and support the scientific community at Mass General and beyond. In 2019, we saw steady growth of 150+ followers per month and added 1,897 new followers over the course of the year for a total of 4,745 followers.

We have also increased the impact of our research marketing via targeted Facebook and Twitter 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 social

media, and a study about new treatment strategies for depression to individuals who follow organizations that promote mental health awareness.

In the fall of 2019, we relaunched our Instagram account (@MassGeneral_RI) to coincide with announcing the winner of the Image Contest. In the brief time since launching we have accumulated 126 followers.

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

In April, we teamed up for the second year with Mass General investigators to host five tables at the Science Carnival and to host a Science Slam as part of the Cambridge Science Festival. On April 12, we participated in the Science Carnival and Robot Zoo with scientists from the Center for Engineering in Medicine, Wellman Center for Photomedicine, Mucosal Immunology and Biology Research Center and the MGH Institute of Health Professions. Mass General scientists created four interactive displays and the Research Institute team created and distributed a coloring book, managed and coordinated the event, and developed coordinated branding so that Mass General stood out in the crowded room. It was enormously successful.

On April 18th, we co-hosted a Science Slam with the Harvard Health Innovation Network (HHIN) at Daedelus in Cambridge. The Science Slams have been so successful we decided to hold them quarterly. In 2019 we held four Science Slams and have co-hosted with the HHIN, the Mass General Thematic Research Centers and the Martinos Center with plans to co-host with Surgery and the CNY Quality of Life Committee in 2020.

These events gave researchers an opportunity to talk about science in front of a lay audience, and to help foster the development of future scientists.

Internship Program: We also continued our communications internship program, which is designed to give aspiring science writers from local colleges—and from within our own postdoctoral community—an opportunity to write stories and social media posts about Mass General research. We hosted two interns in 2019.

Externship Program: We hosted six educators from the Boston Public School system over April vacation, April 16-19, for a pilot externship program. This was a chance for community teachers in middle and high school settings to learn from scientists and clinicians about opportunities for careers in the biotech and healthcare operations fields. The externship program was developed through collaboration between the Mass General Research Institute, the Mass General Center for Community Health Improvement, and the Boston Public Schools Office of External Affairs.

Collaborative Efforts: We continue to work closely with our colleagues in Public Affairs, Development, and 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). The sharing of content and ideas across these departments has continued to improve 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.

Development

We work closely with our colleagues in the Development Office to inspire donors and friends 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 2019, we selected five new MGH Research Scholars, bringing the total number of MGH Research Scholar awards given over the past nine years to 60. This remarkable donor-supported program has had a substantial impact on the careers of the awardees and the advancement of research at Mass General. In addition, we have established four Endowed MGH Research Institute Chairs, thanks to the generosity and vision of donors who recognize that talented scientists transform the compassionate care our patients receive. We continue to work towards our goal of supporting more members of our research community with MGH Research Scholar Awards and Endowed MGH Research Institute Chairs.

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

The Research Institute leadership team hosted numerous meetings, lunches, and lab tours with individual donors and prospective donors in 2019, including the wildly popular LAB DAY hosted in September. Eight scientists across two campuses opened their labs to groups of donors, their friends and family members. Guests included donors to the MGH Research Scholars program and other programs across the hospital. The full day tour gave donors the ability to see first-hand the impact of their support.

In 2019, we continued our work with the Research Institute Advisory Council. With leadership provided by our new Chair, Dr. David Altshuler, we organized an annual meeting followed by a luncheon with a Science Slam that was exceptionally well attended. With the Council's guidance we will continue to raise awareness for the Mass General research community especially now that The Campaign for Mass General is gearing up for public launch next year. Overall, the success of our collaboration with the Development Office can be seen in their willingness to offer donors the opportunity to make research a philanthropic priority and in the growing portfolio of support for our scientists.

Strategic Alliances
We developed the Strategic Alliances Initiative with the objective of helping our investigators establish productive collaborations with industry, biotech and venture communities at all stages of their work; from fundamental research and proof of concept (early translation), to development and transfer to market and patient care (late translation). With the incredible support of the Strategic Alliance (SA) Committee composed of key leaders in the field of biomedical research from industry and venture capital, we were able to push many of our programs forward in 2019. The Strategic Alliance Initiative focuses on three key areas: building the research portfolio, assembling thematic programs and launching a unique translational training program.

Research Portfolio: In 2016, we initiated the Mass General research portfolio initiative as a key mechanism to build common understanding of the scope of research at Mass General. This portfolio serves as a comprehensive scientific foundation for promoting our research, enables programmatic efforts across departments and centers and establishes a sound mechanism to define well-informed strategies and tactics for engaging with industry across different themes. In 2019, we continued using collected research outlines to invite researchers to present their work for colleagues from Mass General Development and Partners Healthcare Innovation at our monthly Research Portfolio Café Sessions. Over the past three years, 49 investigators from 17 departments and centers presented at 17 sessions. In addition, researchers who engaged with the Research Institute by submitting scientific outlines were often selected to have their work highlighted by our marketing team.

Thematic Programs: The RIAC Strategic Alliance Programs (RIAC-SA) come from research "themes" that were collected from departments, centers and institutes across campus. In total, we have built seven SA programs around Epigenetics, Cancer Immunotherapy, Neuroinflammation in Neurodegeneration, the Microbiome, Cardiometabolics, Rare Diseases, and Antimicrobial Resistance that bring together 189 investigators from many departments and thematic centers across the institution. In total, we organized 24 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.

Bridging Academic with Industry Course: Given the vital importance of the academic-industry bond in transforming discoveries into new and affordable cures and medical solutions for patients in need, we developed and launched an innovative translational training program co-directed by Gabriela Apiou, PhD, Director, Strategic Alliances, and Robert Tepper, MD, Partner, Third Rock Venture. The program teaches Mass General faculty (MD and/or PhD) and aims to teach them: Why and how to think about the potential applications of their research early in the discovery process; how to develop a translational plan that includes research, intellectual property, and business perspectives; how to build and manage a translation team; and how to interact with industry.

The program involves a 14-week course on research strategy and tactics and a solution-driven project competition. The inaugural program

was very successful with a class of 12 faculty trainees from 8 departments and centers across the institution. Five project teams competed and two awards of $150,000 each were given to the winning two project teams. Our faculty included 21 instructors from academia and 18 from industry. Importantly, the awards for the best translational projects were funded through philanthropy. We launched our second class in January 2020 with 19 faculty trainees from 13 departments and centers at Mass General.

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

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

https://www.massgeneral.org/research/division-clinical-research/

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 24th year.

Since its inception, the DCR has had a simple and constant mission: to increase the quality, quantity, and efficiency of translating basic science advances into improved care for our patients. Last year, DCR Faculty had provided over 650 individual consultations to Faculty and Staff from over 25 divisions and departments across MGH and PHS. DCR Education Center had offered 200 live and online courses with over 6,000 participants.

More recently, DCR has become the hub for all PHS services (CTO, IRB, QI, Innovation), as well as the Harvard Catalyst.

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

DCR Centers

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

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

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

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

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

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

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

Yvonne L. Munn Center for Nursing Research, Gaurdia Banister, PhD, RN
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 such as 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 nurse scientists at MGH through dissemination in high-impact journals and presentation at internal and external scientific meetings.

DCR Units

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

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

Global Health Research Unit (GHRU), Jessica Haberer, MD, MS
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, neurology, psychiatry, and behavioral science. Research methods are both quantitative and qualitative. Funding experience includes the US National Institutes of Health, the Bill and Melinda Gates Foundation, other foundations, USAID, and philanthropic support. The GHRU also includes experts in grants administration and management of global health research projects.

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

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

Mentoring Corner, Karen K. Miller, MD
The Mentoring Corner Unit assists mentees in identifying appropriate mentors, mentorship tools and provides advice on all aspects of K-award applications.

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

Patient-Centered Outcomes Research (PCOR) Unit, Andrew Nierenberg, MD
The Patient-Centered Outcomes Research (PCOR) Unit was established to address the research needs and funding opportunities provided by the creation of the Patient-Centered Outcomes Research Institute (PCORI). The PCOR Unit seeks to facilitate research by providing support in each of these domains. Specifically, the PCOR Unit advances work through four complimentary strategies: working with the DCR Center for Clinical Research Education to host a series of educational seminars and workshops to prepare investigators to submit PCORI applications; providing project specific consultative services through review of investigator-initiated proposals in the pre-award phase; supporting the expansion and evaluation of methods for collecting patient-reported outcome measures, specifically as routine components in clinical care settings; establishing best practices for patient and community engagement strategies and disseminating these resources to investigators.

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

Qualitative and Mixed Methods Research Unit, Elyse Park, PhD, MPH, Christina Psaros, PhD & Lara Traeger, PhD
The Qualitative and Mixed Methods Research Unit helps researchers investigate the "why" and "how" of questions related to healthcare and biomedicine. The Unit provides free consultations in qualitative and mixed methods study design and execution. The Unit's consultations

advise investigators on all aspects of qualitative study design, data collection, interpretation and publication of study findings, feedback on draft research proposals and identification of potential collaborators.

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

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

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

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

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

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

The Partners Biobank at MGH was devised to be a collaborative effort among patients, clinicians, and scientists to better understand disease, identify novel targets for therapy, and enable personalized medicine, by collecting and storing fully consented blood, serum, and plasma samples, linked to electronic medical records and lifestyle and family history survey data, from patients across the institution. Through the Mass General Research Institute, resources were committed to add personnel, space, and equipment to jumpstart the consent and collection program at Mass General. In its first five years of operation, the Biobank collected only 8,500 samples across all of Partners. With the additional resources contributed over the past five years, we have seen a dramatic increase in patient recruitment to over 113,000 consented patients. Through the dedicated efforts of the team, including site-Principal Investigators Drs. Kerry Ressler (McL), Ross Zafonte (SRN), Lucia Sobrin and Janey Wiggs (MEEI), and Mass General-based managers Joe Coletti and Tasha Tchamitchian, the Biobank program has enjoyed great success since the implementation of the strategic plan. From a recruitment standpoint, the Mass General program met and exceeded recruitment metrics in 2019 thanks to the sustained growth of our team and successful partnerships with high volume clinical departments and research teams including Pathology; the Cancer Center; Neurology; Urology; Center for Perioperative Care; the Emergency Department research team; DOM, General Medicine, Surgery, and Oncology inpatient units, and collaborating studies including the Cardiovascular Biorepository; the Biorepository for Neurological Injury; the MGH Department of Neurology Biobank; the Biorepository for Thyroid, Parathyroid, and Adrenal Disease; the SNP study; and the Partners Calciphylaxis Biorepository. Inpatient recruitment is now one of the Mass General Biobank's most successful recruitment sites and a testament to the synergistic collaboration between our clinical and research teams at Mass General.

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

The Mass General Research Institute continues to be committed to increasing awareness of the Biobank, and now All of Us, to patients and investigators. Our 2017 investment in the creation of two interactive electronic "kiosks" in the Wang and Yawkey lobbies greatly expanded visibility of these programs in the MGH community and have drawn publicity and recognition by local media (NPR). Because the kiosks have been so well received, they will be "refreshed" in the spring of 2020. Two dedicated consent and collection rooms on Wang 2 and Yawkey 3 solidify the link between research and clinical care, as patients who come to the Biobank labs can contribute both research and clinical samples at the same time. The Community Advisory Panel (CAP) that launched in 2015 has expanded its membership and has added All of Us to its purview. The CAP continues to be a tremendous success with members contributing valuable input on patient engagement efforts. Biobank sample collection has been accelerated Partners-wide by the integration of Sunquest sample collection orders into Epic, which has made contributing a sample to the Biobank significantly easier for our patients. The Biobank has also expanded its services to investigators and enhanced the profile of research activities at Partners sites both at an institutional and national level. Partners efforts to genotype 40,000 Biobank samples continues to generate research requests with data for over 36,000 genotyped patients to date freely available to investigators via the Biobank Portal. To date the Biobank has supported over 240 studies with specimens and data. In parallel to the genotyping work, the Biobank continues to return medically actionable genetic results for pathogenic variants within 59 genes (as recommended by the American College of Medical Genetics and Genomics) to Biobank participants. The Biobank provides genetic counseling services to return these results and assist with clinical confirmation. Over 100 medically actionable results have been returned to patients so far.

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

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

Translational Research Center (TRC) — Mason Freeman, MD

Goals

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

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

These activities are typically time-intensive projects and require significant commitments on the part of the TRC staff. The TRC must become familiar with the details of individual investigator's projects to facilitate meaningful interactions with the FDA, external contract research organizations, or third-party vendors whose expertise is needed to enable a translational project to advance.

Accomplishments

During fiscal year 2019, the TCRC was engaged in conducting 69 active clinical trials sponsored by industry. This represents a growth in trial activity from 28 studies in FY 2017, when the new facility opened, followed by 49 studies in FY 2018. The indirect cost recovery to the

hospital from this trial work was $940k. The trials were again distributed among many of the Hospital's clinical departments including Dermatology, Medicine, Neurology, Pediatrics, and Surgery. Neurology and Medicine PI's continue to constitute the most active group of investigators. The breadth of diseases under investigation reflects the wide array of research interests and patient populations that can only be assembled at a general hospital. These include conditions such as severe alopecia areata, hereditary angioedema, recurrent C. difficile infections, idiopathic pulmonary fibrosis, gout, ALS, disorder of bone metabolism, Alzheimer's disease, adrenomyeloneuropathy, cystic fibrosis, multiple sclerosis, GM2 gangliosidosis (Tay-Sachs and Sandhoff diseases), severe peanut allergy, and precocious puberty. Most of these studies are testing novel, experimental drug therapies in their respective patient populations and are leveraging the connections made possible by having a large local biopharma ecosystem adjacent to the MGH. Therapeutic modalities for the treatment of these disorders range widely from traditional oral small molecules to engineered proteins, gene therapy mediated viral vectors, or various new forms of ribonucleic acid containing anti-sense technologies. The influx in new studies has, of course, been accompanied by a substantial rise in the number of patient visits to the TCRC facility, more than tripling in the past 3 years to ~1100 in 2019.

One of the areas the TRC chose to focus on in the past year was the underutilization of the White 12 TCRC facility's overnight care capacity. While all of the rooms on White 12 unit are used on a daily basis, a small percentage of the studies actually require an overnight stay. The use of an inpatient bedroom during the day, rather than an outpatient clinic examining room, is necessitated by study requirements (e.g., significantly ill or fragile patient, prolonged IV infusion, very frequent (q 10 min) blood draws over several hours). In the original specifications for utilization of the new Translational and Clinical Research Centers space on White 12, a robust overnight trial business was anticipated. It has been more difficult than anticipated to recruit such studies to the unit. Most of the difficulty resides in the nature of the studies that require prolonged stay and our lack of investigator interest or time in committing to perform those. To further enable this effort, the TRC hired Dr. Rick Mofsen in the summer of 2019 to build out this activity. Dr. Mofsen ran a very successful phase 1 facility in St. Louis, MO for many years before coming to the MGH and has an extensive network of biopharma relationships arising from that experience. He has begun to recruit trials requiring overnight stays to the MGH and we anticipate that work will begin to affect our workload by the summer of 2020. These trials will initially focus on treatments that fall within his area of expertise, which is acute psychiatric illness, but it is anticipated that this will expand over time. Dr. Mofsen will not only recruit these trials but also serve as the PI for most of them. He becomes the first full time clinical investigator employed by the TRC. This model for investigator involvement in the TRC was proposed in the original business plan outlined in the MGH Strategic Plan that led to the creation of the TRC and renovated TCRC unit, but funding constraints precluded its adoption previously. The expectation is that a small number of these prolonged-residence trials performed yearly can generate sufficient resources to enable the TRC to hire more clinical investigators who are interested in devoting their careers to the task of improving clinical therapeutics in their specialty. The studies typically have only 1-3 patients housed at any one time, so should not adversely affect the conduct of other studies in the unit. A key to the success of this plan is the ability of the trials to recruit substantial numbers of patients who are willing to participate. Dr. Mofsen's experience in running a very successful facility previously has brought a host of new ideas to the TRC for ways we can improve patient recruitment, a challenge that affects almost all academic medical centers and, if implemented, could potentially benefit trial recruitment broadly at the institution.

Improvements in administrative processes have continued. Lynelle Cortellini, who previously served as the TRC administrative director, assumed the role of the administrative director for the combined TRC/CRC programs in May 2018. She now manages both the industry trial work and the NIH-funded (or departmentally funded) investigator portfolio of the CRC that is overseen via the Harvard Catalyst grant. Lynelle has brought new administrative methods to the overall TCRC operation and is working hard to streamline the burdens of study initiation that continue to frustrate busy PI's. Many of the computer tools used to improve efficiency were originally developed in the Translational Medicine Group/Translational Research Center and were ported over to support CRC investigators as well. This includes the development of a new TCRC website and database that features capabilities such as staff training record tracking for audit purposes, protocol metadata tracking, and access-based file management. A new module planned for 2020 is a robust sample tracking system to follow samples from time of blood draw to final disposition out of the unit.

The TRC study staff has continued to advance programs and build new relationships that are designed to enhance the trial work conducted in the TCRC. The excellent working relationship between Dr. John Stone in Rheumatology and the TRC has led to a sponsored grant to Dr. Stone and the TRC to jointly conduct a multi-center clinical trial on behalf of Principia using their novel anti-inflammatory drug directed at IgG4RD. The consulting work performed last year for Drs. Robert Levine and Jacob Dal-Bianco of Cardiology has resulted in trial initiation of a new therapeutic approach to improving outcomes in children with rheumatic heart disease in South America. During 2019, the

TRC director and program manager both met with a growing number of faculty members and trainees individually to discuss careers in translational medicine both in academia and in industry. These meetings included individuals from Endocrine, Pediatrics, Emergency Medicine, Radiology, Infectious Disease, Pulmonary, Gastroenterology, Cardiology, Surgery, and Oncology. It is clear that the pull of companies from the biopharma world in the Boston-Cambridge area is growing and the TRC serves as a resource for our trainees to learn more about what a career in that sector entails. The TRC director continues to mentor fellows in the Innovation Office's external biopharma fellowship program as well as faculty in the Research Institutes Bridging Academia to Industry course.

The long-standing TMG/TRC oral diabetes drug development program, sponsored by Theracos, completed its last phase 3 trial in November 2019. This 1700 patient international trial easily met its primary endpoint objective of demonstrating significant hemoglobin A1c lowering but also produced a clear reduction in major cardiovascular events in the active treatment group compared to those receiving placebo. The TMG/TRC team is now preparing to file the NDA on behalf of Theracos in mid 2020 with anticipated approval of the drug being the first half of 2021. As mentioned in last year's summary, we believe this effort is unprecedented in the history of an academic drug development group. The TRC program manager, Dr. Yuan-Di Halvorsen, is primarily responsible for this achievement.

Adaptation Planned
The major new initiative the TRC has undertaken in 2020 was outlined above in response to the need to improve the TCRC overnight bed utilization rate. Dr. Rick Mofsen was hired to recruit trials that require a domiciled stay for study completion which will improve our bed utilization and enhance revenue generation in the TCRC.

SUPPORT

MGH Research Institute Hits $1 Billion! — 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.)*

The MGH Research Institute reached a very impressive milestone in FY 19. Research revenues finished the year at $1,013M ($779M direct costs and $234M indirect), a $85M increase (9.2 %) from FY18. Our awarded dollars from the National Institutes of Health (NIH) in FY18 increased from $466M to $500M (7.3% increase). In FY19, MGH ranked #11 in NIH funding for all institutions, and continues as the #1 ranked independent hospital, a spot we have held for the past 20+ years. The percentage of funding awarded to MGH from the entire NIH extramural grant pool (market share) grew slightly to 1.7%, up from 1.6% the previous fiscal year.

Overall, MGH submitted 4,335 research proposals to all sponsors in FY19, down 1.8% from the prior fiscal year. This marks the third straight year that research applications submitted to all sponsors has deceased. This may be due to the dramatic increase (26.7%) in NIH dollars awarded to MGH over the past three years. DHHS success rates for MGH proposals is an impressive 30%, which is ten points higher than the NIH national average of 20%.

Research expenditures from direct DHHS funding (which consists mostly of NIH funding and excludes incoming subcontracts), accounts for 43% of MGH research. DHHS-sponsored research expenditures increased from $386M in FY18 to $432M in FY19. In addition, Federal Subcontract (predominately NIH) expenditures were $105M in FY19, increasing from $101M in the previous year. This is an indication that our collaborations with NIH funded investigators at other academic institutions continue to remain strong and increase.

Research expenditures for all of our other non-NIH sponsor types were strong in FY19 and totaled $475M. The overall growth rate was 8% over FY18. The Non-Profit (13.9%), Industry/Corporate (6.2%) and All Other Sponsor (15.1%) categories saw increases from the previous fiscal year. Both Foundations (-5.2%) and Other Federal (-8.1%) categories saw decreases from FY18. Over the past decade, MGH research expenditures across all sponsor types has grown 61.3%.

Our research activity type is split evenly between clinical (clinical trials and other clinical research) and basic/fundamental research at 47% each of the total research portfolio. Training activities make up the remaining 6%.

In aggregate, research activity (direct + indirect dollars) continues to comprise slightly under one quarter (22%) 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

Thank you, Michael!
Beginning in January 2020, leadership in our Research Space Management Group (RSMG) will transition with the retirement of Michael Fisher to Wendy Hobbs and Patricia (Trish) Frederico. Wendy will become Director of RSMG and Trish will assume an expanded role as Director for Research Building Management.

Working with Rick Bringhurst (former SVP for Research), Michael literally created RSMG in 1997. He has been at MGH for over 27 years, joining the hospital as a manager in Materials Management before transitioning to research in 1997. Michael became Director of RSMG in 2005; during his tenure, MGH research space more than doubled from 600,000 SF to over 1.2M SF on multiple campuses. He worked closely with Principal Investigators and other scientists to develop new research space paradigms and ensure the successful completion of every research space renovation and construction project, large and small, since 1997. These projects, beginning with the major renovation of the second floor in Building 149, through construction of the Simches Building, the fit-out of the Ragon Institute in Cambridge, and the recent spectacular renovation of the tenth floor in Building 149, all stand as a testament to Michael's vision, dedication, and leadership.

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

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

MGH currently owns or leases approximately 1.31M net assignable square feet (nasf) of space, essentially the same amount as last year, but nearly double the amount of research space that existed in 2000. Research sites now exist in forty-four buildings across seven campuses in five cities. The percent allocations amongst the campuses are 42% in the Charlestown Navy Yard campus, 22% on the Main Campus, 22% in Charles River Park, 7% on the Boston Campus, and the remainder in various metro Boston and Cambridge locations.

This year the Indirect Cost (IDC) density (defined as the recovered indirect costs per square foot) increased from an average $183 per square foot in Fiscal Year 2018 to $185 per square foot. The main causative factor for this increase was the increase in the Research Portfolio. Of the major campuses listed above, the Boston Campus has the highest IDC density, $292. Major research groups contributing to the high IDC density have research sites at Simches, Building 149, 100 Cambridge St., 165 Cambridge St., Thier, 101 Merrimac St., 125 Nashua St.

Fulfilling outstanding space requests remains one of RSMG's most difficult challenges, particularly when there are few if any opportunities to add new space to our current inventory; thus, the only option available is to renovate existing space to make it more efficient. RSMG works with the research community to better understand the true space requirements and promote space adjacencies amongst collaborative groups. In September of this year space requests increased to 62,925 nasf for wet space and 55,150 nasf for dry space, a total of 118,075 nasf.

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

In Fiscal Year 2019, thirty-three renovation projects, whose costs totaled approximately $7M, were completed. These projects included CVRC Zebra Fish Core on B149-04, Radiology New Imaging Technologies Lab renovations on B75-01, CCM Satellite Housing on 65L-05, and the completion of the Simches-08 CCM Storage to Housing. Thirty-eight projects, totaling $43.6M in project costs, are in process. Major ongoing projects include the i3/IBC Research Program on B149-02 and 10, Cardiology Lab renovation on Simches-03, Wellman Lab renovation on Bartlett-04, and Neurology Office renovation on 101 Merrimac-03. Depending on the outcome of Capital Requests for Fiscal 2020, there could be as many as twenty-five to thirty additional projects totaling $20M initiated over the next few months.

RSMG continues to work with the Partners' Research Applications and Analytics team to update and improve the functionality of the Research Space Management System and the Microstrategy Reporting module. In Fiscal Year 2019, yearly certification of space, agreements, and people integrated into Insight and was certified by the Departments electronically. Work will begin in the new year on implementing new space performance metrics which are designed to more accurately capture the cost of research at any designated research site. This detail is invaluable for senior management when assessing space requests and planning for new program initiatives and Institutional expansion needs. Additionally, this provides a new tool to the Department in managing their space.

In addition to space-related responsibilities, RSMG also operates a Support Core which services 75 research laboratories. To accommodate a growing research need, Ethylene Oxide Sterilization was added to the core services. RSMG is responsible for updating all floorplans for research space and designing and approving furniture purchases for research areas. As part of the ongoing award process, RSMG, in conjunction with Research Management, documents site locations for all research grants, helping to ensure the correct IDC rate is applied. This year RSMG, in collaboration with BWH, worked to provide system access to the Department's space data through the new Insight Space Module. In additional to Departmental reporting, RSMG is in process designating sites as Wet or Dry and reporting out on those attributes.

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

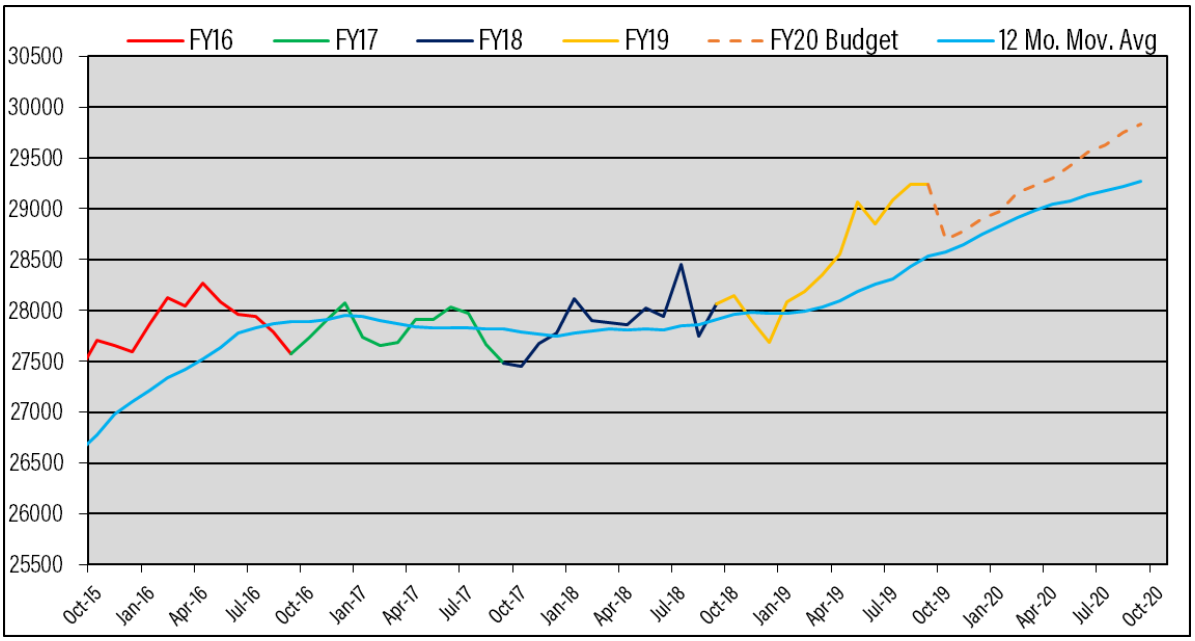
On any given day, approximately 105,000 mice, rats, guinea pigs, rabbits, sheep, pigs, non-human primates, and amphibians plus more than 35,000 zebrafish are housed and used within 95,000 square feet dedicated for such purposes on all 3 MGRI campuses. In addition, the MGRI operates two off-site facilities including a BL-2/BL-3 rodent facility that supports the Ragon Institute in Cambridge, MA, and a rodent facility at 65 Landsdowne Street. An additional 40-50 non-human primate housing units are maintained under a contractual agreement with Biomere (Worcester, MA) . And, in an effort to offer relief in our heavily utilized in-house space, additional collaborative agreements were established in 2019 between MGH and Accuro Farms, Inc (Southbridge, MA) and Tuft's University (North Grafton, MA) for livestock housing.

The Center for Comparative Medicine (CCM) is the central laboratory animal care service for MGRI investigators and is led by Donna Matthews Jarrell, DVM, DACLAM, who also serves as the MGH Attending Veterinarian. CCM facilities are located on the main Boston research campus, the Charlestown Navy Yard (CNY) Campus and the Cambridge Campus. Its activities include husbandry, animal procurement, importing and exporting mouse lines from other academic institutions, inter-institutional transportation, preventive and clinical veterinary care, training in animal manipulative techniques, surgery and post-operative support, mouse breeding and colony preservation, and consultation in animal modeling and protocol design. There are approximately 120 employees, including seven staff veterinarians (six of whom are board-certified in laboratory animal medicine) and a leadership team of 24 mid- and director-level managers, who provide these services throughout the MGRI. In addition, CCM has a training program in Laboratory Animal Medicine and Management (LAMM), offering a veterinary residency with an equal focus on clinical laboratory animal medicine and program management. This residency is recognized by the American College of Laboratory Animal Medicine (ACLAM) as well as MGH's Graduate Medical Education (GME) Program.
Specific efforts were taken in 2019 to:

- Continue to partnership with the MGH IACUC in the improvement of IACUC operating systems and animal welfare educational tools for the research community. Educational materials focus on innovative methodologies including video demonstrations and visual or pictorial-based descriptions for utilization in the laboratory areas.
- Expand Veterinary Services research collaboration capabilities especially in the areas of environmental enrichment and behavioral training, anesthesia monitoring and post-operative care for USDA-regulated species. This resulted in an 13% increase in hours while controlling staffing levels in the division. In addition, they established new animal care standard work for unique species

such as snakes for new research initiatives in imaging.

- Complete the implementation of key capital projects on both the Boston area campus as well as the CNY to increase the utilization of rodent caging capacity as well as address on-going HVAC environmental deficiencies. While rodent occupancy continues to increase, it is not meeting the overall needs of the MGRI with the funding growth observed on the past year.



- Control operational costs through continued elimination of non-valued added activities and process improvements resulting in a positive operating margin (OM) for FY19. The outcome of these efforts is that MGH per diems remain within the lower third for all Boston/Cambridge academic animal programs.

Lastly, CCM continued to host site visits in 2019 from manufacturing, healthcare, research and laboratory animal leaders who expressed interest in adopting a lean operations model in their facilities and programs. Seminars and webinars on this subject were presented at annual conferences of the American College of Laboratory Animal Medicine, the American Association of Laboratory Animal Science and the Public Responsibility in Medicine and Research and through our on-going affiliation with the Vivarium Operations Excellence Network (http://www.voenetwork.com).

The Institutional Animal Care and Use Committee (IACUC) governs the use of research animals at MGH. The Committee is fully constituted in accordance with regulatory requirements and is comprised of 30 members including veterinary staff, IACUC administrators, volunteer research investigators from many departments and research centers throughout the MGH Research Institute, and two community representatives. The IACUC Chair is Dr. Warren Zapol, Reginald Jenney Professor of Anesthesia and (HMS) Chief Emeritus, Department of Anesthesiology and Critical Care Medicine (MGH). Dr. Zapol is supported by Dr. James Allan, Assistant Professor of Surgery and Associate Vice Chair-IACUC and Mark Randolph, M.A.Sc., Director, Plastic Surgery Research Laboratory, and Assistant Vice Chair-IACUC. The IACUC professional staff office supporting the IACUC is called the Office of Animal Welfare Assurance and is led by Anne Clancy, PhD. A membership drive is currently underway for the IACUC. The goal of the drive is to add new members and ensure representation from all departments who submit transactions to the committee for review. Having additional members covering more areas of expertise will allow for a more efficient and meaningful review.

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 approximately 920 active protocols being performed by over 370 Principal Investigators.

A primary role of the IACUC is the review and approval of IACUC applications. Over 3,700 transactions were processed by the MGH IACUC in the past year, an almost 50% increase in volume from fiscal year 2018, comprised of new protocols, triennial reviews and study amendments. "Bridge-the-Gap" amendments accounted for much of the increased volume; these were transactions necessary to transition protocols from Insight 3.6 to the new Insight 4.0 system. Relative to the prior year, there was a decrease in IACUC protocol review processing times across all transactions for fiscal year 2019. Median turn-around-times for new applications decreased 7 days (Full Board) and 19 days (Designated Review), triennial review applications decreased 11 days (Full Board) and 17 days (Designated Review), while Amendments decreased 24 days (Full Board) and 14 days (Designated Review). Complete metrics data for the MGH IACUC are available on the Partners Research Navigator website, Research-Analytics-Reporting.

A primary focus for the Office of Animal Welfare Assurance this past year was to work with Partner's Research Applications and Analytics, and the other Partner's IACUC offices, to implement the new Animals Module in Insight 4.0. This new module went live in Sept 2018, but the work continued throughout 2019 to transition all protocols to the new system and to implement updates and revisions to the new Animals and Meeting Management modules in Insight 4.0 to maximize functionality. The IACUC used the Insight 4.0 release as an opportunity to make significant improvements to IACUC protocol review procedure. Of note: (1) Reduction in wait time for review. The regulations allow IACUCs to review protocols by Full Committee Review (FCR) or Designated Member Review (DMR). DMR requires the committee be provided a 48-hr. period to decide whether a study must be reviewed by FCR or can be reviewed by representative members of the committee, assigned by the Chair. Historically the IACUC had one agenda per month identifying studies assigned to FCR and DMR. Now, the IACUC has one FCR agenda per month (convened meeting of the members) and weekly DMR agendas. This provides up to 5 agendas per month to which a study can be assigned, significantly reducing the "wait time" while studies are in queue ready to be assigned to a review agenda. (2) Reduction in review time. Working with the IACUC membership, target review completion times, we well as reminders, alerts, and other notifications were implemented to promote a timely review for protocols. The IACUC membership is committed to supporting research and completing protocol review within a reasonable time frame, no easy task given how busy our scientific volunteer members are with their own research! (3) Amendment review procedures. The IACUC understands the need to have nimble review procedures for protocol amendments to support the changing needs of research. A focus of the support office was to reduce turn-around-time for the prereview of amendments. The IACUC also released a new amendment review policy that documents the level of review required for different types of amendments. A new level of review – Veterinary Verification and Consultation (VVC) - was implemented in collaboration with the CCM Veterinary team. This allows for certain significant changes be reviewed by the veterinarian without needing FCR or DMR. Taking advantage of this new flexibility in the regulations can directly support the research community when critical changes are needed to studies already underway. Defining amendment review procedures in policy, together with information on turnaround times in our metrics reports, will help the community better plan for research by predicting the length of time it may take for protocol/amendment review.

Other areas of significance in the past year:
The IACUC released a new website, thanks to the help of Samantha Molle and the MGH Research ECOR office. The new website is on a platform consistent with the rest of the research community, is easier to navigate, and includes key information requested by the community. The website has information on the program that is needed for grant applications and sponsor contracts (accreditation dates etc.), tools and checklists to promote regulatory compliance, aids for navigating Insight 4.0 and a new, searchable, policy binder that allows researchers to find policy statements of interest based on key word searches. The new IACUC Web site can be found at: https://mghresearch.partners.org/iacuc-home/

The IACUC strives to effectively interact with the research community to support research, promote compliance, and protect animal welfare. The office released quarterly newsletters that detail, amongst other items, programmatic updates and changes, tips to successfully interact with the Insight and information on compliance issues so that labs can avoid the same problems. The newsletters are sent by email but can also be found on IACUC Web site. In an effort to "build-in" compliance, the office also developed checklists for laboratories to use to prepare for semiannual inspections. These checklists, and similar tools, define the regulatory standards we are all held to and allow the labs to self-audit and correct to ensure successful inspections by the IACUC and outside inspection agencies.

2019 brought a focus on reducing administrative burden and the "21st Century Cures Act" requiring NIH to conduct a review of applicable regulations and policies for the care and use of laboratory animals and to make revisions, as appropriate, to reduce administrative burden on investigators while maintaining the integrity and credibility of research findings and protection of research animals. MGH, with our fellow

Partner's IACUC offices and Partner's Research Compliance, reviewed and responded to solicitations from the Federal agencies regarding potential ways to reduce burden. The agencies have proposed modest changes which are still under review. For example, the USDA may align with OLAW and eliminate the need for Annual Review of IACUC protocols (Triennial Review will still be required). These changes will be implemented at MGH once approved by the Federal Government. While these efforts are appreciated, it must be noted that 2019 also brought a change in culture in agencies such as the USDA Animal and Plant Health Inspection Service (USDA APHIS). USDA, and OLAW, have increased the expectations of programs to identify and report noncompliance with the standards and are requiring the IACUC to implement more detailed and program-wide corrective actions when noncompliance is identified. The institution is strategizing our response to this increased scrutiny and changing regulatory environment and will share information about that over the coming year.

Research Support IS Committee — Harry W. Orf, PhD

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.

Over the past two years, the projects the committee worked on were directed toward working groups with different individuals from research administration leading each group. The committee structure loosened, and eventually gave way to a format where the working groups began to function more independently, interacting directly with research leadership to garner resources. Accordingly, for FY20, leadership has decided to reorganize research IS support by naming a Director for Research IS Support. The Director will restructure the RSIS committee and more actively guide its projects.

In FY19, under the individual working groups, progress was made in several areas.

- **Applications for Research Administration**: (a) streamlined Research Staff Cohort Identification System for further automation and delegation, (b) refined the Lab Safety Survey App and added an escalation module, (c) added features to the research training survey application for broader rollout, (d) expanded HR online evaluations across MGH.
- **Work on Applications for Research Training and Education**: (a) Continued work on LEARN to better support the research community's education and research training needs, (b)generalized educational event attendance tracking application to track general research events using badge readers and iOS devices.
- **Infrastructure Improvements**: (a) Broadened WIFI coverage of research space at CNY to near 100% and improved coverage in key areas on the MGH main campus, (b) facilitated network upgrades to bring 10 Gigabit to desktops, (c) added encrypted storage option to internal cloud platform so that it can be used for projects that need to store sensitive research data in an encrypted format.
- **Committee Work**: (a) Established a user group for telecommunication and video conferencing, (b) explored technology upgrades for shared conference rooms, (c) leveraged local expertise to solve problems and identify areas where consolidation of resources, services, and procedures can help leverage limited research resources, (d) worked with in-house departmental technical support groups to outline strategic needs for the coming years.

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

The Research Institute Training and Education Committee (RITE) continues to search for solutions to minimize the burden of research compliance and voluntary trainings while following required regulations. RITE is starting an initiative to make trainings unified, efficient, and streamlined with the goal of allowing researchers to conduct research across the newly named Mass General Brigham system (formerly Partners Healthcare).

The primary initiative in FY19 involved improvements to the new research hire survey that identifies which training the employee will need. The survey was refined and, instead of just notifying new employees by email of the requirement for them to complete the survey, time is now set aside during the formal MGH orientation for employees to complete the survey before going to their new labs to work.

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

Update – Isuggest Surpasses 1,400 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 2019, Isuggest received 200 new suggestions, bringing its total to over 1,400. Of these, over half (754) have been implemented. Since its renewed launch in 2016, Isuggest has been receiving 3-5 new suggestions a week, indicating that the program has effectively reached a steady state where it is known and used routinely across the research enterprise. This success has in large part been due to the continual upgrades to the program to make it more intuitive and user friendly, and to the continued promotion of the "Suggestion of the Month" campaign, where a slide describing a successfully-implemented suggestion along with a photo of the suggestor is shown at the beginning of every research meeting (ECOR, Research Council, RADG, etc.).

While many of the working groups within the Isuggest structure are functioning well and addressing their suggestions in a timely manner, some were lagging in their responses. To address this issue, new metrics were developed in 2018 to show both working group leaders and the Isuggest administrative management group which working groups are not operating effectively. Use of these metrics throughout FY19 has resulted in increased attention being paid to previously neglected suggestions.

Update – Research Safety Committee Completes Its Seventh Year

Meeting #28 of the Research Safety Committee (RSC) took place in December, marking the end of seven full years of the committee's existence. Formed in late 2012 and meeting quarterly since its inception, the RSC has a membership of over 70 people, including departmental safety coordinators from every research department and center in the hospital, as well as representatives from Compliance, Environmental Health & Safety (EH&S), Police and Security, and the Research Space Management Group. Task forces are formed on an as-needed basis to work on major safety projects. The committee meetings consist of an incident update from the MGH Director of EH&S, reports from active safety task forces, and presentations on various topics of safety and security of interest to the research community.

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

Goals for 2019 include: 1) Develop a controlled substance database to allow us to track permit holders and proactively notify them about renewals and training; 2) Roll out the "Help and Safety" app across the entire hospital; 3) Get full compliance with the new, mandatory employee research training survey, having it completed by all employees during orientation; 4) Led by our Research Compliance Officer, establish a comprehensive Research Safety Risk Assessment Program; 5) Deploy a glove and hand hygiene program across all research labs to include new signage on all research lab doors.

Update – MGH Onsite Indirect Cost Rate Holds Steady

In 2017, the federal government changed the indirect cost (IDC) negotiation schedule for MGH from a 3-5-year fixed rate basis to an annual rate negotiation with carry-forward adjustments. While this process is more labor intensive, it does provide the hospital with a more accurate annual picture of the cost of our research support elements and allows adjustments to be made to streamline them more quickly and reflect them in the published overhead rate. As a result of this new process, the government onsite IDC rate was reduced in 2017 from its previous fixed rate of 71% down to 68.5% for 2018 and down again to 68% for 2019. During this same time period, the offsite rate was increased from 27% in 2017 to 32% in 2018 and then increased again to 34% in 2019.

The federal negotiators were not able to site visit MGH in FY19, but their review of our submitted documentation resulted in them agreeing to hold our onsite and offsite fixed rates for 2020 at 68% and 34%, respectively. We also received approval to hold these numbers as

provisional rates for 2021 and 2022, subject to their next site visit, scheduled for next year. Overall, we were pleased that the 2020 rates held steady given that our research revenues grew while our space and associated indirect costs remained relatively static.

Update – Research Orientation

The restructuring and addition of new support components that led to the formation of the Research Institute were substantial and somewhat complex. These changes left many members of our research community without a good understanding of the new organizational structure or new services created to improve the enterprise. Accordingly, Research Management developed a comprehensive one-hour "Research Road Show" to explain the new structure and services available. The show consists of a slide presentation featuring an overview of organization and services and is followed by a live demo of the "Top Ten Things Every MGH Researcher Should Know" using links on the MGH research intranet page. To date, 50 road shows have been given at various departments and centers to audiences ranging from 20 to over 200. Given the implementation of formal research orientations for all new employees that began last year (see below), fewer formal road shows were given in 2019.

In 2018, Research Management developed a thirty-minute, condensed version of the Research Road Show that is now presented to new research employees during the weekly employee day-and-a-half orientation and the professional staff benefits orientation. The orientations began in Spring 2018 and are given by a rotating group of young research administrative and scientific leaders. The orientations have been very well received and have now become integral parts of the overall orientation process for all research employees. For 2019, we produced a thirty-minute video of the orientation that can be shown to the small cohort of new research employees (such as some transferred faculty and graduate students) who are not able to attend the in-person orientations. For 2020, we have updated the orientation with new facts and figures about the Research Institute and have also made the research training survey a mandatory component to be completed during the formal new employee orientation.

Initiative – IP Policy Change Re: Inventor Revenue Sharing Consensus

Recently, concern has been raised about the method by which inventor revenue sharing is determined when there are multiple inventors. Specifically, if any one inventor did not agree to the percent contributions agreed to by the other inventors, then the default was to require all inventors to share equally. Leadership was asked to review this policy and they devised a new process aimed to be more equitable and avoid a situation where one inventor can essentially force a distribution felt to be unequal by the others. Therefore, for each newly executed license, the following process will occur:

If more than one inventor was involved in the creation of an invention, the inventors will endeavor to unanimously designate in writing to the Chief Innovation Officer how the creator shares should be apportioned among the inventors of record. If the inventors fail to make such unanimous written designation in the time reasonably allotted by Innovation, the principal investigator (in the case of works produced under a grant or other sponsored research) or lab/unit chief (in other cases) shall escalate the matter to the appropriate institution leadership which, in most cases, is the applicable department/service chief(s) or chair(s). If the chief(s)/chair(s) have a conflict of interest or are unable to resolve the matter, the matter shall be referred to the institution senior leadership, such as a senior vice president for research or president, as appropriate. Whenever institution leadership is required under this policy to make share allocation designations among multiple inventors, the designation will be based on such criteria as the applicable leadership deems, in its discretion, to be appropriate.

If more than one department or service, more than one lab or unit, from one institution was involved in the creation of the intellectual property, the department/service share and the lab/unit share of annual net income shall be apportioned among the involved departments/services and labs/units in the same proportion as the creators' share is apportioned among the inventors, unless otherwise unanimously designated by the departments/services or labs/units prior to distribution.

Initiative – Improved Processes for Controlled Substances

Several years ago, the Mass State Department of Public Health (DPH) informed MGH that licenses for all controlled substances used in research would have to be held individually by each lab PI. Applications were filed hurriedly before the hospital could put a systematic process in place to track who had licenses and where their substances were stored. This year, new the MGH Research Compliance Officer, Kele Piper, began a process to document all MGH licenses and develop new tools to assist PI's in properly storing, tracking, and documenting controlled substance use. She created a new logbook that covers all the DEA and DPH regulatory requirements. She gave a

series of presentations to educate our researchers, she worked with the Partners Purchasing Department to get better documentation about drug sales from our vendors, and she commissioned the development of a web-based interface that will assist PI's with license tracking and renewal. This information will be stored in a hospital-wide database and will be particularly helpful during federal and state inspections/ audits.

Partners Research Departments

Office of the Chief Academic Officer (CAO) - Ravi Thadhani, MD, MPH

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

The office of the Partners CAO directly oversees several departments that support a $1.8 Billion research enterprise, including the IRB, Research IS & Computing, the Clinical Trials Office, Personalized Medicine (Partners Biobank and associated research cores). Together, these offices provide critical infrastructure that enable an efficient and innovative research enterprise. Research infrastructure at Partners also includes Research Management, Research Compliance, the Biosafety Office and the Office of Industry Interactions to ensure that all aspects of MGH's research are supported. In addition, Innovation and the Office of Industry Interactions ensure that industry engagements and our efforts to commercialize innovations developed by faculty are driven forward in a collaborative and compliant manner.

Human Research Affairs – Martha F. Jones, Vice President

Human Research Affairs (HRA) includes four areas: (1) the Partners Human Research Committees (Institutional Review Boards or IRBs); (2) the Partners IRB Operations Office; (3) the Partners Quality Improvement Program (QI) and (4) the Human Embryonic Stem Cell Research Oversight Committee (ESCRO).

The HRA provides oversight of all research involving humans conducted by employees from MGH, BWH, McLean, North Shore, Spaulding, Newton Wellesley and, most recently, Mass Eye & Ear. Under new nation-wide efforts to streamline the IRB review process for multi-site research and as required by new federal regulations, IRB review of research may be ceded to outside IRBs. Partners may also take on IRB review of research conducted by researchers at other entities participating in multi-site research.

IRBs: Research that is not exempt from the regulations must be initially approved by an IRB before any subject is recruited or enrolled. During the life of the protocol, the IRBs are then responsible for continuing review, review of any change to the protocol (amendments), adverse events, unanticipated problems, and deviations from the approved protocol. Details of each these reviews are mandated and informed by federal and state laws as well as myriad conditions of grant award. IRB review requires close

HRA IRB and IRB Office Activity
10/1/18 - 9/30/19 (FY19)

Activity	Full	Expedited	Administrative
Initial protocol review	338	2,396	
Continuing review	814	5,801	
Staff amendments	1	9	16,621
Non- staff amendments	174	6,838	
Other Events (e.g., adverse events	53	1,344	
Cede Reviews			167
Total transactions	**1,380**	**16,388**	**16,788**

coordination and communication with Research Management, Clinical Trials Office, Office of General Counsel, Office of Interaction with Industry as well as Partners- and institution-level signoffs and ancillary reviews.

IRB Operations Office: The IRB Operations Office provides administrative support for the IRBs, manages the application and processing of all protocol applications to the IRB, and acts as a liaison between the IRBs and the broader research community. Designated staff also provide determination under the federal regulations for research that is exempt from IRB review and research that falls outside of the definition of human subjects research. The Operations office also provides education and support to the research community, maintains policies and procedures, and documentation required by the federal regulations.

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

HRA QI Program Activity 10/1/2018-9/30/2019 (FY19)	
Type of Activity	**Number**
On-site reviews	121
Consultations	149
Presentations/education	58

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

As HRA supports the large and complex PHS research portfolio, it constantly encounters advances in science and research that present new ethical and regulatory challenges. Research has changed dramatically in the past several years. The single-site study has given way to multi-site (often multi-national) studies. New challenges of risk/benefit analysis that must be addressed include research in genetics, Big Data, data sharing, mobile apps, gene therapy and perhaps soon CRISPR. The HRA must be able to effectively implement changes that keep our researchers compliant with ethical and regulatory requirements while maintaining the ability to lead nationally and internationally in the conduct of important human subjects research.

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

- Mandated use of a single IRB for domestic multi-site research included in the 2018 Common Rules requires significant changes in HRA operations and coordination as PHS increasingly provides single IRB review, relies on external IRBs at other academic institutions and expands the use of commercial IRBs.

The 2018 Common Rule (the main federal regulation regarding the oversight of human subjects research) has undergone a major revision, effective January 21, 2019. Implementing this revised rule with currently little formal guidance from federal regulators will continue to challenge HRA and researchers. Additionally, the FDA is expected to revise its humans subjects regulations to harmonize with the 2018 Common Rule in the near future which will require additional adjustments to IRB and operational oversight activities.

In summary, the health of the PHS research enterprise relies on our ability to conduct safe, ethical, compliant, and leading research. The entities within the HRA are critical to support these areas in collaboration with the research community.

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

The Partners Clinical Trials Office (CTO) serves to facilitate, support and expand the conduct of clinical trials at PHS through service excellence and effective collaboration between investigators and industry sponsors. The CTO is responsible for services to the MGH research community including contracting, budget development/negotiation and electronic resources for clinical trials management. These service areas are designed to provide clinical researchers with resources to engage in local, national and international clinical trials

initiated by both industry and our investigators. Through participation in these trials, MGH is able to provide its patients with the most innovative and state of the art treatments for a variety of disease states and contribute to medical knowledge in support of the Hospital's scientific mission.

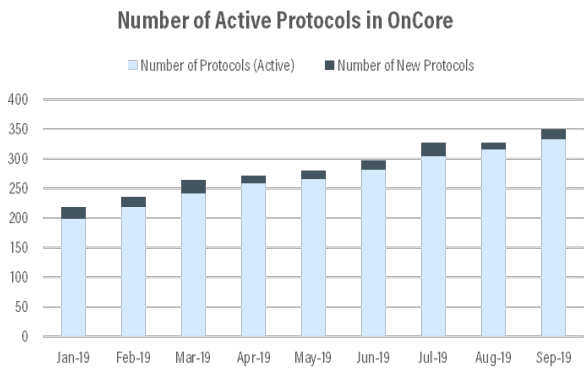
The Clinical Trials Office (CTO) achieved a number of important goals in support of MGH investigators and leadership this year. There are presently master clinical trials agreements with more than 50 industry sponsors, and an additional 40 department or investigator specific master agreements. These master agreements allow for efficient start-up of new clinical trials. Overall volume of executed agreements was steady between FY18 and 19 (Table), with an increase by 9% overall from 1,623 to 1,772. Amendments, support agreements and subcontracts were all increased while new clinical trials agreements decreasing by 9% at MGH from 214 to 195. In addition, there was a slight increase by 4% for trial budget approvals.

Agreement Type	FY19	% change FY19-18	FY18	% change FY18-17	FY17
Clinical Trial Agreements	366	-1%	370	15%	323
Amendments	451	17%	387	-20%	481
Support & Other* Agreements	239	14%	210	15%	182
Confidentiality Disclosure Agreements	598	3%	581	13%	512
Subcontracts	118	57%	75	-49%	147
Total	**1772**	9%	**1623**	-1%	**1645**

Executed Agreements Volume (all-PHS)

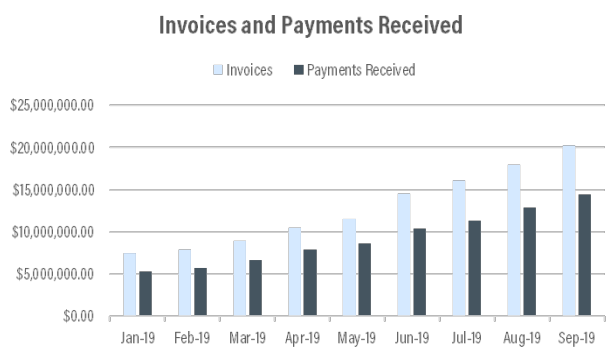
Significant advances in FY 19 have been achieved in the area of electronic clinical trial support services. OnCore CTMS optimization and utilization were the primary focus areas. The OnCore CTMS monthly metrics dashboard was developed and published to senior research leadership and department administrators. The dashboard provides insight to leadership on key financial metrics of accounts receivable and unbilled revenue for industry sponsored clinical trials. (Figures below).

OnCore CTMS

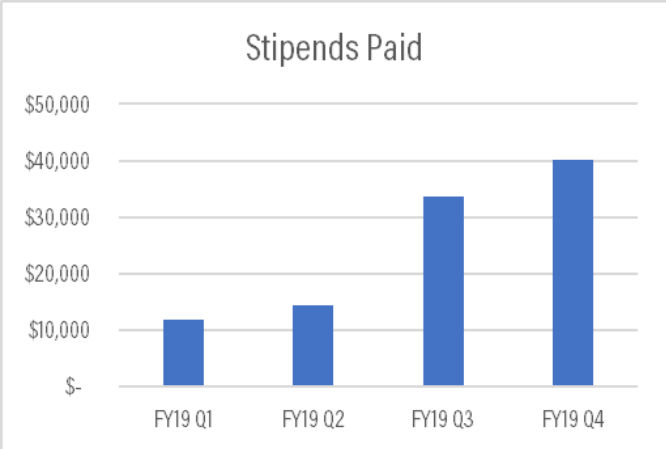


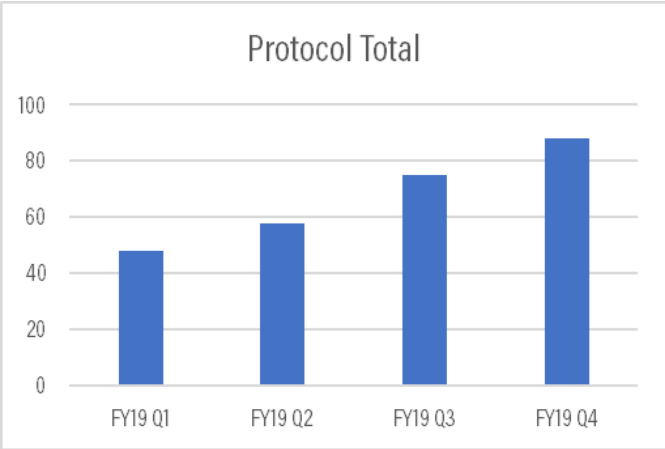
88	752	481	323
Onsite training sessions	Invoices Created in FY19	Payments recorded in FY19	Users trained

472 Active OnCore Users



Additionally, the clinical trials office implemented interfaces between OnCore CTMS and Partners PeopleSoft. This integration has reduced the manual workflow for study teams and also has provided the Partners more visibility into industry sponsored clinical trial revenue. The CTO expanded the availability of Forte Payments, a streamlined, real-time subject payment system across the organization for all clinical trials. The roll out of Forte Payments was completed December 2019. There has been a great demand in both the industry sponsored and non-industry sponsored clinical trials to use Forte Payments.





To increase the utility of the OnCore CTMS for investigators and administrators, the CTO also piloted central billing office at MGH and BWH. Based upon the success of the pilot so far, research leadership was interested in exploring models for expanding a centralized billing service. The CTO will be evaluating the pilot sites through Spring 2020 and plan the program expansion in FY20.

In addition to these new initiatives, CTO strives to continue to work with industry sponsors to bring new clinical trials opportunities to the outstanding investigators at MGH through direct outreach and building on existing relationships between sponsors and CTO and to provide continued efficiency in in core contracting and budgetary services.

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

Mary Mitchell leads the Partners Research Compliance Office (RCO) which was established in 2007 to provide system-wide leadership and coordination of research compliance activities for consistency in interpretation, application and monitoring of regulations, sponsor policies, and Partners research policies. The RCO works collaboratively with Partners Research Management/Finance, hospital-based Research Compliance or Corporate Compliance offices, the hospital Sr. Vice Presidents for Research, and the Partners offices that manage the human subjects, animal research, and biosafety compliance programs. A new MGH Director of Research Compliance (Kele Piper) was recruited in early 2019 which has invigorated the Partners and MGH compliance collaboration.

International Research Collaborations: International collaborations are an important and growing aspect of the Partners and MGH research enterprise. During 2018-19, in response to new requirements of NIH, NSF, and other federal funding agencies to monitor so-called "foreign influence" in research, a significant amount of Research Compliance activity was devoted to (and continues to be) understanding new and existing federal requirements related to foreign support of research and the risks posed to the individual researcher and the institution. A Foreign Collaboration Working Group (WG) was convened to conduct risk assessments of research activities and mitigation planning in the areas of conflict of commitment, sponsored projects, conflicts of interest, export controls, visiting appointments, and research integrity. MGH and Partners institutions receive information regarding research activities through a variety of channels. The WG is looking at how to streamline and revise how this information is collected and used to fulfill federal compliance obligations, e.g., in reporting Other Support on federal grant applications and progress reports and disclosing foreign components of federal awards to sponsors. The WG is also focused on developing new tools and guidance documents to enable investigators and research administrators to meet federal requirements. While the WG's focus in 2018-19 has been on research activities, we recognize that international collaborations are not limited to research and also involve clinical activities. Thus, the WG has been engaging with the Chief Medical Officers, Development, and Human Resources at all the Partners hospitals to alert them to the relevant foreign influence issues that impact their areas.

Training and Education: A key component of the RCO's role in supporting the research hospitals is maintenance of a training and education program for investigators, postdoctoral fellows, and research administrators. RCO educational activities in 2019 consisted of:

- Managing and delivering three Partners Responsible Conduct of Research (RCR) seminars for the 300+ trainees and career awardees across the Partners system required to complete this training
- Offering three specialized RCR seminars at MGH on:
  - Animal Research Compliance
  - Biological Materials
  - Rigor and Reproducibility
- Information seminars at MGH to Research Leadership and a variety of faculty groups on:
  - General Data Protection Regulation (GDPR)
  - Data Management Template (DMP)
  - Electronic Lab Notebooks (ELNs)
  - Federal Agency Requirements Related to "Foreign Influence"
  - Export Controls Requirements
  - Transporting Biological Materials
- Continued oversight of the PI Research Education series to ensure completion of required education by new MGH PIs

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

The division of Research Information Science and Computing (RISC) is the cornerstone of the scientific utilization of Information Technology at Partners. It provides the bridge for scientists who work in big data to access the electronic health record (EHR), imaging repositories, genomics repositories, and healthcare registries, and it provides the power for scientists to perform computation upon Partners-supported, privacy-aware, processing platforms at-scale. More information can be found on our website, https://rc.partners.org.

Queries against integrated healthcare data can be initiated through the Research Patient Data Registry (RPDR), a centralized clinical data registry that gathers electronic healthcare data from across all Partners institutions. With a self-serve query tool, researchers can define patient cohorts of interest for further study and, with proper Institutional Review Board (IRB) approval, obtain detailed clinical data on these patients within the guidelines of the IRB. The RPDR is utilized by over 1400 scientists every year, obtaining over 4,200 sets of EHR data supporting over $1.2 billion in healthcare research. The RPDR has been actively improving the quality of data available to researchers – providing 85 high-quality phenotypes to be used as the basis of research queries, growing the repository of data sources in lockstep with site acquisitions and new partnerships, and integrating new or emerging data types from the EHR.

The **Partners Big Data Commons** enables integration of Big Data with the RPDR and tighter integration of the RPDR with Epic. It allows more types of data to be integrated and become discoverable by researchers in a format they can easily consume. For example, the Partners Biobank Portal, one component of the Big Data Commons, is a web-based application that contains EHR and genomic data that can be queried online for over 113,000 consented Biobank subjects. Another component of the Big Data Commons, the Clinical Image Bank, is a web-based application that contains integrated disease registry data, EHR data, and imaging studies. There are currently over 900 investigators using these portals.

RISC's patient recruitment strategy encompasses several pathways to optimize the number of patients involved in research. Any Partners patient or member of the public can volunteer through Rally, a research portal for patients (rally.partners.org), contacting studies they found by searching for their areas of interest in an online catalog that presents studies in an attractive and informative format. More than 53,000 people have identified themselves to over 900 studies using this system. At patient registration, patients can opt into being contacted for studies that researchers determine may be a good fit for the patient; consented patients can be messaged directly using outreach tools built into Epic. For patients that have not opted in to be contacted directly by researchers, a workflow to contact patients through their providers is provided by the RPDR.

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

Enterprise Research IS (ERIS) provides technology services, platforms, tools, applications and solutions architecture consulting to enable and drive the research and innovation communities across the System. ERIS is composed of service-oriented teams who collaborate with researchers to solve their digital challenges. At the heart of the services are DIPR, the shared, hosted systems for research IT needs, ERISOne, the High Performance Computing environment with GPUs, and IDEA, the Big Data Platform for data analytics. The ERIS computational systems support over 2500 scientists, $275M in grants and 1800 apps that utilize 60 thousand CPU days of computing per quarter on 9 million gigabytes of files. Additionally, ERIS provides the interface for the research community to Partners IS. We provide advocacy and guidance on behalf of research to the many enterprise projects that involve Partners Information Security, ITS, Network Engineering, Security and other corporate departments.

RISC's Research Applications' data capture services are enabled through a suite of secure HIPAA-compliant data collection and survey tools such as Research Electronic Data Capture (REDCap), Lab Archives, GitLab and Freezerworks. The Research Applications Support team will help identify the optimal study tool given the investigator's requirements and facilitate the training of personnel in its uses and functions. In 2019, the team onboarded 3000 PIs to LabArchives as part of an institution-wide Electronic Lab Notebook initiative. In addition, REDCap supports over 16,000 research projects and is now integrated with EPIC and Responsy, a participant facing mobile app.

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

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

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

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

Partners Biobank: The Biobank is a data and sample repository that contains DNA, serum, and plasma of consented patients linked to clinical and research data. The Biobank includes samples and data from across Partners HealthCare hospitals and community sites and enables individual investigators at MGH to access this resource for research with IRB approval. It leverages a common electronic health record which spans PHS. As of December 2019, 113,000+ participants consented and 81,000+ samples have been collected. In addition, the Biobank has supported over $330M in research activities through the distribution of Biobank samples and data as well as through the sample management services, such as DNA Extraction services, cell lines, and discarded samples distribution.
The key value/services provided to Partners HealthCare investigators are:

- Access to serum, DNA, or plasma
- Access to a large cohort of patients who are consented for broad-based research and recontact
- Powerful tools that query across previously disconnected data (e.g. clinical data, research data, and specimen data)
- Rich, curated phenotype data (validated disease populations and calculated healthy controls) as well as additional research data (e.g. self-reported surveys)
- Sample management services
- GWAS Data and Imputed Genomic Data
- Participation in a NIH-funded longitudinal research program, *All of Us*, which aims to consent over 90,000 participants in New England (as part of the larger goal of 1M+ participants over next 5 years) via a $53M grant at MGH that includes BWH and Boston Medical Center.
- Participation in a NIH-funded research network, *eMERGE IV*, that aims to develop polygenic risk scores for 15 medical conditions and disseminate those risk scores in clinical practice at 8 academic medical centers and assess the impact of this genetic information on health care quality and cost. The grant is for $6.7M over 5 years.

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

- Genotyping and Next Gen Sequencing
- DNA analysis and serum/plasma miRNA analysis platforms optimized for sample types collected/extracted from Biobank patients
- Sequencing (Next Gen and Sanger) to support the Partners Biobank
- Novel sequencing workflows developed in partnership with Partners investigators (e.g. Parkinson's biomarkers study using a 7Mb sequencing panel)
- Identification of novel methodologies that can be used for Partners Biobank samples. On-going or recent development efforts include: miRNA from serum/plasma (supports use of Biobank samples), targeted methyl-seq capture (supports use of Biobank samples), and 16s microbial sequencing in whole blood (supports use of Biobank samples)
- Basic and advanced analysis options for genomic and expression analysis, in partnership with the PPM Bioinformatics team.

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

- Supporting NIH-funded genomic medicine programs requiring cutting edge clinical genetic and genomic testing

Personalized Medicine IT and Bioinformatics: The Partners Personalized Medicine IT and Bioinformatics teams supplies IT and computing support for the Biobank, LMM, TGC Core as well as assisting on numerous grant-based projects. The team's key functions are to:

- Support operations and maintain application infrastructure for the Biobank, LMM and TGC
- Develop functionality required to maintain near real-time programmatic access to patient genetic data for the LMM and Biobank
- Offer custom analysis for NGS data to Partners Investigators thru the TGC, such as: Genome/Exome/Panel variant calling and filtration
- Support data processing, analysis, and storage of Genotyping results for Biobank participants' samples
- Assist in the development of the Health Innovation Platform (HIP) and associated apps to improve clinical workflows
- Support eMERGE from both lab processing and clinical results delivery perspectives

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

Partners Innovation monetizes the unique assets of MGH and its Harvard faculty. Its business development responsibilities include company creation, license transactions, international consulting, securing research collaborations, technology development funding and managing intellectual property including patent prosecution. Partners Innovation is the largest academic organization of its kind with 125 staff that includes 7 MDs, 30 PhDs, 26 MBA/MAs, and 20 JDs. Total FY19 revenue exceeded all other universities and hospitals in Massachusetts combined at $348.5 million with 90% of that tied to MGH. These totals include the favorable impact of an orthopedic royalty buyout. Excluding the buyout, system revenues were up by 13% for a total of pre-buyout total of $156M.

MGH Outcomes	FY14	FY15	FY16	FY17	FY18	FY19
Licensing Activity	113	127	130	133	198	197
Material Transfer Agreements	1,073	987	1067	1360	1374	1,537
New Disclosures	408	318	365	311	366	355
Patents Filed (US)	253	228	910	1091	1643	1,593
Patents Filed (Int'l)	644	399				
Patents Issued (US)	86	89	126	136	150	165
Patents Issued (Int'l)*	172	120	311	421	317	464
Royalty and Licensing Income	$68.9M	$80M	$77M	$87.7M	$94.6M	$298.0M

** FY16-FY18 re-stated for "Patents Issued (Int'l)"; re-statement necessitated by actual patent issue dates recorded post-reporting period due to delays in reporting by country.*

More than 300 companies have been established based in whole or in part on the work of Partners HealthCare investigators with 2/3 of those tied to MGH. The Partners Innovation Fund I and II (collectively referred to as "PIF") has $171 million in capital under management that includes strategic investment from Astellas Pharma, Eli Lilly, Fosun Pharma, ShangPharma, and Simcere Pharmaceutical Group. It has invested in more than 42 companies, a dozen of which have gone public or been acquired. Its net internal rate of return is nearly 20% which equates to top quartile performance in the venture industry and is largely unrivaled in the academic realm. A translational innovation fund to drive MGH developed technologies into clinically useful applications and an artificial intelligence and digital innovation fund were launched in October 2019. Plans are underway for launching raising PIF III in FY20.

The World Medical Innovation Forum will be held May 11-13, 2020 in Boston. It will feature fast growing research areas such as cell therapy as well as the role of inflammation in disease. It will also focus on predictive analytics, machine learning and AI in research, diagnosis, therapy, management and operations. More than 2000 registrants from around the globe representing more than 600 organizations will register with nearly a third being PHS faculty and trainees who will experience first-hand how commercial innovation priorities are set.

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

Partners Research Management is comprised of four, distinct disciplines, each supporting the Research community throughout the grant life cycle from proposal submission to award close out. Throughout all phases of the grant, Research Management teams provide expert knowledge on federal regulations, contracting, processes and oversite of all financial data and reporting. These teams act as stewards who must balance adherence to the rules and regulations governing grants while providing support and guidance to the MGH Investigators and their Department Grant Administrators.

Within the grant's continuum, Research Management staff strive to deliver the highest level of service to the MGH research community throughout each segment of the grant. The Pre Award team reviews and supports the submission of proposals to sponsors. Next, the Post Award staff supports the execution of agreements and subcontracts then the management and oversight of the award for the duration of the grant. The third team, Research Finance, monitors the financial activity and supports the billing, reimbursement, and financial reporting for the project. There are also groups who support the oversight of research cores as well as a training team. Our final and newest segment of Research Management is the Research Support Services (RSS) team. Research Support Services was created to directly support the PIs and Departments who may be short staffed, dealing with a leave of absence, or just needs an extra pair of hands during a peak proposal deadline. RSS staff are proficient in all phases of the grant and their services have been enthusiastically embraced by many departments and PIs at MGH.

FY19 was another record-breaking year for research across Partners with over $1.8B in Research revenue. MGH continued to lead the way achieving the $1.0B threshold for the first time! Being in Assembly Row with the other Partners research support teams, including the Clinical Trials Office and Innovation, has allowed us to better manage research activities that are increasingly becoming more complicated and span government, industry, and non-profit sponsors.

To support the success of the MGH research community, Research Management continues to make improvements to systems and the support infrastructure for the MGH investigators. Last year, enhancements and improvements to systems continued to further reduce time and improve data capture in the Research community. Jointly, Research Management and Clinical Trials offices collaborated to successfully build an interface between Oncore and PeopleSoft to support the billing and oversight of clinical trials. This enhancement increased visibility into the status of the clinical trial and provides a platform for an organized, cash collection process. Research Management also deployed its first Robotic Process Automation (RPA) interacting with multiple systems to efficiently and effectively complete a higher volume transaction, allowing some team members to focus on more complicated issues. The team will continue to build out more RPA capabilities including the use of Optical Character Recognition over the next year. Finally, with the growing volume and complexity of the Research Portfolio and the overall pressure to contain costs, Research Management continues to improve upon the reporting tools available to departments. A new Departmental Dashboard was developed and launched providing increasing transparency into research support operations. This dashboard is sent to all MGH departments on a quarterly basis whereby they can see their activity at a department level down to a PI level.

A formal training curriculum for Hospital Grants Administrators, Research Staff, and Investigators continues to be a focus for Research

Management as part of the Partners 2.0 Research Workstream. A foundation is in place to launch a mandatory training curriculum for grants administrators across MGH. We will build of off the existing 30 trainings offered tri-annually to the MGH community via online courses or in person sessions to increase content and move more trainings online. This is training initiative will both level set expectations for a professional grants administrator and help drive improved understanding of challenging and often changing regulations and sponsor requirements.

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

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

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

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

OII staffs the above three committees. In order to fulfill its responsibilities, 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 and the Partners and Harvard Medical School conflict of interest policies.
- The Outside Activities section reviews the outside activities (personal consulting arrangements and the like) of physicians and staff to ensure they are consistent with Partners policy and is responsible for obtaining COA and PICC review of outside activities of senior institutional officials.
- The Educational Grants section oversees the receipt of industry funding in support of Partners educational activities, to ensure compliance with Partners policy. This section also handles conflicts arising in purchasing and similar types of transactions and has responsibility for handling gifts from industry to support research activities.
- The Systems and Education section works with Partners Research Applications Group to design the online conflict of interest disclosure system; administers the Annual Disclosure process to physicians and staff; provides online and in-person training to the Partners community; maintains the OII web site; and coordinates the distribution of educational materials to the Partners community.

Over the course of the last year, OII has made a focused effort to improve integration amongst the four substantive sections of the office detailed above. OII has put particular emphasis on the importance of cross-training members of the office in order to enhance efficiency and to provide a better, more seamless experience for investigators and members of the broader community when they interact with our office. Additionally, and as further detailed below, FY19 was the first full fiscal year of Mass Eye and Ear and Schepens Eye Institute as part of the Partners System. Accordingly, all sections of OII worked closely with the MEE/SERI community on policy and system education and implementation.

Significant accomplishments in each of the OII sections during FY19 included the following:

1. Research Activities – in addition to handling, as part of the normal workflow, the processing of over 22,000 financial interest disclosures

needed for compliance with PHS regulations and HMS and Partners COI policies:

- Worked with the staff of HMS and affiliated hospitals regarding the revision of the definition of "Clinical Research" under the HMS COI policy. The revised definition removes from the scope of the Clinical Research Rule clinical research that the reviewing IRB determines to be "Minimal Risk."
- Continued to advance system improvements 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.
- First annual COI review of MEE/SERI researchers engaged in projects funded by the Public Health Service and introducing them to Partners policies on conflicts of interest in research.

2. Outside Activities – In addition to handling, as part of normal workflow, over 2,300 consulting and related agreements:

- Developed system requirements for new functionality in Insight for the review and processing of outside activities in order to more effectively service the Partners community. Once completed, the system will involve a platform that integrates with the Partners CTO, Innovation and Research Management offices; increases efficiency in the review and processing of agreement; and streamlines the overall tracking and metrics associated with outside activities.
- Continued streamlining processes for handling consulting and other outside activity agreements, in part by developing alternative approaches to the review of certain outside activities; developed more robust guidelines and management for the review of part-time employees' outside activities.
- Continued to integrate and educate MEE/SERI faculty engaged in personal outside relationships to ensure consistency with relevant Partners policies on outside activities.
- Maintained approach of constantly revisiting policies leading to revisions in several Partners policies, specifically:
    i. Guidelines for the review of Industry-Physician Appointments in consultation with the Committee on Outside Activities and senior clinical and research leadership; and,
    ii. Guidelines for the review of Non-Institutional Official Fiduciary positions.

3. Educational Grants – in addition to handling, as part of the normal workflow, over 290 educational grants bringing in about $5M in funding:

- Continued a Process Improvement initiative, focusing on clarifications and revisions to numerous policy and process standards, including:
    - Multifunder Rule Guidelines;
    - Guidelines on Acceptance of Textbooks to Support Educational Activities and Clinical Training Programs;
    - Guidelines for Promotional Opportunities; and,
    - Budget Guidelines for Partners Educational Activities.
- Continued to integrate and educate MEE/SERI on Partners Education Review Board policies and procedures.
- Continued process improvement and continued the review and approval of industry gifts for research, coordinating with the hospital Development Offices, Partners Innovation, Partners Clinical Trials Office, and the Office of the General Counsel. During the year, OII finalized 37 industry gifts for research, totaling over $5M.
- Reviewed over 90 purchasing and other transactions for conflicts of interest, and improved OII's process for handling the transactions.

4. Systems and Education – in addition to handling, as part of the normal workflow, the distribution and completion of annual disclosure forms to nearly 13,000 Partners staff:

- Working with Partners Research Applications & Analytics, continued to refine and enhance the functionality of the Insight Disclosures Module. This past year, the focus was on improving navigation and instructions; reducing the number of forms for reporting relationships between research projects and disclosures; and simplifying reporting of equity holdings and intellectual property payments.
- Integrated Mass Eye and Ear physicians and researchers into the Partners Disclosures process; held training sessions for faculty on what to disclose and for supervisors on how to review Disclosure Forms.
- Prepared training materials and held user training sessions for the Disclosures module and assisted users in completing their Annual Disclosure and Financial Interest Update Disclosure Forms.
- Facilitated the Conflicts of Interest in Research online training course for over 900 faculty.
- Continued emphasis on integrating OII systems with the systems of other Partners offices in order to assist end-users in a more seamless navigation of Partners offices, policies and processes.

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 2019 implementing the strategic plan for research and improving the services that support the Research Institute. Looking ahead to 2020, there are many opportunities for strengthening the research enterprise as well as challenges to be met to sustain our standing as a leader in academic medicine and biomedical research. The most challenging of these is the need for additional research space, as discussed in the final segment of this section, The Case for Space.

Mandatory Electronic Lab Notebooks. With a continued increase in the number of research misconduct cases related to the inability to produce original experimental data, MGH (and all of Partners) mandated use of approved electronic lab notebooks (ELN's). An enterprise-wise license for Lab Archives was procured and made available at no cost to all researchers, and a target date of October 1, 2019 was set to have every research lab registered. Throughout 2019 and into early 2020, the Partners IS team, working with research and IS administrators from the hospitals, onboarded over 3000 PIs to Lab Archives. While most labs are now using Lab Archives, a few have been granted exceptions to use other systems that have been vetted and approved by Partners IS Security. As difficult as it has been to get everyone using ELN's, the preservation of original research data and, with it, the protection of the PI's and researchers who generated it from those who would manipulate or falsify research data has been well worth the effort.

Leadership Changes. 2019 saw three major leadership changes across the MGH research community. When Dr. Anne Klibanski became the Partners Healthcare CEO, she had to relinquish her role as Partners Chief Academic Officer (CAO) and her role as MGH Director of the Center for Faculty Development (CFD). Earlier in the year, Dr. Sek Kathiresan left MGH to lead a biotech start-up company, leaving his position as Director of the MGH Center for Genomic Medicine.

Center for Faculty Development. Major programmatic and staffing changes to the Center for Faculty Development (CFD) have signaled a new era for the Center. A new Director, Dr. Miriam Bredella from Radiology was named to replace Dr. Klibanski. Donna Lawton, long-time CFD Executive Director, retired this past year and a search will begin soon for her replacement. Director positions for the Office of Research Careers and the Graduate Student Division will also soon be filled by Dr. Bredella. Finally, the entire CFD staff will relocate from their isolated location in Bulfinch to 125 Nashua Street, adjacent to the ECOR and Research Institute administrative offices, allowing for better support from and integration into the Research Institute support staff team.

Partners Chief Academic Officer. After an extensive internal search, Dr. Ravi Thadhani, former MGH Chief Renal Division Chief, returned to MGH from Cedars-Sinai, where he had spent the last two years as its Vice Dean of Research and Graduate Research Education. In his new role, Ravi will chair the Partners Academic Executive Committee and co-chair with Peter Markell the Research Operations Management Committee. Ravi will also play a key role in ensuring that the research components of the new Partners five-year System Strategy plan are implemented.

Center for Genomic Medicine. In June of 2019, Dr. Sek Kathiresan announced he would be leaving MGH and his position as Director of the Center for Genomic Medicine (CGM). MGH named Dr. Sue Slaugenhaupt, the Scientific Director of the Mass General Research Institute and longtime member of CGM, as the interim CGM Director. A search committee chaired by Dr. Merit Cudkowicz, MGH Chief of Neurology, was formed to conduct an international search for a permanent Director. Since the Director will have to qualify as a member of the Harvard Medical School faculty, the search process is following the Harvard University faculty search guidelines . As if the writing of this report, the search committee has identified four semi-finalist candidates and hopes to have a new Director named by summer.

A New Name and a New System Strategy: The Strategic Plan for Innovation. After almost a year of internal discussion and debate, trustee leadership of Partners Healthcare agreed to a new brand identity, Mass General Brigham, to highlight the system's two founding academic medical centers. Partners CEO, Dr. Klibanski stated that the rebranding is part of an effort to "better articulate what we offer patients and more closely reflect the vision for our system.....As we build both our system strategy and our new identity, we will focus on how we leverage the full range of capabilities of our world-class clinicians and staff at our academic medical centers, renowned specialty hospitals, our community hospitals and our community sites. Our goal is to have an even greater impact on our patients and the health of the communities we serve locally, nationally and globally."

Along with the rebranding, Dr. Klibanski also outlined five themes that will anchor the system's new five-year strategy: 1) Recognition as the "go to" place for care; 2) Expand the system's impact on health, both nationally and internationally; 3) Innovation in diagnostics, therapeutics,

devices, and data analytics; 4) A value-based model that delivers affordable primary, secondary, and behavioral health care in the community; 5) Lead in community health impact.

The Innovation strategy team, led by Chris Coburn, Partners Chief Innovation Officer, has identified five objectives to realize its strategic goals: 1) Expand impact of MGB innovation engine and enhance future revenue streams through new business development, increased commercialization, translational support, asset creation, process enhancements, significantly increased equity investment, and expanded strategic alliances/collaborations; 2) Create and incubate new high value assets through setting strategic commercial development priorities in high potential technology/disease areas, new translational capabilities including investments and dedicated incubation space, enhanced IP prosecution resources and strategies, increased internal senior industry expertise especially in shaping commercial opportunities from early stage research findings, increased market research, expansion of innovator base and commercial competencies, new digital investment and acquisition tools and structured corporate development (M&A) capabilities; 3) Enhance PI engagement and increase pool of innovators through focused human, financial and electronic support, process improvements and prioritized PI user interface as a key initiative to increase commercially actionable output; 4) Optimize current capabilities to increase scale and timing of transactions. Parallel goals to increase large scale deal making and high workflow processing; 5) Better position the system, including through co-investment, to become a more desired industry partner.

Center for Innovation in Digital Health (CIDH). The creation of CIDH in 2018 at MGH was accompanied by the creation of the Enterprise Data & Digital Health (EDDH) program at Partners. EDDH was stood up as a major initiative across the entire Partners network to provide infrastructure and programmatic support for all digital aspects of patient care, the physician experience, and research. Leadership at CIDH, which initially was co-led by Dr. David Ting, MD, Chief Medical Information Officer of the MGPO, and Dr. Shawn Murphy, MD, PhD, Chief Research Information Officer at Partners, was consolidated under David in 2019. Shawn continues to be involved, Dr. David Louis, MD, MGH Chief of Pathology, continues to serve as Executive Sponsor for the Center, and Ms. Sara Silacci continues to serve as its Director for Strategic Alliances. In 2019, CIDH has begun negotiations for major projects with a variety of companies, including Apple, Astra-Zeneca, Merck, Gaido, and Biofourmis. Projects are being developed in close collaboration with Dr. Adam Landman and the iHub staff at Brigham Health, and with Trung Do in Partners Innovation.

The MGH Capital Campaign. [Excerpted in part from internal Development Department documents produced under the direction of Susan Buchanan] The MGH Capital Campaign had its beginnings in late 2017 when Dr. Slavin asked the Mass General community to contribute "Big Ideas" to fuel our vision for a fundraising campaign. He received over 250 responses (and replied to each one) that were distilled into 13-15 ideas. With the help of our campaign consultant, these ideas boiled down to three themes: Bold Breakthroughs. Compassionate Care. Revolutionary Results. These themes serve to distinguish Mass General and why we are having the campaign.

We began counting gifts received towards the Campaign total on 1 October 2019, at the beginning of FY18. During the current "silent phase" (prior to public announcement) of the campaign, we have met the ambitious goal of $360M per year and are optimistic this trend will continue. FY19 ended this past September with total of $592M raised, exceeding our previous record of $347M in FY18. Even when discounting the one-time, transformative gift of $200M from Terry and Susan Ragon to endow the Institute that carries their name, we still exceeded the FY19 goal. To date, we have now raised $1.055B, more than one-third of our $3B working goal for the campaign, in 28% of campaign time elapsed, putting us (for now) ahead of schedule.

While the campaign overall is progressing well, much work remains to be done to achieve the campaign goals of the Mass General Research Institute (MGRI). Of the $1.055B raised thus far, $464M has been for research. However, of this total, $416M is for specially targeted programs, leaving only $48M of unrestricted funding for the MGRI. If we can successfully raise our goal of $500M for the MGRI, we will be able advance all fields of medicine by providing our investigators with the resources and support they need to translate new laboratory discoveries into better treatments for patients. Specifically, we will be able to: 1) Retain our best and brightest scientists through Research Institute Endowed Chairs; 2) Fully support future classes of MGH Research Scholars; 3) Fund our researchers' most transformative new ideas; 4) Increase diversity in our research community by supporting women and minorities in Science; 5) Stabilize our current research infrastructure; 6) Launch new cross-disciplinary thematic research centers that will transform patient care.

The Case for Space – Sustained Growth Leads to Overcrowding

Over the last two decades, research revenues at MGH have grown from $242M to $1,013M annually. This unprecedented growth has occurred in literally every department across the hospital, making MGH not only the largest, but also the most diverse biomedical research enterprise in the country. But this growth has come at a price. In the last decade, research space at MGH has grown 18.9%, while the number of research employees has grown at twice that rate, and research revenues have grown at three times that rate, even when adjusted for inflation. Consequently, overcrowding in research spaces is approaching a critical level.

The recent dramatic (18%) increase in the amount of long-term NIH grant funding awarded to our investigators combined with significant increases in the number of collaborations with pharma/biotech companies project that strong growth in research revenues will continue at an even greater pace in the future. This activity has brought our space shortage to a critical stage in 2019. This critical space shortage has also been felt in our animal housing facilities, with rodent rooms near or at capacity and continuously on "red" status, meaning no new cages may be placed in the rooms.

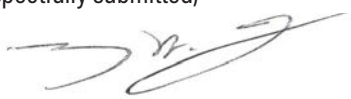
New Space Metrics to Help Manage Current Resources. While the overall density of space usage at MGH is significantly higher than neighboring institutions, not all MGH labs are overcrowded. At the extremes, we have PIs with lab MTDC densities over $1700/SF and some under $100/SF. So, there are pockets of space where opportunities exist to reallocate space to those overcrowded by taking from those with more than they are using. In 2019, a new set of space metrics and management processes have been developed which fairly compare space utilization by both people occupying the space and the amount of research funding spent during the year in the space. These metrics will be made available to hospital and research leadership and department and unit chiefs in the first quarter of 2020. While these metrics will be used to help relieve small pockets of overcrowding, large scale relief from overcrowding will not be possible until a significant amount of new research space is identified and made available.

The Search for Nearby Immediate Space. With the hospital's plans to construct a major new clinical building currently under review by the city, all other formal searches for research space must be held until the clinical building is fully permitted. Still, RSMG and the Planning Office have been informally exploring nearby options. However, the huge and growing pharma/biotech/academic research ecosystem in Boston ensures that any space that becomes available will be purchased quickly and at a premium.

As of the writing of this report, the only potential short-term option for MGH research space relates to the development of the Allston site by Harvard. MGH, through Partners, has expressed interest in relocating components of the Wellman Center, the Center for Engineering in Medicine, and the Center for Systems Biology (all components with significant engineering assets) to Allston. These components would go into a major new research building to be constructed by Harvard's newly-chosen third party developer. Unfortunately, the developer has stated that this new building will likely not be ready for three years. Fortunately, however, the large (500K+ SF) new Harvard Applied Engineering building in Allston is nearing completion and is expected to open in the summer of 2020. A major programmed occupant (60K+ SF) of the building, the Wyss Institute, recently informed Harvard that it would not be relocating to the engineering building. Accordingly, MGH has requested that some of its engineering programs be allowed to occupy the space programmed for the Wyss Institute until the new developer building becomes available. While we continue to search for potential new research spaces near the MGH main campus, the Allston Applied Engineering building is, at this time, the only option that could be realized within 2020.

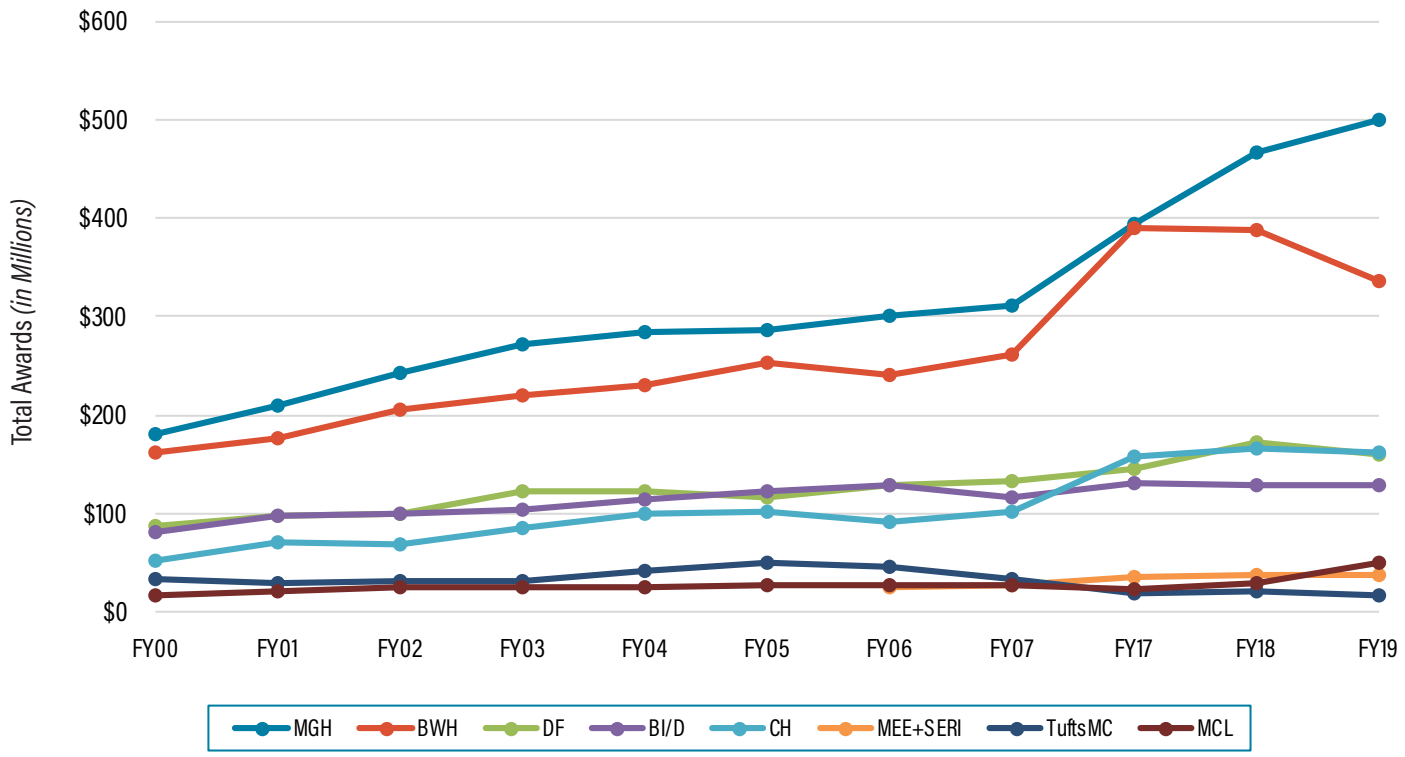
The record setting $1 billion research revenue landmark the Research Institute reached in 2019 is a testament to the extraordinary group of hospital and Partners leaders, faculty, and staff whose dedication has been so vital to maintaining our position as a preeminent biomedical research institution. Collectively, they are responsible for all of the progress documented in this report and they will continue to rise to the challenges we face in the coming year. On behalf of the entire Mass General Research Institute, I offer our thanks and appreciation for their dedication to constantly improve and strengthen our research enterprise.

Respectfully submitted,

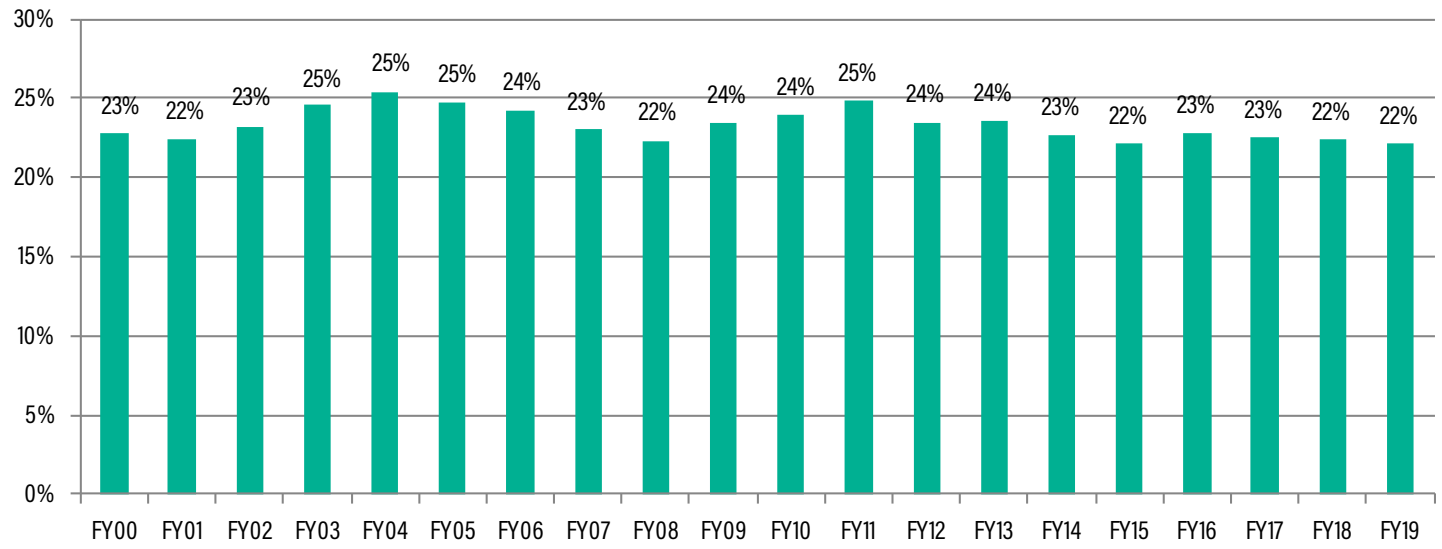


Harry W. Orf, PhD
Senior Vice President for Research
Massachusetts General Hospital

NIH Extramural Awards - Top Local Hospitals
FY00-FY19



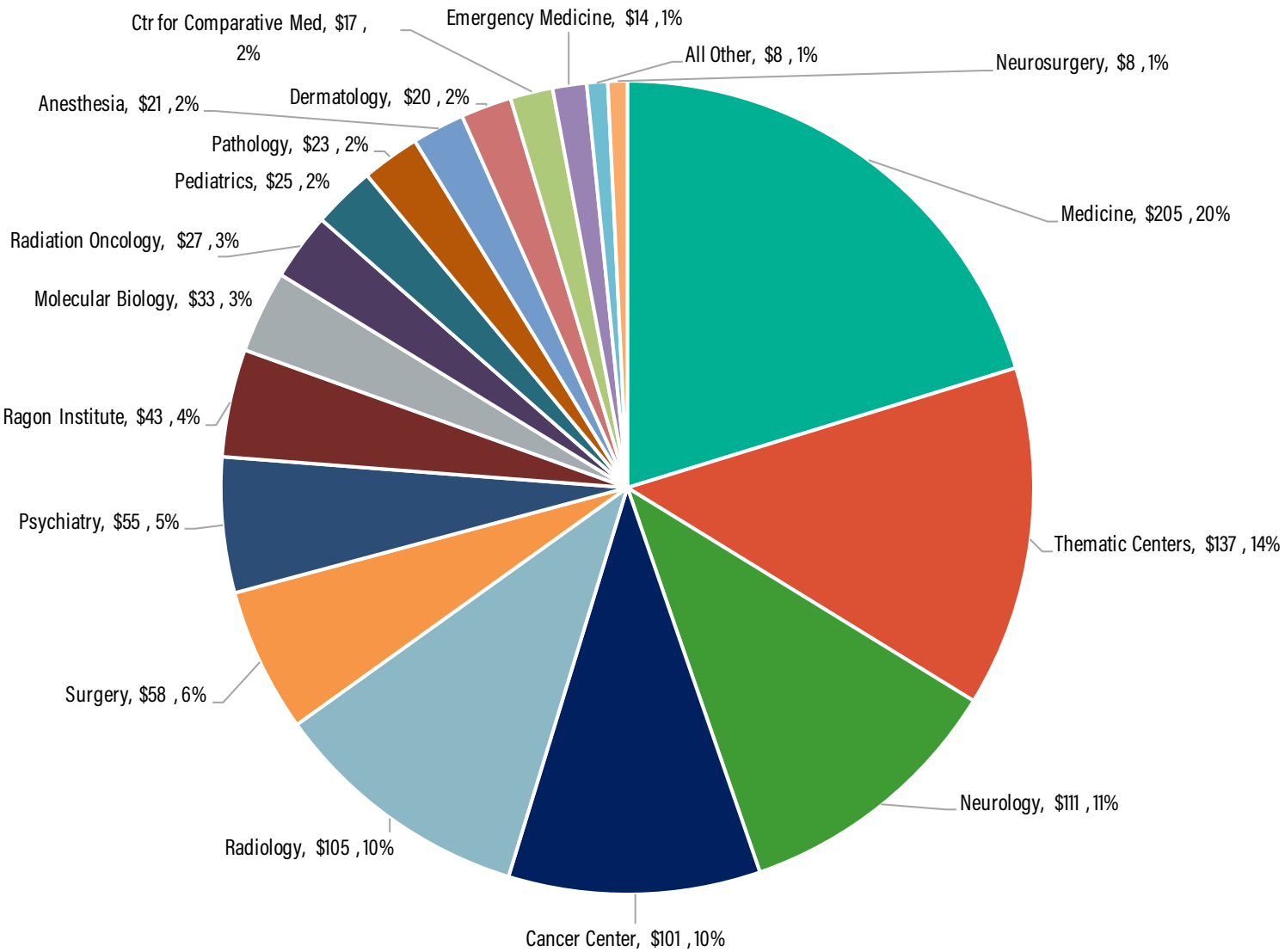
MGH Research Revenue as a Percentage of Total MGH Operating Revenue
FY00-FY19



MGH Research Expenditures by Department

FY19 Direct & Indirect Expenditures - $1.013 Billion

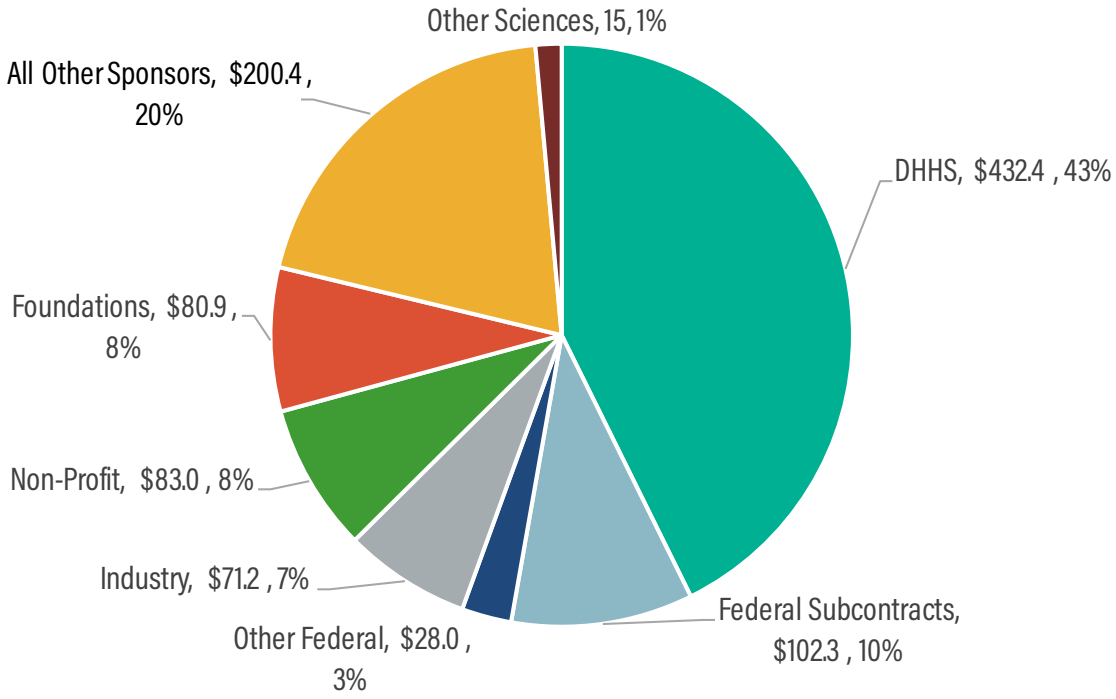
(shown in Millions)



MGH Research Expenditure by Sponsor

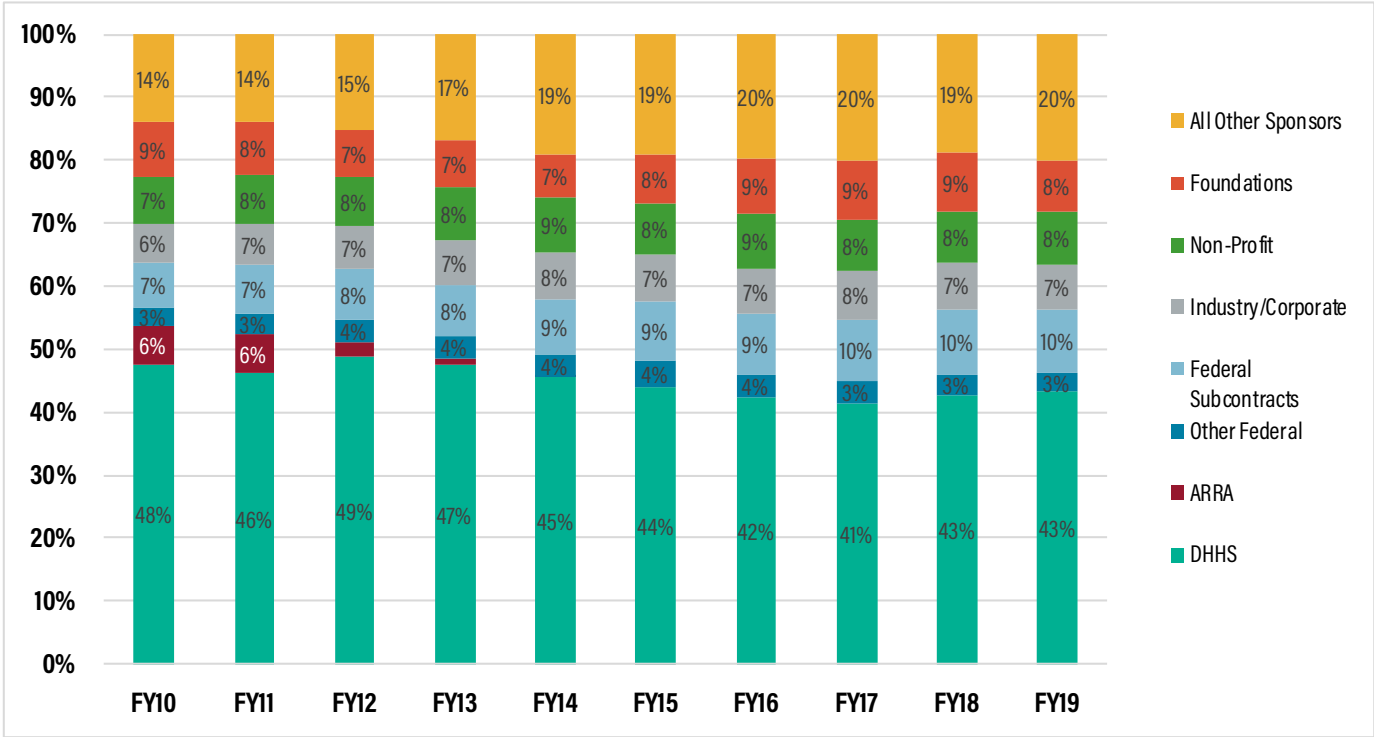
FY19 Direct & Indirect Expenditures - $1.013B

(shown in Millions)



MGH Research Expenditure by Sponsor

FY10-FY19

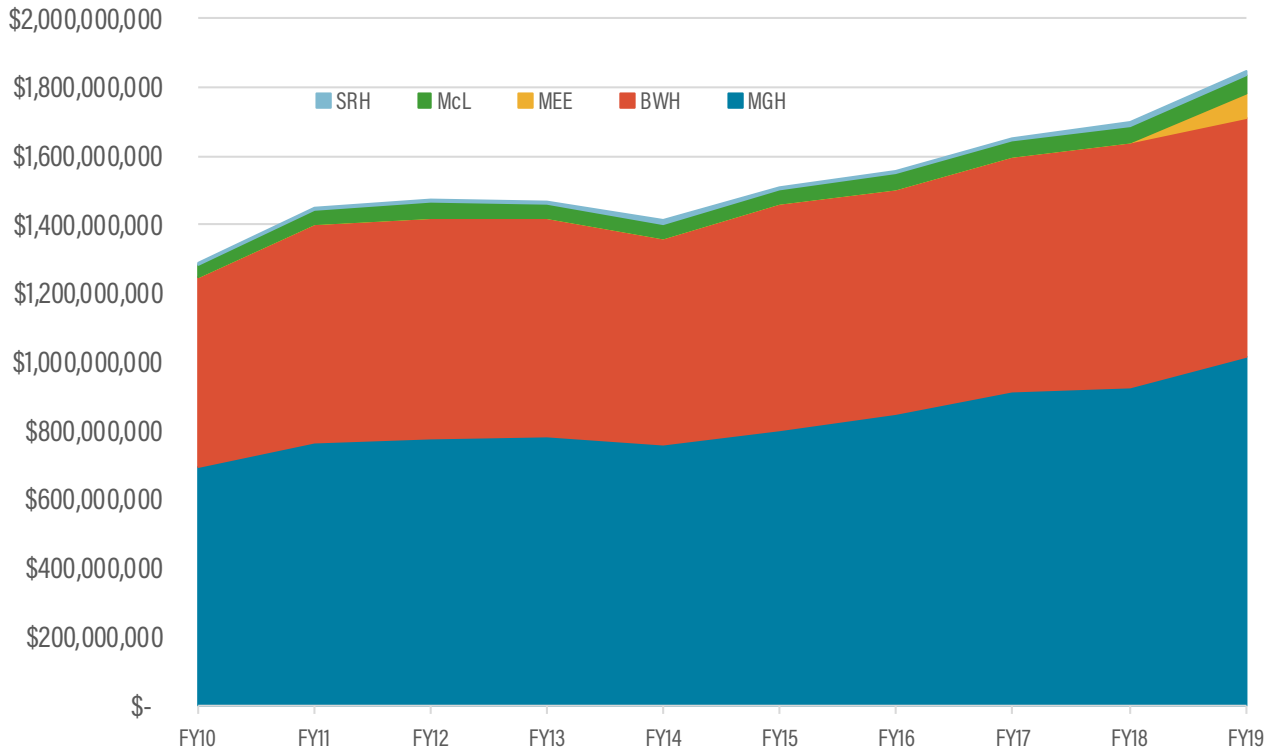


MGH Science Activity by Sponsor

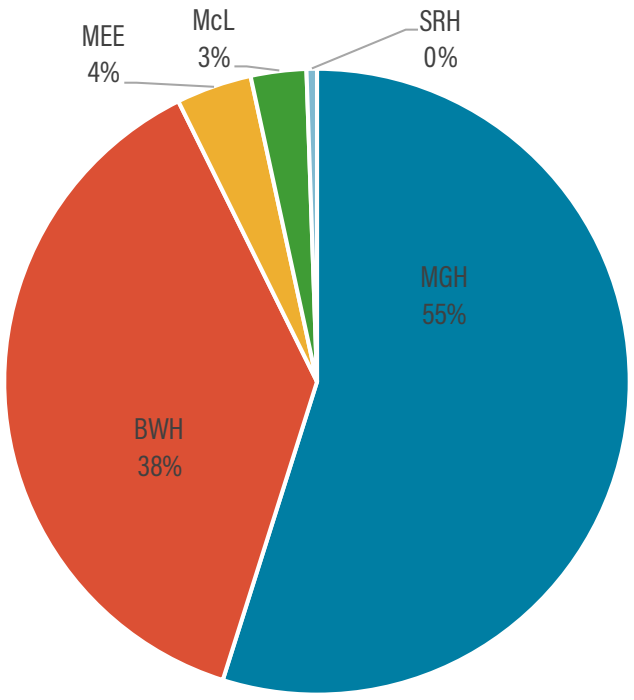
FY19 - 10/01/18-09/30/19

Type of Activity	Direct	Indirect	Total
Federal & State	$ 334,492,199	$ 132,382,954	$ 466,875,154
Non-Federal	$ 444,265,472	$ 101,780,266	$ 546,045,738
Total Expenses FY 19	$ 778,757,672	$ 234,163,220	$ 1,012,920,891
Federal Activity by Sponsor			
NIH	$ 311,185,552	$ 122,095,749	$ 433,281,301
DOD	$ 12,578,395	$ 6,858,894	$ 19,437,289
DARPA	$ 3,870,532	$ 1,564,392	$ 5,434,924
NASA	$ 190,582	$ 129,521	$ 320,102
NSF	$ 655,750	$ 421,652	$ 1,077,402
Other Federal	$ 1,264,204	$ 498,566	$ 1,762,770
Total Other Federal Activity	$ 18,559,464	$ 9,473,023	$ 28,032,487
Subtotal Federal	$ 329,745,016	$ 131,568,772	$ 461,313,788
State	$ 4,747,183	$ 814,182	$ 5,561,366
Total State Activity	$ 4,747,183	$ 814,182	$ 5,561,366
Total Federal and State	$ 334,492,199	$ 132,382,954	$ 466,875,154
Non-Federal Activity by Sponsor			
Industry	$ 54,639,706	$ 21,714,595	$ 76,354,301
Foundations	$ 72,464,043	$ 9,256,986	$ 81,721,029
Subcontracts/Other Nonprofit	$ 130,061,804	$ 46,750,625	$ 176,812,429
MGH Endowment & Gifts	$ 185,968,721	$ 24,058,060	$ 210,026,781
Total Non-Federal Activity	$ 443,134,274	$ 101,780,266	$ 544,914,539
Total Expenses	$ 777,626,473	$ 234,163,220	$ 1,011,789,693
Harvard Medical School	$ 1,131,198	$ -	$ 1,131,198
Grand Total	**$ 778,757,672**	**$ 234,163,220**	**$ 1,012,920,891**

Partners Healthcare Total Research Activity



Partners Healthcare Total Research Activity by Institution



Elena B. Olson, JD, Executive Director

MISSION

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

FOCUS

CDI accomplishes its mission through three focus areas:

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

STRATEGIC PRIORITES

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

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

NOTABLE ACHIEVEMENTS FOR THE 2019 YEAR

1. In 2019, the Mass General appointed an inaugural VP and Chief Equity and Inclusion Officer.
CDI is now reporting directly to this executive leader, who's strategic priorities include addressing disparities, and diversifying researchers, research participants and the research agenda; and other clinical, education, and community health hospital-wide priorities.

2. Expansion of the Physician/Scientist Development Awards
At the 2019 Scientific Advisory Council, CDI proposed expanding the Physician/Scientist Development Award (PSDA) and the Summer Research Trainee Program (SRTP) to enhance research faculty retention and build a pipeline of students committed to academic medicine who could return to MGH. In 2019, ECOR approved funding 5 PSDAs, more than doubling the number of awards and increasing the amount of funding for each award to $180,000 cost-sharing with the recipient's department for 2020. Typically saddled with huge debt and a challenging national funding landscape, more URiM researchers will now be able to take advantage of these PSDA funds to help them build a successful research program at Mass General and alleviate debt burden.

3. Implementation of a resident stipend pilot program.
The high cost of living in Boston has consistently been identified as a barrier by many residency applicants - especially URiMs - who could have come to train here. To address this issue, the CDI worked closely with various strategic partners including Partners Graduate Medical Education, Human Resources, and the BWH Physicians Organization and Center for Diversity and Inclusion to create a pilot program based on national criteria for economic need last year. We now have a few exciting outcomes. 65% of the stipend recipients in the first-year pilot program are URiM. As part of the second year roll out, we incorporated more expansive criteria for all Partners residents within their first 3 years of training.

4. Metrics and Evaluation of CDI impact and Summer Research Trainee Program
CDI worked closely with the Mongan Institute for Health Policy to develop metrics of diversity and inclusion for our URiM researchers, clinicians and trainees, as well as for participants of the Summer Research Trainee Program (SRTP). For 27 years, SRTP has brought talented URiM college, graduate and medical students from across the country to engage in a novel research project with an MGH investigator (see description below). We evaluated the impact of this program on both current students (pre and post surveys) and alumni. In eight short weeks, 100% of participants

reported that this program made a significant positive impact on students' interest in pursuing research careers. 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.

5. Record match of URiM residents to MGH training programs.
CDI helped recruit record numbers of URiMs in residency spots: In 2019, 17% (n=40) of the residents who matched in 20 MGH/integrated residency programs were URiM, with several programs exceeding 27%. This is above the percentage of URiM national medical graduates. CDI worked closely with all MGH affiliated residency programs in their recruiting efforts. CDI hosted 11 applicant receptions during the interview season to provide an opportunity for applicants to meet the CDI community of URiM 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).

6. Champions in race discussions.
Both in our community and across the hospital, CDI and the RFC led important and difficult discussions about race. The CDI was a signature sponsor for several annual Stand Against Racism events at the MGH in 2019, featuring Dean for Diversity from UMass Medical School, a discussion on the outcomes of the hospital-wide culture survey and the desegregation of the health care system in the U.S. These discussions and education sessions help us create an environment of inclusion and belonging at Mass General.

Overall
In 2019-20, CDI met individually with Chairs and MGH affiliated residency program directors to help implement diversity and inclusion efforts for trainees and faculty in all MGH departments. During this past year, CDI served over 450 URiM students, trainees and faculty, and provided cross-cultural education and unconscious bias training to approximately 2,500 physicians, scientists and interdisciplinary teams.

Professional Workforce Diversity
We recognize that decisions of faculty recruitment occur at the departmental level, and that the focus must be deliberate if we expect to achieve results. CDI is now providing more intentional guidance and resources to assist with faculty recruitment, like we have done with our trainee recruitment efforts. Over the past few months, CDI leadership has been meeting individually with Department Chairs and their appointed diversity leaders to understand challenges, provide advice and share successful best practice strategies.

The good news is that the hospital is making positive strides in faculty retention and career advancement, and our CDI research focused programs are helping with this success. Mass General recently appointed Seun Johnson Akeju as Chair of the department of Anesthesia, Critical Care and Pain Medicine. Seun is a past PSDA recipient, which is part of our faculty development award program. Many departments are already in the process of hiring URiM graduates to join our faculty in 2020. One example is Brian Mugo, a Medicine resident who will soon become one of our primary care attendings in the Internal Medicine Associates. Brian is also an SRTP alumnus.

CDI continues to promote many clinical and research faculty through our faculty development award program. With funding from ECOR and the MGPO, CDI sponsored seven faculty development awards in 2019. Since 2004, CDI has awarded 53 faculty development awards totaling over $6.3 million in funding. The purpose of this program is to increase opportunities for URIM faculty, and who are committed to diversity, inclusion and equity, to advance to senior positions in academic medicine and leadership at MGH.

The Summer Research Trainee Program (SRTP) was recognized as a program leader for mentorship of the student pipeline. Founded in 1992 to inspire students who are underrepresented in medicine (URiM) to consider careers in academic medicine and biomedical research, SRTP brings in 20 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. In 2019, students were assigned to investigators in 13 different departments for an eight-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. 370 students have participated in SRTP since its founding. Several participating students have returned to train at MGH; a number have stayed on in labs and have published their work. In 2019, 4 presented posters in MGH's Clinical Research Day (one received the Departmental award); and two returned as medical students to

work with their assigned PIs. Previous SRTP participants state that the program added tangible value to their subsequent training and career decision making and had a marked impact on their decision to pursue careers in an academic setting.

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

Center for Faculty Development (CFD)

Programmatic Report

Anne Klibanski, MD, Director / Theodore Stern, MD, Interim Director

Mission/Focus

The Center for Faculty Development (CFD) facilitates the career advancement and job satisfaction of faculty, research fellows and graduate students at the MGH. It is the 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 Careers (ORC) 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 ORC branch to address the needs of the graduate student and post-doctoral communities.

Achievements

In 2019, the CFD and its offices saw continued success in the integrated approach to providing services and resources to our faculty and trainees. It sponsored approximately 85 professional development programs for approximately 2,400 faculty, fellows, students and other professional staff. The CFD also expanded the OWC gender parity initiatives support by the Mass General Physicians' Organization with the additional support from Executive Committee on Research (ECOR). The initiatives include Scholarly Writing Awards (SWA), Advancing Careers through Editing (ACTE) awards and facilitated negotiation skill building training.

The CFD presented "Facilitating Career Development" at the 2019 Scientific Advisory Council event and facilitated four sessions of the new Mass General Research Institute Orientation this year. The CFD and its offices have given presentations to departments and have represented the MGH at various events including the annual HMS New Faculty Orientation.

In addition, over 300 individuals visited the CFD and/or one of its offices in 2019 for almost 360 office consultations. Approximately 230 of these consultations were with a CFD staff member (59% faculty, 41% fellows, graduate students, residents and other staff) and about 130 consultations were with an external advisor (44% faculty, 56% fellows, graduate students, residents, and other staff). The clear majority of the consultations were for career advice (including individual coaching sessions on negotiation and having difficult conversations), promotion, and grant funding.

Strategic Priorities

- Collaborate with department specific faculty development liaisons to leverage best practices and resources.
- Design and develop a new CFD website to enhance ease of use and communication of resources.
- Continue to automate CFD processes where indicated and practical to enhance efficiencies.
- Continue to collaborate with the Mass General Physician's Organization on gender parity issues.
- Continue to meet with all new Chiefs to review departmental faculty data and CFD resources.
- Provide professional development programs and workshops that meet the needs of our faculty and trainees, as well as networking opportunities for the faculty and trainees.
- Facilitate the annual New Faculty Orientation to familiarize new faculty with MGH/MGPO senior leadership and available resources to enhance their MGH experience.
- Recognize and celebrate outstanding mentorship by continuing to sponsor the annual John T. Potts, Jr., MD, Faculty Mentoring Award.
- Sponsor and administer the Caring for Dependent(s) (CFD) Travel Awards to help defray additional dependent care costs that go above and beyond care needs while a faculty member is traveling to an academic/society meeting.
- Offer individual consultations to help faculty, research fellows and graduate students 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.
- Facilitate the implementation of an online system to track the process/status of postdoctoral fellowship.
- Collaborate with the MGH Diversity Committee, MGH Center for Diversity and Inclusion, Harvard Medical School and its affiliates.
- Continue to collaborate with CHADD on faculty development best practices. Co-chair the annual Mentoring Course at Harvard Medical School along with the Consortium of Harvard Affiliated faculty Development and Diversity Offices (CHADD).

Office for Research Careers (ORC) - Dennis Brown, PhD, Director *(formerly Office for Research Career Development)*
Graduate Student Division (GSD) - Thilo Deckersbach, PhD, Director / Karen K. Miller, MD, Interim Director
Post Doctoral Division (PDD) – Marcia Goldberg, MD, Director

ORC, GSD and PDD Achievements

- Completed the fifth cohort 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, over 20 faculty met nearly every month to hear from senior members of the MGH research community and discuss important topics for a successful career.
- Provided English as a Second Language (ESL) classes specifically designed for researchers. Two 12-week semesters of ESL each served 80-90 students, divided into four class levels based on their English skill.
- Continued to advise the MGPA, which offers research fellows leadership opportunities, and the chance to develop their own career and networking events.
- Presented the "GSD Select Paper of the Year" Award to Daniel Montoro, PhD Candidate, a PhD student in Dr. Jayaraj Rajagopal 's lab; his paper, "A revised airway epithelial hierarchy includes CFTR-expressing ionocytes" was published in Nature journal.
- Sponsored the 2019 GSD Mentoring Award to recognize a PI for his outstanding contribution in helping graduate students to advance their skills and provide academic support; Recipient: Alex Soukas, MD, PhD, the Weissman Family MGH Research Scholar 2018-2023, Physician Investigator, MGH Center for Genomic Medicine, and Associate Professor of Medicine, HMS.
- Facilitated the GSD International "Buddy" System program to help connect new international students with graduate students who have been at MGH for a longer period.
- Offered the GSD T-Pass Savings to help eligible graduate students to defray their T-Pass transportation costs.
- Continued to sponsor and administer the GSD Graduate Student Travel Awards to help graduate students when travelling to an academic/society meeting related to their advancement.
- Processed about 45 post doc extensions using the new Post Doc Extension Policy process on the online platform which enhanced the efficiency significantly.
- Shepherded a change in MGH policy to require that each postdoctoral trainee identify a secondary mentor.
- Modified the Annual Career Planning Form to promote the requirement for a secondary mentor.
- Initiated twice-yearly MGH Post Doctoral Division travel awards in the amount of $1,000 per awardee to support the travel of two postdoctoral fellows to academic/society meetings.
- Sponsored the 13th annual Research Fellows Poster Celebration to recognize the excellent research conducted by MGH postdoctoral fellows. Research fellows presented their work, and prizes were awarded to the top research. Short lectures at the awards ceremony offered advice on career development.

Strategic Priorities - ORC

- The ORC will work with hospital leadership and departments to clarify the process and resources for resolving authorship disputes. The goal of this initiative is the development of written guidance that can be used by authors to avoid disputes when possible and understand the resolution process when disputes arise.
- The ORC will continue focus on the needs of research faculty in developing lab management skills.
- Continue to provide programming and advocacy for MGH research faculty geared toward career development, guidance and career satisfaction, especially considering the complex and difficult funding climate.
- Contribute to efforts to assist researchers in transition due to funding issues or the shrinking faculty job market, including:
    - Raising awareness of the non-faculty track Research Scientist position to retain highly trained individuals.
    - Increasing awareness of programs for alternative career opportunities (e.g., industry, scientific publishing, college teaching, lab management or administration), and encouraging faculty to support postdocs in career exploration.
    - Educating faculty on the availability of and application process for MGH interim funding.
- Continue to facilitate collaborations between the ORC, Graduate Student Division and the Post-Doctoral Division to create programs that serve some of the overlapping needs of members of the research community.

Center for Faculty Development (CFD)

Programmatic Report

Strategic Priorities - GSD

- Enhance communication with graduate students and PIs through digital tools including email and new website resources.
- Expand educational offerings to CNY and add 1:1 counseling sessions and career consultation with Director at CNY location monthly.
- Collaborate with other offices within the CFD to build strong support for the research community at MGH.
- Support scholarly activities of PhD graduate students who are currently doing research at MGH by offering the GSD Travel awards, T-Pass savings, GSD Select – Paper of the Year Award and PI Mentoring awards.
- Collaborate with Post-Doctoral Division to connect graduate students with MGH post docs and develop graduate student and post docs mentoring program.

Strategic Priorities - PDD

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

Office for Women's Careers (OWC) – Nancy Rigotti, MD, Director

Achievements

The OWC continued efforts to support and advance the careers of women faculty in 2019. Highlights of OWC activity:

- Continued to offer a series of initiatives, supported by the Mass General Physicians Organization (MGPO) and the Executive Committee on Research (ECOR), designed to enhance gender parity in MGH faculty. Initiatives include:
- Expansion of the Caring for Dependents Travel Awards, which offer up to $500 reimbursement to help faculty parents cover child travel/extra childcare expenses during a scientific/medical conference.
- The Advancing Careers Through Editing (ACTE) initiative, which offers editing services on journal manuscripts and the Scholarly Writing Awards (SWA), offering extra child/dependent care reimbursement to allow faculty 'protected' time to finish a manuscript.
- A Negotiation Bootcamp workshop, which ran twice with full capacity, to help women faculty negotiate for career advancement.
- Offered individual negotiation coaching consultations to women faculty who attended the Negotiation Bootcamp as an opportunity to enhance the skill set they learned at the session.
- Organized the highly successful 22nd annual Women in Medicine celebration which recognizes past year achievements by MGH female faculty, especially highlighting women who achieved the rank of Professor in the past year. The event includes a lecture from a distinguished female leader. The 2019 speaker was Dr. Iris Bohnet, Academic Dean of Harvard's Kennedy School of Government, who spoke about strategies to overcome barriers to achieving gender equity in academic institutions.
- Received endowment funds from Dr. Slavin to honor of Cathy Minehan's leadership of the MGH Board of Director. These funds will support the Cathy Minehan Fellowship in Leadership Development for Women. This annual award will provide salary support and funding to allow an aspiring female leader to attend an off-site intensive leadership training program and return to conduct a mentored leadership project.
- Supported the growing community of Claflin Distinguished Scholars with a panel discussion for prospective applicants and the Claflin

Consultation Initiative (CCI) to provide individual coaching to applicants by alumnae, and the annual Claflin Luncheon to welcome the newest scholars.
- In 2019 the CCI assisted a record number of applicants (39) for the upcoming award cycle.
- Five of the six 2019 Claflin winners volunteered to coach the new applicants. In addition, four of the six winners had participated in the CCI initiative when they applied the previous year.
- Received results of questions on gender equity and maternity leave and lactation support that OWC advocated for including on the biennial 2019 MGPO faculty survey. The results are being shared with stakeholders to support gender equity efforts across the hospital.
- Collaborated with MGH Human Resources and other offices to expand awareness of the sexual harassment policy and resources.

Strategic Priorities
- Continue collaborations with the MGPO and ECOR to refine initiatives and provide/expand resources to ensure gender equity in career advancement at MGH.
- Continue advocacy efforts to acknowledge and address gender bias and sexual harassment at MGH.
- Expand professional development programs for women faculty that address the challenges of achieving academic promotion, preparing for leadership roles, and integrating career and parenting. Programs include negotiation training and leadership skill building for women, supporting rising female leaders to take advantage of outside resources such as the Executive Leadership in Academic Medicine (ELAM) program, and advocating for parental leave, lactation, and child care initiatives.
- Create the program structure and identify the first awardee for the Cathy Minehan Fellowship in Leadership Development for Women.
- Offer the Claflin Consultation Initiative and panel to support Claflin Distinguished Scholar Award applicants.
- Collaborate with other institutional stakeholders, including the MGH Diversity Committee, MGH Center for Diversity and Inclusion, and the HMS Joint Committee on the Status of Women.
- Collaborate with MGH Development to advocate for increased funding for initiatives that support the advancement of women.

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

Achievements
- Advised over 90 faculty and trainees from most departments, in approximately 100 consultation sessions, regarding: career advice, CV/cover letter critique, mentorship, and promotion.
- Collaborated with the CFD to hold Crafting Your CV Narrative and Promoting Academic Advancement to help "demystify" the HMS promotions' process.
- Participated in departmental outreach by speaking at departmental meetings to present on the CFD, facilitate career advancement via seminars, and discuss how to give and receive an Annual Career Conference.

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

Center for Computational and Integrative Biology

Thematic Center Report

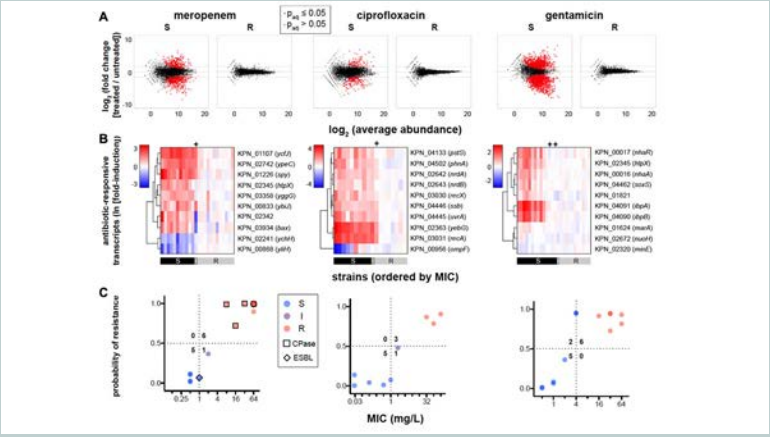
Ramnik J. Xavier, MD, PhD, Director

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 signaling pathways, to identify important mediators of host-microbe interactions, to understand and simulate the conditions associated with the emergence of life, and to directly address human diseases through therapeutic intervention. Center investigators also conduct translational research to explore the potential utility of early stage drug candidates that are developed either in the local academic community or presented to the Translational Medicine Group from the biopharmaceutical industry.

In this year's images we highlight four stories from CCIB laboratories who are working toward more efficient diagnostics, deeper understanding of mechanisms underlying disease and better treatments for infectious, neurological, inflammatory and metabolic diseases.

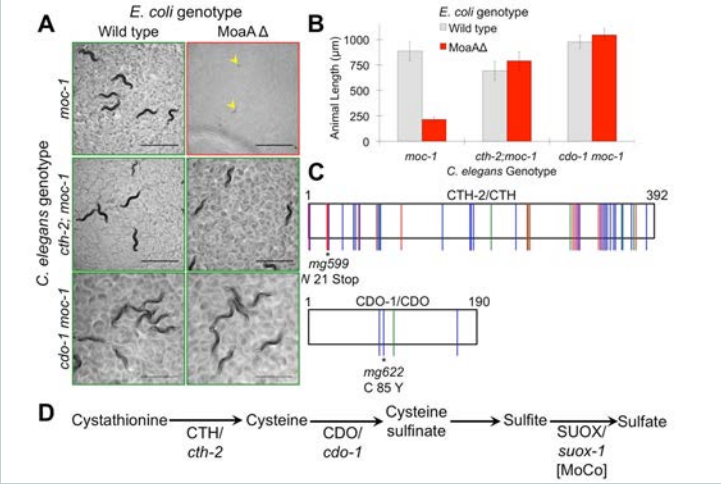
Achievements:

Multidrug resistant bacteria are a serious threat to human health killing 35,000 people in the States each year per a recent CDC estimate. Accurately and rapidly identifying the correct antibiotic to use against these microbes is critical to avoid mortality and decrease the use of broad-spectrum antibiotics which, in a vicious circle, give rise to antimicrobial resistance. The gold standard in antibiotic susceptibility testing (AST), takes several days since it involves growing the pathogen in the presence of various antibiotics. In the December issue of Nature Medicine, Bhattacharyya et al. in the Hung lab describe GoPhAST-R, or Genotypic and Phenotypic AST through RNA detection, a new diagnostic approach that rapidly identifies the correct antibiotic to use within hours rather than days [PMID:31768064]. GoPhAST-R leverages the rapid transcriptional response of a microorganism when treated with an antibiotic to which it is susceptible (phenotype) and combines it with sequence information to determine whether the bacteria carries key genes known to cause drug resistance (genotype). The lab demonstrated this approach works for three major antibiotic classes in common clinical use—fluoroquinolones, aminoglycosides and carbapenems—in five pathogens with a propensity for multidrug resistance through diverse mechanisms. Importantly, they describe a generalizable process to extend this approach to any pathogen–antibiotic pair of interest, requiring only that an antibiotic elicit a differential transcriptional response in susceptible versus resistant isolates, a biological phenomenon that to date appears universal.



Differential gene expression on antibiotic exposure distinguishes susceptible and resistant strains. A, RNA-seq data from two susceptible (left panels) or two resistant (right panels) clinical isolates of K. pneumoniae treated with meropenem (60 min), ciprofloxacin (30 min) or gentamicin (60 min). B, Heatmaps of normalized, log-transformed fold-induction of top ten antibiotic-responsive transcripts from K. pneumoniae treated at CLSI breakpoint concentrations with meropenem (left, 24 clinical isolates), ciprofloxacin (center, 18 clinical isolates) or gentamicin (right, 26 clinical isolates). C, GoPhAST-R predictions of probability of resistance from a random forest model trained on NanoString data from the derivation cohort and tested on the validation cohort (y axis) are compared with standard CLSI classification based on broth microdilution MIC (x axis) for K. pneumoniae isolates treated with meropenem, ciprofloxacin and gentamicin.

Human molybdenum cofactor (MoCo) is a coenzyme required for the incorporation of molybdenum into several essential enzymes across archaea, bacteria and eukaryotes. MoCo deficiency in humans causes seizures, progressive neurological damage, and neonatal death. In a recent study published in Nature Chemical Biology [PMID:30911177], Kurt Warnhoff and Gary Ruvkun identify the metabolic pathway responsible for symptoms of MoCo deficiency and describe for the first time the transfer of MoCo from one species to another. The authors initially observed that mutant C. elegans unable to synthesize Moco (moc-1) are not viable unless fed on a diet of bacteria that can provide the coenzyme. Their search for genetic suppressors of this lethality uncovered cystathionine gamma-lyase (CTH) and cysteine dioxygenase (CDO), enzymes that catalyze sequential steps in the catabolism of methionine and cysteine. Subsequent genetic and pharmacological studies demonstrated that sulfite produced by these enzymes is the key toxin that causes developmental arrest in the absence of MoCo. Molecular insights from this study suggest novel therapeutic approaches to treat MoCo deficiency. Inhibition of CTH or CDO in human patients suffering from Moco

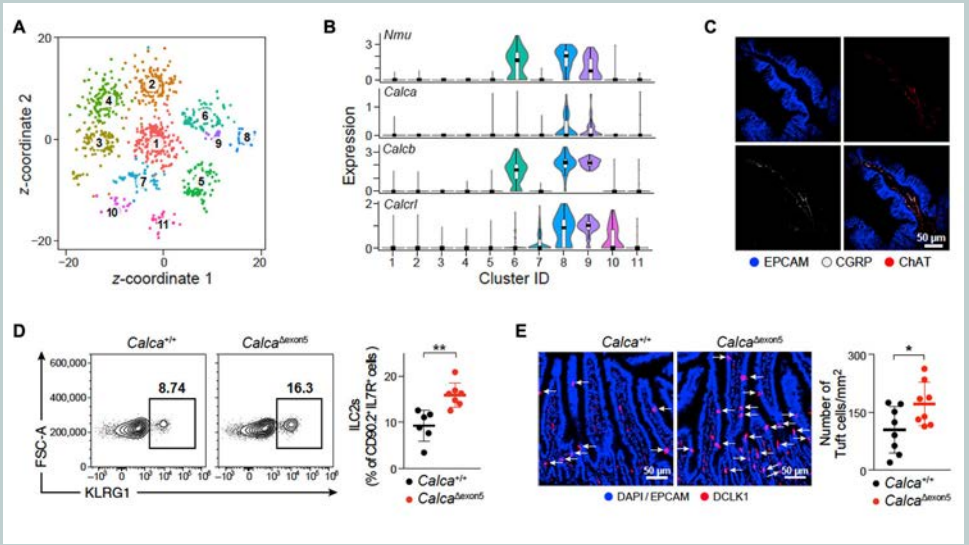


cth-2 and cdo-1 are necessary for the growth arrest and death caused by Moco deficiency. A. Mutant animals were synchronized at the L1 stage and cultured on wild-type and MoCo deficient (ΔMoaA) E. coli for approximately 48 h. Animal lengths were determined for each condition. B. Bar graph representation of animal length. C. Cartoons of CTH-2 (upper) and CDO-1 (lower) proteins. Coloured vertical lines indicate amino acid substitutions identified in our screen as suppressors of MoCo deficient C. elegans when cultured on ΔMoaA E. coli. Asterisks indicate reference alleles for each gene. D. Simplified cartoon of sulfur amino acid catabolism that highlights the roles of CTH (encoded by cth-2), CDO (encoded by cdo-1), and the Moco requiring enzyme SUOX (encoded by suox-1).

deficiency or sulfite oxidase deficiency has the potential to alleviate the toxicity of endogenously produced sulfites. A second approach involves leveraging the ability of C. elegans to utilize MoCo from its microbiome. This ability provides a potential route for delivering MoCo to patients that are unable to synthesize it on their own.

The immune system in the gut is composed of a complex network of innate and adaptive components that sense and respond to antigens from the diet, commensal microbiota, and pathogens. Dysregulated immune reactions often lead to chronic inflammatory responses, which in turn play a key underlying role in inflammatory diseases including inflammatory bowel disease (IBD) and food allergy. The Xavier lab is using single cell genomics approaches to examine the gut as a circuit composed of intra- and inter-cellular interactions that determine health and disease. Single-cell RNA sequencing (scRNA-seq) allows them to dissect cellular diversity on a large scale and identify cell states of individual cell types in response to different stimuli. Two recent studies from the lab published in Cell and Immunity underscore the impact of cell types and cell states on inflammation and allergies, respectively. In one study, Smillie et al. [PMID:31348891] performed scRNA-seq of the human colon during ulcerative colitis (UC), a form of IBD, and established a map to enable discovery of mechanisms of inflammation and treatment response by describing the cell populations that expand with disease, associate with resistance to anti-TNF therapy, and transcribe susceptibility UC genes. To gain a better understanding of the cellular participants in type 2 inflammation in the context of allergies, Xu et al PMID 31618654] combined scRNA-seq with physiological and genetic perturbations. The study uncovered a neuro-immune cellular circuit that modulates type 2 inflammation, identifying a role for alpha-CGRP-mediated neuronal signaling in maintaining homeostasis of ILC2s and the type 2 immune machinery. Such studies outline a path from primary cells to pathology: single-cell genetic and expression data reveal cell type-specific functions that inform hypotheses and focus subsequent investigations on disease-relevant biological contexts.

Since inception, the Translational Medicine Group (TMG) has successfully managed fourteen different therapeutic development programs ranging from pre-INDs through ANDAs for new drug candidates, repurposed drugs and biologics. These projects represent a mixture of internal therapeutics programs involving faculty from many departments including Surgery, Medicine, Neurology, and Psychiatry as well as external programs performed in collaboration with several biotech companies. The projects have ranged from developing a small molecule oral drug type 2 diabetes (Theracos, Inc) to assisting in a program to re-engineer bacteria enabling the metabolism of oxalate to avoid hyperoxaluria (Novome).

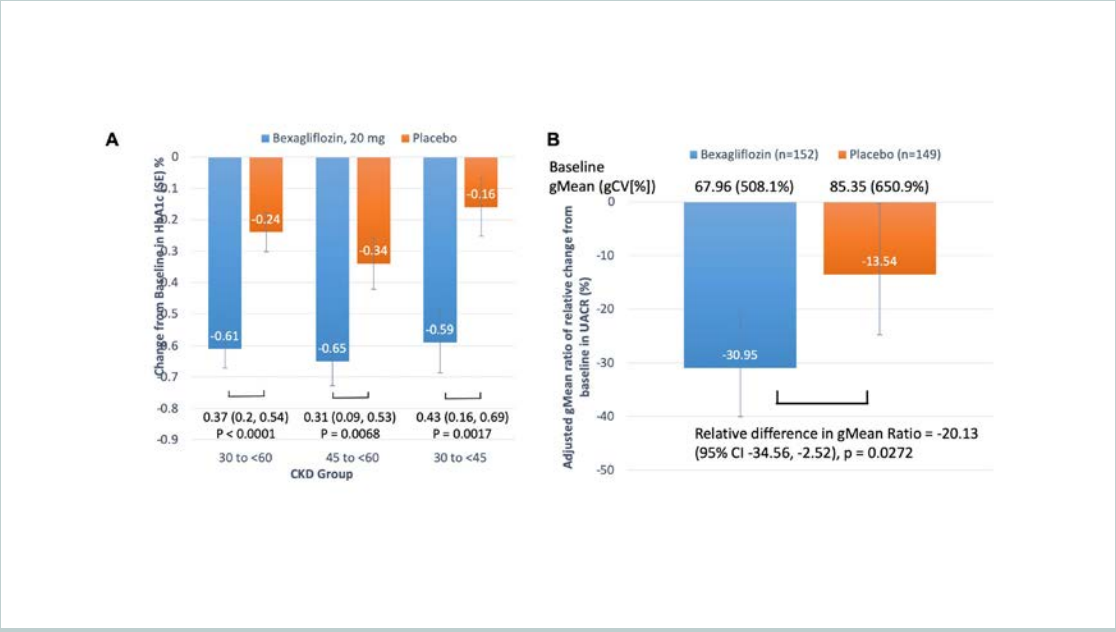


Alpha-CGRP Is Produced by ChAT+ Enteric Neurons in Steady States and Maintains Intestinal KLRG1+ ILC2 Homeostasis In Vivo. (A and B) ChAT+ enteric neurons express a-CGRP. C. Co-localization of ChAT and CGRP in the small intestine of WT mice. Scale bar, 50 mm. (D and E) The deficiency of a-CGRP affects ILC2 expansion in vivo. D. Left: flow cytometry analysis of LP ILC2s in WT and CalcaDexon5 mice in homeostasis. E. Left: representative IF images of tuft cells (arrows) in the small intestine of WT or CalcaDexon5 mice. Scale bars, 50 mm. Right: density of tuft cells (y axis, number per mm2) in WT and CalcaDexon5 mice. Points represent individual mice.

Center for Computational and Integrative Biology

Thematic Center Report

The internal programs have involved collaborations on projects ranging from a vaccine for Shigella (Ed Ryan, MGH ID) to testing new biologic therapies for patients with IgG4RD (John Stone Rheumatology). The TMG's most advanced program involves a collaboration with Theracos, Inc in the development of a novel SGLT2 inhibitor, bexagliflozin. TMG has managed the entire development program for bexagliflozin, from first in human studies to the most recent phase 3 cardiovascular outcome study. This has involved the design and oversight of more than 20 separate clinical trials involving ~ 5000 patients, the largest of which (1700 patients) was completed in December 2019. That study, a combined glucose-lowering and cardiovascular outcome trial in diabetics at increased risk for heart disease demonstrated a significant reduction in HgbA1c levels accompanied by a substantially reduced rate of major CV events in the patients receiving bexagliflozin compared to those on placebo. The TMG faculty overseeing this program, Yuan-Di Halvorsen and Mason Freeman, along with multiple collaborators published four studies in 2019 [PMID: 31297965, PMID: 31161692, PMID: 31101403, PMID: 31749238] evaluating the safety and effectiveness of bexagliflozin in differing diabetic populations, all of which will be included in the anticipated 2020 NDA submission for marketing approval of bexagliflozin in the U.S.



Bexagliflozin treatment for 24 weeks improved HbA1c and lowered UACR. A. Estimated mean change from baseline in hemoglobin A1c (HbA1c) level by treatment and kidney function group at week 24. B. Adjusted geometric mean (gMean) ratios of relative change from baseline in urine albumin-creatinine ratio (UACR). Abbreviations: CKD, chronic kidney disease; SE, standard error; gCV, geometric coefficient of variation.

Susan A. Slaugenhaupt, PhD, Interim Director

Overview:

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.

Achievements:

The CGM is a large and diverse thematic research center comprised of 45 faculty from several clinical departments, with a total of 267 full time FTEs. In 2019, CGM Faculty submitted a total of 148 grant proposals and we saw a 37.2% increase in research funding to 37M in total direct costs.

CGM faculty published 314 scholarly articles in 2019. Of the 55 MGH researchers named to Clarivate Analytics's annual Highly Cited Researchers List in 2019, six are faculty in CGM: Ben Kleinstiver, Sek Kathiresan, Vamsi Mootha, Ben Neale, Mark Daly and Steve Haggarty. Moreover, Ben Neale's paper, "Large-Scale GWAS Reveals Insights Into the Genetic Architecture of Same-Sex Sexual Behavior", is in the Altmetric Top 100, which is an annual list of the research that most caught the public's imagination.

The NHGRI awarded an NIH Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grant (T32), "Partners Training Program in Precision and Genomic Medicine" in 2019, led by Dr. Jordan Smoller and Dr. Heidi Rehm, and we enrolled our first two trainees.

Led by CGM faculty Amit Khera and Heidi Rehm, MGH launched a new Preventive Genomics Clinic in November 2019. This clinic — embedded within primary care — empowers patients to better understand, predict and prevent disease using genetic information. The clinic brings together a team of genetic counselors, clinical geneticists and physicians to provide individualized testing and treatment plans based on state-of-the-art genome interpretation. We work with our patients and their health care teams to develop a plan aimed at minimizing any risks identified for patients and their families, including helping to decide if genetic testing is right for you and discussing previous genetic testing results. published in *Cell.*

Scientific Progress:

Jim Gusella published "CAG Repeat Not Polyglutamine Length Determines Timing of Huntington's Disease Onset" in *Cell.* This groundbreaking paper overturned the three-decade-long and generally accepted view that the timing of neurological onset in Huntington's disease (HD) and the other polyglutamine diseases is actually due to polyglutamine. Using data from over 9,000 HD subjects, the investigators discovered that the age at onset is determined by a special property of the CAG expansion mutation and not by the polyglutamine that it encodes. That property is hypothesized to be a predisposition to further expansion in somatic cells since genome-wide genetic analysis implicated six different genes involved in DNA maintenance/repair as naturally occurring modifiers of the timing of HD onset. This pioneering human modifier study will affect the ways that clinical trials are designed to include consideration of genetic modifier influences in a range of inherited neurologic diseases and, most importantly, provides the proof-of-principle from human subjects themselves, for an entirely new therapeutic approach to HD and to other DNA repeat diseases by targeting the DNA maintenance genes that influence somatic expansion of these repeats to delay or prevent disease onset.

Jonathan Rosand and Chris Anderson's lab published the paper "Genome-wide association study of cerebral small vessel disease reveals established and novel loci" in Brain. They conducted a genome-wide association study (GWAS) across pathologically-related forms of cerebral small vessel disease, including intracerebral hemorrhage and small vessel ischemic stroke. Using a new bioinformatics tool called "Multi-trait Analysis of GWAS", or MTAG, we integrated GWAS from each of these individual traits into a single analysis, replicating prior GWAS associations at 1q22, and identifying novel associations at 2q33 and 13q34. Leveraging additional informatics tools including PrediXcan and the BRAINEAC database, we found that genes at these loci are widely expressed across nerve and vascular tissues, with distinct expression patterns that differ across CNS tissues, including neurons, oligodendrocytes, and endothelial cells. Overall, these results provide new information on genes, tissues,

and cell types central to the development of cerebral small vessel disease, a highly prevalent condition of aging that increases the risk for stroke, cognitive decline, late-life depression, and gait disorders. Studies building on these discoveries will bring us closer to rational therapeutic approaches to prevent or limit morbidities related to cerebrovascular disease.

Jose Florez participated in the study, published in Nature, "Exome sequencing of 20,791 cases of type 2 diabetes and 24,440 controls." Highlights of the study include:

1. Whole-exome-sequencing analyses of 20,791 individuals with type 2 diabetes (T2D) and 24,440 non-diabetic control participants from 5 ancestries
2. Gene-level associations of rare variants in 4 genes at exome-wide significance, including a series of more than 30 SLC30A8 alleles that conveys protection against T2D
3. Significant associations in 12 gene sets, including those corresponding to T2D drug targets and candidate genes from knockout mice
4. Refined assessment of genetic architecture for T2D, with the strongest T2D gene-level signals for rare variants explaining at most 25% of the heritability of the strongest common single-variant signals
5. Introduction of sample size calculations and a method to interpret modest rare-variant associations and to incorporate these associations into future target or gene prioritization efforts

Ben Neale was part of the study "Large-Scale GWAS Reveals Insights Into the Genetic Architecture of Same-Sex Sexual Behavior" in *Science*. Twin studies and other analyses of inheritance of sexual orientation in humans has indicated that same-sex sexual behavior has a genetic component. Previous searches for the specific genes involved have been underpowered and thus unable to detect genetic signals. Ganna et al. perform a genome-wide association study on 493,001 participants from the United States, the United Kingdom, and Sweden to study genes associated with sexual orientation. They find multiple loci implicated in same-sex sexual behavior indicating that, like other behavioral traits, non-heterosexual behavior is polygenic.

David Scadden, MD, Director

The Center for Regenerative Medicine is dedicated to stem cell and developmental biology informing novel therapies in regeneration and cancer. It is comprised of a collaborative team of scientists and clinicians with diverse areas of expertise and a shared mission.

Key Scientific Achievements in 2019

- First demonstration of single day hematopoietic stem cell mobilization and collection in healthy volunteers
- Definition of interneurons contributing to PTSD-like fear responses
- Demonstration of tendon resident progenitor cells that can respond to injury
- Development of a bioengineered device capable of enhancing T cell generation

Awards and Honors

- Donald Metcalf Award, International Society of Experimental Hematology (Scadden)
- Honorary Doctor of Science, D. Sci., Case Western Reserve University (Scadden)

Contributions of Laboratories

SAHAY LAB

The Sahay lab published a study in Nature Neuroscience demonstrating the role of a previously underappreciated neural circuit in regulation of fear. This study may illuminate new circuits to target in PTSD.

Dorsolateral septum somatostatin interneurons gate mobility to calibrate context-specific behavioral fear responses. Besnard A, Gao Y, TaeWoo Kim M, Twarkowski H, Reed AK, Langberg T, Feng W, Xu X, Saur D, Zweifel LS, Davison I, Sahay A. at Neurosci. 2019 Mar;22(3):436-446. doi: 10.1038/s41593-018-0330-y. Epub 2019 Feb 4.

https://hsci.harvard.edu/news/threat-sensors

https://www.massgeneral.org/news/press-release/mass-general-study-identifies-brain-cells-that-modulate-behavioral-response-to-threats

The Sahay lab published a Review in Nature Neuroscience that describes a model for thinking about how new brain cells contribute to memory processing.

Functions of adult-born neurons in hippocampal memory interference and indexing. Miller SM, Sahay A. Nat Neurosci. 2019 Oct;22(10):1565-1575. doi: 10.1038/s41593-019-0484-2. Epub 2019 Sep 2. Review

SYKES LAB

Lab focus:

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

Publications Include:

The novel dihydroorotate dehydrogenase (DHODH) inhibitor BAY 2402234 triggers. differentiation and is effective in the treatment of myeloid malignancies Christian S, Merz C, Evans L, Gradl S, Seidel H, Friberg A, Eheim A, Lejeune P, Brzezinka K, Zimmermann K, Ferrara S, Meyer H, Lesche R, Stoeckigt D, Bauser M, Haegebarth A, Sykes DB, Scadden DT, Losman JA, Janzer A..
Leukemia. 2019 Oct;33(10):2403-2415..

Insights From a Patient With Lung Cancer-Party Therapy Is Way Better Than Chemotherapy. Sykes DB .JAMA Oncol. 2019 Sep 12. PubMed PMID: 31513260.

A man with polycythemia vera, myelodysplastic syndrome and acquired microcytosis.Mann M, Kreuzbauer T, Sykes DB. BMJ Case Rep. 2019 Aug 13;12(8)..

Immune neutropenia mediated by micafungin. Ameri AH, Curtis BR, Sykes DB. Am J Hematol. 2019 Jul;94(7):830-832.

Frontline Science: Employing enzymatic treatment options for management of ocular biofilm-based infections. Kugadas A, Geddes-McAlister J, Guy E, DiGiandomenico A, Sykes DB, Mansour MK, Mirchev R, Gadjeva M. J Leukoc Biol. 2019 Jun;105(6):1099-1110..

GALLOWAY LAB

The Galloway lab is focused on identifying the molecular and cellular regulators of tendon development and regeneration. We use genetics, chemical screening, and live imaging in zebrafish to identify and characterize new pathways important for tendon formation and regeneration. As there was no prior molecular description of zebrafish tendons, we established the zebrafish as a model to study tendon biology and have shown that they are homologous in their formation, regulation, ultrastructure, and mechanical properties to mammalian tendons. We have recently completed a zebrafish high-throughput chemical screen to identify tendon promoting drugs and we are functionally characterizing the target pathways (Chen and Niu et al., in revision, Development). Using new genetic and imaging tools, we show that the zebrafish robustly regenerates tendon and tendon-bone attachment structures, or enthesis, and are defining the function of specific pathways and cell types in the regenerative process. This regenerative ability contrasts markedly with mammals, which have limited regenerative potential and primarily heal through scar formation. Our future goals are to further dissect the mechanisms underlying tendon regeneration in the zebrafish and to identify tendon promoting pathways with activity in human pluripotent stem cell model systems. To complement our work in the zebrafish, my lab uses mouse genetic lineage tracing and functional manipulations to identify new pathways regulating mammalian postnatal tendon growth, maintenance, and healing. We defined a key developmental transition in the postnatal tendon, which is characterized by a shift from cell growth to physiological homeostasis and maturation of the collagen matrix. In addition, we definitively showed that adult tendon cells retain detectable proliferative activity throughout adulthood and aging, suggestive of adult progenitor activity. This work has facilitated current work in my lab using next generation sequencing techniques to define gene expression and epigenetic changes that occur during this transition and in a unique adult progenitor cell population during healing.

Publications Include:
Zebrafish: An Emerging Model for Orthopedic Research.
Busse B, Galloway JL, Gray RS, Harris MP, Kwon RY.
J Orthop Res. 2019 Nov 26. doi: 10.1002/jor.24539. [Epub ahead of print] Review.

A distinct transition from cell growth to physiological homeostasis in the tendon.
Grinstein M, Dingwall HL, O'Connor LD, Zou K, Capellini TD, Galloway JL.
Elife. 2019 Sep 19;8. pii: e48689. doi: 10.7554/eLife.48689.

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

SCADDEN LAB

Our emphasis is on translating the biology of blood cell production into therapies. The target areas are blood stem cell transplantation and blood production gone wrong in acute leukemias. We have spun discoveries out to biotechnology start-ups that are now generating the first clinical data on methods for mobilizing stem cells without G-CSF and for non-genotoxic conditioning for transplantation of gene modified cells. We have also defined unanticipated metabolic targets in AML and five clinical trials are underway testing them.

Publications include:
An injectable bone marrow-like scaffold enhances T cell immunity after hematopoietic stem cell transplantation. Shah NJ, Mao AS, Shih TY, Kerr MD, Sharda A, Raimondo TM, Weaver JC, Vrbanac VD, Deruaz M, Tager AM, Mooney DJ, Scadden DT. Nat Biotechnol. 2019 Mar;37(3):293-302.

A Cellular Taxonomy of the Bone Marrow Stroma in Homeostasis and Leukemia. Baryawno N, Przybylski D, Kowalczyk MS, Kfoury Y, Severe N, Gustafsson K, Kokkaliaris KD, Mercier F, Tabaka M, Hofree M, Dionne D, Papazian A, Lee D, Ashenberg O, Subramanian A, Vaishnav ED, Rozenblatt-Rosen O, Regev A, Scadden DT. Cell. 2019 Jun 13;177(7):1915-1932.e16.

Stress-Induced Changes in Bone Marrow Stromal Cell Populations Revealed through Single-Cell Protein Expression Mapping. Severe N, Karabacak NM, Gustafsson K, Baryawno N, Courties G, Kfoury Y, Kokkaliaris KD, Rhee C, Lee D, Scadden EW, Garcia-Robledo JE, Brouse T, Nahrendorf M, Toner M, Scadden DT. Cell Stem Cell. 2019 Oct 3;25(4):570-583.e7.

Selective hematopoietic stem cell ablation using CD117-antibody-drug-conjugates enables safe and effective transplantation with immunity preservation. Czechowicz A, Palchaudhuri R, Scheck A, Hu Y, Hoggatt J, Saez B, Pang WW, Mansour MK, Tate TA, Chan YY, Walck E, Wernig G, Shizuru JA, Winau F, Scadden DT, Rossi DJ. Nat Commun. 2019 Feb 6;10(1):617.

Identification of Functionally Distinct Mx1+αSMA+ Periosteal Skeletal Stem Cells. Ortinau LC, Wang H, Lei K, Deveza L, Jeong Y, Hara Y, Grafe I, Rosenfeld SB, Lee D, Lee B, Scadden DT, Park D. Cell Stem Cell. 2019 Dec 5;25(6):784-796.e5. doi: 10.1016/j.stem.2019.11.003.

Metcalf Lecture Award: Applying niche biology to engineer T-cell regenerative therapies.
Scadden DT. Exp Hematol. 2019 Dec;80:1-10.

Growing old in the age of heterogeneity: the perils of shifting clonality. Gustafsson K, Scadden DT. Curr Opin Hematol. 2019 Jul;26(4):222-227.

Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. Frodermann V, Rohde D, Courties G, Severe N, Schloss MJ, Amatullah H, McAlpine CS, Cremer S, Hoyer FF, Ji F, van Koeverden ID, Herisson F, Honold L, Masson GS, Zhang S, Grune J, Iwamoto Y, Schmidt SP, Wojtkiewicz GR, Lee IH, Gustafsson K, Pasterkamp G, de Jager SCA, Sadreyev RI, MacFadyen J, Libby P, Ridker P, Scadden DT, Naxerova K, Jeffrey KL, Swirski FK, Nahrendorf M. Nat Med. 2019 Nov;25(11):1761-1771.

Programmable microencapsulation for enhanced mesenchymal stem cell persistence and immunomodulation. Mao AS, Özkale B, Shah NJ, Vining KH, Descombes T, Zhang L, Tringides CM, Wong SW, Shin JW, Scadden DT, Weitz DA, Mooney DJ. Proc Natl Acad Sci U S A. 2019 Jul 30;116(31):15392-15397.

Lineage Tracing Reveals a Subset of Reserve Muscle Stem Cells Capable of Clonal Expansion under Stress. Scaramozza A, Park D, Kollu S, Beerman I, Sun X, Rossi DJ, Lin CP, Scadden DT, Crist C, Brack AS. Cell Stem Cell. 2019 Jun 6;24(6):944-957.

The novel dihydroorotate dehydrogenase (DHODH) inhibitor BAY 2402234 triggers differentiation and is effective in the treatment of myeloid malignancies. Christian S, Merz C, Evans L, Gradl S, Seidel H, Friberg A, Eheim A, Lejeune P, Brzezinka K, Zimmermann K, Ferrara S, Meyer H, Lesche R, Stoeckigt D, Bauser M, Haegebarth A, Sykes DB, Scadden DT, Losman JA, Janzer A. Leukemia. 2019 Oct;33(10):2403-2415

Stem Cell Transplant Approaches for Patients With Blood Cancers. Scadden DT. Oncology (Williston Park). 2019 Mar 13;33(3):86-8.

Glucocorticoids Regulate Bone Marrow B Lymphopoiesis After Stroke. Courties G, Frodermann V, Honold L, Zheng Y, Herisson F, Schloss MJ, Sun Y, Presumey J, Severe N, Engblom C, Hulsmans M, Cremer S, Rohde D, Pittet MJ, Scadden DT, Swirski FK, Kim DE, Moskowitz MA, Nahrendorf M. Circ Res. 2019 Apr 26;124(9):1372-1385.

Ptpn21 Controls Hematopoietic Stem Cell Homeostasis and Biomechanics. Ni F, Yu WM, Wang X, Fay ME, Young KM, Qiu Y, Lam WA, Sulchek TA, Cheng T, Scadden DT, Qu CK. Cell Stem Cell. 2019 Apr 4;24(4):608-620.e6.

Center for Systems Biology

Thematic Center Report

Ralph Weissleder, MD, PhD, Director

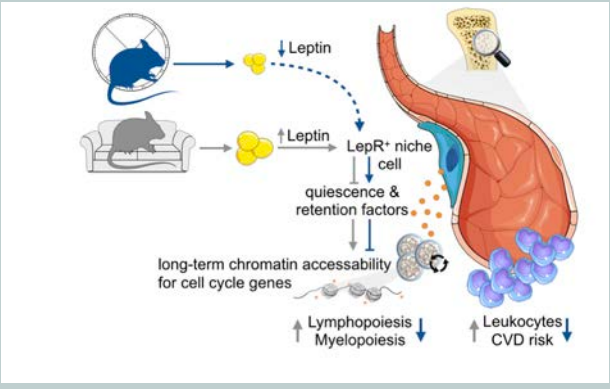
The mission of CSB is to analyze at a systems level how cells, proteins and other biological molecules interact in both healthy and diseased states. Through a multidisciplinary approach that combines clinical insight with powerful analytical technologies, faculty pursue systems-level research that is both fundamental to our understanding of biology as well as directly applicable to the diagnosis and treatment of human disease. While these approaches can be generalizable to a variety of diseases, the Center has particular strengths in complex human conditions such as cancer, cardiovascular and immune diseases. The CSB's mission is enabled by faculty with expertise in advanced bioimaging, immunology, biology, genomics, chemistry, bioengineering and mathematical modeling. The Center is a major node within the Harvard-wide Systems Biology Program, and its faculty maintain joint appointments or affiliations with the HMS Department of Systems Biology, various clinical departments at MGH, other MGH Thematic Centers and the Broad Institute. The CSB is currently structured into 13 PI laboratories (Aguirre, Bernstein, Castro, Higgins, Lee, Lin, Im, Miller, Nahrendorf, Naxerova, Pittet, Swirski and Weissleder), Core Platforms (Imaging, Chemistry, 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 38 faculty.

Achievements:

Study helps solve mystery of how sleep protects against heart disease

Researchers say they are closer to solving the mystery of how a good night's sleep protects against heart disease. In studies using mice, they discovered a previously unknown mechanism between the brain, bone marrow, and blood vessels that appears to protect against the development of atherosclerosis, or hardening of the arteries—but only when sleep is healthy and sound. The discovery of this pathway underscores the importance of getting sufficient, quality sleep to maintain cardiovascular health and could provide new targets for fighting heart disease, the leading cause of death among women and men in the United States. In a study published in Nature, the Swirski Lab identified a mechanism by which a brain hormone controls production of inflammatory cells in the bone marrow in a way that helps protect the blood vessels from damage. This anti-inflammatory mechanism is regulated by sleep, and it breaks down when you frequently disrupt sleep or experience poor sleep quality.

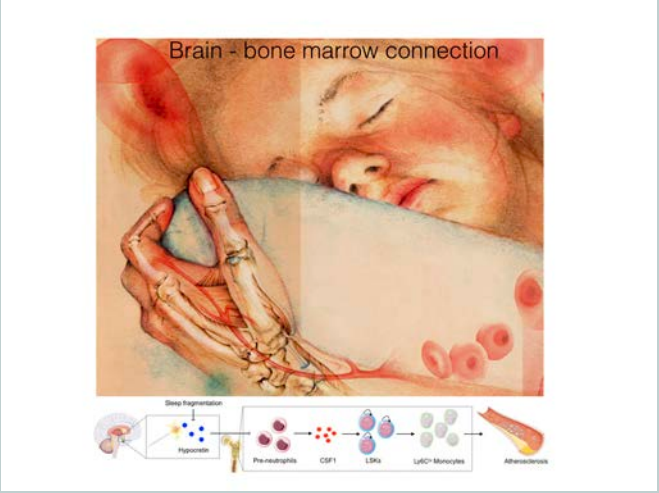
McAlpine CS, Kiss MG, Rattik S, He S, Vassalli A, Valet C, Anzai A, Chan CT, Mindur JE, Kahles F, Poller WC, Frodermann V, Fenn AM, Gregory AF, Halle L, Iwamoto Y, Hoyer FF, Binder CJ, Libby P, Tafti M, Scammell TE, Nahrendorf M, Swirski FK. Sleep modulates haematopoiesis and protects against atherosclerosis. Nature. 2019;566(7744):383-387



Exercise diminishes atherosclerosis
Voluntary physical activity protects against cardiovascular disease (CVD) via reduced chronic hematopoietic output of inflammatory leukocytes, due to diminished leptin signaling to the stromal hematopoietic bone marrow niche. Leptin levels increase when energy is abundant41. The hormone's role in regulating energetically costly hematopoiesis may have evolved to produce blood cells at times of resource sufficiency. However, contemporary sedentary behavior, which increases leptin and consequently hematopoiesis, may have rendered this adaptation a risk factor for CVD, and perhaps also for other diseases with inflammatory components. Nature Med. 2019;25(11):1761-1771

Gene expression profiling maps systemic macrophage responses to sepsis, MI, and stroke

Myocardial infarction, stroke, and sepsis trigger sys- temic inflammation and organism-wide complica- tions that are difficult to manage. Here, we examined the contribution of macrophages residing in vital or- gans to the systemic response after these injuries. We generated a comprehensive catalog of changes in macrophage number, origin, and gene expression in the heart, brain, liver, kidney, and lung of mice with myocardial infarction, stroke, or sepsis. Predomi- nantly fueled by heightened local proliferation, tissue macrophage numbers increased systemically. Macrophages in the same organ responded similarly to different injuries by altering expression of tissue- specific gene sets. Preceding myocardial infarction improved survival of subsequent pneumonia due to enhanced bacterial clearance, which was caused by IFN? priming of alveolar macrophages. Conversely, EGF receptor signaling in macrophages exacerbated inflammatory lung injury. Our data suggest that local injury activates macrophages in remote organs and that targeting macrophages could improve resilience against systemic complica- tions following myocardial infarction, stroke, and sepsis.



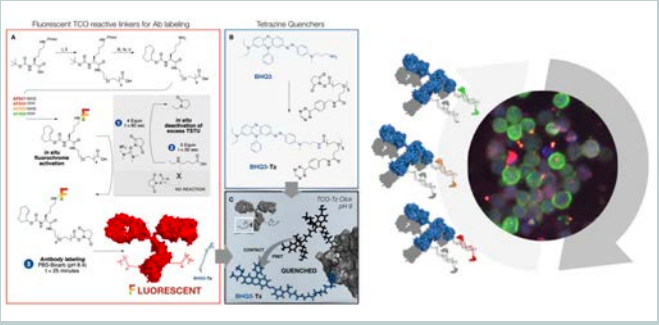
Brain-bone marrow connection
New data indicates that sleep protects against atherosclerosis. Undisturbed sleep maintains proper hypothalamic release of orexin/hypocretin, which limits pre-neutrophil CSF1 in the bone marrow, thereby curtailing haematopoiesis and atherosclerosis. This neuro-immune axis directly connects sleep to immune function and cardiovascular disease. Nature. 2019;566(7744):383-387

Hoyer FF, Naxerova K, Schloss MJ, Hulsmans M, Nair AV, Dutta P, Calcagno DM, Herisson F, Anzai A, Sun Y, Wojtkiewicz G, Rohde D, Frodermann V, Vandoorne K, Courties G, Iwamoto Y, Garris CS, Williams DL, Breton S, Brown D, Whalen M, Libby P, Pittet MJ, King KR, Weissleder R, Swirski FK, Nahrendorf M. Tissue-Specific Macrophage Responses to Remote Injury Impact the Outcome of Subsequent Local Immune Challenge. Immunity. 2019;51(5):899-914.e7

New work discovers exercise benefits on bone marrow

Modern life comes with many dangers. This includes sedentary behavior, as we all spend increasing time sitting: on the office chair, in the car, and on the sofa. This is risky and leads to obesity, myocardial infarction and stroke. A manuscript published in Nature Medicine describes a new pathway how sedentary behavior causes cardiovascular disease. Mice with access to treadmills had lower blood stem cell proliferation in their bone marrow. On the flip side, sedentary mice, resembling a large proportion of the American population, work out 20-fold less. As a result, they had higher blood levels of the hormone leptin, which triggered over-production of inflammatory leukocytes, resulting in more atherosclerosis and heart failure. The team also looked at clinical data from the CANTOS trial, observing similar relationships between physical activity, leptin and leukocytes.

Frodermann V, Rohde D, Courties G, Severe N, Schloss MJ, Amatullah H, McAlpine CS, Cremer S, Hoyer FF, Ji F, van Koeverden ID, Herisson F, Honold L, Masson GS, Zhang S, Grune J, Iwamoto Y, Schmidt SP, Wojtkiewicz GR, Lee IH, Gustafsson K, Pasterkamp G, de Jager SCA, Sadreyev RI, MacFadyen J, Libby P, Ridker P, Scadden DT, Naxerova K, Jeffrey KL, Swirski FK, Nahrendorf M. Exercise reduces inflammatory cell production and cardiovascular inflammation via instruction of hematopoietic progenitor cells. Nature Med. 2019;25(11):1761-1771

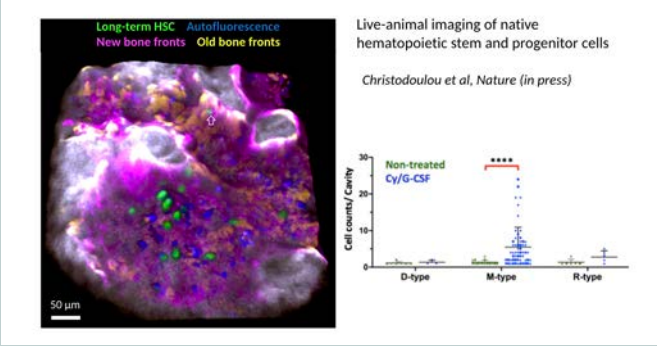


Ultra-fast cycling for multiplexed cellular fluorescence imaging (FAST)
Rapid analysis of single and scant cell populations is essential in modern diagnostics, yet existing methods are often limited and slow. Here we describe an ultra-fast, highly efficient cycling method for the analysis of single cells based on unique linkers for tetrazine (Tz) / trans-cyclooctene (TCO) mediated quenching. This methods multi-cycle staining and immune cell profiling within an hour, leveraging the accelerated kinetics to open new diagnostic possibilities for rapid cellular analyses.A. Synthesis route for preparation of TCO-linked fluorophores (FAST probes) built on a lysine scaffold with a PEG4 linker for efficient antibody conjugation. The core linker can be functionalized with any amine-reactive fluorophore of choice. Inset: Excess TSTU can be used for rapid activation of the PEG4-CO2H and neutralized immediately thereafter with ENBA, circumventing a range of purification and antibody-conjugation obstacles. B. BHQ3-amine is coupled with HTz-PEG5-NHS to yield BHQ3-Tz in one step. C. Structural schematic of the BHQ3-fluorophore quenching interaction after TCO-Tz click; AF647 is depicted here. Angew Chem 2020, in press.

Discovering Myeloid Cells In Lung Tumors

Myeloid cells can promote or limit tumor outgrowth but remain poorly understood. In a study published in Immunity, the Pittet lab at the MGH Center for Systems Biology and the Klein lab at Harvard Medical School teamed up to map myeloid cells at the single cell level in human and mouse lung cancer. They made the following findings: 1) Consistent complexity: the same tumor myeloid populations are repeatedly found across patients, indicating that the myeloid microenvironment within lung tumors is stereotyped. 2) Conservation across species: many myeloid populations are highly conserved across patients and mice, suggesting that studying myeloid cells in mice can help understand the human disease. 3) New therapeutic targets: the map of tumors' myeloid populations identified in this study points to new targets for cancer immunotherapy.

Zilionis R*, Engblom C*, Pfirschke C, Savova V, Zemmour D, Saatcioglu HD, Krishnan I, Maroni G, Meyerovitz CV, Kerwin CM, Choi S, Richards WG, De Rienzo A, Tenen DG, Bueno R, Levantini E, Pittet MJ**, Klein AM** Single-Cell Transcriptomics of Human and Mouse Lung Cancers Reveals Conserved Myeloid Populations across Individuals and Species. Immunity. 2019;50(5):1317-1334.e10



Stem cell imaging in the Lin lab. Live imaging of native HSCs is now possible without transplantation, thanks to a new HSC-specific reporter mouse (MDS Mds1GFP/+ Flt3-Cre) developed by Fernando Camargo's lab at Boston Children's Hospital.
a) HSCs show heterogeneous response to stimulation with cyclophosphamide and G-CSF. Some HSCs proliferate and form clusters (lower part of the image), while others remain quiescent (arrow, pointing to a single cell that did not proliferate).
b) Bone marrow cavities are heterogeneous with respect to stages of bone remodeling (as visualize by in vivo imaging). Remarkably, when we classify the cavities in to three types - those undergoing primarily bone resorption (R-type), new bone deposition (D-type), and mixed (M-type) - we found that while steady state HSCs are distributed in all three cavity types as rare single cells, their expansion after stimulation is restricted to a subset of M-type cavities, as shown in the panel on the right. Christodoulou et al. Nature 2020, in press

High-throughput assessment of hemoglobin polymer in Sickle cell disease

Sickle cell disease (SCD) is caused by a variant hemoglobin molecule that polymerizes inside red blood cells (RBCs) in reduced oxygen tension. Treatment development has been slow for this typically severe disease, but there is current optimism for curative gene transfer strategies to induce expression of fetal hemoglobin or other non-sickling hemoglobin isoforms. All SCD morbidity and mortality arise directly or indirectly from polymer formation in individual RBCs. Identifying patients at highest risk of complications and treatment candidates with the greatest curative potential therefore requires determining the amount of polymer in individual RBCs under controlled oxygen. Here, we report a semi-quantitative measurement of hemoglobin polymer in single RBCs as a function of oxygen. The method takes advantage of the reduced oxygen affinity of hemoglobin polymer to infer polymer content for thousands of RBCs from their overall oxygen saturation. The method enables approaches for SCD treatment development and precision medicine.

Di Caprio G*, Schonbrun E*, Gonçalves BP, Valdez JM, Wood DK, Higgins JM High-throughput assessment of hemoglobin polymer in single red blood cells from sickle cell patients under controlled oxygen tension. Proc Natl Acad Sci U S A. 2019;:ePub

For a complete list of 2019 publications, please see here: https://csb.mgh.harvard.edu/publications?year=2019

R. Rox Anderson, MD, Director

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

Strategic priorities

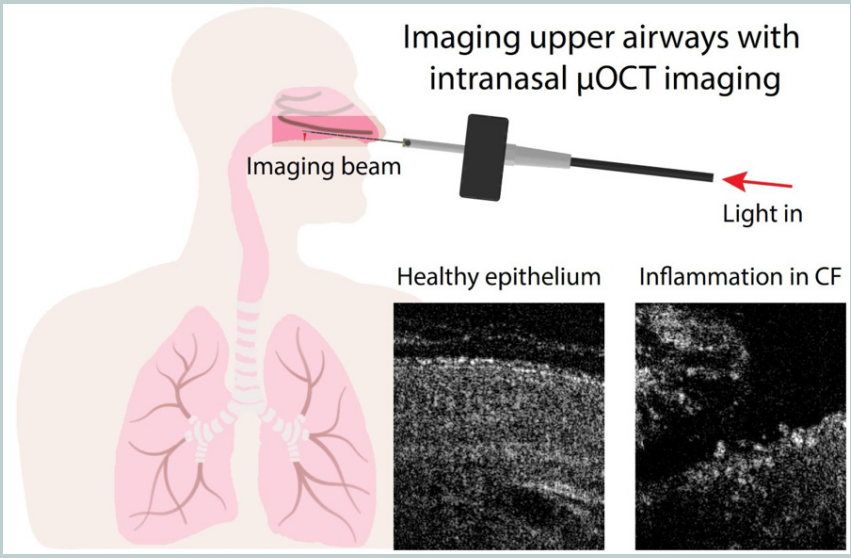
- Leadership and excellent faculty. We are the world's largest research center in a rapidly expanding field, with 280 personnel, and an annual research budget near $30M. Our core strength is the intellectual diversity of excellent faculty who aim for real impact. Prof. Irene Kochevar PhD recently retired. Asst. Prof. Aaron Aguirre MD PhD recently joined our faculty, from the Weissleder lab.
- Innovation. Wellman is the birthplace of many inventions and discoveries now in widespread use. In 2019, we were the leading source of MGH royalty income, there were 36 new invention disclosures, 70 new US and international patents were issued, and 3 new startup companies were formed from Wellman IP licensed by MGH.
- World Health. We are pursuing collaborative research on problems from every continent including Antarctica, with emphasis on environmental change, trauma, malnutrition, child health, infection and cancer in developing countries.
- Education. We offer courses, a regular seminar and lecture series, several CME courses, student and postdoctoral fellow education, an NSF-supported Biomedical Optics summer school for undergraduates, and three endowed competitive research fellowships in biomedical optics (Bullock, Deutsch, Hillenkamp).
- Return value to MGH. Wellman is non-departmental and collaborates broadly (>50 projects) on basic and clinical research at MGH. Our faculty lead or serve on several MGH committees. We welcome, solicit and support collaborative research at all stages.

A Sample of 2019 Research Highlights

Wellman Center published over 150 research papers in 2019. Here are several highlights:

CYSTIC FIBROSIS

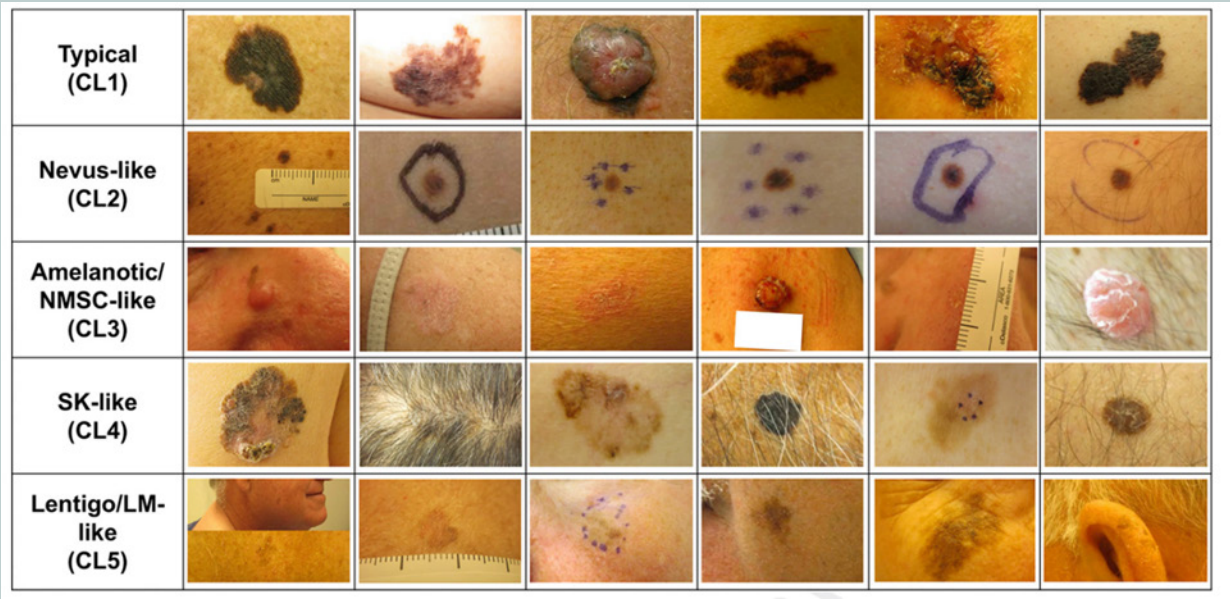
Prof. Gary Tearney leads a large effort for live microscopy/endoscopy that invents, builds, verifies and introduces new technologies into medicine. A unique micro-OCT system illustrated below was used to study respiratory epithelium defects in patients with cystic fibrosis (CF), revealing cell-mediated inflammation, decreased mucus transport, cilia dysfunction, and epithelial loss. This detailed, cellular-resolution, quantitative, completely non-invasive imaging echnology will prove useful in managing CF patients and development of new therapies. Leung, H. M., Birket, S. E.,[...], Tearney G. "Intranasal micro-optical coherence tomography imaging for cystic fibrosis studies." Sci. Transl. Med. 11, eaav3505 (2019).



FINDING MELANOMA

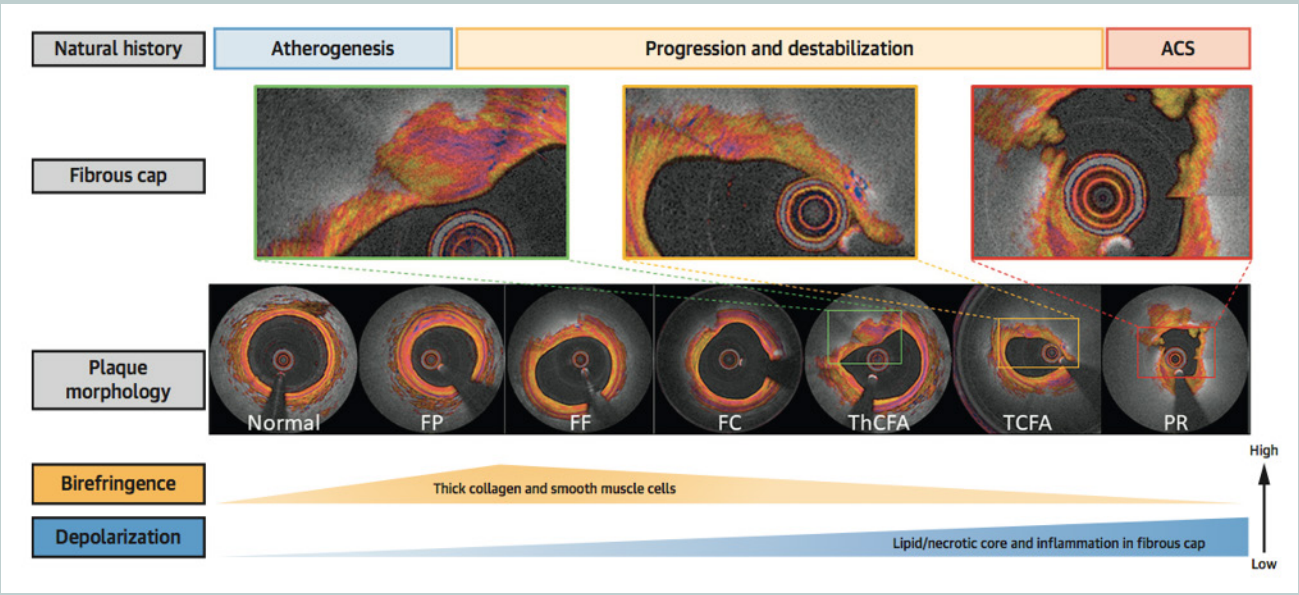
Prof. Hensin Tsao, MD, PhD has in one solid stroke, challenged the way we find these deadly skin tumors. All images of pathologically-diagnosed melanomas taken prospectively over 5 years at MGH were analyzed using "consensus K means clustering". Unlike the classical ABCD (Asymmetry-Border-Color-Diameter) clinical diagnostic criteria, a large fraction of melanomas were symmetric, round, amelanotic, or resembled benign seborrheic keratoses or benign nevi. These findings have tremendous implications for artificial learning and for teaching physicians

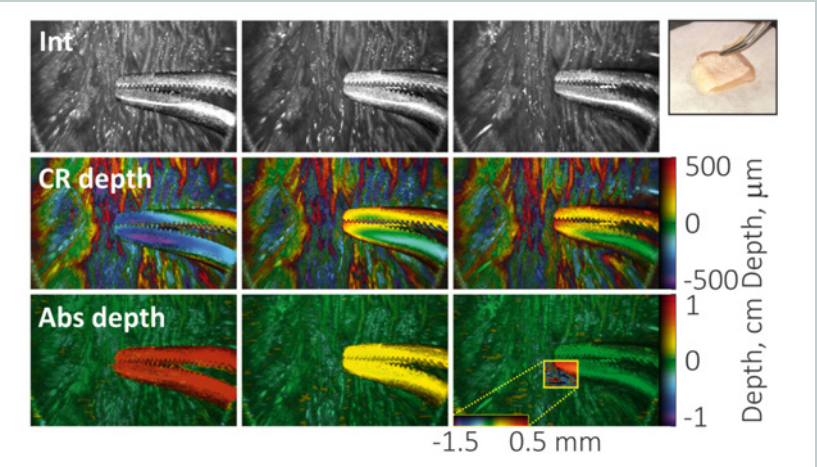
about melanoma. The lesions shown below are all melanomas. Klebanov N, Gunasekera N, [...], Tsao H. "The Clinical Spectrum of Cutaneous Melanoma Morphology" J Am Acad Dermatol. 2019 Jan;80(1):178-188.e3



CORONARY ARTERY IMAGING

Using a novel intravascular OCT imaging system developed in Prof. Bouma's lab, the polarimetric properties of coronary atherosclerosis were imaged in patients undergoing coronary intervention, yielding much better images. Quantitative measures of birefringence and depolarization were found to vary significantly across plaque types, from intimal thickening through thin-capped fibroatheromas. This form of OCT may replace existing versions, open new avenues for studying coronary atherosclerosis, and facilitate automated interpretation of lesion characteristics during percutaneous coronary imaging in patients. Otsuka K, Villiger M, [...], Bouma BE. "Intravascular Polarimetry in Patients with Coronary Artery Disease". J Amer Coll Cardol Img. 2019 Dec 21. Epublished DOI:10.1016/j.jcmg.2019.06.015





DEPTH PERCEPTION MATTERS DURING SURGERY

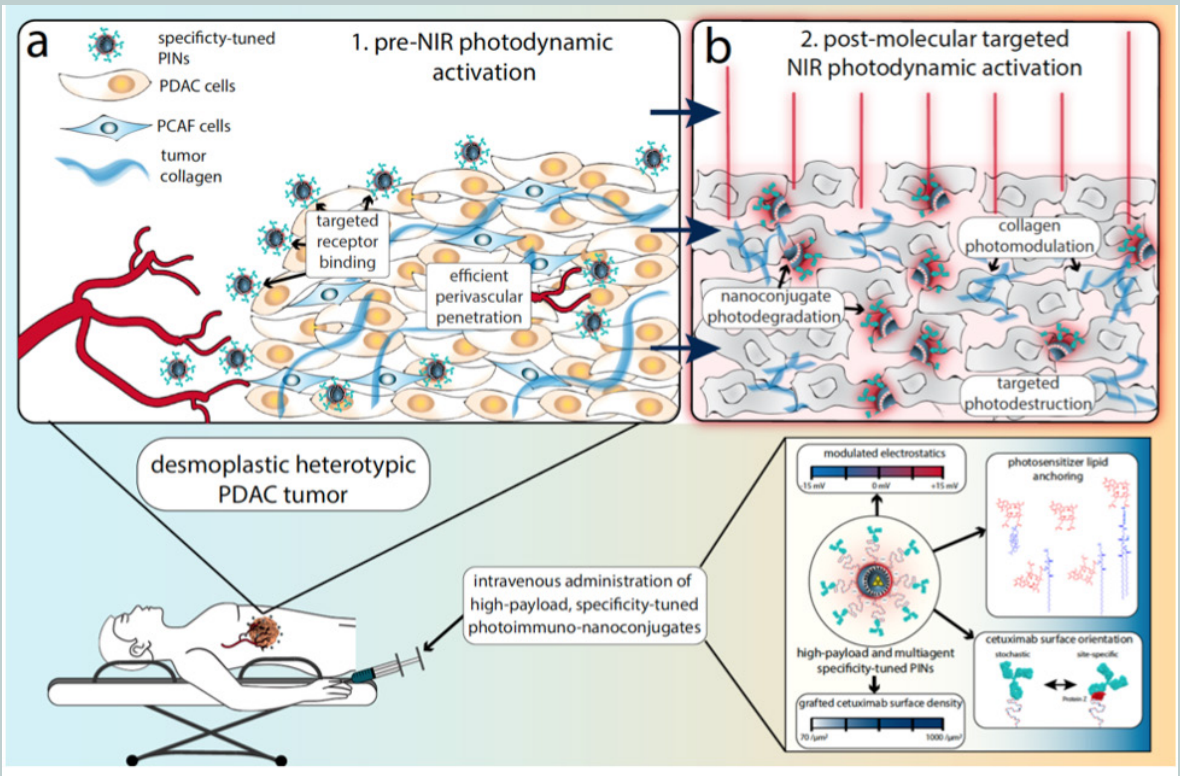
A major challenge of the paradigm shift to minimally-invasive endoscopic surgery, is lack of depth perception. This year, Ben Vakoc's lab demonstrated a smaller, user-friendly version of wide-field OCT that allows imaging, including depth perception, through a very small fiber optic.

Lippok N, Vakoc BJ, "Resolving absolute depth in circular-ranging optical coherence tomography by using a degenerate frequency comb," Opt. Lett. 45, 371-374 (2020)

TACKLING PANCREATIC CANCER

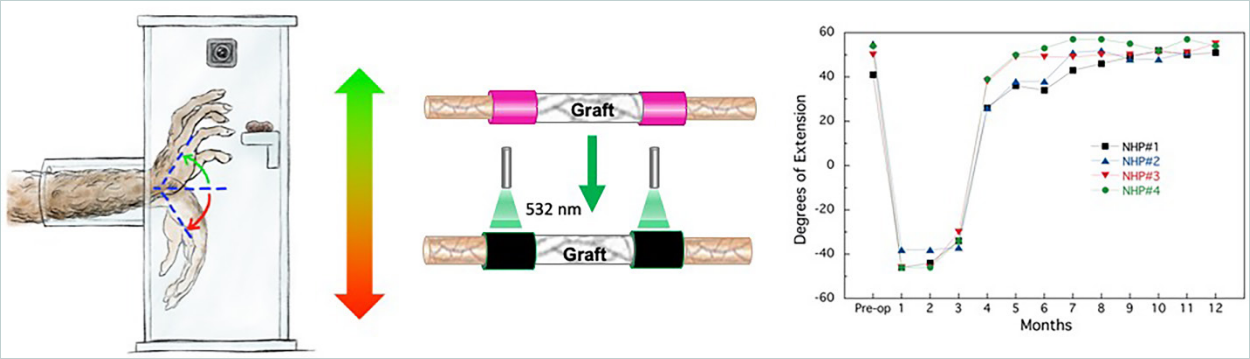
Pancreatic ductal adenocarcinoma is a major cause of cancer death that often defies conventional surgery, radiation and chemotherapy. Prof. Tayyaba Hasan is leading a multiple-hit strategy illustrated below, that uses penetrating near-IR light to release optimally tumor-targeted liposomes that encapsulate high-payload Cetuximab plus an anti-desmoplastic agent. Local potency without systemic toxicity is key. Efficacy was verified in vitro with heterotypic tumor organoids, and in vivo with an animal model of pancreatic cancer.

Obaid G, Bano S, [...], Hasan T. "Impacting Pancreatic Cancer Therapy in Heterotypic In Vitro Organoids and In Vivo Tumors with Specificity-Tuned, NIR-Activable Photoimmunonanoconjugates: Towards Conquering Desmoplasia?" Nano Lett 2019;19:11,7573-7587. doi.org/10.1021/acs.nanolett.9b00859



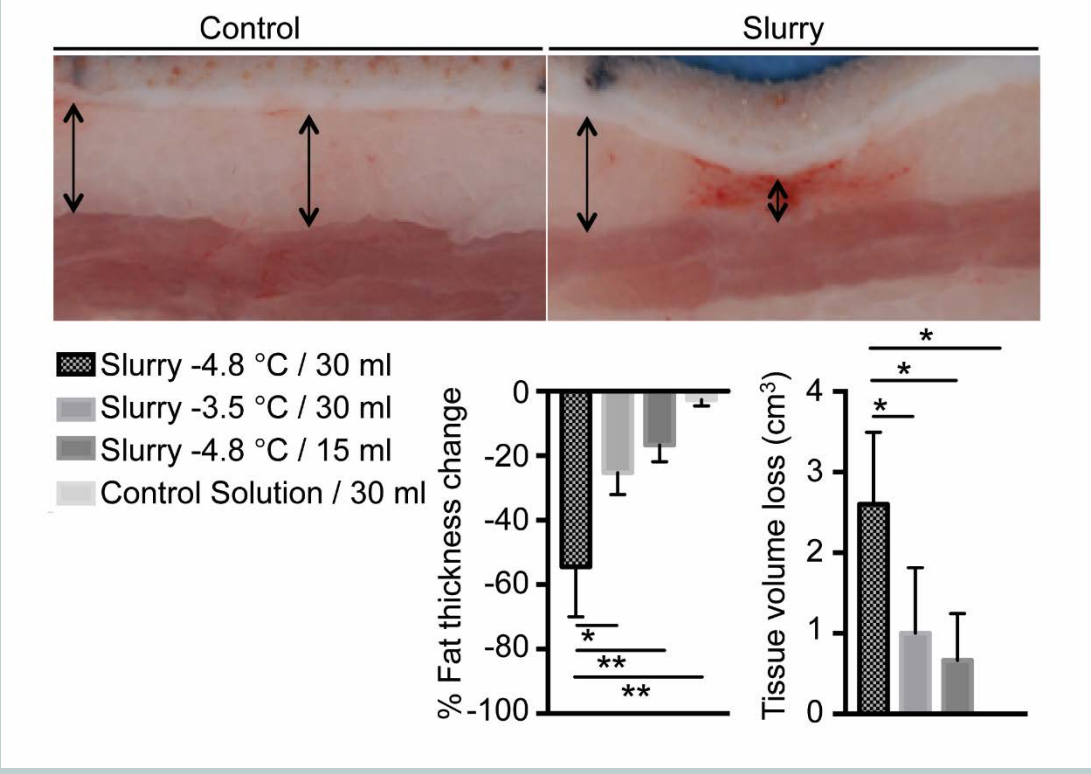
REPAIRING LARGE-GAP NERVE INJURIES

When major trauma destroys or kills a large part of an important nerve, the remaining gap has classically been filled by an autologous nerve graft, but that means another nerve must be harvested and moved. In non-human primates, Robert Redmond and collaborators developed a new non-human primate model to test the functional recovery of wrist extension after radial nerve injury and repair with insertion of a cadaveric nerve allograft (Left). Instead of sutures through the nerve, the nerve graft is secured by bonding a patch of Rose Bengal-stained amniotic membrane is used to attach the nerve allograft to the ends of the severed nerve (middle). Nerve recovery shows return to full extension by 5-6 months after repair (right).



INJECTABLE ICE FOR FAT REMOVAL

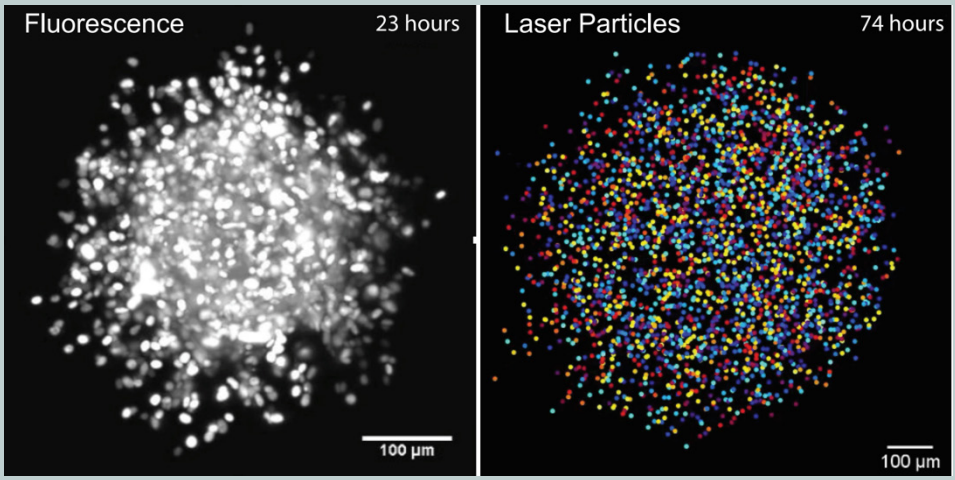
Tissue cooling for selective fat removal was invented in Rox Anderson's lab, and is now a popular treatment for body sculpting. To target deeper body fat, for example visceral fat, Lilit Garibyan, MD, PhD, led the development of physiological ice slurries delivered by local injection. Selective subcutaneous fat removal was demonstrated in animals, and the technology was licensed to a startup company. Garibyan L, Moradi Tuchayi S, [...], Anderson RR. "Subcutaneous fat reduction with injected ice slurry" Plast Reconstr Surg January 7,2020 [epub ahead of print] doi:10.1097/PRS0000000000006658.



ADDRESSING CELLS IN COMPLEX TISSUES

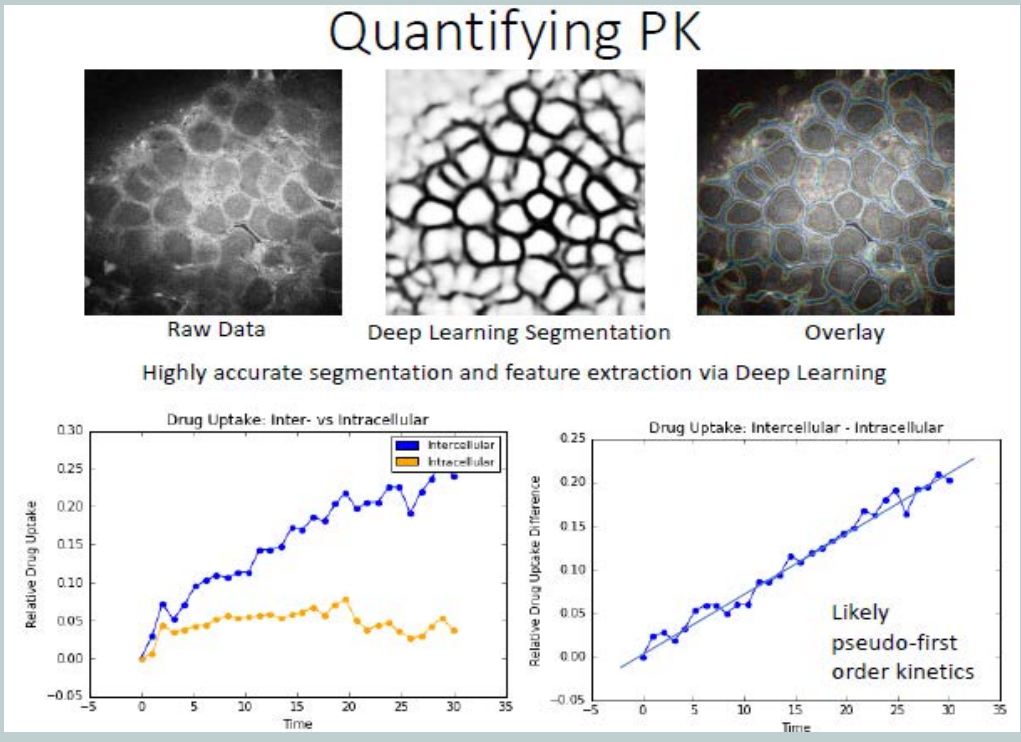
Studying multiple cells or factors at a time is often necessary for understanding complex biological systems. Andy Yun's lab has developed intracellular (1μm diameter) semiconductor laser particles capable of emitting 1,000 colors with line-width 100 times narrower than fluorescence. This new tool allows each individual cell in tissue to be uniquely tagged, tracked and analyzed using high-throughput, comprehensive single-cell techniques. With it, Yun and colleagues simultaneously tracked thousands of individual tumor cells and their progeny during the complex development of tumor spheroids.

Martino N, Kwok SJJ, [...], Yun SH. "Wavelength-encoded laser particles for massively multiplexed cell tagging. Nature Photonics 2019 13:720-727.



QUANTIFYING TOPICAL DRUG PHARMACOKINETICS

Conor Evan's lab has been visualizing and quantifying the uptake of small molecule topical drugs within the skin in clinical settings - a challenging problem. Small molecules can be radiolabeled, but this requires the use of radioactive compounds that are often not compatible with clinical studies. Fluorescent labels are almost always too large and perturbation, making label-free approaches needed. However, tools such as mass spectrometry and chromatography tools require skin tissue samples, necessitating biopsy. They have developed a microscopy imaging tool based on coherent Raman imaging that can detect, track, and quantify topical drug pharmacokinetics directly. By combining coherent Raman imaging with Deep Learning approaches, they have successfully extracted drug uptake profiles, flux, and partitioning coefficients from in situ imaging experiments. This tool is expected to play new and important roles in the development, screening, and regulatory compliance of new topical drugs.

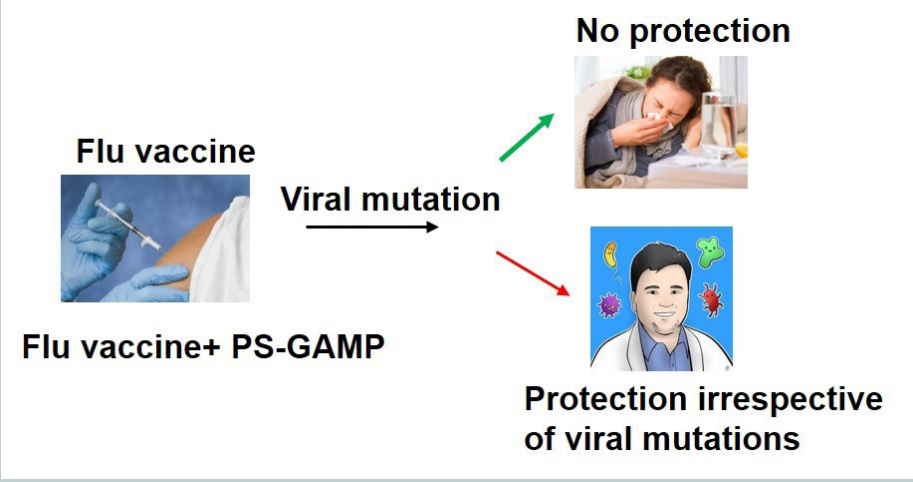


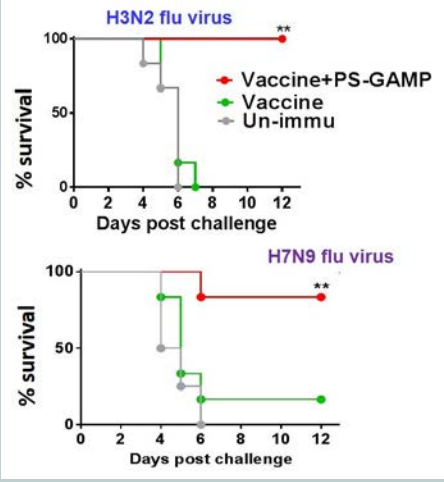
Wellman Center for Photomedicine

Thematic Center Report

NOVEL MUCOSAL ADJUVANT FOR "UNIVERSAL" INFLUENZA VACCINES

Mei Wu's lab has made PS-GAMP by encapsulating an agonist cGAMP for the stimulation of interferon genes (STING) with pulmonary surfactant. All animals (mice and ferrets) were well protected against divergent flu viruses as early as 2 days after vaccination with H1N1 flu vaccines plus PS-GAMP. Annual flu vaccines can be prevented if this is proven effective in humans. Publication: Ji Wang, Peiyu Li, Yang Yu, Yuhong Fu, Zhiping Sun, Shibo Jiang, Lu Lu and Mei X. Wu. Pulmonary Surfactant-Biomimetic Nanoparticles Potentiate Heterosubtypic Influenza Immunity. Science 2020 (In press)





WELLMAN CENTER WELCOMES COLLABORATION AND INQUIRY

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Seun Johnson-Akeju, MD, Chief

Overview:

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, and clinical research. (2) DACCPM has over 175 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 85 grants per year, including 47 NIH grants as of FY 2019. (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 many years, we have provided a significant investment in expanding and retaining our research staff, including salary support to T32/K08 trainees, gap funding for M.D. and/or Ph.D. investigators, and supplemental salary support for basic science and clinical researchers.

(2) Establishing a research platform that promotes integration between basic science and clinical research: We have implemented several initiatives to support clinical and comparative outcome research including competitive intra-departmental clinical research funds and a clinical research core with a first-tier statistical faculty and study coordinators to support clinical investigations. We also have internal clinical research funding mechanisms that provide financial support for conducting clinical research.

(3) Using innovation to advance translational research and expand the overall scope of basic science and clinical research: We have an internal funding mechanism that supports invention and innovation through fruitful translational research. A significant number of pending or awarded patents from our department offer a promising pipeline of innovative products that will ultimately advance patient care and provide sustainable support for research activities in the department. This effort is further strengthened over the last several years.

Achievements:

The excellence of research at the DACCPM is reflected by a combination of basic science, clinical and translational research led by the nation's largest physician-scientist group in the anesthesia field as well as a large group of top-notch non-clinician Ph.D. investigators in our department. The following are the following representative achievements in 2019.

(1) Under the leadership of Dr. Oluwaseun Johnson-Akeju, Chief of DACCPM, our department has recently established the Anesthesia Research Center (ARC), an integrative center for clinical and observational studies. This Center brings together essential clinical and observational research resources within the Department. Central to the departments mission, ARC exists to support investigators throughout the research process in an effort to optimize study design and execution, regulatory oversight and statistical methods for department investigations. ARC is comprised of clinical research coordinators and fellows, data scientists, statisticians and research administrators who leverage their expertise to facilitate all aspects of a research project from study start up to completion. Services within ARC span grant preparation, IRB assistance, subject recruitment/enrollment, study coordination, data collection/entry and statistical analyses. ARC has also established a pathway for department investigators to immerse themselves in observational research, including a team of experts to help investigators and appropriately analyze large internal and external databases. By providing a robust research infrastructure, ARC aims to facilitate and expand both grass roots and funded clinical research endeavors, ensure regulatory compliance, expand the department's data acquisition and analytic capabilities, train the next generation of clinician-scientists, and ultimately produce and publish high-impact clinical investigations.

ARC | MGH ANESTHESIA RESEARCH CENTER

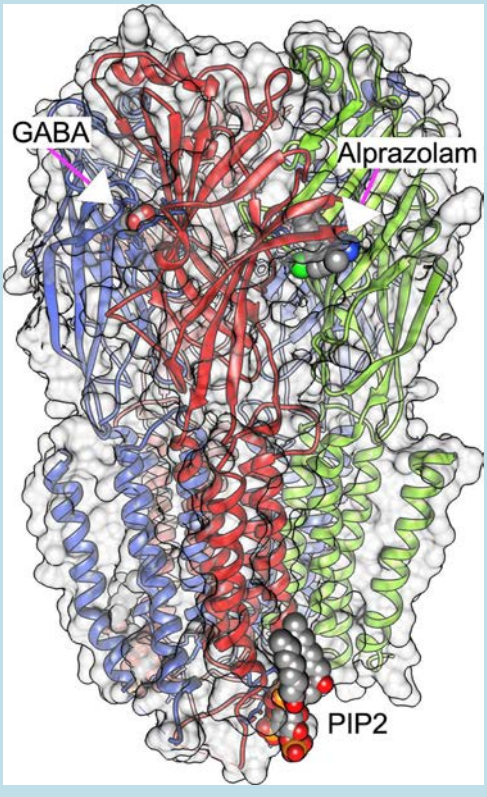
Logo for the newly created MGH Anesthesia Research Center (ARC).

(2) The Keith W. Miller, PhD, laboratory, along with collaborators in Great Britain, published two high-impact manuscripts in the prestigious journal Nature in 2019 [1, 2]. These two breakthrough papers describe the molecular structure of the γ–amino butyric acid type A receptor (GABA(A)R), which is the major inhibitory ligand-gated ion channel in the central nervous system. General anesthetics enhance its inhibitory actions leading to loss of consciousness. It is a very large protein with five subunits (total molecular weight ~250kDa) and the target of many drugs that are employed by anesthesiologists including the general anesthetics and benzodiazepines. The receptor's structure was determined while embedded in a lipid bilayer that maintained it in a functional state in which changes at the GABA binding sites could be detected when anesthetics and benzodiazepines bound to their various different sites. The resolution was sufficient to reveal in molecular detail how important drugs bound to their binding sites. These included benzodiazepines and, very surprisingly phosphatidylinositol-4,5-bisphosphate (PIP2), a lipid signaling molecule involved in the mechanism that traffics receptors to and from the plasma membrane, a process that is likely important in the development of tolerance to benzodiazepines.

This research ushers in an era of molecular pharmacology that will be of particular importance to the practice of anesthesia by enabling the design of anesthetics with fewer side effects and, perhaps, the holy grail of an antagonist for general anesthesia that would allow more rapid recovery for surgical patients [3]. Furthermore, because GABA(A)Rs are involved in many disease states (for example, epilepsy, schizophrenia, anxiety, postpartum depression, etc.), this work has much wider implications.

The research was the result of a long running collaboration between the Miller laboratory in the Mallinckrodt Molecular Pharmacology Research Unit at MGH, DACCPM and Dr. Radu Aricescu's structural laboratory at Oxford University in England (during the latter part of the project he moved to Cambridge University, England).

Citations: [1] D. Laverty, R. Desai, T. Uchanski, S. Masiulis, W.J. Stec, T. Malinauskas, J. Zivanov, E. Pardon, J. Steyaert, K.W. Miller, A.R. Aricescu, Cryo-EM structure of the human alpha1beta3gamma2 GABAA receptor in a lipid bilayer, Nature, (2019). [2] S. Masiulis, R. Desai, T. Uchanski, I. Serna Martin, D. Laverty, D. Karia, T. Malinauskas, J. Zivanov, E. Pardon, A. Kotecha, J. Steyaert, K.W. Miller, A.R. Aricescu, GABAA receptor signaling mechanisms revealed by structural pharmacology, Nature, (2019). [3] C. Ma, E. Pejo, M. McGrath, S.S. Jayakar, X. Zhou, K.W. Miller, J.B. Cohen, D.E. Raines, Competitive Antagonism of Anesthetic Action at the gamma-Aminobutyric Acid Type A Receptor by a Novel Etomidate Analog with Low Intrinsic Efficacy, Anesthesiology, 127 (2017) 824-837.



The molecular structure of the γ–amino butyric acid type A receptor (GABA(A)R).

(3) Dr. Zhongcong Xie of DACCPM is listed as one of the top 25 Massachusetts General Hospital FY19 Sponsored Research Award Recipients. Postoperative delirium (POD) is increasingly recognized as a common phenomenon that occurs after major surgery and has become an important research area in the field of Geriatrics and Aging. Delirium occurs in 25 - 50% of older surgical patients and is associated with the high risk of developing Alzheimer's Disease and Related Dementias (ADRD), greater incidences of postoperative complications, higher mortality, prolonged hospital stays, and higher discharge rates to nursing homes. Specifically, patients with underlying dementia are 2.5 - 4.7 times more likely to develop delirium, and patients with delirium face a 12.5-fold increased incidence of newly diagnosed ADRD. The U.S. healthcare costs attributable to delirium exceed $182 billion per year. At present, there is insufficient knowledge regarding POD pathogenesis due to a lack of mechanistic studies on POD. Dr. Xie's lab has been testing the hypothesis that neuroinflammation from a moderate insult (anesthesia/surgery) plus phosphorylated Tau accumulation from a moderate vulnerability are needed to cause the POD-like behavior in the mice. Dr. Xie has collaborated in other clinical studies demonstrating that the contribution of interaction of gene-protein to the neuropathogenesis of POD, association between c-reactive protein and POD, and association of POD and long-term decline in daily activities. On the other hand, postoperative cognitive dysfunction (POCD) is different from AD or postoperative delirium, is an increasingly recognized common phenomena after major surgery, and has become an important research area in the field of geriatrics and aging. At present, the lack of sufficient POCD mechanistic studies leads to insufficient knowledge regarding POCD pathogenesis. Consequently, there is no prevention or treatment for POCD. This is particularly alarming given the expected increase in POCD patients as the population of geriatric surgical patients grows, and the potential association of POCD

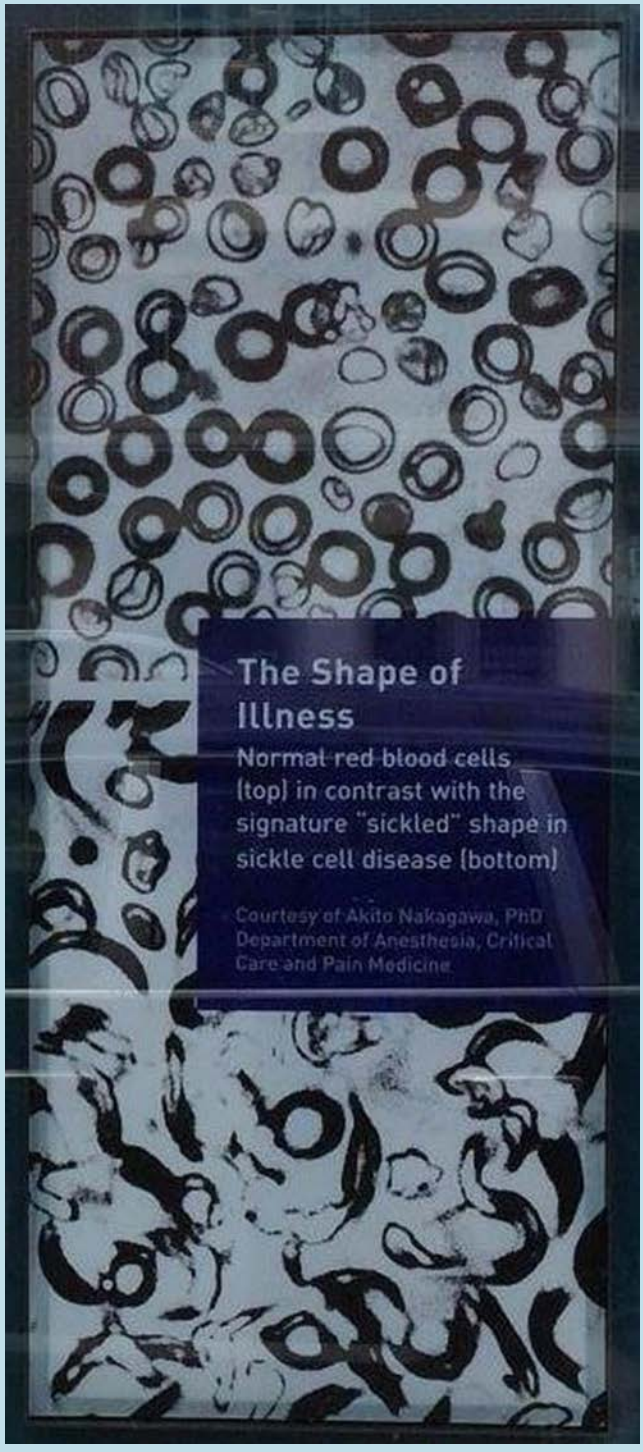


Photo from the Russell Museum display showing normal red blood cells and those with sickle cell disease.

with AD dementia. Dr. Xie's lab has demonstrated that CypD contributes to anesthesia neurotoxicity and cognitive impairment in mice, and anesthesia increases locomotor activity in mice. Dr. Xie has also established a system to test whether Tau or pTau in the blood, urine, feces, and saliva can serve as the biomarker for the anesthesia/surgery-associated neurocognitive outcomes in children. In this area of research, Dr. Xie has published papers show that anesthesia may cause cognitive impairment in young mice via autophagy, that disrupted folate metabolism with anesthesia could lead to myelination deficits mediated by epigenetic regulation of ERMN, and that LncRNA plays a role in the developmental anesthesia neurotoxicity.

(4) Photos from the Akito Nakagawa, PhD laboratory, showing normal red blood cells and those with sickle cell disease, were on display at the Russell Museum at MGH in August 2019. These photos are a part of Dr. Nakagawa's research project, which aims to identify and develop small molecules that could reduce sickling of red blood cells as a way to potentially treat sickle cell disease.

Cancer Center

Department Report

Daniel A. Haber, MD, PhD, Director

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

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

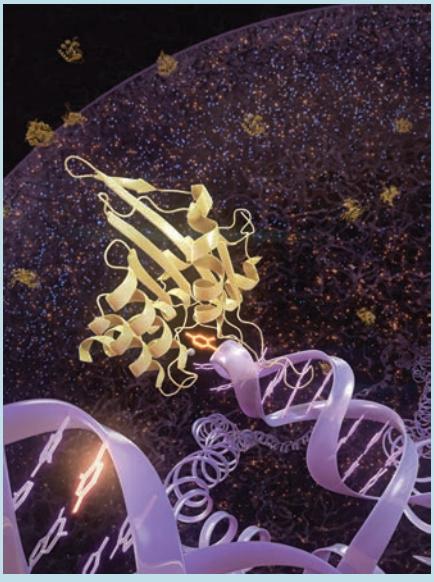
Our research highlights from 2019 include major discoveries and observations from investigators within the multi-departmental Center for Cancer Research (CCR) and the Division of Hematology Oncology (Department of Medicine), both of which are administered through the Cancer Center. Dr. David Ryan is Clinical Director of the Cancer Center and Chief of Hematology/Oncology; Dr. Nick Dyson serves as Scientific Director (CCR); and Dr. Keith Flaherty is Director of Clinical Research.

Total annual research expenditures for CCR and Hematology/Oncology in FY19 were $81.2 million (including industry clinical trials contracts). In 2019, the MGH Cancer Center enrolled 3,947 patients on over 657 clinical trials (1,228 patients on therapeutic/interventional trials, 40% (491) of which were early Phase 1/II trials of first-in-human drugs).

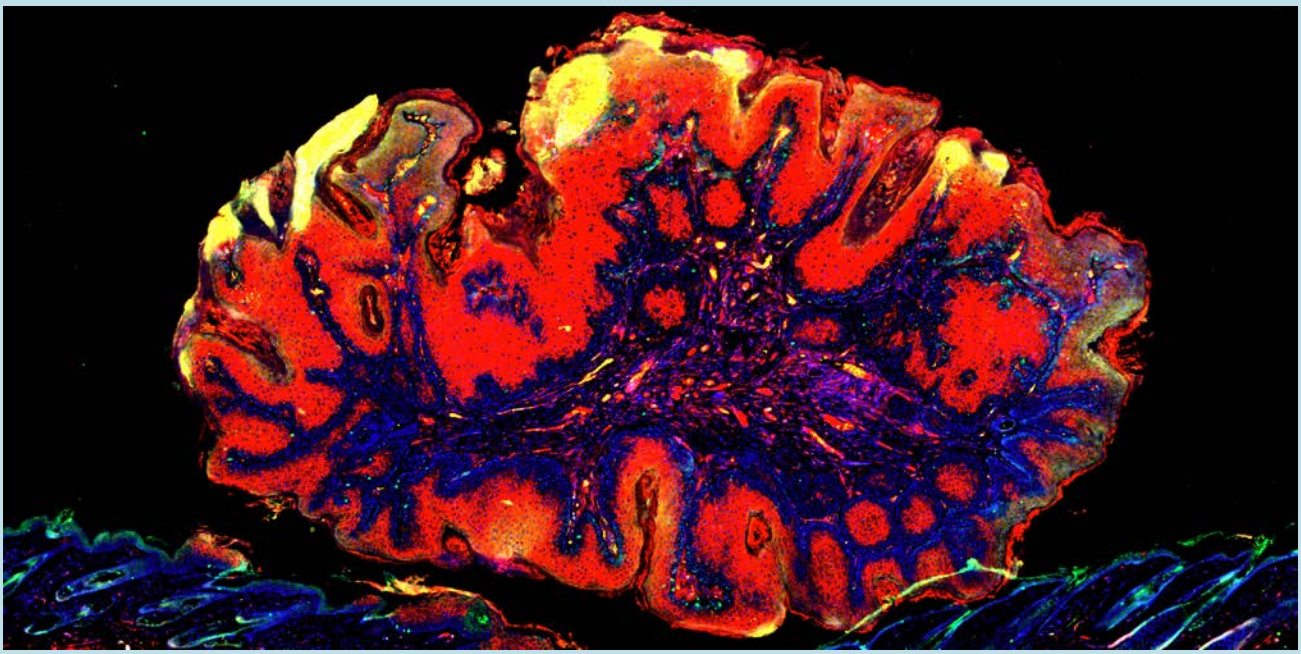
Highlighted accomplishments for the Cancer Center during 2019 are grouped into three thematic areas:

Molecular Genetics

Dr. Michael Lawrence and Dr. Lee Zou and their colleagues discovered that there are certain locations in the genome that can fold into DNA "hairpin" structures whose shape is a perfect fit for the DNA-mutating enzyme APOBEC3A. As such, these site-specific hairpins explain recurrent "passenger hotspots" that are observed in human cancers. (Buisson et al, Science 28;364(6447), 2019). Dr. Mario Suva and his colleagues used an integrative approach spanning single-cell RNA-sequencing, functional approaches, and single-cell lineage tracing to derive a unified model of cellular states and genetic diversity in glioblastoma. They found that malignant cells in glioblastoma exist in four main cellular states that recapitulate distinct neural cell types, are influenced by the tumor microenvironment, exhibit plasticity and are influenced by copy number amplifications of the CDK4, EGFR, and PDGFRA loci and by mutations in the NF1 locus, with each favoring a defined state. (Neftel et al, Cell. 8;178(4):835-849.e21, 2019). Dr. Gad Getz' group developed a method to detect mutations from RNA sequencing data and found that somatic mutations were detected in nearly all individuals and across many normal human tissues in genomic regions called cancer hotspots and in genes that play a role in cancer. Interestingly, the skin, lung, and esophagus exhibited the most mutations, suggesting that clonal expansion is associated with environmental factors, aging, and risk of disease (Yizhak et al, Science, 7;364(6444) 2019). Dr. David Ting and his collaborators combined single-cell RNA and protein analytics to study the role of stromal cancer-associated fibroblasts (CAFs) in modulating heterogeneity in pancreatic cancer by altering inherent patterns of tumor glands. (Ligorio et al, Cell, 27;178(1):160-175.e27, 2019). Results published by Dr. Ryan Corcoran and his team highlight the potential advantages of monitoring serial cfDNA over tissue biopsy to identify acquired drug resistance mutations, demonstrating the profound genetic heterogeneity that underlies cancer evolution under therapeutic pressure (Parikh et al, Nature Medicine, 25(9):1415-1421, 2019)



DNA editing enzyme APOBEC3A (yellow) attacking a cytosine nucleotide (gold) at the tip of a DNA hairpin structure (purple) formed while DNA is transiently single-stranded. Image courtesy of Lawrence/Zou Labs.



Early skin cancer that is colonized with a commensal papillomavirus looks like a wart to the immune system and is effectively eliminated. Keratin 6+ hyperplastic epidermis (red) and Ki67+ proliferative cells (green) mark a wart-like skin tumor. Cell nuclei are seen in blue. Image courtesy of Jon Messerschmidt/Demehri Lab; Member of CBRC and CCR.

Cancer Immunology

Dr. Marcela Maus and colleagues developed a novel CAR-T cell construct targeting EGFRvIII, a glioblastoma-specific tumor antigen, and encoding a bispecific T-cell engager (BiTE), that is released within the local tumor environment, mediating a profound immunological response against the brain tumor cells in mouse models. Adaptation for human clinical trials is under consideration (Choi et al, Nature Biotechnology 37(9):1049-1058, 2019). Dr. Shawn Demehri and his team reported a beneficial role for commensal viruses in the skin, showing that T cell immunity against commensal papillomaviruses suppresses skin cancer in immunocompetent hosts. (Strickley et al, Nature 575(7783):519-522, 2019). Dr. Noopur Raje led a trial of anti-BCMA CAR T-Cell therapy in relapsed or refractory multiple myeloma and showed that CAR T-cell expansion was associated with responses, with CAR T cells persisting up to 1 year after the infusion. Some responding patients had no detectable minimal residual disease (Raje et al, N Engl J Med 2;380(18):1726-1737, 2019).

Early Phase Clinical Trials

Dr. Dejan Juric led a major clinical trial of the PIK3CA inhibitor alpelisib, together with the estrogen receptor degrader fulvestrant, showing that the treatment prolonged progression-free survival among patients with advanced, previously refractory PIK3CA-mutated, hormone receptor (HR)-positive, HER2-negative advanced breast cancer. (André et al, N Engl J Med. 16;380(20):1929-1940, 2019). Dr. Aditya Bardia directed a breakthrough clinical trial of the antibody-chemotherapy conjugate Sacituzumab Govitecan-hziy, targing the Trop2 cell surface epitope on triple negative breast cancer (TNBC), reporting durable responses in patients with heavily pretreated metastatic disease. (Bardia et al, N Engl J Med. 21;380(8):741-7512019). Leading a multi-institutional, randomized clinical trial, Dr. Matthew Smith reported that treatment of men with non-metastatic, castration-resistant prostate cancer using the androgen-receptor antagonist, darolutamide results in significantly improved metastasis-free survival (Fizazi et al, N Engl J Med 28;380(13):1235-1246. 2019). Finally, Drs. Nabeel Bardeesy and Lipika Goyal demonstrated that the irreversible FGFR inhibitor TAS-120 shows efficacy in patients with FGFR2 fusion-positive Intrahepatic Cholangiocarcinoma and provides clinical benefit in patients with resistance to BGJ398 or Debio 1347. (Goyal et al, Cancer Discovery, 9(8):1064-10792019).

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.

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 Clinical Impact Study (CIS) were that the $50M of projects studied resulted in: 1) More than $500M in follow-on funding at CIMIT institutions plus another $600M in commercial investment; 2) Over 460 issued US patents and 2,300 publications; 3) Over 70 NewCo's or commercial licenses with more than 20% had received regulatory approval for human use and 4) more than 30% of the PI's surveyed reported that the project support made a major impact on their career development. Based on this experience, CIMIT has developed state-of-the art tools and facilitation to accelerate medtech development around the world.

Point-of-Care Translational Research Network

The Point-of-Care Technologies Research Network (POCTRN) was created by NIH to drive the development of appropriate point-of-care diagnostic technologies though collaborative efforts that simultaneously merge scientific and technological capabilities with clinical need. Additionally, the Network provides parallel educational activities that advance evidence-based medical practice in point-of-care testing in primary outreach, and low-resource environments, including global health settings. In 2019, CIMIT served as the Coordinating Center for the third 5-year cycle of POCTRN and in that role assists each of the 4 other Centers across the U.S. to create multidisciplinary partnerships necessary to move technologies from an early stage of development into clinical testing.

CIMIT® CRAASH

Commercialization Readiness Assessment and Accelerator for Solutions in Healthcare

CIMIT's CRAASH Course

In 2019, CIMIT continued to hold healthcare commercialization boot camps, including in Europe. With funding from the National Science Foundation, CIMIT customized the traditional I-Corps program to focus on healthcare. The 10-week program facilitates the acceleration of healthcare innovations from the academic lab through commercialization. It is taught by industry veterans and is based on decades of experience from the Coulter Foundation, MIT, Yale, and CIMIT. The program formalizes development of a tested business model through the process of validating business hypotheses. Emphasis is placed on understanding economic buyers and their problems to be solved. Teams from around the country collect evidence to support the assumptions around the entire business (not just the science) through interviews and market testing. Each week teams present and defend findings to a panel of experts, attend lectures, and complete readings. Teams develop a commercialization roadmap based on data from actual customers and other stakeholders. Teams also receive 1:1 mentoring from successful healthcare entrepreneurs and group coaching from commercialization experts and investors.

GAITS

Guidance and Impact Tracking System (GAITS)

CIMIT's GAITS

Based on lessons learned since its first Clinical Impact Study in 2010, CIMIT created the CIMIT Innovation Guidance and Impact Tracking System (GAITS) in 2017 and further developed its functionality in 2019. GAITS parallels the Department of Defense's well-established Technology Readiness Levels (TRLs) and establishes a sequence of 10 healthcare specific milestones. GAITS helps innovators navigate the complex journey of innovation in healthcare and adds significant guidance to teams by defining core set of deliverables at each milestone in four domains critical to success in healthcare innovation: Clinical, Market/Business, Regulatory/ Approvals, and Technology. In addition, GAITS curated resources (descriptions, videos, templates, examples, etc.) are provided to help teams complete the deliverables. It also enables funders/ institutions to provide teams with a secure site to track their progress and measure their impact. CIMIT has organized a consortium of leading healthcare innovation organizations across the globe to use GAITS and to build on CIMIT's experience of facilitating teams by providing an online tool that supports teams and portfolio managers to -increase the likelihood of innovations reaching patient care. The consortium will provide a robust database to study the innovation process in healthcare to establish and share best practices.

David E. Fisher, MD, PhD, Chief

The Dermatology Department at MGH is a historically important contributor to the modern field of skin biology and cutaneous medicine. Its distinguished faculty dates back to the 1800's and included many innovators for whom clinical conditions are named and through whom the modern field of dermatology was derived. One notable feature of MGH Dermatology faculty was the first female physician at MGH, Dr. Loretta Cummings, a Dermatologist working at MGH in the early 1900s who subsequently left a portion of her estate to the MGH Dermatology Department. The proceeds of that fund are currently utilized to fund an annual research award pertaining to a female-related dermatologic study. The department's core missions are to deliver excellent clinical care, research, education, and community outreach. The department is also deeply committed to close collaborations with colleagues across nearly all departments at MGH, and numerous colleagues at other academic institutions. The Department has a global dermatology interest with faculty representation on WHO dermatologic leadership (Dr. Esther Freeman). And the care of the homeless remains a high priority for which the department commits resources in a program spearheaded by Dr. Jennifer Tan. On an annual basis MGH Dermatology delivers care in approximately 90,000 patient visits. Care is provided at MGH main campus as well as multiple community care centers and MGH-Northshore in Danvers. In collaboration with MGH Pathology, an outreach community-based Dermatopathology Lab has become one of the busiest of its type in New England. In addition to providing general medical dermatologic care, the department also provides specialty clinics in topics including Pediatric Dermatology, High-Risk Non-melanoma Skin Cancer, Pigmented Lesions/Melanoma, Dermatologic & Mohs Surgery, Hair-loss, Urgent-care, Rheumatologic Dermatology, Laser and Cosmetic Unit, and Inpatient-Consultation Services. The Pigmented Lesions/Melanoma Clinic was the first of its kind in the US, and celebrated its 50 year anniversary recently. Aside from the Clinical Service, the MGH Dermatology Department contains multiple research-oriented programs. These include the Clinical Trials Unit (CURTIS: Clinical Unit for Research Trials In Skin) and the Cutaneous Biology Research Center (CBRC). CURTIS typically runs 15-20 clinical trials, with a combination of Industry Sponsored and Investigator Initiated investigations. The Cutaneous Biology Research Center was founded in 1990 and currently houses 13 Principal Investigators who collectively represent a highly distinguished center for skin research. The Center has attracted substantive federal grant support as well as Industry funding that includes a longstanding and deep collaborative relationship with Shiseido Cosmetics. A highlight of this relationship was a celebration during the past year of the 30th anniversary of the CBRC-Shiseido program which provided one of the largest Industry-Academic collaborations in modern history. At the celebration, leadership from both groups signed a Memorandum of Understanding to extend the collaboration for an additional six years. CBRC faculty direct research laboratories which study topics including melanoma, non-melanoma skin cancers, hair, cryobiology, itch, stem cells, inflammatory pathways, drug discovery, UV radiation, pigmentation, epigenetics, cancer immunotherapy, laser biology, targeted therapy, metabolomics, RNA biology in skin, and developmental/differentiation pathway control. Particularly close collaborations exist with MGH Cancer Center (in which several CBRC faculty hold joint appointments) as well as collaborations with MGH Dermatopathology and numerous additional departments. Additional research faculty whose academic home is in Dermatology include many researchers in the Wellman Center for Photomedicine, an MGH Thematic Center that has made seminal contributions to the current practice of dermatology largely through the development of devices used in the diagnostic or therapeutic aspects of medicine (including dermatology).

During 2019, two endowed MGH Dermatology Chairs were established: the Lancer Chair (generously contributed by Harold Lancer MD, who carried out his Dermatology residency training at Harvard in the 1980's) and the Richard Johnson MD Chair (generously contributed by Dr. Richard Johnson, a current and beloved faculty member within the department). The first incumbent of the Lancer Chair is Dr. R. Rox Anderson, who also serves as Director of the Wellman Center and Professor of Dermatology. The first incumbent of the Richard Johnson Chair is Dr. Hensin Tsao, who also serves as Director of the Pigmented Lesions Clinic at MGH Dermatology and also Professor of Dermatology. During 2019 faculty members from the Department of Dermatology published 161 scholarly articles and gave 220 speaking engagements. During this period $20.5M in research support was spent, which included funds from NIH, Dept of Defense, numerous Foundations, Industry partners, royalties, and philanthropy. The Department also holds the leadership role in a Harvard-wide NCI-sponsored multi-million dollar Program Project Grant on Melanoma, which is highly collaborative with investigators across Harvard Medical School. The Department also hosts numerous visiting trainees including specific initiatives to enhance diversity representation in the field of Dermatology and skin research. Finally, MGH Dermatology particularly prides itself on its close interactions and collaborations with most departments across the hospital—in clinical care initiatives, research projects, medical education, and community outreach.

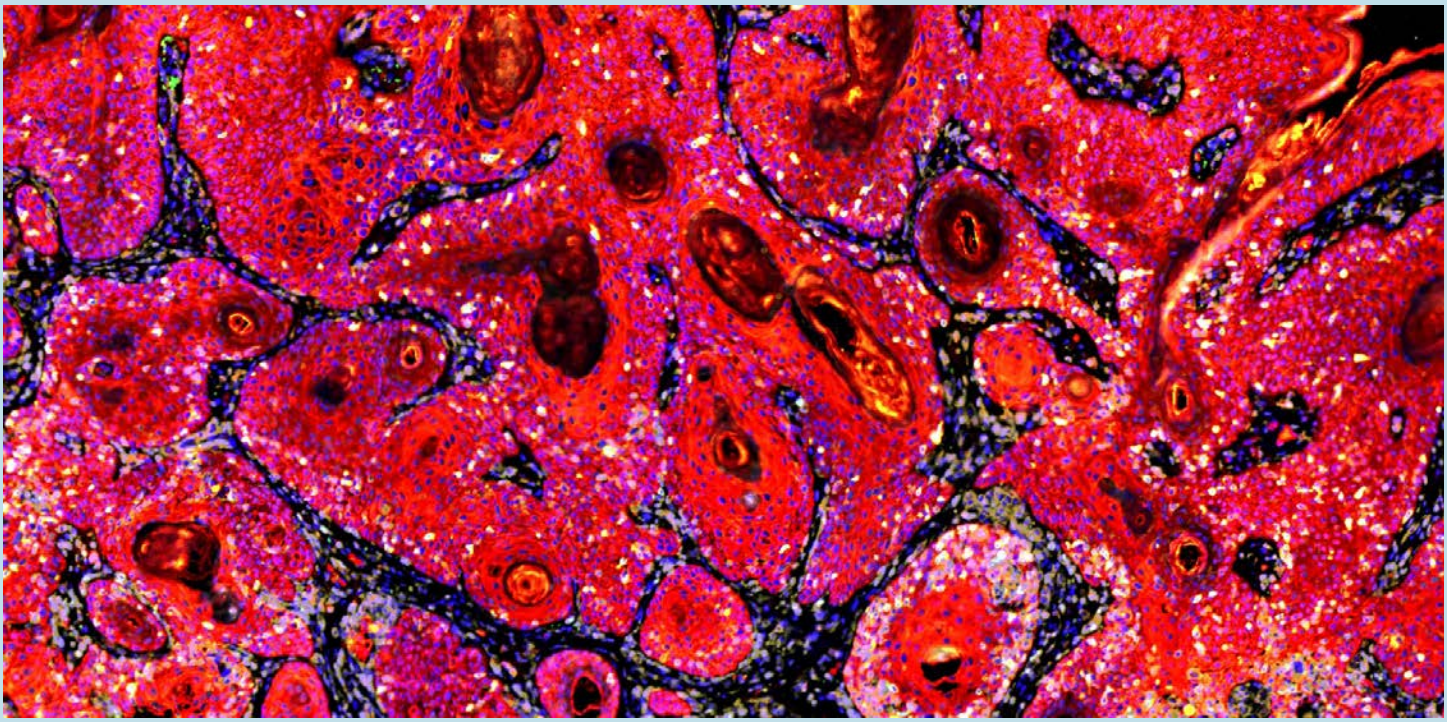
Examples of Research Achievements

Jixiao Niu, Yang Sun, Baoen Chen, Baohui Zheng, Gopala K. Jarugumilli, Sarah R. Walker, Aaron N. Hata, Mari Mino-Kenudson, David A. Frank, and Xu Wu Fatty acids and cancer-amplified ZDHHC19 promote STAT3 activation through S-Palmitoylation, Nature, 2019, 573, 139–143.
This study demonstrates that lipids can regulate inflammation and immunity though modification of the transcription factor STAT3. The process is mediated by the enzyme ZDHHC19, which is highly expressed in multiple cancers. The work provides a key link between lipid metabolism, cancer, and inflammation.

Bordignon P, Bottoni G, Xu X, Popescu AS, Truan Z, Guenova E, Kofler L, Jafari P, Ostano P, Röcken M, Neel V, Dotto GP. Dualism of FGF and TGF-β Signaling in Heterogeneous Cancer-Associated Fibroblast Activation with ETV1 as a Critical Determinant. Cell Rep. 2019 Aug 27;28(9):2358-2372.
The role of fibroblasts within the cancer stroma has been increasingly recognized to shape the tumor microenvironment. This study examines key signaling events underlying this activity.

Fogel AL, Kvedar JC, Reported Cases of Medical Malpractice in Direct-to-Consumer Telemedicine. JAMA. 2019 Apr 2;321(13):1309-1310. doi: 10.1001/jama.2019.0395. PMID:30938788
In the era of increasing use of technology for direct-to-consumer medicine, this study examines malpractice considerations.

Strickley JD, Messerschmidt JL, Awad ME, Li T, Hasegawa T, Ha DT, Nabeta HW, Bevins PA, Ngo KH, Asgari MM, Nazarian RM, Neel VA, Jenson AB, Joh J, and Demehri S. Immunity to commensal papillomaviruses protects against skin cancer. Nature. 2019 Nov;575(7783):519-522. PMID: 31666702.
The findings described in this publication provide the first evidence that viruses can have a beneficial health effect both in experimental models and also in humans. This beneficial effect involves cancer protection by skin dwelling viruses. Commensal papillomaviruses are found to induce CD8+ T cell immunity in the skin that is then able to protect patients from squamous cell carcinoma.



Robust T cell immunity against an early cancer clone arising in the skin that has been colonized with a commensal virus. CD45+ leukocytes (grey) and CD3+ T cells (yellow) attacking cancer cells infected with commensal papillomavirus (red). Image courtesy of Jon Messerschmidt.

David F. M. Brown, MD, Chief

Mission

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

Focus

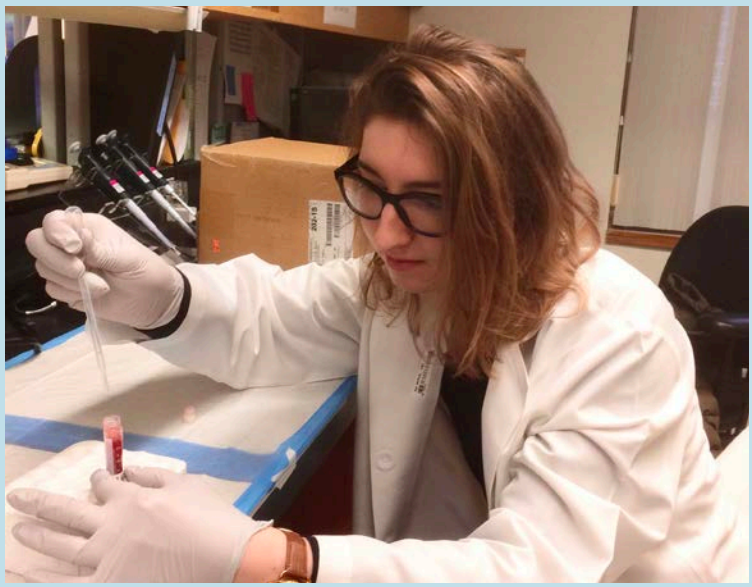
The role of the emergency physician is to provide rapid diagnostics and therapies for those with acute illness and injury. As such, our research focuses on the development and validation of new diagnostic strategies, treatments, and care delivery systems across a broad range of health conditions. Areas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

Brendan Lilley in the MGH ED

Over the past year we have continued to broaden our research portfolio, with more investigators contributing to our increasing publication volume. We continue to increase our research support from federal sponsors, and continue to grow our research faculty, fellows and clinical research coordinator team.

Goals for 2020:

1. Continue to develop a strong pipeline of clinical investigations, and clinician and non-clinician researchers, to support a robust research infrastructure that can drive forward the departmental research mission.
2. Increase expertise in sample processing to facilitate expanded investigation in proteomics, metabolomics, genomics, and human microbiome. Explore expanding laboratory space and capabilities to allow for more sophisticated in-house processing with the goal of increasing opportunity for NIH- and industry-sponsored funding in these areas.
3. Develop a consistent mechanism for providing Epic data to investigators to carry out health record-based research.
4. Continue to hone departmental resources available to support and optimize our research infrastructure, including grants administration and finance, statistical support, and mentoring for young investigators.



Brenna McKaig processing a patient sample in the Emergency Medicine lab

Achievements in 2019:

1. Kabrhel C, Rosovsky R, Baugh C, Connors J, White B, Giordano N, Torrey J, Deadmon E, Parry BA, Hagan S, Zheng H. Multicenter Implementation of a Novel Management Protocol Increases the Outpatient Treatment of Pulmonary Embolism and Deep Vein Thrombosis. Acad Emerg Med. 2019 Jun;26(6):657-669.

This study reports outcomes of a novel outpatient treatment pathway for patients with acute venous thromboembolism (VTE), including those with pulmonary embolism (PE), utilizing a direct-acting oral anticoagulant (DOAC). A total 2,212 patients were enrolled before and after implementation of the pathway in two academic hospitals. Most notably, outpatient management of pulmonary embolism increased from 12% to 18%, with a total of 120 patients post-implementation with PE discharged from the

Emergency Department (ED) with treatment and follow-up, without increase in adverse event. Discharge rate of PE from the MGH ED was 24%. This first pragmatic demonstration of the safety and feasibility of outpatient treatment for PE in selected low-risk cases is catalyzing a shift in the standard of care for treatment of this common disease.

2. Hasegawa K, Mansbach JM, Bochkov YA, Gern JE, Piedra PA, Bauer CS, Teach SJ, Wu S, Sullivan AF, Camargo CA Jr. Association of Rhinovirus C Bronchiolitis and Immunoglobulin E Sensitization During Infancy With Development of Recurrent Wheeze. JAMA Pediatr. 2019 Jun 1;173(6):544-552.

This study leverages the Emergency Medicine Network sponsored Multicenter Airway Research Collaboration (MARC-35), enrolling 716 infants age <12 months admitted to hospitals with rhinovirus and respiratory syncytial virus (RSV) bronchiolitis, the most common causes of bronchiolitis. Of these infants, 231 (32%) had developed recurrent episodes of wheezing by the age of 3 years, as defined by asthma guidelines. Compared with RSV-only bronchiolitis, infants with rhinovirus C had a significant increase in the risk of wheeze by the age of 3 years, whereas this was not observed with other subtypes of rhinovirus. This association was even stronger in infants with IgE sensitization during the index hospitalization, indicating underlying interplay between respiratory viruses and host immune response. This study signifies impactful research on a difficult to study population, and demonstrates an important association between specific viral pathogens, IgE sensitization, and subsequent development of disease long after resolution of acute infection.

3. Marill KA, Salcido DD, Sundermann ML, Koller AC, Menegazzi JJ. Cardioplegia defibrillation of circulatory and metabolic phase ventricular fibrillation in a swine model. Resuscitation. 2019 Nov; 144:123-130.

This study investigates the concept of potassium cardioplegia followed by calcium reversal (Kplegia) in ventricular fibrillation (VF) in a swine model, previously shown by the authors to terminate VF without the need for electrical cardioversion. The current study aimed to optimize the dosing and timing of potassium and calcium administration in 3 separate experiments of VF of different durations. They found improvement in shorter duration VF with Kplegia versus a control model, achieving spontaneous return of circulation from VF in 25% of animals. Pre-human research in resuscitation of cardiac arrest is critical to advancing the field given the high mortality of the condition and the difficulty of studying novel therapies in this population.

4. Salas RN, Jha AK. Climate change threatens the achievement of effective universal healthcare. BMJ. 2019 Sep 23;366:l5302.

This publication summarizes the key barriers created by climate change to achieving Universal Health Coverage (UHC) targeted by the United Nations by 2030. These barriers include direct effects of increased temperature on both non-communicable diseases and the nature and spread of infectious diseases. It analyzes the effects of weather-associated population displacement and migration, rising poverty, and the disruption of healthcare infrastructure and care delivery. This work exemplifies an emerging field of medicine within the scope of healthcare policy that is receiving increased attention within the medical community, and for which a deeper understanding is required to address the increasing threats to population health due to climate change and to prepare healthcare systems for future hazards.

MGH Emergency Medicine Clinical Research Team:
1st Row: Jim Lu, Carl Lodenstein; 2nd Row: Michael Filbin, MD, MSc, (research director), Hargun Khanna, Kyle Kays, Kendall Lavin-Parsons, Brenna McKaig, Jasmine Torrey, Nicholas Giordano, Brendan Lilley, Blair Alden Parry (senior manager)

Not pictured: Nicole Charland, Shane Donnelly, Allison Keach, RN, Caroline Rizzo

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

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

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

The **Division of General Internal Medicine's** research efforts in 2019 had tremendous impact across health care from preventive services to physician burnout to substance use disorders. As part of the US Preventive Services Task Force, an independent, volunteer panel of national experts in disease prevention and evidence-based medicine, Michael Barry (1-4) played a key role in establishing guidelines on screening for abdominal aortic aneurysm, on medications to reduce the risk of breast cancer, on screening for Hepatitis B virus infection in pregnant women, and on interventions to prevent perinatal depression. All of these guidelines and others from the task force are available in JAMA. Sara Kalkhoran and Nancy Rigotti (5) led the national dialogue surrounding e-cigarettes and cigarette abstinence. In a nationally representative longitudinal cohort study of U.S. adult cigarette smokers, compared to no e-cigarette use, daily e-cigarette use, was associated with a 77% increased odds of prolonged cigarette smoking abstinence over the subsequent 2 years, meaning regular use of e-cigarettes may help some smokers to stop smoking combustible cigarettes. Arabella Simpkin (6) conducted a faculty survey on job satisfaction and feeling valued in medicine. Among 988 faculty surveyed, job satisfaction was significantly associated with feeling valued, feeling treated with respect, and working in a social and supportive environment. It was not associated with gender, race, rank, or feeling fairly compensated. She concluded that at a time when faculty appear to be becoming increasingly unhappy, dissatisfied, and burnt out in their work environment, with much speculation about the causes, dedicating efforts to ensure employees feel valued, respected, and supported appears imperative. Sarah Wakeman (7) continued her transformative efforts to address substance use disorders. In a study of 40,885 adults with opioid use disorder that compared the effectiveness of 6 different treatment pathways, only treatment with buprenorphine or methadone was associated with reduced risk of overdose and serious opioid-related acute care use as compared with no treatment during 3 and 12 months of follow-up. And Jennifer Haas' (8) retrospective analysis of data from 3 research centers found that compared with screening examinations using digital mammography, screening examinations using digital breast tomosynthesis (DBT) detected breast cancers with increased specificity and that a higher proportion of those detected were associated with a better prognosis. and to compare the detection rates by patient age and breast density. The largest increase in cancer detection rate and the greatest shift toward smaller, node-negative invasive cancers detected with DBT was for women aged 40 to 49 years.

In 2019, the **Disparities Research Unit** took the research information it has produced and shared it with institutions and organizations both home and abroad. Under the direction of Margarita Alegria (9), the DPU partnered with policy agencies in New York, California, and Massachusetts to advise on new initiatives on mental health and substance use treatment; presented work on innovation for the National Institute of Mental Health Director and at the National Academy of State Health Policy; trained on its interventions in Maryland and Spain; and chaired the Forum of Mental Health and Substance Treatment at the National Academies of Medicine in October. Among the unit's numerous publications was a study evaluating the effectiveness of the Integrated Intervention for Dual Problems and Early Action (IIDEA) program compared with enhanced usual care among Latino immigrants. Over a three-year period at 17 clinics or emergency departments and 24 community sites in Boston, Madrid, and Barcelona, participants were assigned randomly to either the IIDEA treatment group (n = 172) or the enhanced usual care control group (n = 169). Intent-to-treat analyses assessed effectiveness, and post hoc analyses examined whether results varied by symptom severity or treatment dose. The study found no statistical significant effects of IIDEA on primary drug and alcohol outcomes, but statistically significant beneficial effects were observed in the IIDEA group for secondary mental health outcomes.

In **Infectious Diseases**, Michael Mansour, Sarah Turbett, and Libby Hohmann (10) described two patients who acquired infection due to extended spectrum beta-lactamase-producing E. coli from fecal microbiota transplant. Using genomic sequencing, they demonstrated that the source

was a single stool donor. They conclude that enhanced screening of donors to limit the transmission of organisms with the potential to cause adverse infectious events is critical. Lisa Goer and Cammie Lesser (11) helped demonstrate that IpaH7.8, secreted by the intracellular bacterial pathogen Shigella, specifically inhibits NLRP1B, a murine inflammasome protein, even though Shigella is not a natural pathogen of mice. IpaH7.8 is a ubiquitin E3 ligase that targets NLRP1B for degradation, releasing a fragment of NLRP1B that is active. Jason Harris, Steve Calderwood, and Edward Ryan (12) were part of a team that developed a serological profile of recent cholera infection by using machine learning on more than 1,500 serologic samples from individuals in Bangladesh recovering from cholera or their uninfected contacts. The assay can be used to estimate the annual incidence of cholera in both endemic and epidemic settings. Roby Bhattacharyya (13) extended a novel RNA-based diagnostic he developed for use in the rapid detection of antibiotic resistance phenotype and genotype. Phenotypic diagnosis is based on machine learning analysis of the transcriptional response of the microbe to growth in the presence of antibiotics. The method classified bacterial strains with an accuracy of 94-99% and can be performed in less than 4 hours, which is 24-36 hours faster than standard-of-care antibiotic resistance diagnostics. Camille Kotton and Jay Fishman (14) investigated the safety of transplanting hearts from hepatitis C virus-infected donors unto uninfected recipients. In a study of 20 uninfected recipients, they examined whether pre-emptive administration of hepatitis C virus (HCV) antiviral therapy prevents the development of chronic hepatitis C infection. They found that this approach resulted in rapid HCV suppression, prevention of chronic HCV infection, and excellent function of the allografts.

In **Pulmonary & Critical Care**, Melissa Suter (15, 16) was an author on two important publications in 2019. The first paper addresses the challenge obtaining tumor biopsies that contain sufficient tumor tissue (rather than associated fibrotic tissue) for diagnostic studies. Within ex vivo lung nodule samples, polarization-sensitive optical coherence tomography (PS-OCT) enables accurate detection of areas of fibrosis and can identify regions containing tumor with little fibrosis. PS-OCT therefore has significant potential to increase diagnostic tumor yield by guiding intraprocedural tissue sampling in vivo and by rapidly assessing biopsy adequacy ex vivo. In the other paper, analysis of airway microstructure using endobronchial optical coherence tomography revealed functional and structural differences between allergic airways with asthma and allergic non-asthmatic airways, demonstrating that a comprehensive microstructural approach to assessing the airways may be important in future asthma studies as well as in the monitoring and treatment of asthma. Michael Gillette (17) had a paper that described a blood-based host response that can help to differentiate active tuberculosis from other causes of persistent cough in patients with and without HIV infection from Africa, Asia, and South America. In the area of by impaired mucociliary clearance, Raghu Chivukula (18) led a study that identifies a novel and potentially targetable signaling axis that controls motile ciliary function in humans, which has implications for other respiratory disorders characterized by impaired mucociliary clearance. And David Christiani (19) provided editorial comments on the recent rise in cases of vaping induced lung injury and its possible causes.

The **Cardiology Division** had a number of impactful investigations and publications last year, including Pradeep Natarajan (20), who performed a large-scale GWAS for venous thromboembolic (VTE) disease, identifying previously unknown risk loci and highlighting common origins with arterial disease. He and his colleagues also developed a polygenic risk score, identifying 5% of the population as at high risk. Jason Roh (21), working in the Rosenzweig Lab, identified a new causal link between aging and heart failure that involves activin signaling. Using 2 different clinical grade inhibitors of the pathway, Jason reversed established heart failure in multiple independent animal models, suggesting therapeutic potential for multiple forms of heart failure. Raj Malhotra's (22) work reveals an important role for HDAC9 in aortic vascular calcification, which together with independent work published in Nature Communications the year before by Mark Lindsay, places HDAC9 at the center of a variety of vascular pathologies. Since it's potentially a druggable target, the work has generated a lot of interest in the pharmaceutical industry and academia. Amit Khera and Sek Kathiresan (23) developed a polygenic risk score for obesity that quantitatively assesses inherited susceptibility to obesity and offers opportunities for clinical prevention and mechanistic assessment. And Jim Januzzi (24) published an analysis of the effects of sacubitril-valsartan on ventricular remodeling, providing potential mechanistic insight into how sacubitril-valsartan promotes the survival of heart failure patients.

In the **Renal Division**, Andrew Allegretti (25) evaluated the safety and effectiveness of bexagliflozin, a novel sodium/glucose cotransporter 2 (SGLT2) inhibitor, in patients with type 2 diabetes and chronic kidney disease (CKD). Hyperglycemia exacerbates the progression of CKD, but most glucose-lowering therapies do not address morbidities associated with CKD. SGLT2 inhibitors offer potential benefits to patients with diabetes and CKD, but their effectiveness may be diminished with decreased kidney function. This phase 3, double-blind, placebo-controlled, multicenter, multinational, randomized trial included 312 patients at 54 sites across 4 countries. The SGLT2 inhibitor bexagliflozin was associated with significantly lower hemoglobin A1c levels, including among patients with CKD stages 3a and 3b, decreased body weight, systolic blood pressure, fasting plasma glucose level, and albuminuria, compared with placebo. Urinary tract infection and genital mycotic infections were more common

in the bexagliflozin group; otherwise, frequencies of adverse events were comparable between groups. Eugene Rhee co-authored a paper along with Jose Florez (26) of Endocrine showed that D5D/D6D, enzymes involved in the synthesis of highly unsaturated fatty acids, provide a mechanism for glycolytic NAD+ recycling that permits ongoing glycolysis and cell viability when the cytosolic NAD+/NADH ratio is reduced, analogous to lactate fermentation. Although lesser in magnitude than lactate production, this desaturase-mediated NAD+ recycling is acutely adaptive when aerobic respiration is impaired in vivo. Notably, inhibition of either highly unsaturated fatty acids synthesis or lactate fermentation increases the other, underscoring their interdependence. Megan Sise, Harish Seethapathy, Frank Cortazar, and Yaa Oppong, together with Chloe Villani from Rheumatology, Allery, and Immunology, and Kerry Reynolds, Ryan Sullivan, and Meghan Mooradian (27) from the Cancer Center, examined the frequency, severity, cause, and predictors of AKI in 1,016 patients receiving checkpoint inhibitors. Seventeen percent experienced AKI (defined by an increase in creatinine at least 1.5 times the baseline within 12 months), 8% experienced sustained AKI (events lasting at least 3 days), 2% patients experienced stage 3 sustained AKI, and 0.4% of patients required dialysis. In 3% of patients, the AKI was potentially checkpoint inhibitor–related. The first episode of sustained AKI occurred on average 106 days (S.D. 85) after checkpoint inhibitor initiation. Proton pump inhibitor use at baseline was associated with sustained AKI. The causes of sustained AKI in this population are heterogenous and merit thorough evaluation. Jenny Lu (28) was part of a team that, using tissue-specific genetically engineered mice, identified a previously unrecognized important role of integrin-linked kinase (ILK) in mediating necroptosis in collecting duct epithelial cells. And Jodie Babitt (29) co-authored a study in mice that investigated the role of SMAD1, -5, and -8, major regulators of hepcidin production in response to iron, in hepcidin and iron homeostasis regulation and liver injury. They found that SMAD8 plays a redundant but critical role in hepcidin and iron homeostasis regulation, additionally showing that hepatocyte Smad1/5/8 knockout mice are a model of hemochromatosis that encompasses liver injury and fibrosis seen in human disease.

In the **Division of Rheumatology, Allergy & Immunology and the Center for Immunology & Inflammatory Diseases**, Thorsten Mempel's (30, 31) laboratory had two high-impact research findings last year, including a demonstration that TGF-beta signals epigenetically precondition some naive CD8+ in their resting state in lymph nodes to develop into a particular subset of memory cell, so-called epithelial tissue-resident memory cells that are important for antiviral protection at barrier tissues such as the skin. This finding suggests a fundamental shift in our understanding of T cell differentiation, since it indicates that the differentiation path of T cells can already be biased by events that precede antigenic priming, which was previously thought to be the initiating event for their functional diversification. The lab also produced a manuscript that immunosuppressive, tumor-infiltrating regulatory T (Treg) cells can be reprogrammed into IFN -secreting effector T cells through either genetic or pharmacological disruption of the CARMA-BCL10-MALT1 pathway. They found that this resulted in tumor inflammation that rendered tumors sensitive to immune checkpoint therapy. Andrew Luster's (32, 33) lab similarly had a pair of significant research findings. His lab describes an important role for the CXCR3 chemokine system in responsiveness to anti-PD1 therapy. Given the known role of CXCR3 in mediating effector T cell migration, researchers were surprised to find that the CXCR3 chemokine system was not required for CD8+ T cell migration into the tumor, but rather was required for the enhancement of the intratumoral CD8+ T cell response in the context of PD-1 blockade. The Luster lab also used an immune complex–induced arthritis murine model to show that neutrophil arrest requires endothelial expression of the atypical complement C5a receptor 2 (C5aR2) to drive transport of C5a into the vessel lumen, which is required for initiation of C5aR1-driven neutrophil arrest. is a chronic immune-mediated disease of unclear etiology. Cory Perugino, working with John Stone and Shiv Pillai (34) on IgG4-Related Disease (IgG-RD) generated recombinant patient-derived human mAbs and used them to identify disease-relevant antigens using immunoaffinity chromatography and mass spectrometry. One such protein identified as an auto-antigen in IgG4-RD was galectin-3. This work has helped to define IgG4-Related Disease as autoimmune in etiology.

The **Division of Endocrine** (35) had a significant collaborative research effort across the division of whole-exome sequencing of 45,000 samples of type 2 diabetes cases and controls to elucidate the contribution of coding variants to the genetic architecture of type 2 diabetes. The results of this work were published in Nature. Alexander Soukas (36) and his colleagues conducted a study that may improve the understanding of how mitochondrial permeability determines the impact of autophagy in aging. Takara Stanley and Lindsay Fourman were lead authors on a study that included colleagues from the Metabolism Unit and Kathleen Corey and Raymond Chung (37) in the Liver Center that demonstrated the growth hormone-stimulating agent Tesamorelin reduces hepatic fat and prevents liver fibrosis progression in HIV lipodystrophy. Hank Kronenberg's (38) lab showed salt-inducible kinases transduce the parathyroid hormone 1 receptor signals in bone development and remodeling. And Joy Tsai (39) led a study that found a combination therapy with denosumab and high-dose teriparatide is highly effective in the treatment of post-menopausal osteoporosis.

In the **Neuroendocrine Unit**, Anna Aulinas and Elizabeth Lawson (40) reported the first evidence of a new hormone deficiency syndrome

in patients with hypopituitarism. They demonstrated that men with hypopituitarism and diabetes insipidus (deficiency of posterior pituitary hormone vasopressin) have low serum levels of oxytocin (also a posterior pituitary hormone) and increased psychopathology. Future research will focus on the role of oxytocin replacement in such patients. Allison Kimball, Laura Dichtel, and Karen Miller (41) studied the neuroactive steroid 3α-5α-tetrahydroprogesterone (allopregnanolone), a metabolite of progesterone, which is a positive allosteric modulator of GABA-A receptors. They demonstrated that the serum allopregnanolone/progesterone ratio decreases 8-fold from the follicular to luteal phase and is lower at mid-cycle and in the luteal phase than in postmenopausal women, which may have implications for luteal phase mood disorders. Laura and Karen (42) also published guidelines for plasma free cortisol level cut-offs for adrenal insufficiency in patients with altered binding globulins, such as those in intensive care units or with cirrhosis. These guidelines have the potential to reduce the need for glucocorticoid administration – with its attendant risks -- in these patients. Melanie Schorr Haines and Karen Miller (43) showed that men with anorexia nervosa (both low-weight and normal-weight "atypical" forms) or with avoidant/restrictive food intake disorder (ARFID) represent new groups of patients who are at risk for low bone mineral density. Alex Faje and Nicholas Tritos (44) demonstrated that the phenotype of patients with hypophysitis caused by PD-1 inhibitor therapy is distinct from that of patients with hypophysitis caused by CTLA-4 inhibitor therapy.

The **Reproductive Endocrine Unit** developed a new diagnostic test to differentiate between children who are late, but will eventually enter puberty, from children who are late and who will never start puberty. The neuropeptide kisspeptin, which stimulates GnRH release, can be used to probe the integrity of the reproductive endocrine axis. Stephanie Seminara, along with Yee-Ming Chan at Boston Children's, demonstrated that responses to kisspeptin can predict outcomes for individuals with pubertal delay. Those who responded to kisspeptin initiated puberty on their own, whereas those who did not respond to kisspeptin did not initiate puberty. Thus, kisspeptin-stimulation is a promising novel tool for predicting pubertal outcomes for children with delayed puberty. Ravikumar Balasubramanian was key in initiating a systematic genetic interrogation of families with isolated hypogonadotropic hypogonadism, a Mendelian disorder caused by a defect in the biosynthesis, secretion or action of GnRH. He discovered eleven families with an anosmic form of IGD (Kallmann syndrome; KS) with autosomal dominant heterozygous loss-of-function mutations in TCF12, a locus also known to cause syndromic and non-syndromic craniosynostosis. Loss of tcf12 in zebrafish larvae perturbs GnRH neuronal patterning. The genetic landscape uncovered indicates highlights genetic links between craniofacial patterning and GnRH dysfunction and begins to assemble the functional network that regulates the development of the GnRH axis. Using a similar approach, Meg Lippincott identified 7 novel loss-of-function mutations in two new genes causing hypogonadotropic hypogonadism: RhoGTPase-activating proteins 5 and 35. It is thought that these genes activate RhoGTPases that initiate signal cascades that regulate the actin cytoskeleton.

In the Department's **Core Educator Faculty**, Steven Knuesel joined Josh Metlay, Marjory Bravard, and Melissa Mattison (45) from DGIM to research the impact of length of stay on a hospital medicine Emergency Department (ED) boarder service (defined as patients waiting for more than two hours for an inpatient bed). The study found that admitted patients who were not boarders had the shortest LOS. Among boarded patients, coverage by a hospital medicine-led ED boarder service was associated with a reduced hospital LOS. There was no difference in 30-day ED readmission rates.

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39. Publication: Tsai JN, Lee H, David NL, Eastell R, Leder BZ. Combination denosumab and high-dose teriparatide for postmenopausal osteoporosis (DATA-HD): A randomised, controlled phase 4 trial. Lancet Diabetes & Endocrinology 2019;7:767-775. (PMID: 31447409).
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Molecular Biology

Department Report

Robert E. Kingston, PhD, Chief

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

At present, approximately 228 people, including 17 faculty, 172 postdoctoral fellows and graduate students, and 39 staff members, comprise the Department of Molecular Biology. Our areas of excellence include:

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

The Department of Molecular Biology congratulates Dr. Lauren Orefice, our newest faculty recruit, for winning of the 2019 Eppendorf and Science Prize for Neurobiology. Dr. Orefice was recognized for her work on autism spectrum disorders (ASD), showing the importance of peripheral somatosensory neurons in influencing brain function. A full press release on Dr. Orefice's award is available at https://www.aaas.org/news/lauren-orefice-wins-2019-eppendorf-science-prize-neurobiology.

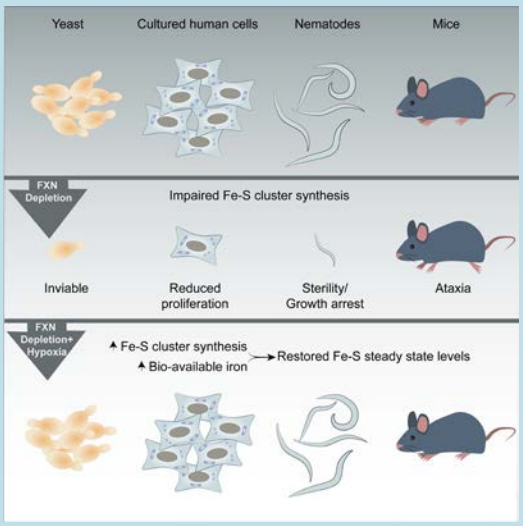


Figure 1. Work from the Mootha lab, done in collaboration with several investigators at MGH, characterized a dramatic impact of oxygen levels on the progression of Friedrich's ataxia. (Ast et al, Cell 2019; 177(6):1507-1521).

Our department takes pride in the breadth of our work, including our translational research. In one recent example, the Mootha lab turned their attention to Friedrich's Ataxia (FRDA), a progressive, neurodegenerative movement disorder caused by mutations in the gene FXN, which encodes the protein frataxin (Ast et al, Cell 2019; 177(6):1507-1521). Surprisingly, the Mootha lab showed that loss of FXN can be completely buffered by hypoxia in both yeast, human cells, and nematodes, while simply housing an FRDA mouse in low oxygen can attenuate the progression of ataxia (Fig. 1). Their work identifies oxygen as a key environmental variable in the pathogenesis associated with FXN depletion, with important mechanistic and therapeutic implications for FRDA.

Our department also has a long tradition of supporting fundamental biological research. Focusing on cellular signaling, the Subramanian lab turned their attention to the Sonic Hedgehog (Shh) pathway, which is central to embryonic development and tissue homeostasis (Jiang et al, Dev Cell 2019; 49(5):711-730). The correct localization of Hedgehog effectors to the tip of primary cilia is critical for proper signal transduction. The conserved non-motile kinesin Kif7, a conserved component of the Shh pathway, defines a "cilium-tip compartment" by localizing to the distal ends of axonemal microtubules. How Kif7 recognizes microtubule ends has not been understood. The Subramanian lab found that, unlike other kinesins, Kif7 recognizes and stabilizes a GTP-form of tubulin to promote its own

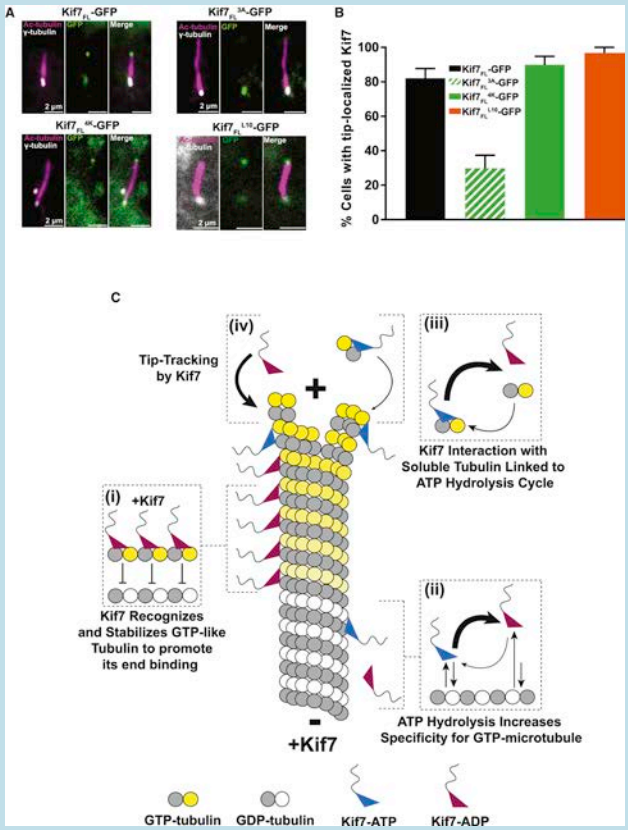


Figure 2. Radhika Subramanian's lab showed that Kif7 recognizes and stabilizes a GTP-form of tubulin to promote its own microtubule-end (Jiang et al, Dev Cell 2019; 49(5):711-730).

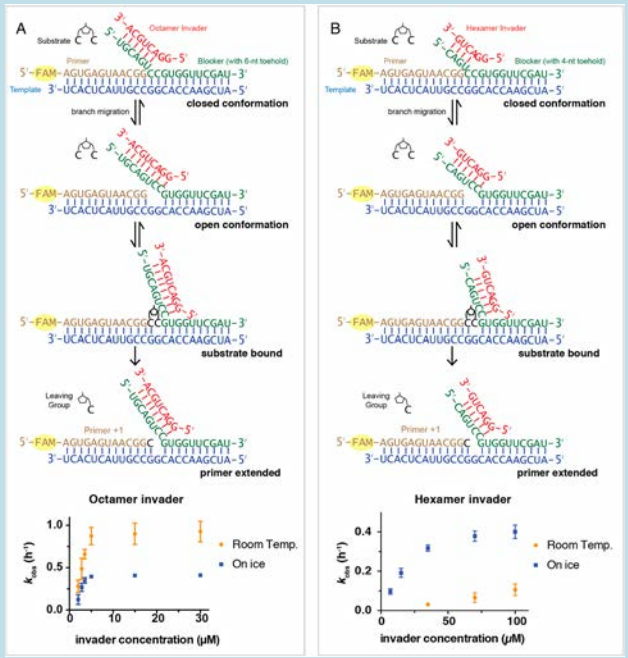


Figure 3. Jack Szostak's lab published a report showing that short RNA oligonucleotides can catalyze strand displacement synthesis by opening up a duplex through a toehold and branch migration mechanism (Zhou et al, Elife; 2019 Nov 8;8).

microtubule-end localization (Fig. 2). They propose that the ubiquitous kinesin fold has been repurposed in Kif7 to facilitate organization of a spatially restricted platform for localization of Hedgehog effectors at the cilium tip.

Focusing on even more fundamental questions, the Szostak lab explores the nonenzymatic replication of RNA, which is thought to be a crucial development leading to the earliest forms of life (Zhou et al, Elife; 2019 Nov 8;8). The replication of the genetic material in all living systems proceeds through strand displacement synthesis, in which sophisticated enzymes open up the DNA duplex ahead of the replication fork. Because of the complexity of this process, it was not previously thought to be applicable to the much simpler nonenzymatic forms of replication that were important during the origin of life. Jack's lab has shown that short RNA oligonucleotides can catalyze strand displacement synthesis by opening up a duplex through a toehold and branch migration mechanism (Fig. 3).

Neurology

Department Report

Merit Cudkowicz, MD, MSc, Chief

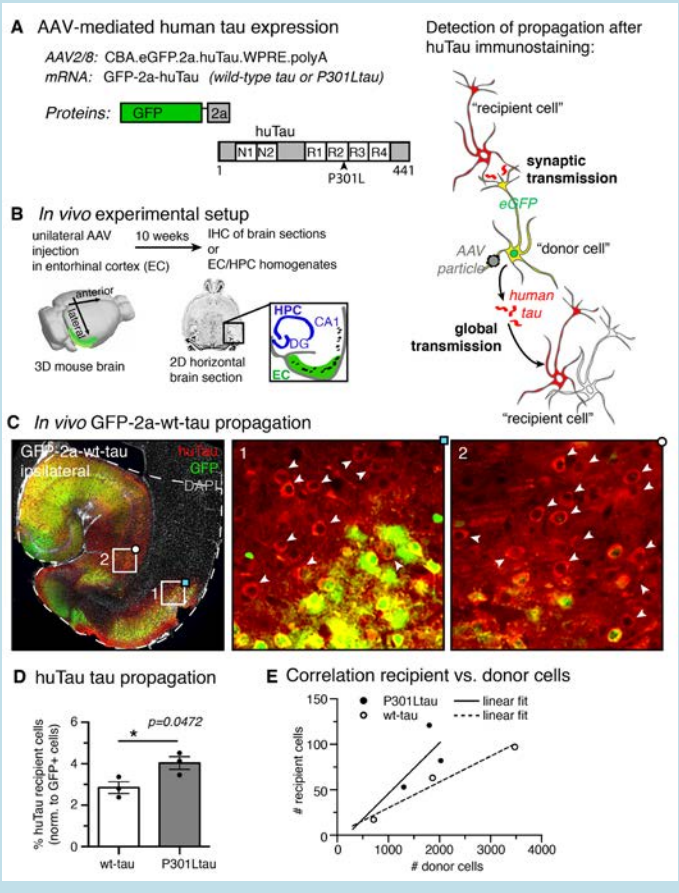
The mission of the Department of Neurology is to be the preeminent academic neurology department in the US by providing outstanding clinical care while rapidly discovering new treatments to reduce and eliminate the devastating impact of neurological disorders; training the very best neurologists and scientists of the future; and improving the health and well-being of the diverse communities we serve.
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. 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. The Department of Neurology research revenue continues to increase over prior years, bringing in over $132M in total research revenue and maintains an average NIH success rate of 28%.

Departmental Strategic Research Priorities

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

Breakthroughs in Research and Therapeutics

Experimental evidence for the age dependence of tau protein spread in the brain. The incidence of Alzheimer's disease (AD), which is characterized by progressive cognitive decline that correlates with the spread of tau protein aggregation in the cortical mantle, is strongly age-related. It could be that age predisposes the brain to tau misfolding and supports the propagation of tau pathology. To address this hypothesis, Drs. Wegmann, Hyman and colleagues used an experimental setup that allowed them to explore age-related factors of tau spread and regional vulnerability. They virally expressed human tau locally in entorhinal cortex (EC) neurons of young or old mice and monitored the cell-to-cell tau protein spread by immunolabeling. Old animals showed more tau spreading in the hippocampus and adjacent cortical areas and accumulated more misfolded tau in EC neurons. No misfolding, at any age, was observed in the striatum, a brain region mostly unaffected by tangles. Age and brain region dependent tau spreading and misfolding likely contribute to the profound age-related risk for sporadic AD.



Enhanced neuron-to-neuron propagation of mutant P301Ltau in vivo.
(Pictured to the right)

(A) Schematic showing the AAV sequence, the mRNA, and the proteins encoded in AAV CBA.eGFP.2a.huTau (WTtau and P301Ltau), as well as the tau protein propagation principle and detection methodology. Using a self-cleaving 2a peptide, transduced "donor" neurons express both eGFP and human tau as individual proteins. The propagation of tau can be visualized by immunofluorescence labeling of postmortem brain sections or fixed neurons in culture: Human tau detected in "recipient" neurons that do not express the fluorescence transduction marker eGFP indicates the propagation of tau between cells. Thereby, the upstream location of the GFP

transduction marker prevents the detection of false positives that could occur due to incomplete translation of the mRNA. (B) Schematic for the unilateral injection of AAV eGFP-2a-huTau into the EC (green) and the experimental work flow. The location of the EC, the HPC (and subregion CA1), and the dentate gyrus (DG) in horizontal mouse brain sections is indicated. (C) Example of the immunofluorescence labeling of human tau (red) and GFP (green) in a horizontal brain section of a GFP-2a-WTtau–injected mouse with many huTau recipient cells: [huTau+/GFP−] cells, which received tau by cell-to-cell propagation (white arrowheads in close-ups 1 and 2), can be seen adjacent to the EC injection side (1) and in synaptic connected area CA1 (2). Cells transduced with the AAV (GFP+) can, in this specific case, be found in the EC and CA3. (D) Quantification of tau propagation (no. of recipient cells/no. of transduced cells) was done by counting all recipient (huTau+, red) and donor neurons (GFP+, green) in the entire ipsilateral EC and HPC formation (dashed white line). A higher propagation ($P = 0.0472$) was detected for P301Ltau compared to WTtau. (E) Scatterplot shows the average of recipient versus donor cells per mouse. Mean ± SEM, $n = 3$ animals per group and $n = 4$ to 5 brain sections per animal; single data points represent the mean per animal; unpaired two-tailed Student's t test with Welch's correction.

Wegmann S, Bennett RE, Delorme L, Robbins AB, Hu M, McKenzie D, Kirk MJ, Schiantarelli J, Tunio N, Amaral AC, Fan Z, Nicholls S, Hudry E, Hyman BT. Experimental evidence for the age dependence of tau protein spread in the brain. Sci Adv. 2019 06; 5(6):eaaw6404.

Cromolyn sodium delays disease onset and is neuroprotective in the SOD1G93A Mouse Model of ALS. Research led by Dr. Sadri-Vakili shows that treatment with an anti-inflammatory drug delayed the onset of disease in a mouse model of ALS. Accumulating evidence suggests that neuroinflammatory processes are implicated in the initiation and progression of amyotrophic lateral sclerosis (ALS). Previous reports have demonstrated an increase in microgliosis and astrogliosis in the lumbar spinal cord of SOD1G93A transgenic mice before the onset of symptoms, a neuroinflammatory response which correlated with disease progression. Importantly, early stage homeostatic microglia enhanced motor neuron survival, while pro-inflammatory microglia were toxic to motor neurons in the SOD1G93A mice. Recent studies from this group have demonstrated that cromolyn sodium, an FDA approved compound, exerts neuroprotective effects in mouse models of Alzheimer's disease by altering microglial cell activation. Here, they tested the neuroprotective and anti-inflammatory effects of cromolyn sodium in the SOD1G93A mouse model of ALS. Results indicate that cromolyn sodium treatment significantly delayed the onset of neurological symptoms, and improved deficits in PaGE performance in both male and female mice, however, there was only an effect on survival in female mice. Furthermore, there was a significant increase in motor neuron survival in the lumbar spinal cord as well as a significant decrease in the denervation of the neuromuscular junction of the tibialis anterior muscle in cromolyn treated transgenic SOD1G93A mice. Lastly, cromolyn treatment decreased the expression of pro-inflammatory cytokines/chemokines in the lumbar spinal cord and plasma and decreased mast cell degranulation in the tibialis anterior muscle of transgenic SOD1G93A mice. Together, these findings suggest that cromolyn sodium provides neuroprotection in the SOD1G93A mice by decreasing the inflammatory response.

Granucci EJ, Griciuc A, Mueller KA, Mills AN, Le H, Dios AM, McGinty D, Pereira J, Elmaleh D, Berry JD, Paganoni S, Cudkowicz ME, Tanzi RE, Sadri-Vakili G. Cromolyn sodium delays disease onset and is neuroprotective in the SOD1G93A Mouse Model of ALS. Sci Rep. 2019 Nov 27;9(1):17728. doi: 10.1038/s41598-019-53982-w. PubMed PMID: 31776380

Loss of Ataxin-1 Potentiates Alzheimer's Pathogenesis by Elevating Cerebral BACE1 Transcription. An impactful article published in Cell by Drs. Suh, Tanzi, and colleagues showed that expansion of CAG trinucleotide repeats in ATXN1 causes spinocerebellar ataxia type 1 (SCA1), a neurodegenerative disease that impairs coordination and cognition. While ATXN1 is associated with increased Alzheimer's disease (AD) risk, CAG repeat number in AD patients is not changed. Here, the consequences of ataxin-1 loss of function was investigated and it was discovered that knockout of Atxn1 reduced CIC-ETV4/5-mediated inhibition of Bace1 transcription, leading to increased BACE1 levels and enhanced amyloidogenic cleavage of APP, selectively in AD-vulnerable brain regions. Elevated BACE1 expression exacerbated Aβ deposition and gliosis in AD mouse models and impaired hippocampal neurogenesis and olfactory axonal targeting. In SCA1 mice, polyglutamine-expanded mutant ataxin-1 led to the increase of BACE1 post-transcriptionally, both in cerebrum and cerebellum, and caused axonal-targeting deficit and neurodegeneration in the hippocampal CA2 region. These findings suggest that loss of ataxin-1 elevates BACE1 expression and Aβ pathology, rendering it a potential contributor to AD risk and pathogenesis.

Suh J, Romano DM, Nitschke L, Herrick SP, DiMarzio BA, Dzhala V, Bae JS, Oram MK, Zheng Y, Hooli B, Mullin K, Gennarino VA, Wasco W, Schmahmann JD, Albers MW, Zoghbi HY, Tanzi RE. Loss of Ataxin-1 Potentiates Alzheimer's Pathogenesis by Elevating Cerebral BACE1 Transcription. Cell. 2019 Aug 22;178(5):1159-1175.e17. doi: 10.1016/j.cell.2019.07.043. PubMed PMID: 31442405; PubMed Central PMCID: PMC6726125.

TREM2 Acts Downstream of CD33 in Modulating Microglial Pathology in Alzheimer's Disease. The microglial receptors CD33 and TREM2 have been associated with risk for Alzheimer's disease (AD). Drs. Griciuc, Tanzi and colleagues published a manuscript in Cell that investigated crosstalk between CD33 and TREM2. They showed that knockout of CD33 attenuated amyloid beta (Aβ) pathology and improved cognition in 5xFAD mice, both of which were abrogated by additional TREM2 knockout. Knocking out TREM2 in 5xFAD mice exacerbated Aβ pathology and neurodegeneration but reduced Iba1+ cell numbers, all of which could not be rescued by additional CD33 knockout. RNA-seq profiling of microglia revealed that genes related to phagocytosis and signaling (IL-6, IL-8, acute phase response) are upregulated in 5xFAD;CD33-/- and downregulated in 5xFAD;TREM2-/- mice. Differential gene expression in 5xFAD;CD33-/- microglia depended on the presence of TREM2, suggesting TREM2 acts downstream of CD33. Crosstalk between CD33 and TREM2 includes regulation of the IL-1β/IL-1RN axis and a gene set in the "receptor activity chemokine" cluster. Our results should facilitate AD therapeutics targeting these receptors.

Griciuc A, Patel S, Federico AN, Choi SH, Innes BJ, Oram MK, Cereghetti G, McGinty D, Anselmo A, Sadreyev RI, Hickman SE, El Khoury J, Colonna M, Tanzi RE. TREM2 Acts Downstream of CD33 in Modulating Microglial Pathology in Alzheimer's Disease. Neuron. 2019 Sep 4;103(5):820-835.e7. doi: 10.1016/j.neuron.2019.06.010. Epub 2019 Jul 10. PubMed PMID: 31301936; PubMed Central PMCID: PMC6728215.

Eye Movement Abnormalities Are Ubiquitous in the Spinocerebellar Ataxias. Oculomotor abnormalities are common in the spinocerebellar ataxias (SCAs). In studies of SCAs 1, 2, 3, and 6, eye movement abnormalities correlate with disease severity. Oculomotor abnormalities may be the sole motor manifestation of early and/or premanifest disease; however, not all ataxia rating scales include oculomotor assessment. Drs. Stephen and Schmahmann sought to identify the prevalence and characteristics of oculomotor abnormalities at first presentation in a large SCA cohort, including those in earlier stages of disease. They performed a retrospective assessment of initial clinical examinations of SCA patients followed in the Massachusetts General Hospital Ataxia Unit and assessed with the Brief Ataxia Rating Scale (BARS). One hundred thirty-four SCA patients were assessed: 17 SCA1, 13 SCA2, 55 SCA3, 2 SCA5, 22 SCA6, 11 SCA7, 9 SCA8, and 5 SCA17, mainly in the early stages of disease (67.2% stage 0–1). Oculomotor abnormalities were present on initial assessment in 94.8%, including 7/9 stage 0 and 77/ 81 stage 1 patients. Stage 0/1 patients had frequent saccadic intrusions, nystagmus, and hypo/hypermetric saccades. Saccadic slowing was present even in early stage SCA7 and SCA2, eventually leading to ophthalmoplegia. The burden of oculomotor abnormalities correlated with disease stage, duration, and severity, remaining highly significant even when controlling for age. The ubiquitous presence of oculomotor abnormalities in the SCAs, particularly early in the course, underscores the importance of oculomotor assessment in ataxia rating scales such as BARS. These findings highlight the potential for quantitative physiological oculomotor measures as clinical biomarkers in natural history studies and clinical trials.

Stephen CD, Schmahmann JD. Eye Movement Abnormalities Are Ubiquitous in the Spinocerebellar Ataxias. Cerebellum. 2019 Dec;18(6):1130-1136. doi: 10.1007/s12311-019-01044-2. PubMed PMID: 31175630.

Big Data Approaches to Phenotyping Acute Ischemic Stroke Using Automated LesionSegmentation of Multi-Center Magnetic Resonance Imaging Data. This comprehensive study evaluated deep learning algorithms' segmentation of acute ischemic lesions on heterogeneous multi-center clinical diffusion-weighted magnetic resonance imaging (MRI) data sets and explored the potential role of this tool for phenotyping acute ischemic stroke. The study used Ischemic stroke data sets from the MRI-GENIE (MRI-Genetics Interface Exploration) repository consisting of 12 international genetic research centers that were retrospectively analyzed using an automated deep learning segmentationc algorithm consisting of an ensemble of 3-dimensional convolutional neural networks. Three ensembles were trained using data from the following: (1) 267 patients from an independent single-center cohort, (2) 267 patients from MRI-GENIE, and (3) mixture of (1) and (2). The algorithms' performances were compared against manual outlines from a separate 383 patient subset from MRI-GENIE. Univariable and multivariable logistic regression with respect to demographics, stroke subtypes, and vascular risk factors were performed to identify phenotypes associated with large acute diffusion-weighted MRI volumes and greater stroke severity in 2770 MRI-GENIE patients. Stroke topography was investigated. Results showed that the ensemble consisting of a mixture of MRI-GENIE and single-center convolutional neural networks performed best. Subset analysis comparing automated and manual lesion volumes in 383 patients found excellent correlation (ρ=0.92; P<0.0001). Median (interquartile range) diffusion-weighted MRI lesion volumes from 2770 patients were 3.7 cm3 (0.9-16.6 cm3). Patients with small artery occlusion stroke subtype had smaller lesion volumes (P<0.0001) and different topography compared with other stroke subtypes. The study concluded that Automated accurate clinical diffusion-weighted MRI lesion segmentation using deep learning algorithms trained with multi-center and diverse data is feasible. Both lesion volume and topography can provide insight into stroke subtypes with sufficient sample size from big heterogeneous multi-center clinical imaging phenotype data sets.

Wu O, Winzeck S, Giese AK, Hancock BL, Etherton MR, Bouts MJRJ, Donahue K, Schirmer MD, Irie RE, Mocking SJT, McIntosh EC, Bezerra R, Kamnitsas K, Frid P,Wasselius J, Cole JW, Xu H, Holmegaard L, Jiménez-Conde J, Lemmens R, LorentzenE, McArdle PF, Meschia JF, Roquer J, Rundek T, Sacco RL, Schmidt R, Sharma P, Slowik A, Stanne TM, Thijs V, Vagal A, Woo D, Bevan S, Kittner SJ, Mitchell BD, Rosand J, Worrall BB, Jern C, Lindgren AG, Maguire J, Rost NS. Big Data Approaches to Phenotyping Acute Ischemic Stroke Using Automated LesionSegmentation of Multi-Center Magnetic Resonance Imaging Data. Stroke. 2019 Jul;50(7):1734-1741. doi: 10.1161/STROKEAHA.119.025373. Epub 2019 Jun 10. PubMed PMID: 31177973; PubMed Central PMCID: PMC6728139.

Rich-Club Organization: An Important Determinant of Functional Outcome After Acute Ischemic Stroke. The objective of this study was to determine whether the rich-club organization, essential for information transport in the human connectome, is an important biomarker of functional outcome after acute ischemic stroke (AIS) Consecutive AIS patients (N = 344) with acute brain magnetic resonance imaging (MRI) (<48 h) were eligible for this study. Each patient underwent a clinical MRI protocol, which included diffusion weighted imaging (DWI). All DWIs were registered to a template on which rich-club regions have been defined. Using manual outlines of stroke lesions, we automatically counted the number of affected rich-club regions and assessed its effect on the National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS; obtained at 90 days post-stroke) scores through ordinal regression. Findings demonstrated that of 344 patients (median age 65, inter-quartile range 54-76 years) with a median DWI lesion volume (DWIv) of 3cc, 64% were male. The authors established that an increase in number of rich-club regions affected by a stroke increases the odds of poor stroke outcome, measured by NIHSS (OR: 1.77, 95%CI 1.41-2.21) and mRS (OR: 1.38, 95%CI 1.11-1.73). Additionally, they demonstrated that the OR exceeds traditional markers, such as DWIv (ORNIHSS 1.08, 95%CI 1.06-1.11; ORmRS 1.05, 95%CI 1.03-1.07) and age (ORNIHSS 1.03, 95%CI 1.01-1.05; ORmRS 1.05, 95%CI 1.03-1.07). In this proof-of-concept study, the number of rich-club nodes affected by a stroke lesion presents a translational biomarker of stroke outcome, which can be readily assessed using standard clinical AIS imaging protocols and considered in functional outcome prediction models beyond traditional factors.

Schirmer MD, Ktena SI, Nardin MJ, Donahue KL, Giese AK, Etherton MR, Wu O, Rost NS. Rich-Club Organization: An Important Determinant of Functional Outcome After Acute Ischemic Stroke. Front Neurol. 2019 Sep 10;10:956. doi:10.3389/fneur.2019.00956. eCollection 2019. PubMed PMID: 31551913; PubMed Central PMCID: PMC6748157.

Neuropathologic correlates of amyloid and dopamine transporter imaging in Lewy body disease. The goal of Dr. Gomperts and colleagues was to develop imaging biomarkers of diseases in the Lewy body spectrum and to validate these markers against postmortem neuropathologic findings. To accomplish this, four cognitively normal participants with Parkinson disease (PD), 4 with PD with cognitive impairments, and 10 with dementia with Lewy bodies underwent amyloid imaging with [11C]Pittsburgh compound B (PiB). All 18 had annual neurologic examinations. All cognitively normal participants with PD developed cognitive impairment before death. Neuropathologic examinations assessed and scored Braak Lewy bodies, Thal distribution of amyloid, Consortium to Establish a Registry for Alzheimer's Disease neuritic amyloid plaques, Braak neurofibrillary tangles, and cerebral amyloidangiopathy, as well as total amyloid plaque burden in the superior frontal, superior parietal, occipital, and inferior temporal cortical regions. PET data were expressed as the standardized uptake value ratio with cerebellar reference. Analyses accounted for the interval between imaging and autopsy. This study found that all 18 patients met neuropathologic criteria for Lewy body disease; the DAT concentration was low in each case. All patients with elevated [11C]PiB retention measured in a neocortical aggregate had β-amyloid deposits at autopsy. [11C]PiB retention significantly correlated with neuritic plaque burden and with total plaque burden. [11C] PiB retention also significantly correlated with the severity of both Braak stages of neurofibrillary tangle and Lewy body scores. Neuritic plaque burden was significantly associated with neurofibrillary tangle pathology. The overall conclusion of the study was that antemortem [11C]Altropane PET is a sensitive measure of substantia nigra degeneration. [11C]PiB scans accurately reflect cortical amyloid deposits seen at autopsy. These findings support the use of molecular imaging in the evaluation of patients with Lewy body diseases.

Shirvan J, Clement N, Ye R, Katz S, Schultz A, Johnson KA, Gomez-Isla T, Frosch M, Growdon JH, Gomperts SN. Neuropathologic correlates of amyloid and dopamine transporter imaging in Lewy body disease. Neurology. 2019 Jul 30;93(5):e476-e484. doi: 10.1212/WNL.0000000000007855. Epub 2019 Jun 26. PubMed PMID: 31243072; PubMed Central PMCID: PMC6693430.

Cholinergic modulation of hippocampal calcium activity across the sleep-wake cycle. Calcium is a critical second messenger in neurons that contributes to learning and memory, but how the coordination of action potentials of neuronal ensembles with the hippocampal local field potential (LFP) is reflected in dynamic calcium activity remains unclear. Here, De Gomperts and collaborators recorded hippocampal calcium activity with endoscopic imaging of the genetically encoded fluorophore GCaMP6 with concomitant LFP in freely behaving mice. Dynamic

calcium activity was greater in exploratory behavior and REM sleep than in quiet wakefulness and slow wave sleep, behavioral states that differ with respect to theta and septal cholinergic activity and modulated at sharp wave ripples (SWRs). Chemogenetic activation of septal cholinergic neurons expressing the excitatory hM3Dq DREADD increased calcium activity and reduced SWRs. Furthermore, inhibition of muscarinic acetylcholine receptors (mAChRs) reduced calcium activity while increasing SWRs. These results demonstrate that hippocampal dynamic calcium activity depends on behavioral and theta state as well as endogenous mAChR activation.

Zhou H, Neville KR, Goldstein N, Kabu S, Kausar N, Ye R, Nguyen TT, Gelwan N, Hyman BT, Gomperts SN. Cholinergic modulation of hippocampal calcium activity across the sleep-wake cycle. Elife. 2019 Mar 7;8. pii: e39777. doi: 10.7554/eLife.39777. PubMed PMID: 30843520; PubMed Central PMCID: PMC6435325.

Clinical EEG slowing correlates with delirium severity and predicts poor clinical outcomes. The overall goal of this study was to determine which findings on routine clinical EEGs correlate with delirium severity across various presentations and to determine whether EEG findings independently predict important clinical outcomes. To accomplish this the group led by Dr Westover prospectively studied a cohort of nonintubated inpatients undergoing EEG for evaluation of altered mental status. Patients were assessed for delirium within 1 hour of EEG with the 3-Minute Diagnostic Interview for Confusion Assessment Method (3D-CAM) and 3D-CAM severity score. EEGs were interpreted clinically by neurophysiologists, and reports were reviewed to identify features such as theta or delta slowing and triphasic waves. Generalized linear models were used to quantify associations among EEG findings, delirium, and clinical outcomes, including length of stay, Glasgow Outcome Scale scores, and mortality. 200 patients were evaluated (median age 60 years, IQR 48.5-72 years); 121 (60.5%) met delirium criteria. The EEG finding most strongly associated with delirium presence was a composite of generalized theta or delta slowing (odds ratio 10.3, 95% confidence interval 5.3-20.1). The prevalence of slowing correlated not only with overall delirium severity ($R^2 = 0.907$) but also with the severity of each feature assessed by CAM-based delirium algorithms. Slowing was common in delirium even with normal arousal. EEG slowing was associated with longer hospitalizations, worse functional outcomes, and increased mortality, even after adjustment for delirium presence or severity. This study concluded that generalized slowing on routine clinical EEG strongly correlates with delirium and may be a valuable biomarker for delirium severity. In addition, generalized EEG slowing should trigger elevated concern for the prognosis of patients with altered mental status.

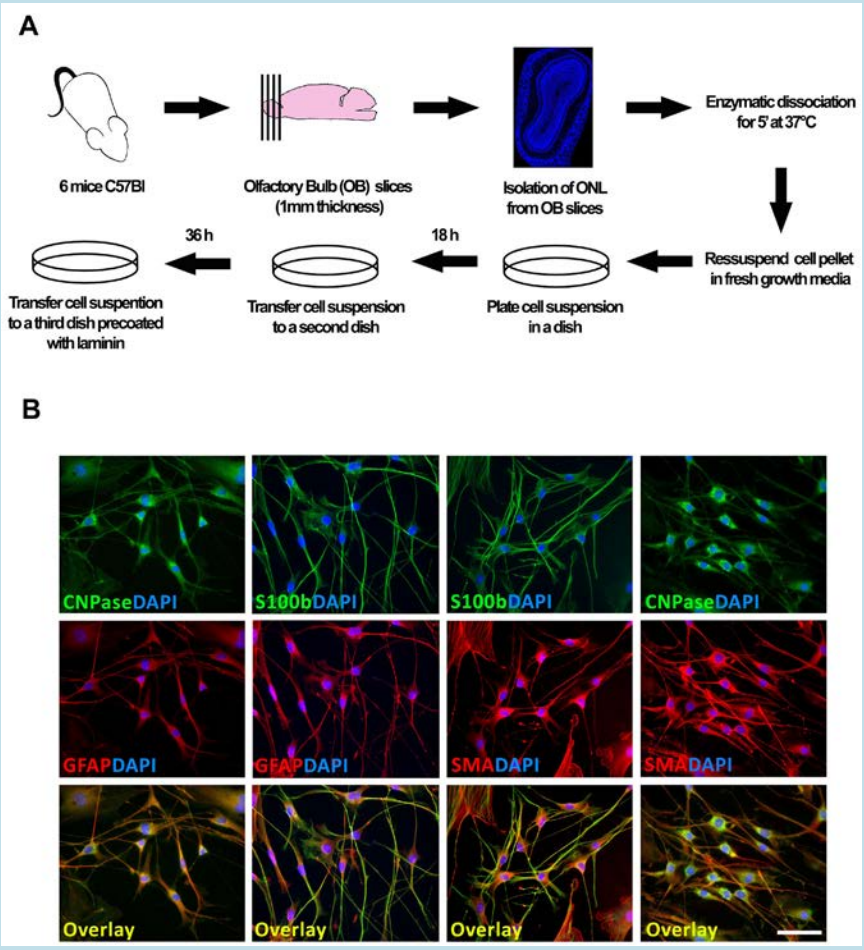
Kimchi EY, Neelagiri A, Whitt W, Sagi AR, Ryan SL, Gadbois G, Groothuysen D, Westover MB. Clinical EEG slowing correlates with delirium severity and predicts poor clinical outcomes. Neurology. 2019 Sep 24;93(13):e1260-e1271. doi: 10.1212/WNL.0000000000008164. Epub 2019 Aug 29. PubMed PMID: 31467255.

Radiation-Induced Targeted Nanoparticle-Based Gene Delivery for Brain Tumor Therapy. Targeted therapy against the programmed cell death ligand-1 (PD-L1) blockade holds considerable promise for the treatment of different tumor types; however, little effect has been observed against gliomas thus far. Effective glioma therapy requires a delivery vehicle that can reach tumor cells in the central nervous system, with limited systemic side effect. In this study, Dr. Tannous and collaborators developed a cyclic peptide iRGD (CCRGDKGPDC)-conjugated solid lipid nanoparticle (SLN) to deliver small interfering RNAs (siRNAs) against both epidermal growth factor receptor (EGFR) and PD-L1 for combined targeted and immunotherapy against glioblastoma, the most aggressive type of brain tumors. Building on recent studies showing that radiation therapy alters tumors for enhanced nanotherapeutic delivery in tumor-associated macrophage-dependent fashion, they showed that low-dose radiation primes targeted SLN uptake into the brain tumor region, leading to enhanced downregulation of PD-L1 and EGFR. Bioluminescence imaging revealed that radiation therapy followed by systemic administration of targeted SLN leads to a significant decrease in glioblastoma growth and prolonged mouse survival. This study combines radiation therapy to prime the tumor for nanoparticle uptake along with the targeting effect of iRGD-conjugated nanoparticles to yield a straightforward but effective approach for combined EGFR inhibition and immunotherapy against glioblastomas, which can be extended to other aggressive tumor types.

Erel-Akbaba G, Carvalho LA, Tian T, Zinter M, Akbaba H, Obeid PJ, Chiocca EA, Weissleder R, Kantarci AG, Tannous BA. Radiation-Induced Targeted Nanoparticle-Based Gene Delivery for Brain Tumor Therapy. ACS Nano. 2019 Apr 23;13(4):4028-4040. doi: 10.1021/acsnano.8b08177. Epub 2019 Mar 27. PubMed PMID: 30916923.

Olfactory Ensheathing Cells: A Trojan Horse for Glioma Gene Therapy. The olfactory ensheathing cells (OECs) migrate from the peripheral nervous system to the central nervous system (CNS), a critical process for the development of the olfactory system and axonal extension after injury in neural regeneration. Because of their ability to migrate to the injury site and anti-inflammatory properties, OECs were tested against

different neurological pathologies, but were never studied in the context of cancer. Here, Dr Tannous and colleagues evaluated OEC tropism to gliomas and their potential as a "Trojan horse" to deliver therapeutic transgenes through the nasal pathway, their natural route to CNS. To accomplish this OECs were purified from the mouse olfactory bulb and engineered to express a fusion protein between cytosine deaminase and uracil phosphoribosyltransferase (CU), which convert the prodrug 5-fluorocytosine (5-FC) into cytotoxic metabolite 5-fluorouracil, leading to a bystander killing of tumor cells. These cells were injected into the nasal cavity of mice bearing glioblastoma tumors and OEC-mediated gene therapy was monitored by bioluminescence imaging and confirmed with survival and ex vivo histological analysis. All statistical tests were two-sided. The study found that OECs migrated from the nasal pathway to the primary glioma site, tracked infiltrative glioma stemlike cells, and delivered therapeutic transgene, leading to a slower tumor growth and increased mice survival. At day 28, bioluminescence imaging revealed that mice treated with a single injection of OEC-expressing CU and 5-FC had tumor-associated photons (mean [SD]) of 1.08E + 08 [9.7E + 07] vs 4.1E + 08 [2.3E + 08] for control group (P < .001), with a median survival of 41 days vs 34 days, respectively (ratio = 0.8293, 95% confidence interval = 0.4323 to 1.226, P < .001) (n = 9 mice per group). This study shows for the first time that autologous transplantation of OECs can target and deliver therapeutic transgenes to brain tumors upon intranasal delivery, the natural route of OECs to the CNS, which could be extended to other types of cancer.



Isolation and characterization of olfactory ensheathing cells (OECs) from the mice olfactory bulb. *(Pictured to the left)* A) Schematic overview of OEC isolation from the mouse olfactory bulb. B) Phenotypic characterization of OECs by co-immunostaining for 2′,3′ cyclic nucleotide 3′-phosphodiesterase (CNPase), calcium-binding protein β (S100b) (green), smooth muscle α-actin (SMA), and glial fibrillary acidic protein (GFAP) (red). Nuclei were also stained with 6-diamidino-2-phenylindole (DAPI) (blue). Scale bar, 50 μm. ONL = olfactory nerve layer.

Carvalho LA, Teng J, Fleming RL, Tabet EI, Zinter M, de Melo Reis RA, Tannous BA. Olfactory Ensheathing Cells: A Trojan Horse for Glioma Gene Therapy. J Natl Cancer Inst. 2019 Mar 1;111(3):283-291. doi: 10.1093/jnci/djy138. PubMed PMID:30257000; PubMed Central PMCID: PMC6410949.

Amyloid Imaging of Dutch-Type Hereditary Cerebral Amyloid Angiopathy Carriers. The objective of this study, led by Dr. Greenberg, was to determine whether amyloid imaging with the positron emission tomography (PET) agent Pittsburgh compound B (PiB) can detect vascular β-amyloid (Aβ) in the essentially pure form of cerebral amyloid angiopathy associated with the Dutch-type hereditary cerebral amyloid angiopathy (D-CAA) mutation. PiB retention in a cortical composite of frontal, lateral, and retrosplenial regions (FLR) was measured by PiB-PET in 19 D-CAA mutation carriers (M+ ; 13 without neurologic symptoms, 6 with prior lobar intracerebral hemorrhage) and 17 mutation noncarriers (M-). Progression of PiB retention was analyzed in a subset of 18 serially imaged individuals (10 asymptomatic M+ , 8 M-). Associations between PiB retention and cerebrospinal fluid (CSF) Aβ concentrations in 17 M+ and 11 M- participants who underwent lumbar puncture and compared the findings to PiB-PET and CSF Aβ in 37 autosomal dominant Alzheimer disease (ADAD) mutation carriers were also analyzed. D-CAA M+ showed greater age-dependent FLR PiB retention (p < 0.001) than M- , and serially imaged asymptomatic M+demonstrated greater longitudinal increases (p = 0.004). Among M+ , greater FLR PiB retention associated with reduced CSF

concentrations of Aβ40 ($r = -0.55$, $p = 0.021$) but not Aβ42 ($r = 0.01$, $p = 0.991$). Despite comparably low CSF Aβ40 and Aβ42, PiB retention was substantially less in D-CAA than ADAD ($p < 0.001$). These studies indicate that Increased PiB retention in D-CAA and correlation with reduced CSF Aβ40 suggest this compound labels vascular amyloid, although to a lesser degree than amyloid deposits in ADAD. Progression in PiB signal over time suggests amyloid PET as a potential biomarker in trials of candidate agents for this untreatable cause of hemorrhagic stroke.

Schultz AP, Kloet RW, Sohrabi HR, van der Weerd L, van Rooden S, Wermer MJH, Moursel LG, Yaqub M, van Berckel BNM, Chatterjee P, Gardener SL, Taddei K, Fagan AM, Benzinger TL, Morris JC, Sperling R, Johnson K, Bateman RJ; Dominantly Inherited Alzheimer Network, Gurol ME, van Buchem MA, Martins R, Chhatwal JP, Greenberg SM. Amyloid Imaging of Dutch-Type Hereditary Cerebral Amyloid Angiopathy Carriers. Ann Neurol. 2019 Oct;86(4):616-625. doi: 10.1002/ana.25560. Epub 2019 Aug 12. PubMed PMID: 31361916; PubMed Central PMCID: PMC6876775

Bob S. Carter, MD, PhD, Chief

Massachusetts General Hospital's Department of Neurosurgery is one of the nation's leading neurosurgery centers, treating around 70-90 patients a day, and we perform more than 4000 neurosurgical procedures each year. This unique scale fuels a research enterprise that focuses on bringing cutting-edge science and technology to bear on the most difficult problems in the field of neuroscience. Indeed, across the diverse areas of neurosurgery practice (tumor, cerebrovascular, functional/epilepsy, spinal disorders, peripheral nerve, trauma, and pediatrics), a vision for integrating research into our centers is a hallmark of the department.

Functional neurosurgery

Dr. Mark Richardson was recruited to MGH as our new Director of Functional Neurosurgery and as leader of new collaborative initiative with the Department of Brain and Cognitive Sciences at MIT in neurosurgical brain modulation (see photo). He joins Dr. Ziv Williams, Co-Director of Functional Neurosurgery, and Director of the Neuronal Communication and Restoration Laboratory, and Dr. Jeffrey Schweitzer, Director of the Neurosurgery Stem Cell Therapeutics Laboratory, to create one of the nation's most innovative centers for functional neurosurgery, with leading clinical programs in surgical based care for epilepsy, movement disorders, psychiatric, and pain conditions. Dr. Richardson hails from the Epilepsy and Movement Disorders Surgery program at the University of Pittsburgh, where he launched the Brain Modulation Laboratory (www.brainmodulationlab.org), a human systems neuroscience lab that studies brain electrophysiology and cognition in patients undergoing surgery for epilepsy and movement disorders. The overall goal of Dr. Richardson's work has been to facilitate the optimization of brain modulation therapies and the discovery of novel neurobiological targets, by filling critical gaps in the understanding of human brain function.

In the developmental laboratory setting, work from Drs. Seung Woo Lee and Shelley Fried over the last few years has shown that implantable micro-coils are not only effective for driving neurons of the CNS but also that they have several important advantages over conventional micro-electrodes. Although magnetic stimulation is known to have several important advantages over electric stimulation, the shrinking of coils to a size that is safe for implantation into the brain was thought to render them ineffective. For example, the magnetic fields from coils induce electric fields that are spatially asymmetric and therefore, can be harnessed to selectively target specific types of neurons, e.g. vertically-oriented pyramidal neurons, without simultaneous activating other types, e.g. horizontally-oriented passing axons. The ability to avoid axons helps to tightly confine activation (around the coil) allowing for much better resolution with an implant . This benefit is particularly intriguing for implants that target sensory systems as better resolution translates to better acuity (with a visual prosthesis) or higher quality feedback (from feedback with brain-machine interfaces). Initial demonstrations of effectiveness were done in vitro and showed activation could be confined to single cortical columns. More recent in vivo testing has shown dramatic differences in the spatial extent of activation measured via cortical surface (epidural) electrodes. A second important advantage of micro-coils is that the magnetic fields they induce are highly permeable through all biological materials and thus, the foreign body responses and gliosis that plague conventional cortical electrode implants do not similarly diminish the effectiveness of coils. Current translation efforts include a cortical visual prosthesis to restore vision to the blind as well as a next-generation cochlear prosthesis (one that allows for a larger number of independent electrodes). The increased safety and better selectivity with micro-coils suggests they may also be more attractive for other Neural Engineering applications as well, including DBS and Brain-Computer Interfaces. This work is funded by the BRAIN Initiative (NIH/NINDS), the NIH (NEI) and by the DoD Vision Research Program. The work has been published in Science Advances, Nature Communications IEEE Transactions on Neural Systems and Rehabilitation Engineering, and IEEE Transactions on Biomedical Engineering.

Neurovascular neurosurgery

The neurovascular team including faculty members Drs. Paul Chapman, Chris Ogilvy, Aman Patel, Chris Stapleton, Bey Leslie-Mazwi, Josh Hirsch, Bob Carter, and Jim Rabinov analyzed 318 consecutive adult patients with brain AVMs treated at MGH with embolization, surgery, and/or proton beam radiosurgery. The 12 year MGH treatment results with five year follow up are much better than in the ARUBA Trial , suggesting that tertiary care centers with integrated programs, expertise in patient selection, and individualized treatment approaches may allow for better clinical outcomes. The work earned best abstract at World Federation of Interventional and Therapeutic Neuroradiology conference in 2019, and was published "Multimodal cerebral arteriovenous malformation treatment: a 12-year experience and comparison of key outcomes to ARUBA" in J Neurosurg. 2019 Nov 1:1-10. All three modalities of treatment are offered in MGH Neurosurgery.

Pediatric Neurosurgery

Drs. Beth Costine-Bartell and Tina Duhaime published the result of many years of work trying to develop a large animal model of one of the mystery conundrums in pediatric neurotrauma – the profound unilateral damage associated with subdural hematoma in babies, usually (but not exclusively) with child abuse, that wipes out one hemisphere and virtually spares the other. Dr. Duhaime started working on this model more than 15 years ago and optimized it over years until Dr. Costine-Bartell saw success with it as the closest approximation to date of so-called "hemispheric hypodensity", or "big black brain". This work serves as the basis of Dr. Costine-Bartell's current grants and has been featured in invited talks at meetings on child abuse and head injury in infants/young children, as the model may offer many clues to pathophysiology (such as possible spreading depolarization, maturation-dependent channel changes, and others) – and maybe treatments. This work has been published as "Development of a Model of Hemispheric Hypodensity ("Big Black Brain")" in J Neurotrauma. 2019 Mar 1;36(5):815-833.

Tumor Neurosurgery

In the MGH Brain Tumor Research Center, Drs. Sam Rabkin, Hiro Wakimoto, and Bob Martuza continue to explore new therapeutic strategies for the treatment of glioblastoma, using glioblastoma stem-like cells. This year they found that amplification of MYC or MYCN in glioblastoma stem-like cells induced sensitivity to poly(ADP-ribose) polymerase (PARP) inhibitors, FDA approved for the treatment of some breast and ovarian cancers, through suppression of CDK18 expression, a poorly understood cyclin-dependent kinase. CDK18 acts by activating ATR and homologous recombination to make the cells resistant to PARP inhibitors. Combining ATR and PARP inhibitors is effective in treating glioblastoma in mouse models, even in PARP inhibitor resistant tumors, and warrants clinical trial. This work has been published as Ning J, et al. "Myc targeted CDK18 promotes ATR and homologous recombination to mediate PARP inhibitor resistance in glioblastoma." in Nature Communications 10: 2910, 2019.

Additionally, in the Brain Tumor Center, faculty members Drs. Fred Barker, Will Curry, Pamela Jones and Dan Cahill, collaborating with Dr. Priscilla Brastianos of Neuro-Oncology, have provisioned an exciting new treatment approach for craniopharyngiomas. As a histologically benign lesion, these tumors can nonetheless cause high morbidity due to their cranial-base location, causing blindness and hypothalamic-pituitary dysfunction. Papillary craniopharyngiomas are characterized by BRAF V600E mutations. BRAF/MEK therapy can elicit a dramatic radiographic regression of these tumors, and the MGH team is leading a national trial of this therapeutic strategy (ClinicalTrials.gov Identifier: NCT03224767). Looking to the future, prediction of BRAF mutation status before definitive surgery could enable neoadjuvant treatment strategies. Studying 64 patients with craniopharyngioma, the team established a diagnostic rule for BRAF mutation and validated the rule in an independent cohort. Combining three clinical features (age older than 18 years, absence of calcification on routine head CT, and supradiaphragmatic tumor location) provided a sensitivity and specificity for the presence of BRAF mutation were 83% and 93%, respectively. In a validation cohort, the sensitivity was 100% and specificity was 89%. This rule may be useful in identifying patients who could potentially benefit from neoadjuvant BRAF V600E-targeted systemic therapies. This work was published in Neurosurgery. 2019 Aug 1;85(2):204-210. "A Clinical Rule for Preoperative Prediction of BRAF Mutation Status in Craniopharyngiomas."

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

The Yvonne L. Munn Center for Nursing Research (Munn Center) is designed to advance nursing science, foster inquiry and generate funding to promote the development and translation of nursing knowledge through original research and translation of evidence into practice. Nursing research investigations informed by the strategic goals within Patient Care Services (PCS) fosters original research that addresses patient response to illness, promotes the understanding and meaning of the human experience in health and illness and explores issues around Health Promotion and Wellness, Symptom Science (e.g. pain management, wound care), Ethics in Clinical Practice, Complimentary Healing Modalities and Workforce Evaluation. The work of the Munn Center is led by the Director Dr. Gaurdia Banister and facilitated by a team of Nurse Scientists that facilitate the goals of the Center across nursing and other disciplines within PCS.

There are four strategic goals that help to guide the work of the Munn Center. These goals are articulated through a plan that includes specific objectives. Interventions and outcomes are reviewed annually. Examples of these goals and related activities are included below:

GOAL 1: Facilitate MGH nurses' participation in the development of nursing knowledge that aligns with the goals of MGH and Patient Care Services. Objective: Clearly, articulate Nurse eligibility criteria for internal and external grant funding opportunities for dissemination to the broader research community; Seek new funding opportunities aligned with advancing nursing science.

GOAL 2: Foster opportunities within the MGH Research Institute to enhance the unique contributions of nursing science. Objectives: Maintain membership on ECOR, the Research Council and Committee of Clinical Research; Obtain membership on other appropriate committees with established guidelines for research funding, education, and training opportunities for scientists in the MGH community. i.e. ECOTE.

GOAL 3: Partner with academic and clinical settings and industry to improve the health and well-being of the communities we serve. A. Strengthen ties with academic partners. Objective Revise criteria for External Faculty Nurse Scientists (EFNSs) initial and continued appointment to the Munn Center; Continue appointments of EFNSs to the Munn Center. B. Share nursing research resources across practice settings external to PCS. Objectives: Increase participation of nurses from throughout HMS affiliated hospitals in research opportunities, and Center-led initiatives such as Nursing Research Day and Nursing Research Grand Rounds; Share nursing research interests with the MGH research community; Seek out investigators with shared interests.

GOAL 4: Expand the impact of nursing science through the development of financial resources that improve patient care delivery and outcomes. Objectives: Efficient use of Munn Nurse Scientist expertise to support the mission of PCS; Build collaborative research relationships that allow nurses to be Principal and Co-Investigators on funded studies; Identify data sources for inclusion in existing PCS data warehouse (e.g. SPWEI, PCA-WES, Job Enjoyment, Disruptive Behavior Scale) for use in research and evaluation.

The Munn Center for Nursing Research has actively been working to advance nursing research that will improve patient and family care outcomes and fosters an in environment of inquiry for all nurses at the MGH. Nurses participate in the development, use and translation of research and evidence to optimize the delivery of nursing care grounded in knowledge and inquiry. Nurses with research-intensive doctoral preparation (e.g. PhD) are involved in the development of original research, mentor other nurses and collaborate with other disciplines to generate original research. Nurses with a doctorate in practice (DNP) lead, mentor and facilitate the translation of evidence into practice.

The Doctoral Forum is an important opportunity to help advance nursing inquiry through discussion and development of innovative approaches to nursing inquiry. This year the group has been discussing the development of a model to articulate the unique role of doctorally prepared nurses (DNP and PhD) in advancing a research intensive, evidence driven practice environment for all nurses. The ultimate outcome of such initiative builds research in areas that support the strategic goals of nursing/organization, facilitates the translation of nursing research into practice and promotes collaboration with other disciplines to participate in scholarly inquiry to enhance patient care outcomes.

Highlights for 2019

There are 4 Key achievements accomplished by the Munn Center in 2019 that include A) Partnership Activities, B) Workforce Evaluation research; C) Nursing Research Grand Rounds and D1) Nursing Research Day and D2) Grant Funding.

A. Partnerships- The Munn Center works with multiple groups to facilitate a nursing research agenda. Currently, the Center has 37 Partnerships with 26 institutions and has 51 senior ENFSs who participate in mentoring staff in the conduct of research and evidence -based practice initiatives and present research in multiple forums across the year.

B. Workforce Evaluation - Multiple instruments have been developed, tested, revised, and translated by nurses at MGH and research teams in the Munn Center to evaluate professional practice and staff satisfaction in the workplace. These instruments are available on the Munn website and can be requested for use in research investigations by contacting SGOODRIDGE@partners.org. Examples of the available instruments include:

Table I - Instruments to Evaluate Professional Practice and Staff Satisfaction in the workplace

The Professional Practice Environment Tool, (PPE, 2004)
The Revised Professional Practice Environment tool, (RPPE, 2013)
The Professional Practice Work Environment Inventory, (PPEWI, 2017)
The Patient Care Associate's Work Environment Scale, (PCA-WES,2015)
Power Influencing Professional Practice Change Scale PIPPCS, (2020- in publication)

The Staff Perception of the Professional Practice Environment survey (SPPPE, 2019) is administered to over 5,000 staff within Patient Care Service (PCS). Results provide PCS leadership and staff with information that can inform strategic planning and decision making within the organization. Data from this survey and other data sources are being identified for inclusion in PCS Data Warehouse to advance data-driven care delivery and workforce evaluation.

C) Nursing Research Grand Rounds 2019 - Nursing Research Grand Rounds provide nurses an opportunity to share research findings from clinical investigations. During 2019 there were three Grand Rounds presented. Examples include: a) "Understanding parental research participation in the neonatal intensive care unit (NICU) and special care nursery (SCN)" Kim Francis PhD, RN, PHCNS-BC; MGH Infectious Disease Associates, MGH and b) "Understanding Patient Engagement in Breast Cancer Survivorship Care: A National Web-Based Survey" Kathryn E. Post, PhD(c), MS, ANP-BC; Radiation Oncology GI/GYN Services, MGH

D1) Nursing Research Day - Nursing Research Day is a special event within Nurse Recognition Week each May, designed to celebrate nurses who have been involved in original research investigations or evidence –based practice studies. There were 42 abstracts submitted for presentation. Recognition is given to the best posters in the categories of original research, evidence-based practice and quality improvement. The keynote speaker for the 2019 Nursing Research Day was Diane Carroll, PhD, RN, FAHA, FESC, FAAN, a Nurse Scientist at the Munn Center who presented her journey in nursing research, who emphasized the importance of mentorship in supporting the next generation of nurse researchers.

Award co-chair Kim Francis, PhD, RN, PHCNS-BC presented the Yvonne L. Munn Nursing Research Grant to Principal Investigator J. Heidi Jupp, RN, for her study, Validation of a Nausea Assessment Tool in a Pediatric Oncology Population: A Pilot Study in 28 Pediatric Cancer Patients. Also pictured are Rhonda McIntyre, RN (co-investigator) and Jennifer Cahill, PhD, RN (mentor).

Poster Awards

- Maria Michelle Van Pelt, RN; Suzanne Smeltzer, RN; Frederick van Pelt, MD; Farnaz Gazoni, MD; Marcel Durieux, MD; and Rosemary Polomano, RN, won in the category of Advanced/ Mid- Career Nurse Researcher for their poster, "Preliminary Psychometric Evaluation of the Nurse Anesthesia and the Aftermath of Perioperative Catastrophes Survey and Ways of Coping Questionnaire."
- Meghan Noonan Feldpausch, RN; Emma Kileel; Markella Zanni, MD; Sara Looby, RN; Steven Grinspoon, MD; and Kathleen Fitch, RN, won in the category of Emerging Researcher for their poster, "Retention of Research Participants in a Longitudinal HIV Clinical Trial: Best Practices Identified by Systematic Surveys of Study Staff."
- Kathryn Post, RN, won in the category of Original Research for her poster, "Patient Engagement in Breast Cancer Survivorship Care: A National Web-Based Survey."
- Shelly Stuler, RN, and Judi Carr, RN, won in the category of Quality Improvement for their poster, "Improving Consistency and Accuracy in Pressure-Injury Documentation."

- Christina Murphy, RN; Laura Gaudet, RN; Susan Gavaghan, RN; Maria Winne, RN; Regina Gibbons; and Virginia Capasso, RN, won in the category of Evidence-Based Practice for their poster, "Effectiveness of acupuncture/acupressure in the patient with acute pulmonary needs."
- Yvonne L. Munn Grant supports research studies initiated by MGH staff nurses to advance nursing science and improve outcomes for patients and families.

D2) Additional Grant Awards Presented during 2019- The Jeanette Ives Erickson Award

The Jeanette Ives Erickson-Research Institute Grant Promoting Excellence in Patient Care is given annually to a mid-career, PhD-prepared, nurse researcher dedicated to inquiry that improves patient and family outcomes.

Jeanette Ives Erickson DNP, RN, NEA-BC, FAAN, Susan Slaugenhaupt, PhD, and Maurizio Fava, MD presented the Jeanette Ives Erickson – Research Institute Grant to Principal Investigator Katherine Rosa, PhD, CNP, FNP-BC for her study, Psychometric Evaluation of a Tool to measure Patients' Perceptions of Nurse-Patient Relationship as Healing Transformations Scale (RELATE Scale).

National Institute of Occupational Safety and Health (NIOSH) - National Institute of Occupational Safety and Health (NIOSH) - award is supported by the Occupational Health Services and the Harvard Center for Work Health and Well-being. The grant supports studies initiated by MGH nurses for the purpose of advancing science related to the healthcare workforce and improving outcomes for patient care workers by integrating occupational safety and health protection with health promotion to prevent worker injury and illness and to advance health and well-being.

Connell Nurse-Led Team Grant- This grant offers a PhD-prepared nurse the opportunity to lead a multidisciplinary research team in a clinically relevant investigation. The research proposal builds upon the nurse investigator's past work and research trajectory. The proposed science compliments an area(s) of research interest identified by the Munn Center. The goals of the Connell Nurse-Led Team Research Grant include but are not limited to: Advancing

Jane Flanagan PhD, ANP-BC, AHN-BC, FAAN presented the Be Well Work Well Nursing Grant to Principal Investigator Jennifer Repper DeLisi, MSN, RN, PCNS, and team members Robin Lipkis-Orlando MS, RN, NE-BC (co-Investigator), Colleen Gonzales, MSN, RN, NE-BC (co-Investigator; not pictured), and Colleen Snydeman, PhD, RN, NE-BC (mentor; not pictured) for their study, Creating a safe and supportive culture for the nursing workforce: Evaluation of the Staff Perception of Disruptive Patient Behavior Scale as a tool to measure change in staff experience.

Nursing

Department Report

Dorothy Jones, Ed.D., ANP, FAAN presented the Connell Nurse-Led Team Research Grant to Principal Investigator Amanda Coakley, PhD, RN, FNAP, AHN-BC and team Dana Cvrk, MS, CNM; Heather Fraser BSN, RN, Jennifer Healy, BSN, RN, ATC, Emily Dexter BSN, RN, (not pictured) Michele O'Hara, DNP, RN, NE-BC, Joanne Empoliti MSN, RN, ANP-BC, B. Robert Young, RPh (not pictured), Tanya John (Medication Safety Coordinator, not pictured) for their study, Exploring the experience of an aromatherapy intervention in the acute care setting.

nursing science; promoting collaborative research across providers and disciplines; and extending interdisciplinary and intraprofessional research.

Connell Postdoctoral Fellowship in Nursing Research- This postdoctoral fellowship is a unique opportunity within the Munn Center, to support postdoctoral training for a nurse researcher at MGH. The three-year fellowship provides developmental support and resources to advance nursing research in Symptom Science and Nursing Workforce Evaluation. The program's overall objective is to cultivate expertise among nurses in the conduct of clinical studies that will improve patient care delivery. Kirsten Dickins, PhD, AM, MSN, FNP-C is the inaugural recipient of the Connell Postdoctoral Fellowship and will be mentored by Dr. Sara Looby, a Nurse Scientist in Munn Center. Kirstin received her PhD in Nursing Science at Rush University in Chicago, Illinois. Her dissertation focused on primary care access and use patterns among homeless persons, seeking to better understand the facilitators and barriers to establishing and maintain a regular source of care. Kirsten Postdoctoral Fellowship experience will build upon this work while focusing on designing interventions that can improve preventive care and chronic disease management among difficult to engage patient populations, such as homeless persons. She seeks to increase her understanding of health inequities experienced by patients at the social margins and work to develop viable solutions to addressing the impact of chronic diseases in underserved groups, including homeless women.

Kirsten Dickins PhD, AM, MSN, FNP-C is the inaugural Connell Postdoctoral Fellow in Nursing Research

Jeffrey L. Ecker, MD, Chief

Research in Obstetrics and Gynecology at MGH

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

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

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

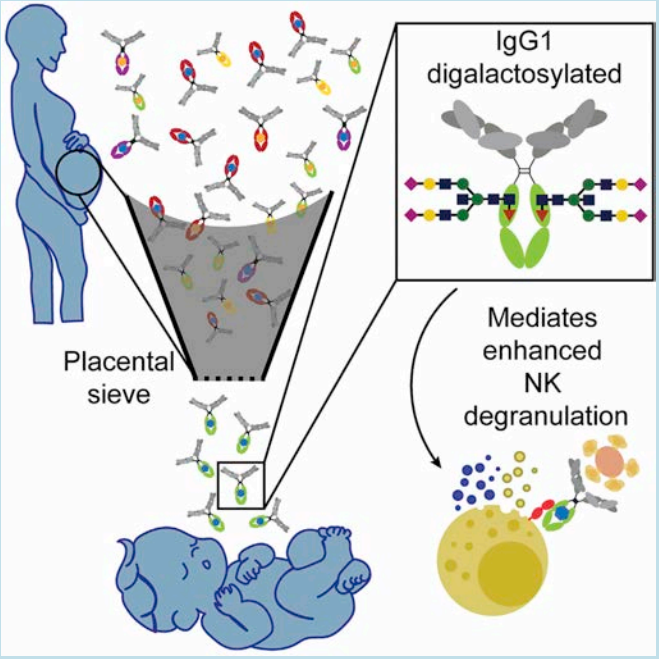
Mass General Global OB/GYN integrates three core missions to address the unmet promise of health care for all women throughout the world by providing care, organizing education and trainings, and conducting research and leading innovation. We strive to ensure that our efforts are guided by locally relevant needs of our partners and the women they serve to help address the unmet promise of health care for all women throughout the world. Within the research arena, Global OB/GYN at Mass General carries out it's mission by conducting innovative and locally-relevant scientific studies to widen the evidence base for the care of women in resource-poor settings both domestically and abroad.

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

Achievements:

Jennewein MF, Goldfarb I, Dolatshahi S, Cosgrove C, Noelette FJ, Krykbaeva M, Das J, Sarkar A, Gorman MJ, Fischinger S, Boudreau CM, Brown J, Cooperrider JH, Aneja J, Suscovich TJ, Graham BS, Lauer GM, Goetghebuer T, Marchant A, Lauffenburger D, Kim AY, Riley LE, Alter G. Cell. 2019 Jun 27;178(1):202-215.e14. doi: 10.1016/j.cell.2019.05.044. Epub 2019 Jun 13. PMID: 31204102. PMCID: PMC6741440.

Abstract: Despite the worldwide success of vaccination, newborns remain vulnerable to infections. While neonatal vaccination has been hampered by maternal antibody-mediated dampening of immune responses, enhanced regulatory and tolerogenic mechanisms, and immune system immaturity, maternal pre-natal immunization aims to boost neonatal immunity via antibody transfer to the fetus. However, emerging data suggest that antibodies are not transferred equally across the placenta. To understand this, we used systems serology to define Fc features associated with antibody transfer. The Fc-profile of neonatal and maternal antibodies differed, skewed toward natural killer (NK) cell-activating antibodies. This selective transfer was linked to digalactosylated Fc-glycans that selectively bind FcRn and FCGR3A, resulting in transfer of antibodies able to efficiently leverage innate immune cells present at birth. Given emerging data that vaccination may direct antibody glycosylation, our study provides insights for the development of next-generation maternal vaccines designed to elicit antibodies that will most effectively aid neonates.

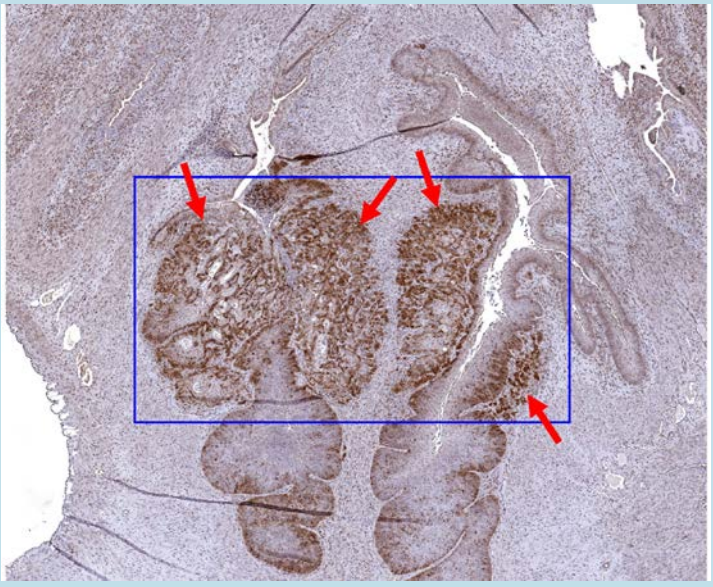


Antibodies with a specific glycan modification and with the ability to activate NK cells are selectively transferred across the placenta to the neonate.

He C, Lv X, Huang C, Angeletti PC, Hua G, Dong J, Zhou J, Wang Z, Ma B, Chen X, Lambert PF, Rueda BR, Davis JS, Wang C. A Human Papillomavirus-Independent Cervical Cancer Animal Model Reveals Unconventional Mechanisms of Cervical Carcinogenesis. Cell Rep. 2019, 26(10):2636-2650.e5. doi: 10.1016/j.celrep.2019.02.004. PMID: 30840887. PMCID: PMC6812687.

Abstract: HPV infections are common in healthy women and only rarely cause cervical cancer, suggesting that individual genetic susceptibility may play a critical role in the establishment of persistent HPV infection and the development of cervical cancer. Here, we provide convincing in vitro and in vivo evidence showing that differential expression and activation of YAP1 oncogene determine individual susceptibility to HPV infection and cervical carcinogenesis. We found that hyperactivation of YAP1 in mouse cervical epithelium was sufficient to induce invasive cervical cancer. Cervical epithelial cell-specific HPV16 E6/E7 and YAP1 double-knockin mouse model demonstrated that high-risk HPV synergized with hyperactivated YAP1 to promote the initiation and progression of cervical cancer. Our mechanistic studies indicated that hyperactivation of YAP1 in cervical epithelial cells facilitated HPV infection by increasing the putative HPV receptor molecules and disrupting host cell innate immunity. Our finding reveals an unconventional mechanism for cervical carcinogenesis.

Edlow AG, Guedj F, Sverdlov D, Pennings JLA, Bianchi DW. Significant Effects of Maternal Diet During Pregnancy on the Murine Fetal Brain Transcriptome and Offspring Behavior. Front Neurosci. 2019; 13:1335. doi: 10.3389/fnins.2019.01335. eCollection 2019. PMID: 31920502. PMCID: PMC6928003.

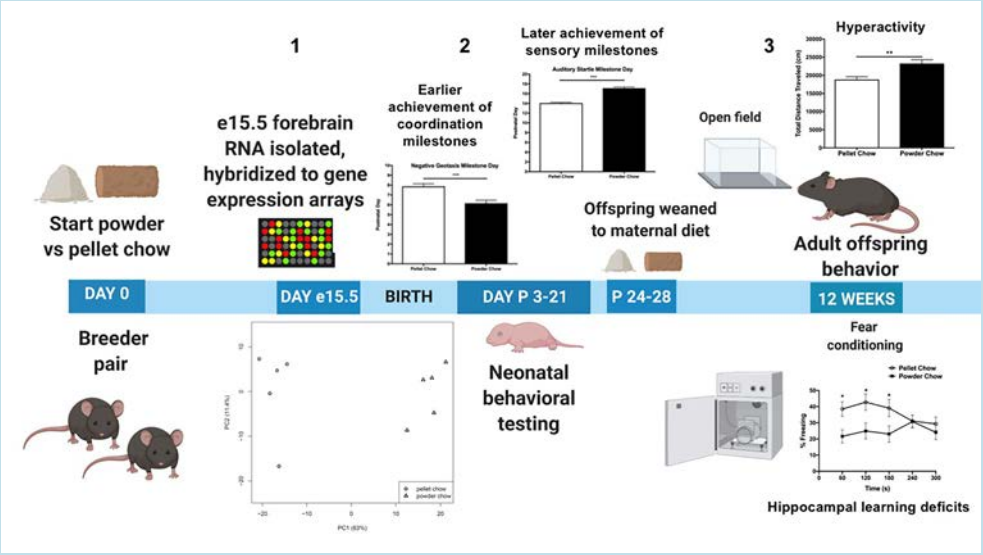


Representative image showing the initiation of invasive cervical cancer (red arrows) from the epithelium of the cervical transformation zone (blue rectangle) in the KRT14-YAPS127A mice. Expression of YAP1 (in brown) in cervical tissue was detected by immunohistochemistry. Nuclei were counter-stained with hematoxylin.

Abstract: Our laboratory has primarily focused on the impact of maternal obesity and high-fat diet in pregnancy on fetal brain development and long-term consequences for offspring behavior. In this investigation, we wanted to examine the impact of two commercially-available chow maternal diets on fetal brain development and offspring behavior, using a C57Bl/6 mouse model. The two diets differed primarily with respect to micronutrient content, with the powdered chow diet relatively deficient in micronutrients compared to the pelleted chow diet.

We evaluated the impact of maternal diet on fetal brain development and offspring behavior using a combination of fetal brain transcriptomics, a validated neonatal behavioral scale, and neurobehavioral testing of adult offspring with fear conditioning (to evaluate hippocampal learning), open field test (to evaluate locomotor behavior) and Rotarod test (to evaluate motor coordination).

We found that a maternal diet relatively deficient in micronutrients was associated with significant dysregulation of fetal brain global gene expression at embryonic day 15.5 (1647 differentially-regulated fetal brain genes). Maternal pregnancy diet accounted for 63% of the variation in fetal brain gene expression. Functional analyses identified



Experimental timeline and results: Relative to pelleted diet, a maternal powder chow diet which is relatively deficient in micronutrients is associated with: 1) more than 1600 genes dysregulated in the embryonic day 15.5 brain (principal component analysis demonstrates strong clustering of fetal brain gene expression by maternal pregnancy diet, with maternal pregnancy diet accounting for 63% of the variation in fetal brain gene expression); 2) more rapid acquisition of strength/coordination-related neonatal milestones (negative geotaxis depicted), and delayed acquisition of sensory maturation reflexes (auditory startle depicted); 3) Increased locomotor activity (increased total distance traveled on the open field test) and hippocampal learning deficits (reduced freezing on day 2 of fear conditioning) in adults. e, Embryonic day; P, Postnatal day.

significant upregulation of canonical pathways involved in cell cycle regulation, synaptic plasticity, and sensory nervous system development in the fetal brain, and significant downregulation of pathways related to cell and embryo death. Pathways related to DNA damage response, brain immune response, amino acid and fatty acid transport, and dopaminergic signaling were significantly dysregulated. There were no differences between groups with respect to maternal weight gain in pregnancy, nor in embryo/neonatal weight trajectories.

On neonatal behavioral testing, neonates exposed to the micronutrient-deficient maternal diet achieved coordination- and strength-related milestones significantly earlier, but had significant delay in acquisition of sensory maturation reflexes. On adult behavioral testing, the micronutrient-deficient-exposed offspring exhibited hyperactivity and hippocampal learning deficits.

We concluded that in wild-type offspring, two diets that differed primarily with respect to micronutrient composition had significant effects on the fetal brain transcriptome, neonatal and adult behavior. These effects did not appear to be mediated by alterations in gross maternal nutritional status nor fetal/neonatal weight. Maternal dietary content is an important variable to consider for investigators evaluating fetal brain development and offspring behavior.

Kaimal AJ, Grobman WA, Bryant A, Blat C, Bacchetti P, Gonzalez J, Thiet MP, Bermingham Y, Kuppermann M. The association of patient preferences and attitudes with trial of labor after cesarean. J Perinatol. 2019 Oct;39(10):1340-1348. doi: 10.1038/s41372-019-0399-5. Epub 2019 Jul 3. Erratum in: J Perinatol. 2019 Dec;39(12):1696. PubMed PMID: 31270433.

Anjali Kaimal, MD, MAS, Chief, Division of Maternal-Fetal Medicine, Director, Deborah Kelly Center for Clinical Research in Obstetrics and Gynecology.

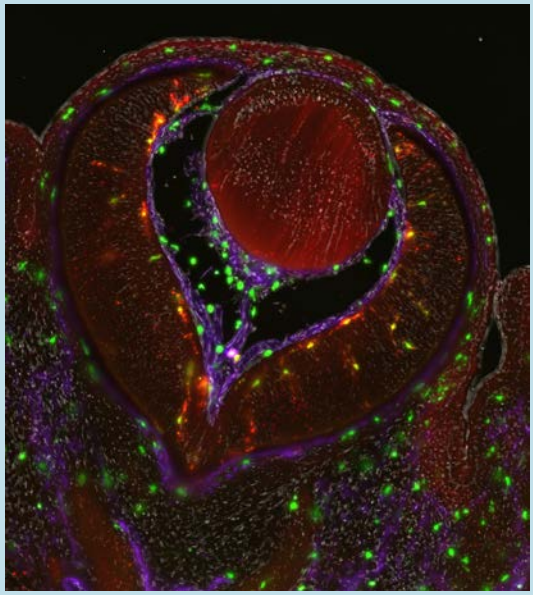
Abstract: The cesarean delivery rate in the United States was 31.9% in 2018, as compared to 20.7% in 1996. This change has been associated with substantial increases in maternal morbidity; safely decreasing the cesarean rate therefore has been identified as an important public health goal. Elective repeat cesarean deliveries (ERCD) contribute significantly to the cesarean rate, resulting from the combination of a high rate of primary CD and a relatively low rate of vaginal birth after cesarean (VBAC), which was 13.3% in 2018 as compared to a high of 28.3% in 1996. In general, the decline in VBAC is attributable to a decline in trial of labor after cesarean (TOLAC), rather than to decreasing rates of VBAC in the setting of TOLAC. A substantial portion of this decrease is related to women foregoing TOLAC even when they are appropriate candidates and this option is available to them. Understanding the impact of patient preferences, attitudes, and perceived social norms on the decision for TOLAC or ERCD and systematically incorporating this information into counseling are important parts of ensuring the delivery of high-quality care to all women. This study sought to evaluate the association of patient preferences (utilities) and attitudes with TOLAC among a

diverse population of English- or Spanish-speaking, TOLAC-eligible pregnant women. We found that strength of preference for vaginal delivery and value placed on the experience of labor and vaginal birth, along with endorsement of TOLAC by the person whose opinion they valued most (other than their provider) were associated with undergoing TOLAC. While discussion of complications of uterine rupture is often a focus in counseling regarding TOLAC, the mean utility scores that participants who underwent TOLAC and ERCD assigned to the maternal and neonatal outcomes associated with uterine rupture did not differ significantly, indicating that both groups are similarly concerned about avoiding these devastating but rare complications. However, the strength of preference for vaginal delivery did differ significantly between groups. These findings suggest that for patients, as for providers, the likelihood of vaginal delivery may be a more critical factor in determining a woman's choice of approach to delivery after prior cesarean than the risk of potential complications. We also found that addition of a measure of patient perception of their provider's opinion attenuated the impact of the opinion of the "important other" but did not affect the relationship between the preference and attitude measures and TOLAC, suggesting that the individual woman's preferences and attitudes remain key determinants of delivery approach. Coupled with the fact that a significant proportion of the participants in our study ultimately chose ERCD despite their initial stated preference for vaginal delivery, they suggest an opportunity for enhanced decision support to ensure that women and their families have the data they need to express informed preferences and participate in shared decision-making regarding TOLAC and ERCD.

Joan W. Miller, MD, Chief

The research mission of the Mass. Eye and Ear/MGH Department of Ophthalmology is focused on eliminating blinding diseases and disorders of the eye and visual system. Tackling blinding diseases using a multifaceted, multidisciplinary approach has been the mainstay of the Department's past success in translational medicine. This approach has led to groundbreaking advancements such as proton beam irradiation, photodynamic therapy, anti-VEGF therapies, the Boston Keratoprosthesis, which together have saved sight or improved vision for millions of people worldwide. The Department's commitment to translational medicine extends into gene-based therapies, with Mass. Eye and Ear serving as a lead site for the first CRISPR-based, gene editing clinical trial for retinal degeneration associated with Leber congenital amaurosis 10 (LCA10). Today, scientific collaboration and information—leveraged from modern genetics and genomics—are accelerating our understanding of blinding diseases and revealing new targets for therapy. Capitalizing on this momentum, the department's research strategy focuses on areas of greatest unmet medical need, including retinal degenerations, macular degeneration, and diabetic eye disease, as well as optic neuropathies, particularly glaucoma. Programs in other areas—cornea and ocular surface, oncology, immunology, infectious disease, and vision rehabilitation—are also an important focus.

Going forward, we are pursuing a range of promising research areas, including artificial intelligence, big data, genetics and gene-based therapy, imaging, and other diagnostic technologies. We are confident that treatment breakthroughs and cures are imminent for many blinding diseases. Highlighted accomplishments for the Department of Ophthalmology in 2019 are grouped thematically below:



Microglia entry in the developing eye. Retinal microglia populating the retina at embryonic day (E) 15.5. Cross section of the developing eye CX3cr1GFP/+ (green) mice mark embryonic yolk sack derived immune cells infiltrating the ocular globe. Microglial marker P2ry12 (red) depicts early microglia entering the superficial neuroretina. DAPI (white) stained nuclei and early blood vessels (CD31, blue) are also depicted.

Cover image for PNAS; from Okunuki, et al., PNAS. 116(20):9989-9998, 2019. (Connor lab).

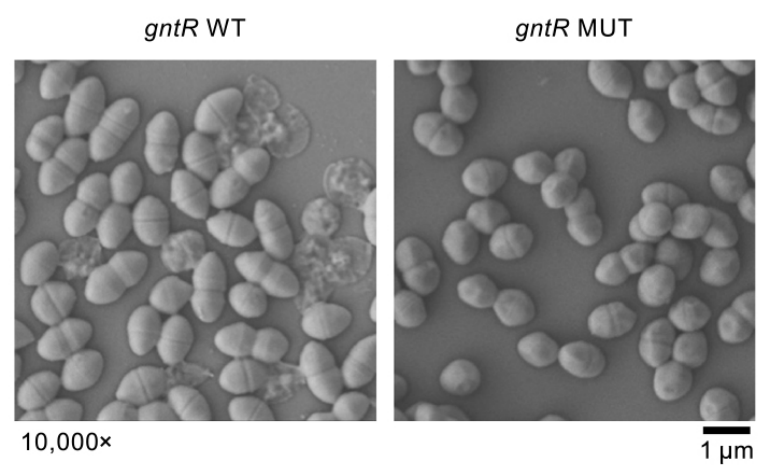
Neural Degeneration/Inflammation

Co-first author Joseph Arboleda-Velasquez, MD, PhD and a team of researchers identified a presenilin 1 (PSEN1) mutation carrier from the largest autosomal dominant Alzheimer's disease kindred in the world, who did not develop cognitive impairment until her seventies—three decades after the expected age of clinical onset. The collaboration across multiple institutions, including Mass. Eye and Ear, Mass General Hospital, the University of Antioquia, and Banner Alzheimer's Institute, demonstrated that the individual had two copies of the very rare APOE3 Christchurch (R123S) mutation, and in spite of unusually high brain amyloid levels, had limited tau accumulation and neurodegeneration. These findings have implications for the role of APOE in the pathogenesis, treatment, and prevention of Alzheimer's disease, and may have application to protection against other neurodegenerations, such as age-related macular degeneration (AMD) or inherited retinal disorders (IRD) (Arboleda-Velasquez, et al., Nature Medicine 25: 1680-1683, 2019).

Work from the laboratory of Kip Connor, PhD, demonstrated that microglia, the resident immune cells in the retina thought to initial retinal inflammation, are essential for the induction of a retinal inflammatory repsonse in a preclinical model of autoimmune uveitis. In response to disease induction, microglia closely associate with the retinal vasculature and facilitate inflammatory immune cell entry past the blood-retina barrier. When microglia are ablated, the circulating immune cells cannot enter the retina, and autoimmune uveoretinitis does not develop (Okunuki, et al., PNAS 116(20):9989-9998, 2019). These findings illustrate that microglia play a critical role in regulating infiltration of inflammatory cells into the retina and offer a potential therapeutic target for the treatment of autoimmune uveitis, a sight-threatening oculuar inflammatory disease that occurs in a variety of diseases such as Bechet's disease, sarcoidosis, and Vogh-Koyanagi-Harada disease, among others.

Antibiotic Resistance

A team led by Michael Gilmore, PhD analyzed the genomes of strains of the multidrug-resistant bacteria Enterococcus faecalis that had been archived from an early outbreak of bloodstream infection in a hospital ward in the mid-1980s. Mutations in a small number of loci, including



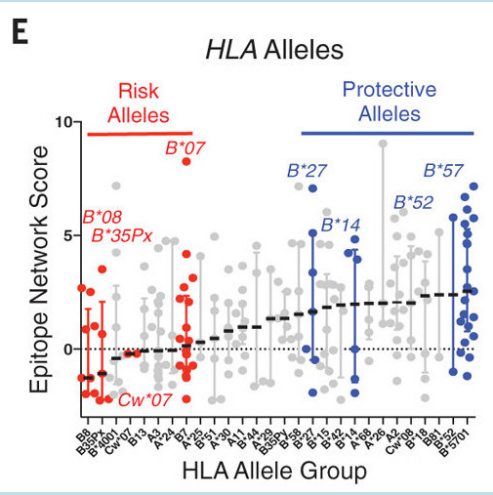
Scanning electron micrographs of gntR WT and MUT E. faecalis strains in culture.

Figure adapted from Van Tyne, et al., Sci Trans Med. 11(487): eaat8418, 2019. (Gilmore lab).

a little studied polysaccharide utilization pathway and the cydABCD locus, rendered E. faecalis better able to withstand antibiotic pressure and innate immune defenses in the human bloodstream (Van Tyne, et al., Science Translational Medicine 11(487): eaat8418, 2019). The findings from this study may help scientists and physicians develop new ways to prevent and manage nosocomial enterococcal infections.

Molecular Mechanisms of Viral Replication and Cellular Entry

Two recent studies from Mass. Eye and Ear address different aspects of viral replication and cellular entry. The first study focused on infection, with co-first author Elizabeth Rossin, MD, PhD, and a team of researchers using a novel approach to identify specific amino acids in the protein structure of HIV that appear critical to the ability of the virus to function and replicate. The collaboration across multiple institutions, including Mass. Eye and Ear, the Ragon Institute of Mass General Hospital, Massachusetts Institute of Technology, and Harvard University, found that the immune system of individuals who are naturally able to control HIV infection target these amino acids with pathogen-killing CD8 T cells, an event seen even in controllers who do not carry versions of the HLA-B protein previously associated with HIV control. These findings could guide the development of broadly protective vaccines to prevent and suppress HIV infection (Gaiha, et al., Science 364(6439):480-484, 2019).



Median epitope network scores of protective HLA alleles, as defined by GWAS, are statistically higher than those of neutral or risk alleles. Ranked median epitope network scores for individual HLA alleles (median, interquartile range). GWAS-defined protective (blue) and risk (red) HLA alleles

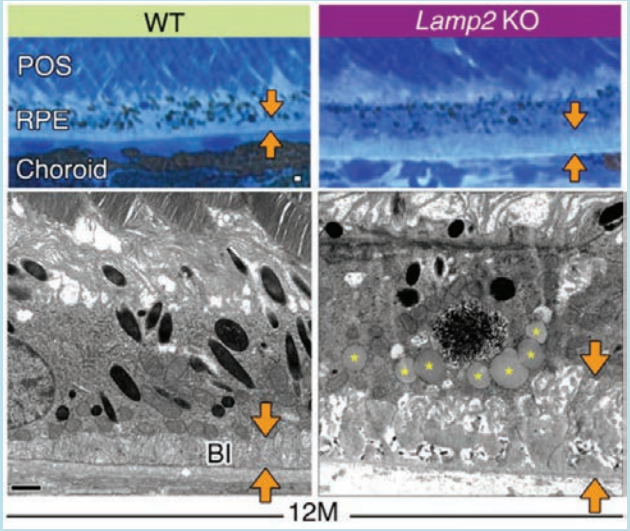
Figure adapted from Gaiha, et al., Science. 364(6439): 480-484, 2019. (Rossin).

Focused on gene-based therapies, the second study from the laboratory of Luk Vandenberghe, PhD, identified that GPR108, a G protein-coupled receptor, as an entry factor for adeno-associated virus (AAV). AAV vectors are the most commonly used viral vectors for in vivo gene therapy, and have shown promise transporting genetic therapy treatments to affected tissues. Since gaining cellular access is a critical step in the delivery of gene therapy, this discovery may provide a crucial piece of information to enable scientists to better predict, and ultimately, direct AAV-mediated gene transfers to specific tissues (Dudek, et al., Molecular Therapy Nov 13: S1525-0016(19)30501, 2019).

Retinal Diseases, Including Age-related Macular Degeneration (AMD)

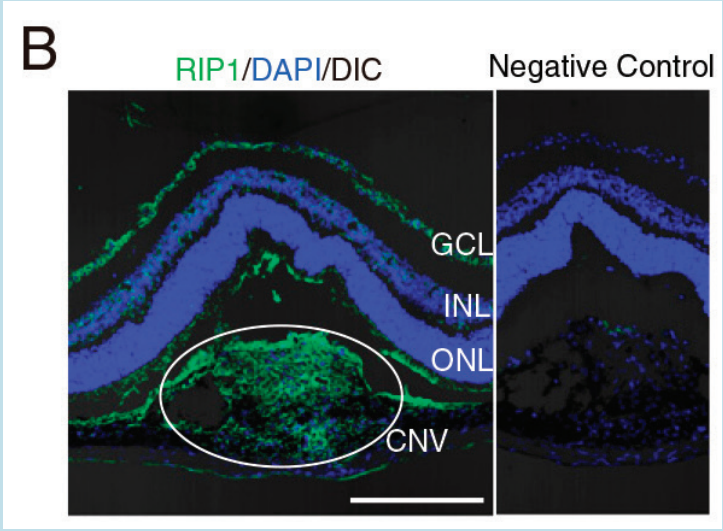
Researchers from the laboratory of Demetrios Vavvas, MD, PhD, examined the role of lysosome-associated membrane protein-2 (LAMP2), a glycoprotein known to be critical in lysosome biogenesis and maturation of autophagosomes/phagosomes, in age-related macular degeneration (AMD). Results from the study indicate that LAMP2—preferentially expressed by retinal pigment epithelium cells (RPE)—plays an important role in biology and pathobiology of the RPE. Reduction of LAMP2 may contribute to and accelerate the formation of basal laminar deposits (BLamD), a characteristic of early stage AMD (Notomi, et al., PNAS 116(47): 23724-23734, 2019).

Demetrios Vavvas, MD, PhD, and team also investigated the role of cell death mechanisms in choroidal neovascularization (CNV) and pathologic angiogenesis. Their data showed that receptor-interacting protein 1 (RIP1) kinase—highly expressed in inflammatory cells and known to play an important role in regulating apoptosis and necrosis—is abundantly expressed in human CNV and infiltrating macrophages during angiogenesis. In a preclinical model of CNV, genetic or pharmacologic inhibition of RIP1 kinase activity attenuated angiogenesis and was associated with caspase activation in infiltrating macrophages and decreased expression of pro-angiogenic M2-like markers, but not M1-like markers. These findings suggest that RIP1 kinase-mediated modulation of macrophage activation may be a therapeutic target of pathological angiogenesis in retinal diseases, including neovascular AMD (Ueta, et al., PNAS 116(47): 23705-23713, 2019).



Images of Azure II stain and TEM of the RPE from 12-month old WT or Lamp2 KO mice. Thick BLamDs were detected in aged Lamp2 KO mice in contrast to the normal structure of basal infoldings WT mice (arrows). Note massive accumulation of lipid droplet-like inclusions in the RPE from aged Lamp2 KO mice (asterisks).

Figure adapted from Notomi, et al., PNAS. 116(47): 23724-23734, 2019. (Vavvas lab).



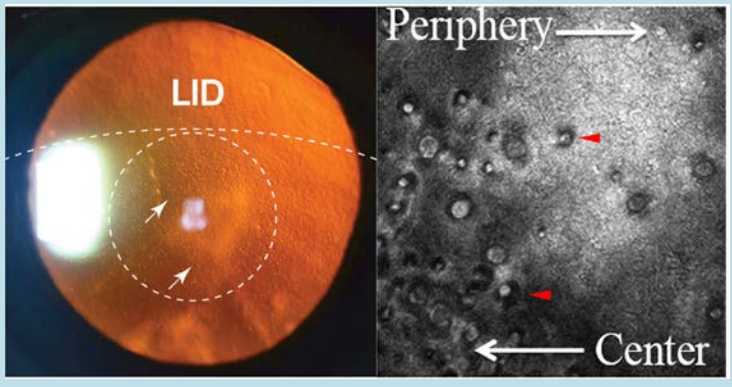
RIP1 expression in CNV. Immunohistochemistry of RIP1 in CNV on day 5 after induction by laser. Scale bar = 100 µm. DIC = differential interference contrast; GCL = ganglion cell layer; INL = inner nuclear layer; ONL = outer nuclear layer.

Figure adapted from Ueta, et al., PNAS. 116(47): 23705-23713, 2019. (Vavvas lab).

Deeba Husain, MD, and collaborators assessed the plasma metabolomic profiles of AMD and its severity stages with the ultimate goal of identifying accessible and reliable biofluid biomarkers for diagnosis, prognosis, and treatment of AMD. The collaboration across multiple institutions, including Mass. Eye and Ear, Harvard T.H. Chan School of Public Health, Channing Division of Network Medicine at Brigham and Women's Hospital, and the University of Coimbra revealed 28 metabolites that were significantly different between AMD patients versus control subjects, and 67 metabolites that were significantly different across disease stages. Analysis identified plasma lipid and amino acid metabolites, in particular those related to glycerophospholipids, taurine and hypotaurine, purines, and nitrogen pathways. Combining metabolomic data with other phenotypic data (including multimodal imaging and functional testing), as well as genomic and environmental data, may help elucidate AMD subtypes and identify potential druggable targets (Lains, et al., Metabolites 9(7): E127).

Corneal Diseases and Bioengineering Advances

Research from the laboratory of Ula Jurkunas, MD, identified ultraviolet A (UVA) light as a possible mechanism to explain why Fuchs' endothelial corneal dystrophy (FECD) affects only central part of the cornea, and why it affects women more frequently than men. The pre-clinical studies found that exposure of the central cornea in adult mice to UVA light resulted in the formation of FECD. Furthermore, the investigators discovered that exposure to UVA light sets off a reaction driven by the activation of CYP1B1, an enzyme that converts estrogen into metabolites that cause DNA damage. This increased estrogen formation correlated with the sex-dependent differences in disease presentation (Liu, et al., PNAS 117(1): 573-583, 2019).



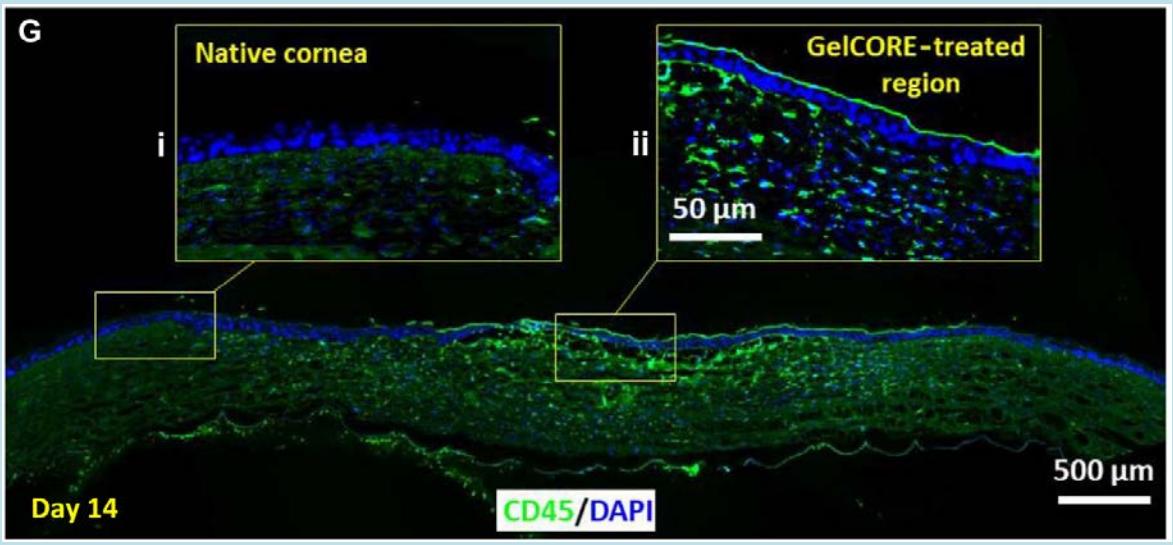
UVA exposure causes progressive middle cornea endothelial cell morphological changes and decreases cell density. (Left) Slit lamp image of FECD patient cornea. White arrows = guttae; dotted circle = central cornea; white dotted line = eyelid boundary. (Right) Corresponding HRT image of the patient cornea. Red arrowheads = guttae.

Figure adapted from Liu, et al., PNAS. 117(1):573-583, 2019. (Jurkunas lab).

A pre-clinical study led by Joseph Ciolino, MD, and scientists at Boston Children's Hospital has developed a contact lens that slowly releases the steroid dexamethasone—commonly used to treat inflammatory eye diseases—successfully preventing damage to the retina. The lenses safely provided sustained drug delivery to the retina for one

week at concentrations that were 200 times greater than that of hourly eye drops (Ross, et al., Biomaterials 217:119285, 2019). These contact lenses represent a minimially invasive, effective topical delivery system for diseases of the retina, which are currently treated with injections or implants.

Reza Dana, MD, MPH, along with scientists from UCLA, has developed a light-activated adhesive gel that can seal cuts or ulcers on the cornea, as well as encourage the regeneration of corneal tissue. The new technology, named GelCORE (gel for corneal regeneration), is applied as a thick liquid which, after exposure to blue light, hardens to match the consistency of the natural cornea and bonds to the native tissue. GelCORE could provide a safer method of treating corneal injury, and reduce the need for surgery to repair injuries to the cornea, including those that would today require corneal transplantation (Shirzaei Sani, et al., Science Advances 20;5(3): eaav1281, 2019).



Fluorescent immunohistochemical images of the cornea (DAPI and DC45 marker). (i) From area without defect. (ii) From corneal stroma defect treated with GelCORE bioadhesive at day 14 after surgery.

Figure adapted from Shirzaei, et al., Sci Adv. 20;5(3): eaav1281, 2019. (Dana lab).

Innovation

The Mass. Eye and Ear/MGH Department of Ophthalmology continues to be a nidus for translational innovations. Programs have resulted in licensing of technology and startups all dedicated to improving the lives of our patients.

- Pykus Therapeutics, founded in 2016, aims to develop synthetic replacement for vitreous humor based on the work of Thomas Stryjewski, MD, and James (Tony) Stefater, MD, PhD. With a license from Mass. Eye and Ear and funded in part by the Partners Innovation Fund (PIF), a proof-of-concept Phase I clinical study is expected to begin in 2020. Mass. Eye and Ear has equity in the company.
- ONL Therapeutics, founded in 2011 and funded in part my Mass. Eye and Ear and the University of Michigan, is focused on preventing Fas-mediated death of key retinal cells, which is a root cause of vision loss, a leading cause of blindness, and a completely unaddressed medical need. Based on technology and licenses from the University of Michigan and Mass. Eye and Ear (David Zacks, MD, PhD, and Joan W. Miller, MD), the first patient was treated in Australia in a first-in-human trial of ONL1204 in October of 2019. ONL1204 was granted orphan drug designation for the treatment of retinal detachment by the U.S. Food and Drug Administration (FDA).
- Touchdown Therapeutics, founded in 2019, is licensing technologies from Mass. Eye and Ear (Luk Vandenberghe, PhD) and Lonza to develop the next generation of AAV gene therapy vectors. Seed financing was provided, in part, by the Partners Innovation Fund (PIF).
- Helio Vision, Inc., founded in 2016, based on technology licensed from Mass. Eye and Ear (Dean Eliott, MD, and Thomas Stryjewski, MD) to develop a therapy for rare, fibroproliferative disorders that lead to abnormal scarring and blindness after retina surgery. Helio Vision, Inc. was acquired by Alderya Therapeutics in January of 2019. ADX-2191 (intravitreal methotrexate), received Orphan Drug Designation from the U.S. FDA. The first patient was enrolled in the Alderya phase III GUARD trial of ADX-2191 for the prevention of proliferative vitreoretinopathy in December of 2019.

- ReNeuron licensed human retinal progenitor cells (hRPCs) scale up manufacturing developed at Mass. Eye and Ear by Michael Young, PhD, for hRPC cell therapy for the blindness-causing inherited retinal disease, retinitis pigmentosa (RP). Jason Comander, MD, PhD, is the Principal Investigator (PI) of the U.S. phase I/IIa clinical trial. Positive safety data were presented at the American Academy of Ophthalmology Annual Meeting in October of 2019.
- Novartis licensed ECF843, a recombinant human lubricin (rh-Lubricin; PGR4) protein, developed by Lubris Biopharma, LLC. and licensed from Schepens Eye Research Institute of Mass. Eye and Ear (David Sullivan, PhD). A phase II clinical study of ECF843 demonstrated the potential to provide immediate improvement of dry eye symptoms, likely by increasing lubrication across various eye and tear surfaces. Improvement in dry eye signs were observed within 28 days of treatment.
- Aramis Biosciences, founded in 2019, is focused on the preclinical development of therapeutics in the areas of ocular inflammation and pain licensing Mass. Eye and Ear technologies (Reza Dana, MD, MPH, MSc.).

Oral & Maxillofacial Surgery

Department Report

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

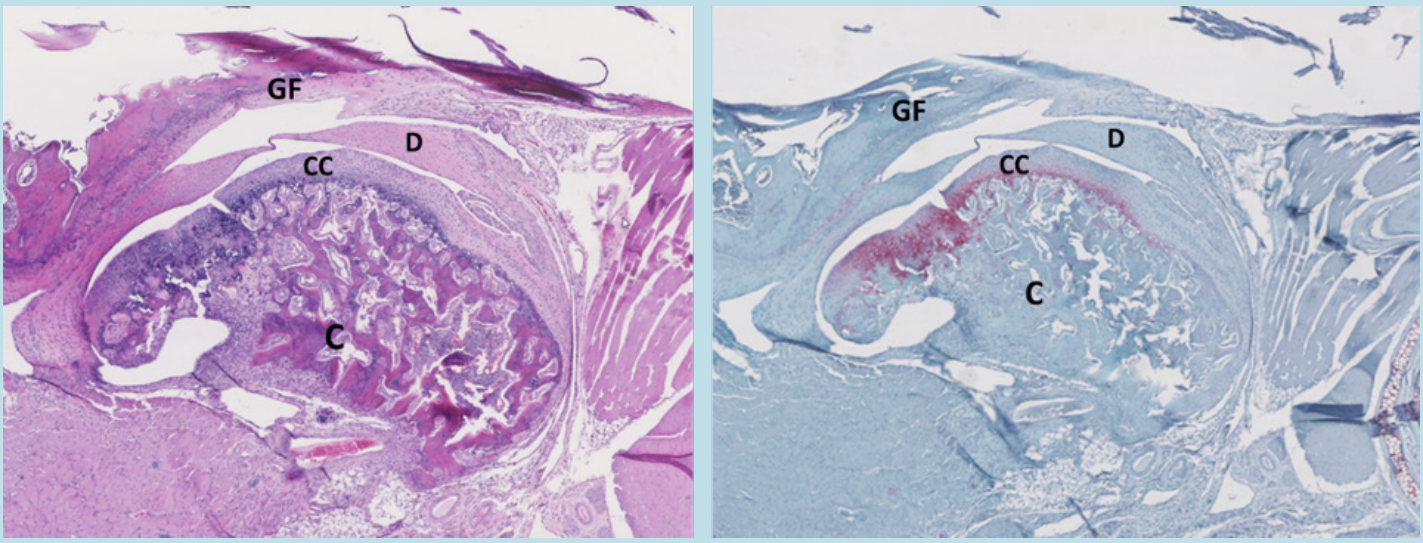
Thematic-driven translational research program continues to thrive in our department. The two research centers are the Skeletal Biology Research Center (SBRC) and the Center for Applied Clinical Investigation (CACI). Both centers promote the introduction to research of trainees at all levels (high school to post-docs). Both centers also are an energetic platform to promote the innovative treatment of disease, via translational science.

Skeletal Biology Research Center (SBRC), located in the Thier 5 Laboratory (approx.1500sq ft.). The science performed focuses on bone biology, tissue engineering and rare tumor biology (giant cell tumor and clear cell odontogenic carcinoma). Another area of study is metabolic/inflammatory bone disorders (MRONJ, microbiology-sterile osteomyelitis/necrosis, synovial chondromatosis). In-vivo tissue engineering (distraction osteogenesis), led by Dr. Peacock and ex-vivo tissue engineering (bone, cartilage, ginigiva and joint), led by Dr. Guastaldi, are being studied. On the focus with scaffold properties. We have developed a standard minipig model for the study of the biology of bone.

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 Obstructive Sleep Apnea (Dr. Lahey) trauma (Drs. Kaban, Tannyhill, Lahey and Peacock), dental implantology (Dr. August) and medication related osteonecrosis of the jaws (MRONJ), maxillofacial pathology (pediatric jaw tumors, rare jaw tumors) Dr. August, facial pain (Dr. Jeffry Shaefer), minimally invasive surgery and, temporomandibular joint surgery outcomes (Dr. McCain).

The center serves to study outcomes (retrospective and prospective) on treatment protocols developed in the Department. We continue with work QI/Safety/Service improvement research (Dr. Lahey) and Education/Simulation research (Dr. Tannyhill).

This year was used to continued to promote and nuture our studies in tissue engineering, TMJ repair/generation. The TMJ component under the direction of Dr. McCain and hard work of the Fellows, Drs. Hakim, Guastaldi, Liapaki and Thamm. Other significant Collaborations include the Department of Pathology, Drs. Haber, Iafrate, Faquin and Rivera (Genetics and Treatment of Clear Cell Odontogenic Carcinoma) and Oncology, Dr. Raje (Genetics of Bone Metabolism and MRONJ). New collaborations include Dr. V. Rosen and Dr. Joe McCain in Temporomandibular Joint Repair; Drs. Yakir Levine and Rox Andersen in attached ginigva reconstruction, in collaboration with Dr. Guaastaldi. Dr. Klein has been leading the study of the effect of marijuana on tooth movements with exiciting preliminary results.



Representative picture of harvested specimen. Histological analysis on mice TMJ. H&E and Safranin O staining. C: condylar head; CC: condylar cartilage; D: disc; GF: glenoid fossa (Guastaldi, Hakim, Liapaki, Lowe, Thamm, McCain, unpublished data)

CACI

A select few ongoing outcome, retrospective and prospective studies include the study of jaw osteomyelitis; Risk factors of suamous intraepithelial lesions undergoing malignant transformation; Skeletal relapse following reconstructive jaw surgery; facial dog bites and how they can be prevented; Heterotopic ossification of the temporomandibular joint (Dr. Keith). Brain absess as a sequela of odontogenic infection. An exciting new collaboration with Drs. Dunn and Lau is the Wisdom in Teeth: exploring the use of teeth as fossil records of early stress exposure and future neuropsychiatric risk.

SBRC

Temporomandibular joint (TMJ) disorders affect up to 10-40% of the population and if left untreated, may eventually lead to osteoarthritis (OA) of the TMJ. In vivo TMJ repair and regeneration has received significant attention and represents a promising approach for the treatment of degenerative TMJ disorders. At the SBRC we developed a preclinical mouse- defect model of TMJ condyle's fibrocartilage. Our current studies focus on a potential tissue engineered TMJ therapy based on mesenchymal stem cells (MSC's) derived from the mice condyle, hydrogel and biosilica nanoparticles (Drs. Guastaldi, Lowe, Hakim, Liapaki, Lowe, Thamm, and McCain).

Otolaryngology

Department Report

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

Driven by a mission to find better treatments and cures for otolaryngologic conditions, including deafness and diseases of the head and neck, the Department of Otolaryngology–Head and Neck Surgery at Massachusetts Eye and Ear/Massachusetts General Hospital is committed to moving science in these areas forward. Being home to a large and productive community of otolaryngology–head and neck surgery researchers, as well as a rich landscape of collaborators, positions us to accelerate the science necessary for the prevention, management, and rehabilitation of human communication disorders. From advancements in facial reanimation to demonstrating that artificial electrical stimulation is a feasible therapeutic modality for anosmia, we strive to always be at the forefront of medicine in order to ensure the best care possible for our patients.

Anatomical image of the middle and inner ear, depicting the various locations where conductive hearing loss can originate.

2019 Research Highlights

Sound deprivation in one ear leads to speech recognition difficulties

Chronic conductive hearing loss, which can result from middle-ear infections, has been linked to speech recognition deficits, according to the results of a study published in Ear and Hearing. Led by Stéphane F. Maison, PhD, of the Eaton-Peabody Laboratories at Mass. Eye and Ear, this study suggests that not properly treating infections or other conditions that chronically affect the middle ear may lead to neural deficits and/or other troubles consistent with cochlear synaptopathy. The researchers retrospectively reviewed the hearing profiles of 240 patients who visited an audiology clinic at Mass. Eye and Ear with either an acute or chronic conductive hearing loss but normal sensorineural function on hearing tests. The researchers found that patients with longstanding conductive hearing impairments of moderate to moderately severe degrees had lower speech-recognition scores on the affected side than on the healthy side, even when the speech was loud enough to be clearly audible. Due to these findings, the authors urge clinicians to consider providing amplification in the management of unilateral conductive hearing loss.

Study questions if tongue-tie surgery for breastfeeding is always necessary

New research raises questions as to whether too many infants are getting tongue-tie and upper lip tether surgery to help improve breastfeeding, despite limited medical evidence supporting the procedure. The number of these procedures has been rapidly rising in recent years. The Kids' Inpatient Database in the U.S. estimated a ten-fold increase in tongue-tie surgeries from 1,279 in 1997 to 12,406 in 2012. Prompted by these rising rates and an influx of parents seeking second opinions, a Mass. Eye and Ear team of medical professionals led by Christopher J. Hartnick, MD, MS, implemented a feeding evaluation program staffed by clinicians and speech-language pathologists. In a study published in JAMA Otolaryngology–Head & Neck Surgery, this team found that nearly 63 percent of children who were referred to a pediatric ear, nose, and throat surgeon for tongue-tie and/or upper lip tether surgery ended up not needing the procedure. Mothers were able to successfully breastfeed following a thorough feeding evaluation instead. A feeding evaluation program implemented on a wider scale may prevent infants from getting a surgery that might not be beneficial for improved breastfeeding. The authors call for best practice guidelines to be developed to help with this decision-making throughout the medical community.

Coat protein PKHD1L1 required for normal hearing in mice

In a study published in Nature Communications, a team including Artur A. Indzhykulian, MD, PhD, of the Eaton-Peabody Laboratories at Mass. Eye and Ear, discovered that the coat protein of hair cell stereocilia, known as Polycystic Kidney and Hepatic Disease 1-Like 1 (PKHD1L1), is required for normal hearing in mice. The bundle of stereocilia on inner ear hair cells responds to subnanometer deflections produced by sound or head movement. Stereocilia are interconnected by a variety of links and also carry an electron-dense surface coat. The study showed that PKHD1L1 mediates the surface coat at the surface of stereocilia. This coat may contribute to stereocilia adhesion or protect from stereocilia fusion, but its molecular identity remains unknown. From a database of hair cell-enriched translated proteins, the investigators identified PKHD1L1, a large, mostly extracellular protein. Using serial immunogold scanning electron microscopy, they showed that PKHD1L1 is expressed at the tips of stereocilia, especially in the high-frequency regions of the cochlea. PKHD1L1-deficient mice lacked the surface coat at the upper, but not lower, regions of stereocilia and developed progressive hearing loss. Therefore, the investigators concluded that PKHD1L1 is a component of the surface coat and is required for normal hearing in mice.

Dr. Artur Indzhykulian working in his laboratory at Mass. Eye and Ear.

Exosomes "swarm" to protect against bacteria inhaled through the nose

A Mass. Eye and Ear research team led by Benjamin S. Bleier, MD, FACS, recently discovered that when bacteria are inhaled, exosomes are immediately secreted from cells that directly attack the bacteria and also shuttle protective antimicrobial proteins from the front of the nose to the back along the airway, protecting other cells against the bacteria before it gets too far into the body. Along with this new understanding of the innate immune system, these findings may have implications in the development of new methods of delivering drugs through the airway. More specifically, as natural transporters, exosomes could be used to transfer inhaled packets of therapeutics to cells along the upper airway—and possibly even into the lower airway and lungs.

Toward the bionic face: A novel neuroprosthetic device paradigm for facial reanimation

Facial palsy is a devastating condition potentially amenable to rehabilitation by functional electrical stimulation. A team of investigators including Nate Jowett, MD, FRCSC, and Tessa A. Hadlock, MD, of the Facial Nerve Center at Mass. Eye and Ear, recently characterized a novel paradigm for unilateral facial reanimation via an implantable neuroprosthetic device and demonstrated its feasibility in a live rodent model. The paradigm comprises use of healthy-side electromyography activity as control inputs to a system whose outputs are neural stimuli to effect symmetric facial displacements. The vexing issue of suppressing undesirable activity resulting from aberrant neural regeneration (i.e., synkinesis) or nerve transfer procedures is addressed using proximal neural blockade. The researchers implanted epimysial and nerve cuff electrode arrays in the faces of rats and delivered stimuli to evoke blinks and whisks of various durations and amplitudes. The dynamic relation between electromyography signals and facial displacements were modelled and facial nerve blockade in awake behaving animals was achieved without detrimental effect, noted from long-term continual use. The researchers note that use of proximal neural blockade coupled with distal functional electrical stimulation may have relevance to rehabilitation of other peripheral motor nerve deficits.

Proof of concept research may accelerate the development of smell restoration technology

Estimated to occur in five percent of the population, anosmia is a phenomenon that reduces and/or eliminates a person's ability to smell. In some instances, anosmia is caused by damage to sensory nerves for which there are currently no proven therapies. Such cases are attributed to the nasal cavity (olfactory) nerves not functioning properly. Taking the cochlear implant as inspiration, investigators from the Virginia Commonwealth University School of Medicine have been testing the idea of an olfactory implant system that uses electrodes to stimulate smell. To determine if this technology is feasible, Eric H. Holbrook, MD, of Mass. Eye and Ear, became the first person to apply an artificial electrical stimulation of smell through the human nasal cavities and sinuses. In a study published in International Forum of Allergy & Rhinology, Dr. Holbrook described that three of five patients reported sensations of smell as a result of the stimulation. This work shows that smell restoration technology is an idea worth studying further.

Dr. Eric Holbrook examining a patient at Mass. Eye and Ear.

Pathology

Department Report

David N. Louis, MD, Chief

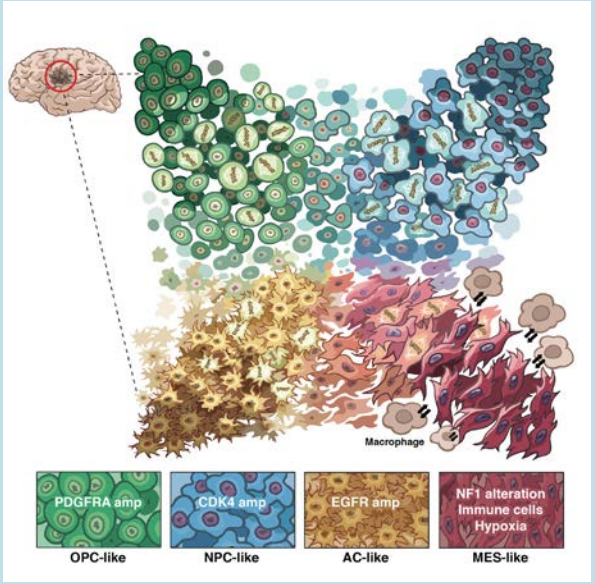
Pathology plays a critical and substantial role in academic medicine, as a natural connection between the diagnosis of human disease and experimental biomedical investigation. Major advances in molecular pathology and pathology informatics continue to accelerate the pace of diagnostic and translational research. In turn, the rapidity and frequency of interactions between clinical and scientifc areas makes this an exciting time in the field of pathology. Laboratory-based scientifc research is a major component 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 grown considerably over the past two decades, building an exceptional and well-funded group of basic science and translational investigators with particular strengths and expertise in cancer biology, genomics, and epigenetics as well as with single-cell and genome editing technologies. Over the past several years, we have implemented initiatives identi?ed 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.

Achievements:

An Integrative Model of Cellular States, Plasticity, and Genetics for Glioblastoma.

Neftel C, Laffy J, Filbin MG, Hara T, Shore ME, Rahme GJ, Richman AR, Silverbush D, Shaw ML, Hebert CM, Dewitt J, Gritsch S, Perez EM, Gonzalez Castro LN, Lan X, Druck N, Rodman C, Dionne D, Kaplan A, Bertalan MS, Small J, Pelton K, Becker S, Bonal D, Nguyen QD, Servis RL, Fung JM, Mylvaganam R, Mayr L, Gojo J, Haberler C, Geyeregger R, Czech T, Slavc I, Nahed BV, Curry WT, Carter BS, Wakimoto H, Brastianos PK, Batchelor TT, Stemmer-Rachamimov A, Martinez-Lage M, Frosch MP, Stamenkovic I, Riggi N, Rheinbay E, Monje M, Rozenblatt-Rosen O, Cahill DP, Patel AP, Hunter T, Verma IM, Ligon KL, Louis DN, Regev A, Bernstein BE, Tirosh I, Suvà ML. Cell. 2019;178(4):835-849. PMID: 31327527.

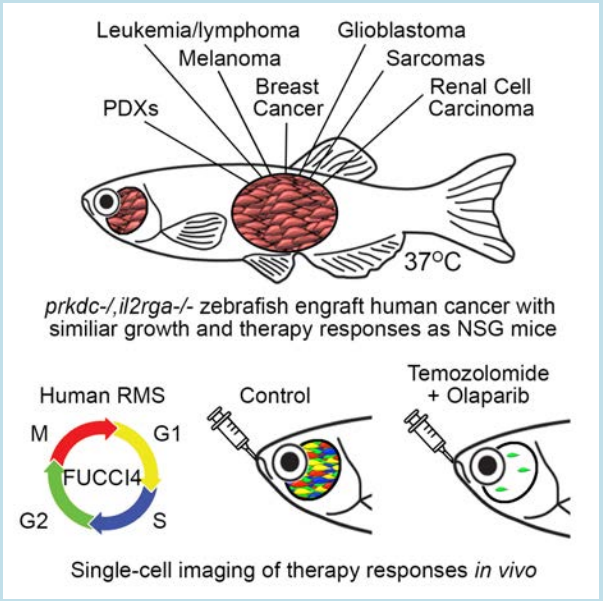


Model for the cellular states of glioblastoma and their genetic and micro-environmental determinants. Mitotic spindles indicate cycling cells. Lighter/darker tones indicate strength of each program. Intermediate states are shown in between the four states and indicate transitions. Abbreviations: OPC oligodendrocyte precursor cell; NPC: neural progenitor cells; AC: astrocytes; MES: mesenchymal (Naftel et al., Cell 2019).

Glioblastoma is the most common primary brain tumor and is incurable. The disease is difficult to treat largely because of its heterogeneity (both within and between patients). Here, the Suva group profiled the gene expression of more than 24,000 individual cancer and immune cells from 28 glioblastoma patients (both adult and children), re-analyzed 401 "bulk" genomic samples through the lens of our single-cell programs and analyzed experimental models in which the fate of cells could be followed over time (lineage tracing). This allowed them to understand glioblastoma with much higher granularity. They propose a model in which each patient tumor is composed of four malignant cellular states, each having a unique gene expression program and that can account for the large variation in the disease. They show how defined genetic drivers of glioblastoma influence the relative frequency of cells in each of the state in a given tumor, while other genetic events have no consequences. They demonstrate the capacity of cells to shift from one state to another (plasticity) and show how one of the glioblastoma state is exclusively cross-talking to immune cells. This work offers a much-needed blueprint to understand glioblastoma and sheds important light on disease biology, glioblastoma classification and will help inform novel therapeutic approaches.

Visualizing Engrafted Human Cancer and Therapy Responses in Immunodeficient Zebrafish.

Yan C, Brunson DC, Tang Q, Do D, Iftimia NA, Moore JC, Hayes MN, Welker AM, Garcia EG, Dubash TD, Hong X, Drapkin BJ, Myers DT, Phat S, Volorio A, Marvin DL, Ligorio M, Dershowitz L, McCarthy KM, Karabacak MN, Fletcher JA, Sgroi DC,Iafrate JA, Maheswaran S, Dyson NJ, Haber DA, Rawls JF, Langenau DM.
Cell. 2019;177(7):1903-1914. PMID: 31031007

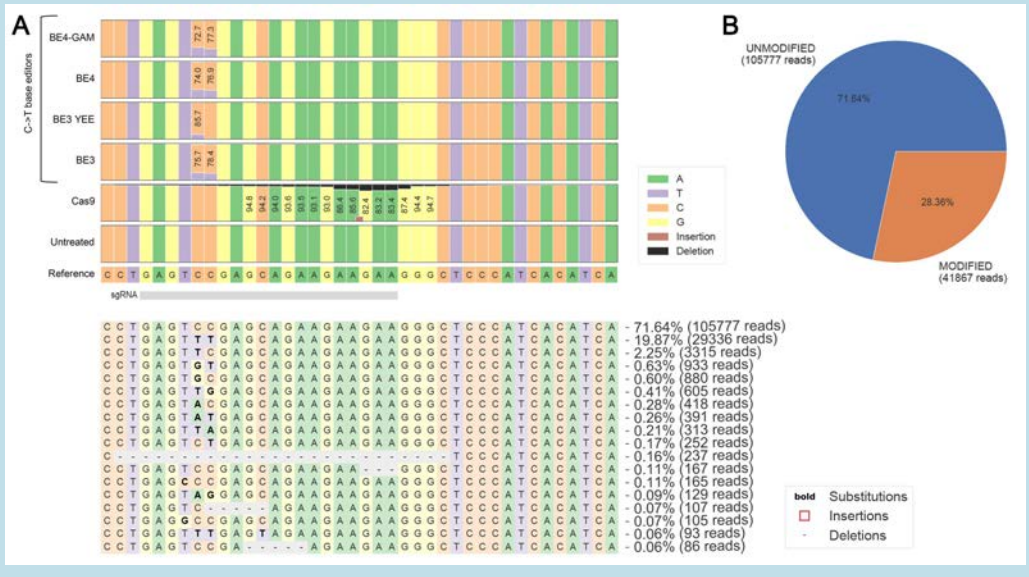


Robust engraftment of human cancers into optically-clear, immune-deficient zebrafish enables dynamic visualization of cell biological phenotypes and therapy responses in single cancer cells over time (Yan et al., Cell 2019).

Immune compromised mice are an invaluable model for xenograft cell transplantation studies. However, mouse models are expensive and single cell imaging of engrafted cells requires complex imaging techniques including surgical window implantation into engrafted mice. Here, the Langenau group has described the first optically-clear, homozygous compound mutant prkdcD3612fs, il2rgaY91fscasper-strain zebrafish that lack T, B and natural killer (NK) cells. These immune deficient animals can survive at 37ºC and robustly engraft a variety of fluorescently-labeled human cancers. Remarkably, the growth kinetics, histology, cell proliferation and apoptotic rates are identical when compared to the same tumor engrafted into NSG mice. This work went on to identify a new drug combination, olaparib PARP-inhibitor and the DNA damaging agent temozolomide, that curbed growth of pediatric rhabdomyosarcoma (RMS) muscle cancers. Moreover, they were able to dynamically visualize therapy responses at single cell resolution in vivo using clinically relevant dosing using oral gavage and the four-color FUCCI4-cell cycle reporter. Importantly, this same drug combination elicited tumor responses in mouse xenograft studies. This work is important because it provided the pre-clinical rationale for assessing this same drug combination in RMS patients, which is now entering clinical trails for this disease at MGH. This is the first example of zebrafish avatars defining a potential therapy in any pediatric cancer to date.

CRISPResso2 provides accurate and rapid genome editing sequence analysis.

Clement K, Rees H, Canver MC, Gehrke JM, Farouni R, Hsu JY, Cole MA, Liu DR, Joung JK, Bauer DE, Pinello L. Nat Biotechnol. 2019;37(3):224-226. PMID: 30809026

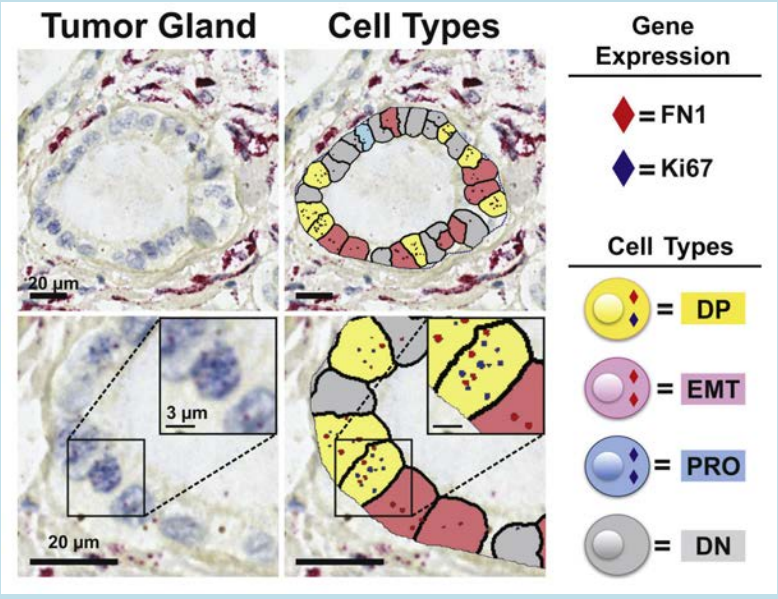


CRISPResso2 allows users to easily interpret genome editing analysis with comprehensive plots comparing different genome editing technologies. Panel A shows the proportion of each base, as well as any indels, in reads at each position in the reference genome. The pie chart in panel B shows the proportion of modified and unmodified alleles in a given sample (Clement et al, Nat. Biotechnol.2019).

CRISPResso2 is an analysis toolkit for analyzing the results of genome editing experiments. After performing a CRISPR experiment, researchers need to measure the types, locations, and frequencies of genome editing events by comparing the reference sequence to next-generation sequencing reads from their experiment. CRISPResso2 introduces a novel, biologically-aware alignment algorithm that dramatically increases the speed and accuracy of the quantification of mutations induced by the CRISPR system. Given the importance of this alignment technology, a patent has been filed. This algorithm has been used to improve analysis and comparison of multiple editing tools, including base editors, a novel class of editors with

dramatic translation potential given their capability of introducing precise target substitutions that could reverse pathogenic DNA alterations. CRISPResso2 offers a user-friendly web interface accessible to users with little computational background, allowing them to easily analyze and visualize genome editing outcomes. The website can be accessed at: http://cripresso2.pinellolab.org.

Stromal Microenvironment Shapes the Intratumoral Architecture of Pancreatic Cancer.
Ligorio M, Sil S, Malagon-Lopez J, Nieman LT, Misale S, Di Pilato M, Ebright RY, Karabacak MN, Kulkarni AS, Liu A, Vincent Jordan N, Franses JW, Philipp J, Kreuzer J, Desai N, Arora KS, Rajurkar M, Horwitz E, Neyaz A, Tai E, Magnus NKC, Vo KD, Yashaswini CN, Marangoni F, Boukhali M, Fatherree JP, Damon LJ, Xega K, Desai R, Choz M, Bersani F, Langenbucher A, Thapar V, Morris R, Wellner UF, Schilling O, Lawrence MS, Liss AS, Rivera MN, Deshpande V, Benes CH, Maheswaran S, Haber DA, Fernandez-Del-Castillo C, Ferrone CR, Haas W, Aryee MJ, Ting DT. Cell. 2019;178(1):160-175. PMID: 31155233



Representative images of RNA In Situ Hybridization (RNA-ISH) of a primary human pancreatic ductal adenocarcinoma (PDAC) tumor gland stained for the proliferation marker, Ki67, and the epithelial-mesenchymal transition (EMT) marker FN1. The second column shows image analysis of the tumor gland using quantitative digital pathology software to classify individual cancer cells within the gland into one of four types (Ligorio et al., Cell 2019).

Pancreatic ductal adenocarcinoma (PDAC) is highly aggressive and is defined by a robust stromal microenvironment. Here, the Aryee and Ting labs combined single-cell RNA sequencing and next generation protein analytics to uncover the microenvironmental programs that shape cancer cell phenotypes, most notably programs that allow cancer cells to invade the blood stream, spread, and lead to metastatic growth. Specifically, they found that stromal cancer associated fibroblasts (CAFs) shift tumor cells towards invasive epithelial-to-mesenchymal (EMT) states and can result in highly proliferative cell states (PRO) linked with MAPK and STAT3 signaling. Using high-content digital imaging of RNA in situ hybridization in 195 PDAC tumors, these EMT and PRO states were assessed in 319,626 individual cancer cells. This classified individual cancer cells within the context of distinct tumor gland "units" within the same tumor. Tumor gland typing provided an additional layer of intratumoral heterogeneity that was associated with differences in stromal abundance and clinical outcomes. This demonstrates the impact of the stroma in shaping tumor architecture by altering inherent patterns of tumor glands in human PDAC.

Ronald E. Kleinman, MD, Chief

The research mission of the Department of Pediatrics is to advance translational basic, clinical and population science related to the health and development of infants, children, and adolescents. Research at MGHfC recognizes the challenges and opportunities for child health research dictated by the changing social, economic and health care policy landscape in the US, including the shift toward Precision Medicine. Across the Department, our research integrates multidisciplinary clinical and scientific expertise with local, regional, national and international collaborations.

With the appreciation that biological events beginning during gestation and continuing into childhood can strongly influence disease onset during childhood and beyond, we intend to expand our integrated models focused on pre-clinical/early and translational clinical studies to provide the rationale for possible therapeutic and/or preventive interventions. Our overarching goal is to improve the lives of children and families through science. A current strategic priority is to develop new effective personalized and preventive strategies for disorders starting in childhood by integrating multi-level, multisystem data ranging from the molecular to the whole child in order to prevent or reverse development of disease. To better coordinate our effort and to integrate our scientific mission within the MGH Research Institute we have established the Pediatric Translational Research Center (PTRC) in which basic, translational, clinical, and community-based research are blended to deliver state-of-the-art clinical care, to provide superb training opportunities, and foster cutting-edge discoveries to achieve our mission. We are currently focused on the following specific research missions:

Allergy & Immunology
The research mission for Pediatric Allergy & Immunology is to partner with our patients to advance new therapeutic, preventative and educational interventions for the millions of children affecting by the spectrum of allergic disease including both IgE- and non IgE-mediated forms of food allergy and asthma. A major research focus within the Division is on the mechanisms of immune-mediated food hypersensitivities including IgE-mediated food allergy, chronic gastrointestinal inflammatory diseases related to food allergy such as eosinophilic esophagitis and allergic proctocolitis. To advance this research effort, The Food Allergy Center at Massachusetts General Hospital (FAC@MGH) was established in 2010 as a multi-disciplinary research and clinical care virtual center with the recruitment of Dr. Shreffler to provide leadership, and the core participation of clinicians and investigators from Allergy / Immunology, Rheumatology, Gastroenterology, Dermatology, Pathology, Psychology, Nutrition, Child Life and the Harvard CTSA-supported, MGH Clinical Research Center (CRC). At the time of its inception, there were no clinical trials, interventional or otherwise, focused on food allergy at MGH. To date, the FAC@MGH has initiated than 40 IRB-approved studies on food allergy. These studies represent almost 3,000 research participants in total, more than 2,000 of whom have undergone oral food provocation tests (food challenges). These include randomized interventional trials for food allergy, including two studies funded by NIAID – (NCT01750879, NCT02698033), enrolling 100s of patients and conducting 1000s of study visits, demonstrating the capacity to carry out randomized interventional trials for the food allergic population, including the necessary regulatory compliance (cGCP and ICH), pediatric and adult patient recruitment, data management and all other necessary requirements.

The Gastrointestinal Microbiome and Allergic Proctocolitis (GMAP) study has demonstrated our capacity to also carry out larger population cohort / low risk interventional trials: GMAP is an observational healthy newborn cohort study that has enrolled >1000 newborns from a single multi-provider general pediatrics site since May 1, 2014. The study aims to identify risk factors for the development of food allergy – allergic proctocolitis (AP) primarily, but immediate hypersensitivity as well – and collects maternal breast milk, infant stool (at <1 week, 2 weeks, 1, 2, 4, 6, 9, 12, 18, 24 months) and blood (at 1, 2 and 3 years of age).

To complement the discovery efforts, Dr. Michael Pistiner leads our program on Prevention, Education and Advocacy. This program is one of the largest in the country targeting high risk infants by collaborating with primary care pediatricians in the MGH/Partners network to lower the barriers of access in order to expand the early childhood diet to include common allergens – the most effective means of allergy prevention currently proven – and to develop a national model for doing this in other settings. Because of Dr. Pistiner's efforts, effective Dec 2018, we have also become the second site for an NIAID-funded prevention study, led by our colleagues at Johns Hopkins University and have attracted other new extramural funding for education and prevention as well.

In 2016, the FAC@MGH was awarded a seven year UM1 award by NIAID to be part of the Consortium for Food Allergy Research (CoFAR), the first time for any center in New England and only one of six in the US. The Division enjoys strong collaborations with academic and industry groups at

BWH (The Channing Laboratory), BCH, MIT, The Broad Institute, Sanofi and others.

Cardiology
The Pediatric/Congenital Cardiology division is involved in research in basic science and health services research to understand the causes of congenital heart disease and to study clinical interventions to improve the provision of pediatric cardiovascular care and foster a patient centered environment. We are fortunate to have a robust clinical and academic environment to promote these research endeavors. Members of our service are engaged in basic science research understanding the genetic etiologies of vascular pathology such as aortopathies (e.g. Marfan and Loeys Dietz syndromes). We are also involved in health services research specifically in the area of patient safety and quality as it pertains to pediatric cardiology. We have ongoing investigations evaluating diagnostic accuracy of cardiac imaging, investigations evaluating of parental health literacy among congenital heart disease families, and studies of resource use among patients undergoing congenital heart surgery. Our preventative cardiology service has collaborated with the Harvard T.H. Chan School of Public Health on projects to examine outpatient and wireless means to track physical activity and caloric intake.

Critical Care Medicine
A major focus of the division of Pediatric Critical Care Medicine is preventing and understanding mechanisms of pediatric traumatic brain injury. Our neurocritical care research efforts include basic science and translational studies to understand cellular and molecular events that occur following brain trauma, with the goal of finding new therapies that mitigate specific maladaptive responses and improve outcome. In addition, we seek to inform public health trauma prevention strategies to reduce pediatric traumatic brain injury through our Trauma and Injury Prevention Outreach Project (TIPOP). This multidisciplinary group focuses research, community outreach, and education on the most common causes of pediatric injuries leading to emergency department visits and PICU admissions, including motor vehicle accidents, window falls, firearms violence, burns and recreational-related trauma. Our division is also dedicated to better understanding the long-term neurological sequelae of critical illness to better inform our practice, particularly as it relates to long-term exposure to pain and sedation medications. Finally, the division is committed to better understanding existing modalities that deliver non-invasive respiratory support during critical illness and to developing innovative technologies for use in low-resource settings.

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 neurobiology of conditions that span the weight spectrum from obesity to exercise induced amenorrhea 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. Other areas of interest include investigations of novel technologies related to diabetes care, and the impact of administration of the growth hormone releasing hormone analog, tesamorelin, on carbohydrate and fat metabolism. We will continue to foster an environment of inquiry and investigation among our faculty and fellows, work on optimizing funding opportunities to maintain a strong research base within the division. This includes intra- and extra-mural collaborations with other laboratories actively engaged in these areas to create a rich and interactive reinforcing environment that will lead to changes in medical care paradigms for children with endocrine disorders.

Gastroenterology, Hepatology & Nutrition
Mucosal Immunology and Biology Research Center
Our mission is to expand clinical, basic and translational research in pediatric gastroenterology and nutrition to provide better outcomes for pediatric patients. Using a multidisciplinary approach, our major basic research mission is to characterize the role of the enteric mucosa and its mucosal barrier function at the interface between microbial luminal stimuli and lymphoid effector responses. We focus on the enterocyte and its involvement in microbial "crosstalk," lymphoid-nerve-epithelial interactions and inappropriate developmental responses secondary to epigenetic pressure by the gut microbiota during the first 1000 days of life. We also look at host-pathogen interactions during infection as well as how the enterocyte functions both as a barrier to antigen trafficking and as a site for the beneficial effects of probiotics in chronic inflammation. Finally, we are interested in the gut-brain axis, particularly as concerns small intestinal and blood brain barriers in the contest of neuroinflammatory diseases. Our researchers examine strategies used by gut microbiota to affect the host and how these interactions lead to both local and systemic chronic inflammation and autoimmunity in the Mucosal Immunology and Biology Research Center. In addition, active clinical and translational research to implement personalized and primary preventive medicine is carried out in our Airway, Voice and Swallowing Center for Children; the Center for Celiac Research and Treatment; the Center for Diagnostic, Therapeutic and Interventional Endoscopy; the Center for

Inflammatory Bowel Disease; the Center for Nutrition; the Center for Pediatric Hepatobiliary and Pancreatic Disease; the Food Allergy Program; the Liver Transplantation Program; the Lurie Center for Autism Pediatric Gastroenterology Program; the Neurogastroenterology Program and the Pediatric Weight Center.

General Academic Pediatrics

Our 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; evaluating the costs and cost-effectiveness of interventions and screening guidelines; and improving the health of populations across the lifecourse through innovations in research, patient care, education, and community advocacy. We also conduct research to prepare and support primary care pediatricians in the delivery of health care innovations, leveraging clinical and community partnerships to implement and sustain effective interventions.

Division faculty have a wide variety of research specialties, including:

- Childhood obesity prevention and treatment, including understanding the role physical activity and other health behaviors play in chronic disease prevention, the development of new, innovative childhood obesity interventions, and the dissemination and implementation of proven-effective programs.
- Providing comprehensive, high quality care to children with special health care needs, including autism spectrum disorder through collaborations such as the Autism Intervention Research Network on Physical Health (AIR-P), Autism Speaks Autism Treatment Network (ATN), and the newly created Autism Learning Health Network (ALHN).
- Strategies to address tobacco use and exposure in families, including the development of the Clinical Effort Against Secondhand Smoke Exposure (CEASE) program available in all 50 states for free, thirdhand smoke, electronic cigarettes, regulating smoking in multiunit housing, and raising the purchase age of tobacco to 21.
- Maternal-child health throughout the life course, including how substance use in pregnant and parenting women impacts the health of children and families, obesity prevention efforts beginning pre-conception and in pregnancy, and the role and influence of fathers in the early life period.
- How the built environment, such as architecture and urban planning, can affect individual and population health.
- Health outcomes of HIV-infected adolescents and adolescents at risk for HIV infection.

Genetics and Metabolism

The Division of Medical Genetics and Metabolism at MGHfC helps with the diagnosis and care of individuals with 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. We perform counseling, diagnostic and management services helping patients and physicians to better understand the genetic contributions to their health and disease and to diagnose and treat a wide variety of genetic/metabolic conditions. We have established specialty clinics in Metabolism, Lysosomal Storage Diseases, Mitochondrial disease, Turner Syndrome, William syndrome, 22q Deletion Syndrome, Stickler Syndrome, Klinefelter syndrome, Hereditary Hemorrhagic Telangiectasia, CHARGE syndrome, a multidisciplinary Sensorineural Hearing Loss Clinic at the MEEI, an Autism Genetics Clinic at the Lurie Center, Pitt Hopkins Syndrome Clinic and Pediatric Cancer Predisposition Clinic. Our multidisciplinary Down Syndrome Clinic leads the way in care and research including participation in groundbreaking clinical therapeutic trials of agents to improve cognitive function in people with Down syndrome. Our Williams syndrome and Pitt Hopkins syndrome clinics are world renown the largest experience with these patients of any site in the world and regularly have international referrals seeking our expertise. Active clinical trials are also underway with lysosomal storage 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 and participates in the NIH sponsored Undiagnosed Diseases Network. Our services impact every field of pediatric and adult medicine. We have active engagement throughout the hospital in advisory and teaching capacities assisting other providers and committees in the implementation of genetics in medicine.

Global Health

Founded in 2010, the Division of Global Health at MassGeneral Hospital is actively engaged in interdisciplinary research, education and clinical care aimed at improving the wellbeing of the most vulnerable children in our global community. The Division includes faculty, research fellows and staff with diverse experiences and interests but a shared dedication to the health and development of children across the globe. Building

upon MassGeneral Hospital for Children's long-standing commitment to scientific and clinical innovation, our faculty and staff work to combat prematurity, birth asphyxia, neonatal sepsis, childhood pneumonia, cholera transmission, and HIV at several sites across the globe.

Hematology/Oncology

The physician scientists and clinicians in the Division of Pediatric Hematology-Oncology have been active in both basic science and translational/clinical research in both cancer and non-malignant hematologic illnesses. Together with our pediatric subspecialists, we have developed multi-disciplinary programs and clinics for children with brain tumors, long-term survivors of childhood cancer, stroke, and hemophilia. In addition to our cooperative group and industry sponsored therapeutic clinical trials, we have important companion imaging and biomarker studies. We also have a research focus examining quality of life and neurocognitive sequelae in children who have been receiving cancer therapies. We are active members of an international clinical research group known as the Children's Oncology Group, as well as members of a Neuroblastoma and Brain Tumor Research Consortium. These groups give us access as participants or co-principal investigators to novel Phase 1,2, and 3 clinical trials. We have ongoing research projects with our colleagues in radiation oncology, molecular pathology, and pediatric radiology. Examples of these collaborations include Dr. Miguel Rivera's research in the Department of Pathology using epigenome editing tools to examine the genetic drivers in Ewing sarcoma and medulloblastoma and Dr. Shannon Stott's research in the MGH Cancer Center isolating exosomes and circulating tumor cells ("liquid biopsy") from the peripheral blood of patients with brain tumors and sarcomas for diagnosis and a noninvasive method to monitor response to therapy. Dr. Verena Göbel in our division has been a leading basic science investigator studying lumenogenesis and cell polarity. These studies have important implications for tumor invasion and metastasis.

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 for Autism

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. There are exciting clinical studies looking at new molecules for the treatment of Angelman syndrome (Dr. Chris Keary), and, along with researchers at the Lincoln Lab of MIT, Dr. Lisa Nowinski has initiated a study of movement and gait in children with ASD. Our collaborative research project with Drs. Jacob Hooker and Nicole Zurcher (Martinos Center), aims to identify an "inflammatory subtype" of autism and has produced very exciting preliminary findings. To identify inflammation within the brains of patients with autism spectrum disorder (ASD), we are assessing translocator protein 18 kDA (TSPO) expression in individuals using [11C]PBR28 positron emission tomography (PET) imaging. Preliminary results show a striking decrease in the expression of this protein in males with ASD compared to age- and gender-matched typically developing controls, indicating a change in neuroimmune activity within the brains of patients. Our publications on methods for preparing adults with ASD for MR/PET scanning highlights our commitment to engaging and preparing patients for success in research. Ongoing work in this model aims to incorporate females in these studies based on evidence in mice and in postmortem human brains that immune system function within the brain differs between males and females, 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. Marcy Kingsbury's lab. Finally, the pre-clinical arm of the Lurie Center and the clinical arm (researchers and clinicians) have established a monthly "think tank" for consistent interaction and cross-fertilization of ideas.

Neonatology and Newborn Medicine

The research efforts in the Neonatology and Newborn Medicine Unit are multifaceted and range from basic science to epidemiology. All research projects share a common mission, which is to advance scientific knowledge aimed at improving the care and treatment of our very vulnerable

patients and their families. Reflective of the broad clinical spectrum of issues in our patient population: from extremely low birth-weight infants and the myriad medical issues they face, to full-term infants with various congenital anomalies or those born with physiologic dependence to opioids due to in-utero exposure, we have the following main research foci: 1. Developmental biology approaches to study how prematurity affects human development and to create new strategies and treatment to mitigate the negative impact of prematurity; 2. Neuroprotection strategies, including an examination of those factors that affect neurodevelopmental outcomes following perinatal neurological insults; 3. interventions to mitigate the effects of substance abuse disorders pre and postnatally.

Nephrology

The Nephrology Division has a significant focus on the discovery of molecular defects that cause rare genetic disorders affecting the regulation of mineral ion homeostasis; particularly on the identification of genetic mutations leading to different forms of pseudohypoparathyroidism and hypoparathyroidism, as well as on the molecular definition of disorders affecting the regulation of phosphate homeostasis. We identified a novel mutation in one of the GNAS exons encoding Gs-alpha, which leads to a very complex phenotype that includes hyponatremia during the neonatal period, agonist-independent precautious puberty, PTH-resistance in the proximal renal tubules, yet evidence for hyperparathyroid bone disease. In vitro the mutant Gs-alpha leads to constitutive cAMP formation when co-expressed with some G protein-coupled receptors, yet resistance when some of these receptors are activated by their cognate ligands indicating that the mutant G-protein interacts differently with different receptors. We furthermore identified a novel splice-side mutation in PTHrP, which leads to a truncated, biologically inactive peptide, thereby explaining the autosomal dominant, shortening of metacarpals and -tarsals. In part based on our retrospective outcome study on Jansen's metaphyseal chondrodysplasia, a very rare disease caused by activating mutations in the PTH/PTHrP receptor and based on our studies describing the efficacy of inverse PTH agonists in vitro and in vivo, we are now supported through the NIH-TRND program. This will facilitate production of large amounts of GMP-grade inverse agonist PTH peptide for toxicology studies in animals and for the first clinical trials in humans affected by this disease. In addition to these genetic studies, we have shown in wild-type mice and animals lacking FGF23 that a novel, orally active NPT2a inhibitor can increase urinary phosphate excretion thereby lowering blood phosphate levels in the latter animals that typically develop severe hyperphosphatemia and die prematurely. Furthermore, the NPT2a inhibitor appears to be efficacious in models of acute and chronic kidney disease, and could thus be beneficial in preventing hyperphosphatemia, vascular calcifications, and elevations in FGF23 levels in patients with these disorders. In addition to these efforts on disorders affecting calcium and phosphate homeostasis, Dr. Tan continues to contribute significantly to the identification of the molecular defects underlying steroid-resistant nephrotic syndrome (SRNS) and various inherited renal disorders. He documented in numerous families known causative mutations in 20 different genes and identified novel candidate genes through the analysis of additional consanguineous and non-consanguineous families. These efforts to identify the underlying genetic defects will allow disease-specific interventions using established medications and will help in the search for novel therapies.

Neurology

The neurology department seeks to directly improve child health through cutting-edge translational projects. These include a bench-to-bedside effort to find more effective therapies for neonatal seizures, improving the detection of active disease in adrenoleukodystrophy, and optimizing genetic therapies and response metrics for leukodystrophies and spinal muscular atrophy, and dietary therapy for hereditary sensory and autonomic neuropathy type 1. Basic studies are focused on metabolic disorders including sulfite oxidase deficiency and the genetic origins of mitochondrial disorders; corticothalamic dysfunction underlying comorbidities of epilepsy including learning disabilities and sleep disorders; the driving forces for neurotransmitter-mediated neuronal inhibition. Clinical studies include characterizing genetically-based epilepsies and neurocutaneous syndromes and testing new therapies for intractable childhood epilepsies. Highlights for 2019 include a paper in Neurology describing MRI findings in adrenoleukodystrophy, a study published in the Journal of Neuroscience describing how seizures start and stop; a trial of dietary therapy for hereditary sensory and autonomic neuropathy type 1 published in Neurology; a paper describing the phenotype of a mitochondrial disorder manifesting with ataxia; and a study describing EEG measures of seizure recurrence risk published in Brain.

Pediatric Palliative Care

In 2019, we embarked on a pilot of a novel model of care for children with serious illness. We have combined the medical home model of the Coordinated Care Clinic with the predominantly inpatient palliative care service to provide more comprehensive and seamless care to a small population of children whose care represents the most expensive and intensive. These patients are characterized by frequent or prolonged admissions to hospital and repeated transitions from home to hospital to outpatient and community services.

Pulmonary

The research focus of the Pulmonary Division encompasses 6 areas.
The first area of research, led by Drs. Bernard Kinane and Lael Yonker, is the genetic basis of lung disease including interstitial lung disease and non-cystic fibrosis bronchiectasis. In collaboration with the Partners Center for Personalized Medicine, we have developed standard diagnostic approaches that are used across the Nation.

The second area, led by Dr. Lael Yonker, is an effort to develop new models of the cystic fibrosis (CF) airway. Dr. Yonker established a cellular model of the CF airway and has defined how bacteria interact with this model system thus broadening our understanding of airway inflammation. She is expanding the model to define how leukocytes from patients with specific diseases might have attenuated airway immune responses.

The third area, led by Drs. Lael Yonker and Shannon Fracchia, is clinical research looking at the use of correctors and potentiators of CFTR to treat cystic fibrosis. This year they were key participants in the clinical trial for the triple combination with tezacaftor and ivacaftor (VX-659-tezacaftor-ivacaftor) to treat cystic fibrosis patients with the most common mutation. This work in part was included in an FDA submission.

The fourth area lead by Drs. Lael Yonker and Bethany Bartley focuses on CF palliative care. They designed primary palliative care interventions in order to provide chronic symptom management at all stages of the disease. Also, they worked on advance care planning (ACP) which is recommended for people with CF. They found that people with CF worry about advanced disease and feel comfortable discussing ACP, but need more guidance to understand and document ACP choices.

The fifth area, led by Dr. Kinane, focuses on genetic correctors for Duchenne's muscular dystrophy (DMD). Dr. Kinane has now demonstrated that eteplirsen reduces pulmonary function decline in patients with DMD. In the next year, he will extend this work for other novel correctors of DMD.

Finally, in the area of education research, Dr. Ben Nelson established a novel mentor program for residents and fellows and is assessing the utility and feasibly of such programs.

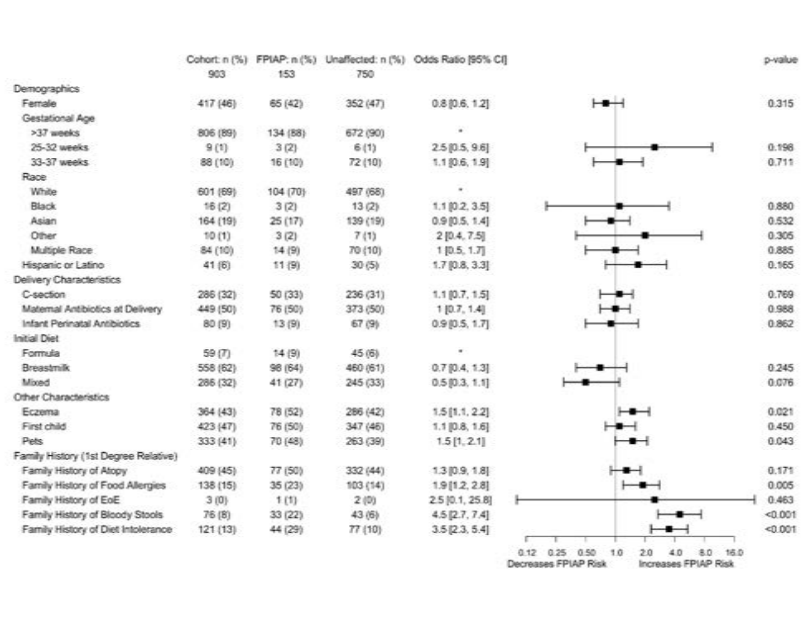
Rheumatology

Investigators in the Pediatric Rheumatology Program lead and participate in clinical research that include observational research studies and randomized clinical trials, as well as investigator-initiated outcomes and adverse event studies, across a wide range of childhood-onset rheumatic diseases. As part of such research efforts, we recently began enrollment of patients as a member site of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, which is a long-term, multi-site prospective observational study focused on safety and disease outcomes that combines FDA Phase IV post-marketing surveillance with outcomes research. In addition, MGH will be an enrolling site for the LIMIT-JIA clinical trial, funded by Patient-Centered Outcomes Research Institute – this is the first FDA Phase III study of prevention of disease progression in patients with limited Juvenile Idiopathic Arthritis (JIA), the most common subtype of JIA. As part of these studies, MGH is also participating in the development of advanced clinical informatics strategies, including development of computable phenotypes for JIA, to improve the efficiency of enrolment for rare disease studies, under the leadership of Marc Natter as site PI.
Other research in our program focuses on creating and improving guidelines for the safety monitoring of children receiving rituximab and strategies for preventing immunosuppression-related infections among high-risk patients with pediatric-onset rheumatologic diseases. Deborah Rothman has received a grant from CARRA to study the association between rituximab and infection risk. We are currently performing a retrospective study of children (<18 years old) who received rituximab using data using EHR data from subjects at MGH and other sites that assesses risk factors such as the immunoglobulin deficit to infection risk following rituximab treatment.

Notable Achievements 2019

Allergy & Immunology

Prospective Identification of Risk Factors for the Development of Food Allergy Early in Life
From the Gastrointestinal Microbiome and Allergic Proctocolitis (GMAP) cohort, we have for the first time prospectively defined the cumulative one year incidence of food protein induced allergic proctocolitis (FPIAP) in a U.S. suburban cohort to be 17% and we have evaluated risk factors for the development of this early form of food allergy, predominantly triggered by cow's milk allergen.

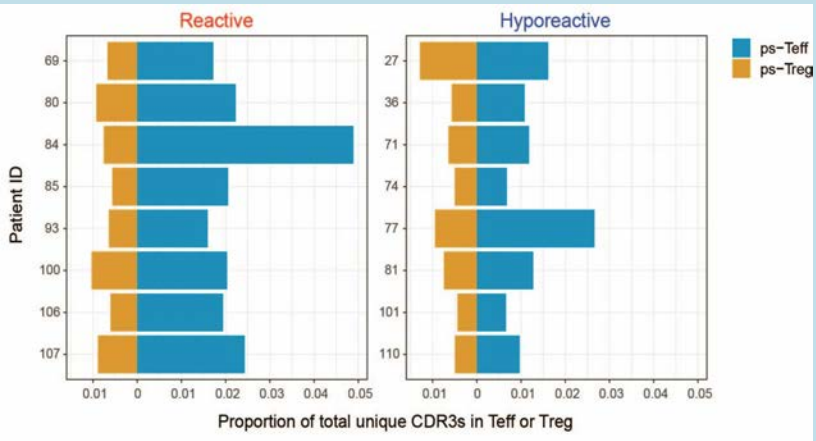


Breastfeeding from the time of initial feeding when combined with formula was associated with almost half the rate of AP ($p<0.05$). Mode of delivery, perinatal antibiotic exposure, and presence of siblings were not associated with AP (not shown), however eczema as well as a family history of food allergies,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

It remains unclear if FPIAP increases the risk of developing IgE-mediated food allergies (FA); it is additionally unclear if FPIAP is part of the atopic march or if the food avoidance necessary to treat AP predisposes to FA by preventing early food introduction.

We used a prospective observational cohort of 903 healthy newborn infants to evaluate the rates of FPIAP and FA in young children. FPIAP was diagnosed by the treating physician with diagnosis requiring blood in the stool. FA was determined by independent agreement of two allergist reviewers based on clinical reactivity and documented IgE sensitivity. Of 903 infants analyzed, 153 (16.9%) children were diagnosed with FPIAP and 56 (6.2%) children were diagnosed with FA. Seventeen (11% of FPIAP; 1.9% of whole cohort) children with FPIAP were diagnosed with FA, while 39 (5%) children without FPIAP developed FA ($p=0.099$). Children with FPIAP were significantly more likely than healthy controls to develop FA to milk (3.9% v. 0.5%, $p<0.001$) and egg (5.9% v. 2.5%, $p<0.04$). There were non-significant trends toward higher rates of FA to peanut as well. Infants with FPIAP were significantly more likely to develop IgE-mediated food allergies to milk and egg, with trends toward higher rates of FA to other foods. FPIAP may represent an early step on the atopic march, possibly compounded by subsequent allergen avoidance, to potentially increase the risk of developing some IgE-mediated food allergies. Longitudinal evaluation of microbiota composition continues in collaboration with Ramnik Xavier as part of the newly established Food Allergy Science Initiative at the Broad Institute.

Peanut Allergy Phenotypes



Peanut allergy is an IgE-dependent condition, however, the clinically observed variability in clinical sensitivity is not adequately explained by assays of peanut allergen-specific IgE. We hypothesize that characterizing differences in the antigen-specific CD4+ T cell phenotypes and the TCR repertoire within various T cell compartments – given their role in disease pathogenesis – may be useful biomarkers of the differences in clinical sensitivity and help meet this important clinical issue. Using an assay to identify antigen specific T cells (CD154 expression after in vitro stimulation), we evaluated the TCR repertoire diversity and size within effector (Teff) or regulatory (Treg) CD4 T cell compartments. Using this approach, we found that the relative expansion of the Teff compartment was associated with greater clinical sensitivity to peanut exposure – defined by the gold standard, double blind placebo controlled food challenges. This phenotypic difference is now being tracked longitudinally as patients undergo immunotherapy to peanut (i.e., desensitization).

Critical Care

With funding from NINDS, Dr. Whalen's lab has developed models of repetitive mild traumatic brain injury (TBI) in adolescent and adult mice and reported that aberrant inflammasome activation in brain endothelium is a potential new therapeutic target to reduce learning and memory deficits. Non-invasive vagal nerve stimulation inhibited brain endothelial IL-1 activation and reduced learning deficits after a single severe concussive injury in mice, suggesting a road to translation for patients1. In a collaboration with the Vaccine and Immunotherapy Center (Mark Poznansky, Co-PI), the Whalen lab is developing cell-based therapy for contusion TBI using autologous B cell transplantation into injured brain. A third translational project is pharmacological MRI to detect dopaminergic dysfunction in striatum as a biomarker of repetitive concussions. Dr. Josephine Lok published on the regulation of oligodendrocyte precursor cell (OPC) survival and differentiation2. OPCs are important as a source of new oligodendrocytes, the cells that produce the myelin sheath around axons. In the setting of brain injury, it is important to find ways to rescue OPCs and to promote their differentiation into mature new oligodendrocytes so that the conduction of nerve impulses can continue along myelinated axons. Dr. Flaherty led studies in pediatric injury caused by firearms violence, falls, and burns and was lead author on a study identifying lapses in screening high risk pediatric patients presenting to the emergency department for access to firearms. In that study he helped develop an electronic smart phrase to improve screening by pediatric residents3. In partnership with Shriners Hospital and the MGH Department of Burn Surgery, he published a study demonstrating an exponential increase in fire pit-related burn injuries in children and identifying common risk factors to aid in prevention efforts5. He also led the first multi-center study of New England pediatric trauma centers looking retrospectively at the risk factors and trends in unintentional window falls, with the goal of guiding preventive and legislative efforts to reduce the incidence of window falls in children. Lastly, Dr. Carroll collaborated with MGH investigators in Respiratory Care to determine the actual positive end-expiratory pressure delivered by high-flow nasal cannulae5, a mode of respiratory support that has redefined how we care for critically ill infants and children with impending respiratory failure and dramatically reduced the number of patients who go on to need tracheal intubation. Dr. Carroll also continued his work to design simple, low-cost, live-saving, non-invasive ventilation devices so that children in low-resource settings presenting with respiratory distress have a better chance of survival.

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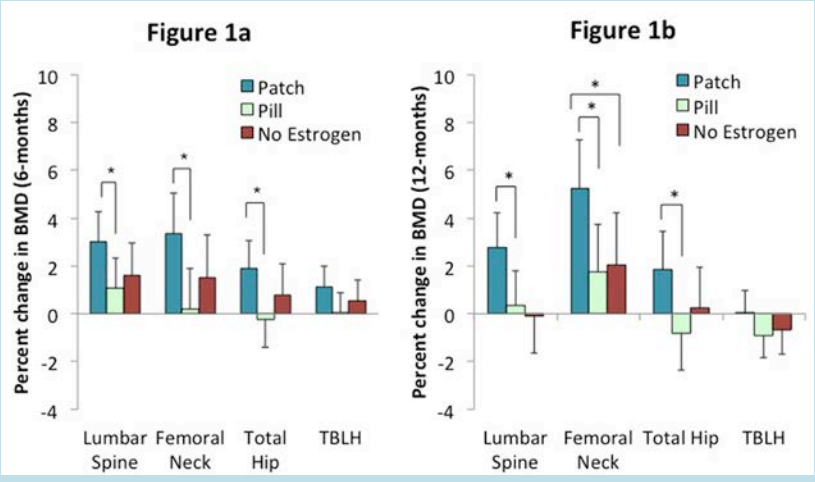
Endocrinology

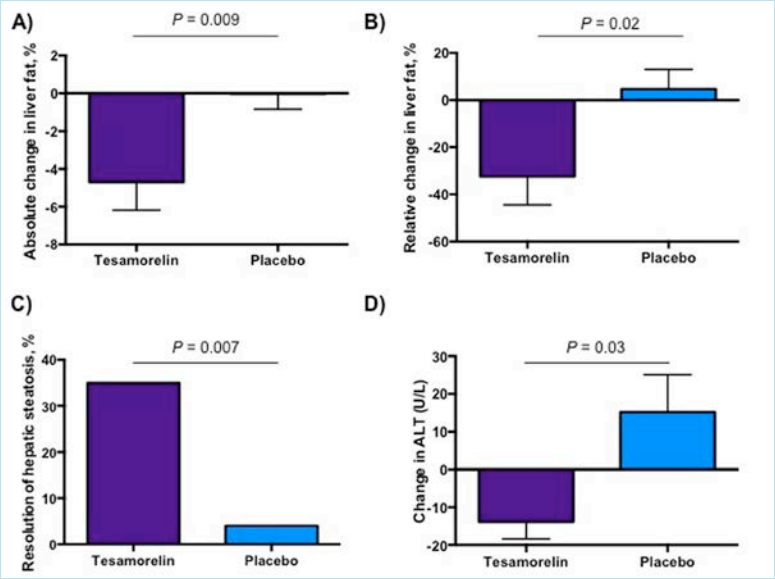


Percent change in bone mineral density (BMD) in completers at 6-months (Figure 1a) and 12-months (Figure 1b) in the PATCH, PILL and No estrogen arms. *Significant at p<0.05. Ackerman et al. Br J Sports Med. 2019 Feb;53(4):229-236

In the past year, Dr. Misra's laboratory reported bone outcomes from a randomized controlled trial of transdermal 17β-estradiol vs. oral ethinyl estradiol vs. no estrogen in 14-25-year-old oligoamenorrheic athletes (OAA). The study showed that transdermal estradiol over 12 months (with cyclic progesterone) improved bone mineral density (BMD) at the spine and femoral neck in young OAA, particularly compared to an ethinyl estradiol-containing oral contraceptive pill (Figure 1). These data indicate that while addressing energy availability and lifestyle remains the first line of management in OAA, transdermal 17β-estradiol may be a therapeutic adjunct to optimize bone accrual, particularly during the critical adolescent and young adult years. This manuscript is now published in the British Journal of Sports Medicine (Impact factor 11.6).

In a subsequent paper, the authors examined mechanisms that may explain the differential effects of transdermal 17β-estradiol vs. oral ethinyl estradiol on bone. The study demonstrated that transdermal 17β-estradiol given over 12 months does not cause the decrease in IGF-I (a bone trophic hormone) or increase sex hormone binding globulin levels (associated with a decrease in bioavailable sex steroids) observed with oral ethinyl estradiol. Transdermal 17β-estradiol also results in decreases in sclerostin, Pref-1 and BDNF, all of which are otherwise deleterious to osteoblastic activity, suggesting additional mechanisms that may mediate the beneficial effects of transdermal estradiol on bone. This manuscript is now published in the Journal of Clinical Endocrinology and Metabolism (Impact factor 5.6).

Dr. Stanley recently published a multi-center randomized controlled trial of tesamorelin vs. placebo in HIV-infected individuals with nonalcoholic fatty liver disease (NAFLD), and demonstrated that tesamorelin, a growth hormone releasing hormone analog, significantly decreased liver fat quantity and also prevented progression of hepatic fibrosis (Lancet HIV 2019 14.7). Tesamorelin is FDA approved to reduce visceral fat in individuals living with HIV, and this study demonstrates that it appears to have the additional benefit of reducing hepatic fat and potentially ameliorating progression of liver damage. This may also have implications for the general population, as there are few pharmacologic strategies for nonalcoholic fatty liver disease (NAFLD), and augmenting growth hormone in those who have reductions in growth hormone due to obesity may be a useful part of a multi-pronged strategy to address NAFLD.



Change in absolute (A) and relative (B) liver fat content between baseline and 12 months, with p-values shown for t-test comparing change between groups. Data are mean ± SEM. C: Percent resolution of steatosis, defined as 12-month hepatic fat fraction <5%, with P-value for Pearson Chi-Square. D: Change in ALT between baseline and 12 months for those with ALT ≥ 30 U/L at baseline, with p-value for t-test comparing change between groups. Data are mean ± SEM. Stanley et al. Lancet HIV. Epub ahead of print 11 Oct 2019. Doi: 10.1016/S2352-3018(19)30338-8.

Further, Dr. Sherwood published a pilot study in patients with cystic fibrosis related diabetes comparing usual care with automated glycemic control using the bihormonal (insulin and glucagon) and insulin-only configurations of the bionic pancreas (J Cyst Fibros. 2019; Impact factor 4.29). Both configurations of the bionic pancreas achieved good glycemic control, with mean glucose levels <150 mg/dl and minimal hypoglycemia. Subjects reported improved treatment satisfaction and reduced burden of diabetes management with the bionic pancreas.

Currently the Pediatric Endocrine faculty include three researchers with R01 funding, and two with K23 funding.

Gastroenterology, Hepatology & Nutrition
Mucosal Immunology and Biology Research Center
Celiac Disease, Genomic, Environmental, Microbiome and Metabolomic (CDGEMM) Study

The Celiac Disease, Genomic, Environmental, Microbiome and Metabolomic (CDGEMM) Study is an international, observational study of approximately 750 infants. By studying infants with a first-degree relative with celiac disease, we are examining environmental factors – such as method of birth delivery, use of antibiotics and breast or formula feeding – as well as the genetic makeup of the infants and their microbial "signature." Using blood, stool, and tissue samples from the mothers as well as the children, along with extensive food and antibiotic use diaries, demographic data, and microbial sequencing data, we are amassing an enormous amount of data to study celiac disease development with the goal of preventing the disease before it occurs. The retention rate of participants is 91% in the United and 84% in Europe;. extensive resource materials, social gatherings and an interactive Facebook group aids in this retention. The Institutional Review Board has approved the continuation of the study for another five years, until participants reach the age of 10 years.

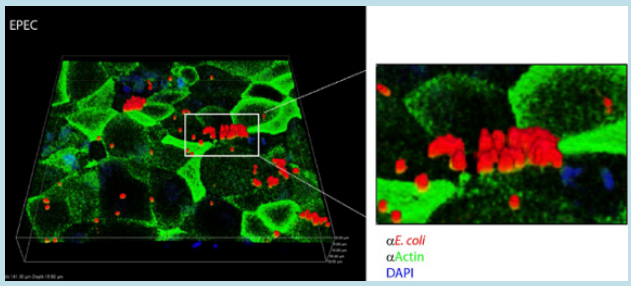
We developed the CDGEMM study following the results of a pilot study of 47 infants, which investigated the timing of introducing gluten into the diet and the resulting changes in the microbiota during the introduction of solid food. Findings from the pilot suggested that understanding how the microbiota of infants with a genetic predisposition to celiac disease differ from infants without the predisposition might help predict celiac disease or another autoimmune disorder. We have enrolled more than 450 infants in Boston, Italy and Spain. Systems Biology Lead Dr. Ali

Zomorrodi joined our group in 2019. Among other tasks, he is performing deep analysis of microbial profiles of infants who develop celiac disease compared to healthy controls. Preliminary data from this small number of infants who have gone on to develop celiac disease show interesting differences in the development of the microbiome of at-risk celiac disease infants and healthy controls. Results from our recently concluded pilot study include:

- Colonization of the microbiome of infants at risk of developing celiac disease is influenced by underlying genetics at the species level.
- We identified significantly different microbial species in infants based on birthing delivery mode, feeding practices, and exposure to antibiotics at birth between from 7 days after birth to 6 months of age.
- Even before exposure to solid foods, including gluten, early environmental factors may predispose the microbiome of infants at risk of celiac disease toward inflammation and autoimmunity or toward immune tolerance and pathogen protection.

In other work, by using RNA sequencing of intestinal tissue from patients with active celiac disease, celiac disease in remission, and non-celiac controls, Dr. Leonard's group gained insights into how the disease develops and identified additional genetic signatures linked to celiac disease. By following up on results published in PloS One in April, our research could eventually lead to possible targets for future therapies to treat or prevent celiac disease. Drs. Fasano and Leonard co-authored a paper examining the correlation between celiac disease and type 1 diabetes (T1D). Through the implementation of a screening program, we were able to identify genetic predictors associated with an increased risk of developing celiac disease autoimmunity in T1D patients and their family members.

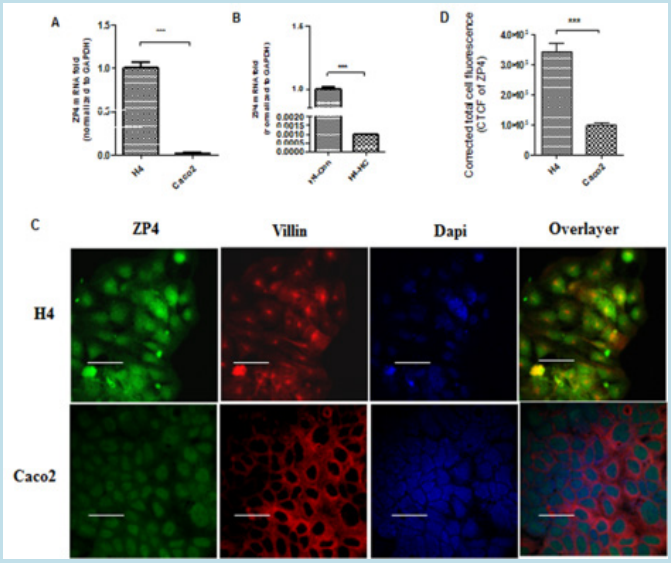
Development and Validation of Human Gut Organoids for the Development of Novel Therapeutic Strategies for Celiac Disease, Necrotizing Enterocolitis and Enteropathogens' Infection



We continue to make great strides in an innovative technique using intestinal tissue from people who have undergone clinically indicated endoscopies. By using this tissue, we have developed gut organoids to study the interaction between the gut tissue and the complex bacterial ecosystem in our intestine. The Program's Director, Dr. Stefania Senger, published a seminal paper in May that firmly establishes the use of "mini-guts" developed in her lab at Charlestown Navy Yard for the study of celiac disease and other conditions. Dr. Senger's team explored how the gut epithelium (layer of cells that form mucous membranes) and microbiota-derived molecules respond to gluten, the protein complex found in wheat and other grains that can trigger celiac disease. By using this human tissue model, Dr. Senger found that these mini-guts express the same molecular markers as the actual epithelium in the celiac tissue. She also discovered that gene expression in the celiac tissue reflects the functional differences that occur when the epithelium from a celiac disease patient is exposed to gliadin (a main component of gluten). Another result of the study shows that bioproducts derived from gut microorganisms can be employed to modify the epithelial response to gluten, a finding that could lead to future treatment strategies. Human intestinal organoids are part of a repository that counts now about 50 samples, derived from multiple regions of the small and large intestine. Based on our own and other studies, organoids express a gene profile that recapitulates the developmental stage and/ or the disease state of the tissue of origin. They can be stored frozen virtually endlessly and resuscitated and handled similarly to cell lines. We have used organoids to derive high throughput assays to study the effect of environmental factors on innate immune response and barrier function of the gut. Our work has generated significant advancement in understanding S. Typhi pathogenesis. We have also shed light on some important functional differences in the development of fetal intestine, which could be crucial in the development of necrotizing enterocolitis (NEC). We have also leveraged the organoids to study alternative strategies for enteropathogens that develop antibiotic resistance. Finally, we have used the organoids platform to study the intestinal epithelium of celiac patients. Our next step is to leverage this model from proof-of-concept to develop new strategies for the treatment of celiac disease, NEC and enteropathogens' vaccine development.

The discovery of Zona pellucida glycoprotein 4 (ZP4) as a new anti-inflammatory gene in human immature enterocytes by Transcription profile may provide a new potential therapeutic strategy for Necrotizing Enterocolitis

Dr. Walker's group has been focused their research effort on initial colonizing bacteria that seem to play a critical role in completing the development of the immune system in the gastrointestinal tract of infants. Yet, the interaction of colonizing bacterial organisms with



the developing human intestine favors inflammation over immune homeostasis. This characteristic of bacterial-intestinal interaction partially contributes to the pathogenesis of NEC, a devastating premature infant intestinal inflammatory disease. However, paradoxically some unique pioneer bacteria (initial colonizing species) have been shown to have a beneficial effect on the homeostasis of the immature intestine and the prevention of inflammation. We have reported that one such pioneer bacterium, Bacteroides fragilis (B. fragilis), and its surface component polysaccharide A (PSA) inhibit IL-1β-induced inflammation in a human primary fetal small intestinal cell line (H4 cells). In this study, using transcription profiling of H4 cellular RNA after pretreatment with or without PSA before an inflammatory stimulation of IL-1 β, we showed that zona pellucida protein 4 (ZP4), is uniquely elevated after IL-1 β stimulation and reduced with PSA exposure. ZP4 was known as a sperm receptor mediating species-specific binding protein in the initial life of mammals. However, its intestinal epithelial function is unclear. We found that ZP4 is a developmentally regulated gene involved with immune function and regulated by both Toll-like receptor 2 and 4. Knockdown of ZP4-affected PSA inhibited IL-8 mRNA expression in response to IL-1β. This represents an initial study of ZP4 innate immune function in immature enterocytes. This study may lead to new opportunity for efficient treatment of NEC.

Studying immune and microbial regulation of obesity induced by high-fat diet

The incidence of obesity and metabolic syndrome is rising globally and is expected to continue to increase. Epidemiological studies indicate an inverse correlation between the prevalence of the so-called western diseases, such as obesity and metabolic syndrome, and the exposure to helminths. However, the precise mechanism by which helminths modulate metabolic syndrome and obesity is not fully understood. Dr. Shi's research group has begun to shed light on this issue by establishing a novel mouse model of high-fat diet (HFD) induced obesity and helminth infection using the intestinal nematode parasite Heligmosomoides polygyrus. Our results show that infection with the small intestinal helminth parasite ameliorates HFD-induced obesity, and provide evidence that the helminth-dependent protection against obesity involves the induction of M2 macrophages. Ongoing studies examine the role of immune function and microbiota in the modulation of obesity. The mechanistic insights provided by these studies will facilitate the development of novel strategies for the better control and treatment of obesity, metabolic disorder, and other immune-mediated diseases.

Studying the Microbiome of the Blood

With new genetic sequencing techniques, we have been able to view bacteria in the blood as well as DNA. We are looking at how bacteria move into the blood under conditions of increased intestinal permeability found in individuals with active celiac disease. Increased intestinal permeability could play a role in the transport of bacteria found in the blood to other parts of the body. We are looking for differences in the microbial component of blood and how this might be expressed in healthy controls, people with celiac disease in remission, and people with active celiac disease. By using stool samples as well as blood samples to measure microbial communities, we can look for correlations in the microbial composition of blood and stool in the three different patient populations. Our pilot study shows that the blood microbiome of active celiac patients has a different composition and microbial diversity as compared to healthy controls and celiac patients in remission. The comparison between the fecal and hematic microbiomes highlights the differences between the two environments in terms of microflora composition and function. A better understanding of the hematic microflora could not only provide new insights into the onset of celiac disease, but also could be instrumental in the development of new therapies and diagnostic tools for this autoimmune disease. A pilot study underway in 2019 is looking at the blood microbiome composition in the pediatric population compared with adult samples.

Shigella flexneri Adherence Factor Expression in In Vivo-Like Conditions

Dr. Faherty's group made an important discovery regarding Shigella pathogenesis. It was previously hypothesized that Shigella does not express adherence factors to facilitate contact with epithelial cells due to gene annotations and a lack of visualization of structures following growth in laboratory media. However, as we published in 2017, exposure to signals in the small intestine (specifically glucose and bile salts), we detected an induced adherence phenotype. This publication demonstrates that both bile salts and glucose result in the production of adherence factors

Scanning electron microscopy image of Shigella flexneri adhering to the apical surface of colonic epithelial cells from HIODEM

in Shigella flexneri. Both signals are required for proper expression, and we identified 3 structural genes required for this phenotype. Most importantly, we demonstrate that these factors facilitate S. flexneri adherence to the apical surface of colonic epithelial cells. In doing so, we used the human intestinal organoid-derived epithelial monolayer (HIODEM) model to visualize and quantitate S. flexneri adherence. Combined with our 2017 publication, this work expands the Shigella infection paradigm: the pathogen utilizes signals during small intestinal transit to regulate virulence factor expression and prepare for infection in the colon.

Center for Pediatric Hepatobiliary and Pancreatic Disease

We have successfully obtained the INSPPIRE 3 grant. This is a NIH multi-center study that is looking at all aspects of acute and chronic pancreatic disease in adult and pediatric patients. We published 12 articles with several abstracts and oral presentations at the Pancreas Conference, DDW and NASPGHAN. INSPPIRE 3 will be looking at chronic pancreatic disease, pancreatic insufficiency and the development of diabetes and malignancy. We have also concluded our aims for The Pediatric Sclerosing Cholangitis study that is based out of Utah. And are now moving into PSC 2, that will be looking at cholangiocarcinoma, the genetics of PSC and novel therapies in the management of pediatric PSC. Our group has received approval to be part of the Cystic Fibrosis TDN grant called PROMISE. This is a prospective, multi-center observational study. The study is designed to measure the clinical effectiveness of elexacaftor, tezacaftor and ivacaftor triple combination therapy (TCT) in people with one or more copies of the F508del mutation, study the effects of TCT across a number of CF disease manifestations, and collect specimens for future research. Subjects in the study will have one "before TCT" visit within 30 days before initiation of the therapy and five "after TCT" visits over a 24-month follow-up period. Most participating sites will be divided into sub-study groups; each sub-study group will have specific non-optional procedures conducted in addition to the "Core" procedures. Finally, there are four optional procedures (pH pill, transient elastography, and nasal cell procurement) that will be offered to subjects at certain sites. The duration of participation for each subject is 25 months.

General Academic Pediatrics

Treating parents for tobacco dependence and preventing children's exposure to cigarette smoke and electronic cigarette aerosol

The Clinical Effort Against Secondhand Smoke Exposure (CEASE) program aims to change pediatric primary care so that every parent who uses tobacco is offered evidence-based treatment during their visits to their child's doctor. CEASE also aims to prevent children's secondhand and thirdhand exposure to tobacco smoke and e-cigarette aerosol. According to CDC data, approximately 38% of US children between the ages of 3 and 11 are exposed to secondhand smoke from tobacco products. The current study was a cluster randomized clinical trial that included 10 pediatric practices in 5 states (North Carolina, Tennessee, Virginia, Ohio, and Indiana). Practices randomized to the CEASE condition were trained to use an electronic screening survey to identify families with a tobacco user and then provide prescriptions for FDA-approved nicotine replacement therapy, offer enrollment to the state's free tobacco cessation quitline and provide instructions to register for a National Cancer Institute text messaging cessation program. Results showed parents who visited CEASE practices received meaningful smoking cessation treatment (defined as prescription of nicotine replacement therapy or quitline enrollment) at much higher rates than parents who visited usual care control practices. A statistically significant reduction in the practices' parent smoking rate was found in CEASE practices compared to control practices at the end of the 2-year study. CEASE practices had a 2.7% decline in population smoking rate whereas control practices had an increase of 1.1%, confirmed by parents' salivary cotinine levels.

NabiBurza E, Drehmer JE, Hipple Walters B, Rigotti NA, Ossip DJ, Levy DE, Klein JD,
Regan S, Gorzkowski JA, Winickoff JP. Treating Parents for Tobacco Use in the Pediatric Setting: The Clinical Effort Against Secondhand Smoke Exposure Cluster Randomized Clinical Trial. JAMA Pediatrics. doi: 10.1001/jamapediatrics.2019.2639. [Advance online publication August 12, 2019].

Risk Factors Associated with Opioid Overdose

The opioid overdose crisis is one of the biggest public health problems in the United States today. Our research continues to investigate factors that are associated with an increased odds of opioid overdose among vulnerable and high risk populations including postpartum women and youth.

Opioid-related overdose is increasingly linked to pregnancy-associated deaths, but factors associated with postpartum overdose are unknown.

In retrospective cohort study using a linked, population-level data set, we aimed to estimate the strength of the association between maternal and infant characteristics and postpartum opioid-related overdose. The primary outcome was opioid-related overdose in the postpartum year. We used multivariable logistic regression to explore the independent associations of maternal (demographics, substance use, pregnancy) and infant [gestational age, birthweight, neonatal abstinence syndrome (NAS)] characteristics with postpartum opioid overdose. Findings were stratified by maternal opioid use disorder (OUD) diagnosis. We found that among women who delivered live infants in Massachusetts, USA between 2012 and 2014, maternal diagnosis of OUD, prior non-fatal overdose, infant diagnosis of NAS and high unscheduled health-care utilization appeared to be positively associated with postpartum opioid overdose. However, more than half of postpartum overdoses in that period were to women without a diagnosis of OUD. Engagement in methadone or buprenorphine treatment in the month prior to delivery was not sufficient to reduce the odds of postpartum overdose.

Nielsen T, Bernson D, Terplan M, Wakeman SE, Yule AM, Mehta PK, Bharel M, Diop H, Taveras EM, Wilens TE, Schiff DM. Maternal and infant characteristics associated with maternal opioid overdose in the year following delivery. Addiction. 2019 Nov 06. PMID: 31692133.

Chronotype, Social Jet Lag, and Cardiometabolic Risk Factors in Early Adolescence

Inadequate sleep duration and quality increase the risk of obesity. Sleep timing, while less studied, is important in adolescents because increasing evening preferences (chronotypes), early school start times, and irregular sleep schedules may cause circadian misalignment.

To investigate associations of chronotype and social jet lag with adiposity and cardiometabolic risk in young adolescents, we conducted a cross-sectional study of 804 adolescents aged 12 to 17 years in Project Viva, a pre-birth cohort study. Adolescents completed 5 days or more of wrist actigraphy, questionnaires, and anthropometric measurements. Chronotype was measured via a continuous scale with higher scores indicating greater evening preferences, and social jet lag was measured as the continuous difference in actigraphy sleep midpoint in hours from midnight on weekends vs weekdays, with higher values representing more delayed sleep timing on weekends. Adiposity was measured via anthropometry and dual-energy x-ray absorptiometry. For a subset of 479 adolescents with blood samples, cardiometabolic risk scores were computed as the mean of 5 sex- and cohort-specific z scores for waist circumference, systolic blood pressure, inversely scaled high-density lipoprotein cholesterol, and log-transformed triglycerides and homeostatic model of insulin resistance. We found that evening chronotypes and greater social jet lag were associated with greater adiposity in adolescent girls, but not boys, independent of sleep duration. There were no associations with a cardiometabolic risk score. This suggests that female adolescents may be more vulnerable to the obesogenic effects of circadian misalignment. Therefore, obesity prevention efforts should consider regular sleep-wake patterns in addition to sleep extension and sleep quality improvement.

Cespedes Feliciano EM, Rifas-Shiman SL, Quante M, Redline S, Oken E, Taveras EM. Chronotype, Social Jetlag, and Cardiometabolic Risk Factors in Early Adolescence. JAMA Pediatrics. 2019 Sep 16. [Epub ahead of print]

Genetics and Metabolism

Down Syndrome Clinic to You (DSC2U), funded with a $2.1M grant from PCORI and additional $350,000 in philanthropic donations, was created by Dr. Brian Skotko and a team of researchers from the MGH Down Syndrome Program, MGH Laboratory of Computer Science, MGH Mongan Institute Health Policy Center, and MGH Biostatistics Center. DSC2U brings the resources of a highly specialized and renown Down Syndrome Clinic to caregivers and providers everywhere. This website allows caregivers to supply information about their loved one with Down syndrome and in return receive up-to-date, personalized health and wellness information as well as the most current recommendations for care that they can share with their primary healthcare provider. In a national randomized control trial, DSC2U was shown to be effective in improving healthcare outcomes for people with Down syndrome. Both families and primary care physicians, alike, found the tool to be helpful and well-designed.

Formulation of International Clinical Care Guidelines in Pitt Hopkins Syndrome

Drawing upon the knowledge and experiences of an international team of leading experts in Pitt Hopkins syndrome, including David Sweetser, Director of the MGH Pitt Hopkins Syndrome Clinic, the first consensus clinical care guidelines for Pitt Hopkins syndrome were developed.

Zollino M*, Zweier C*, Van Balkom ID*, Sweetser DA*, Alaimo J, Bijlsma EK, Cody J, Elsea SH, Giurgea I, Macchiaiolo M, Smigiel R, Thibert RL, Benoist

I, Clayton-Smith J, De Winter CF, Deckers S, Gandhi A, Huisman S, Kempink D, Kruisinga F, Lamacchia V, Marangi G, Menke L, Mulder P, Nordgren A, Renieri A, Routledge S, Saunders CJ, Stembalska A, Van Balkom H, Whalen S, Hennekam RC. Diagnosis and management in Pitt-Hopkins syndrome: First international consensus statement. Clin Genet. 2019 Apr;95(4):462-478. (*contributed equally to this work).

Development of a National Mitochondrial Care Network

The mitochondrial medicine society (MMS) has previously highlighted the clinical landscape and physician practice patterns of mitochondrial medicine in the US and attempted to develop consensus criteria for diagnosis and management to improve patient coordinated care. Most recently, and in collaboration with US-based patient advocacy groups, we developed a clinical care network to formally unify US-based clinicians who provide medical care to individuals with mitochondrial disease; to define, design and implement best practices in mitochondrial medicine building on the current consensus guidelines and to improve patients' clinical outcomes. Here we review the steps taken in collaboration with several stakeholders to develop goals and expectations for a mitochondrial care network (MCN), criteria for MCN site selection and formal launch of the network.

Amel Karaa, Amy Goldstein, Cristy Balcells, Kira Mann, Laura Stanley, Philip E. Yeske, Sumit Parikh. Harmonizing care for rare diseases: How we developed the mitochondrial care network in the United States. Molecular Genetics and Metabolism, Volume 127, Issue 2, 2019, Pages 122-127, ISSN 1096-7192.

Global Health

Advances in cholera research. Jason Harris, an NIH funded investigator, collaborates with investigators in Bangladesh and Haiti to study immunity to cholera and cholera vaccines. During the past year, these research teams made significant contributions including:

- The discovery that long-lasting immunity following oral cholera vaccination is associated with O-antigen specific memory B cell responses (PLoS NTD)
- The discovery that live but not heat inactivated V. cholerae stimulates IL-23 in a manner which is also dependent on active cholera toxin (mSphere)
- Developing immunologic approaches to measuring cholera incidence, though modeling of using cross-sectional serologic data (papers Sci Transl Med and in preparation)

Advances in pediatric HIV. Dr. Kate Powis' work focuses on new treatments for infants diagnosed or exposed to HIV at birth or in utero. With a group of collaborators, Dr. Powis recently completed a study, to be published in JAMA, revealing that antiretroviral prescribing practices in the United States do not correspond well with treatment guidelines. As an expert in pediatric HIV care, Dr. Powis has been recruited to join a task force coordinated jointly by the World Health Organization and UNICEF to optimize the early childhood development of children affected by HIV worldwide. Additionally, in 2019, she received R01 NIH grant to support her research examining the immune correlates of Tuberculosis and HIV in a cohort of Botswanan and South African children exposed to HIV in utero.

Advances in respiratory disease treatment. Dr. Peter Moschovis has dedicated his efforts to improving the treatment of pneumonia, a leading cause of death in young children worldwide. This year Dr. Moschovis secured a K23 funding, a key NIH Career Development award, to support his efforts in identifying the preventing respiratory disease in children who are at the highest risk of dying from pneumonia.

Advances in neonatal care. Dr. Brett Nelson's research focuses on improving the critical care of newborns, particularly in resource-limited settings where children are impacted by poverty, conflict, or disaster. This year, Dr. Nelson was recognized for his contributions to research with the Distinguish Alumnus Award from the Bloomberg School of Public Health at Johns Hopkins University.

Hematology/Oncology

Ewing sarcoma is the second most common bone tumor diagnosed in children and is characterized by a genetic alteration in which the EWRS1 gene on chromosome 22 is most commonly fused to the FLI1 gene on chromosome 11 leading to the fusion protein EWS-FLI1. The Rivera lab has been investigating how the EWS-FLI1 fusion protein regulates gene expression. In Ewing sarcoma, the EWS-FLI1 protein induces chromatin features typical of active enhancers at GGAA microsatellite repeats. In this study they found that a subset of GGAA repeats is transcriptionally active in Ewing sarcoma and that silencing individual repeat leads to markedly reduced expression of target genes. Epigenome silencing of a GGAA repeat that controls SOX@ expression is sufficient to impair the growth of Ewing sarcoma xenografts. Epigenome editing reveals how a

fusion protein found in cancer cells enhances the expression of normally inactive GGAA microsatellites in Ewing sarcoma. Finding regulatory regions, such as enhancers in the genome that are specifically utilized in tumors but not in normal cells, may lead to new therapeutic targets. Genes and Development 2018;32(15-16):1008-1019.

The Göbel lab continues their novel research in C. elegans to study cell polarity and lumenogenesis. All internal organs and the vasculature are built of tubes. Tubes are polarized epithelia or endothelia with distinctive luminal surfaces, constructed for horizontal transport and vertical exchange of liquids, solids, and gases. Defects in tube development and maintenance cause congenital organ and vascular malformations and internal organ dysfunction and vessel disease. Findings in their most recent study characterize a novel mechanism of capillary-like lumenogenesis, where a tensile trilayered cytoskeletal endotube transforms concentric into directional growth. J Cell Biol 2019;Vol 218(7):2403-24.

Fever and neutropenia are the most common toxicities associated with cancer chemotherapy. Friedmann and her colleagues designed a clinical pathway for primary outpatient management of pediatric patients with low-risk febrile neutropenia. Following implementation of this pathway, the majority of patients designated as low-risk were managed primarily in the outpatient setting without major morbidity or mortality. Pediatr Blood Cancer 27 March 2019.

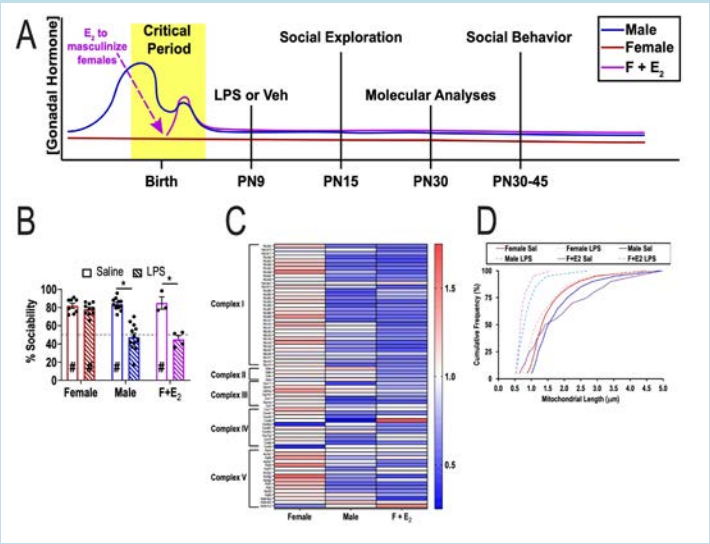
Infectious Disease

Dr. Jason Harris has been actively characterizing the B cell response to cholera and cholera vaccines analyzed at the individual cell / antibody level. (see also Global Health). He has identified the basis of partial serotype specificity and long-term memory against the O antigen, and demonstrated that this serologic reactivity is responsible for protection against clinical infection. In addition, he has demonstrated that changes in the human gut microbiome helps to determine susceptibility to cholera infection.

Dr. Warren has continued his work on heme binding agents to block inflammation and is seeking support to test hemopexin in ARDS in clinical trials. He is also continuing his DARPA funded work focused on understanding the underlying mechanisms explaining the natural innate resistance of rodents and certain other species to pro-inflammatory agonists.

Lurie Center for Autism

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 2019, we have made great progress in advancing our pre-clinical basic science research. Given the male-biased (~4:1 males to females) prevalence of Autism Spectrum Disorder (ASD), our ongoing work is to develop animal models to determine sex-specific alterations in the biological mechanisms that are relevant for ASD-like behavioral, anatomical, physiological and molecular changes. First, we have evidence that a perinatal immune challenge in a mouse model results in male-biased social behavioral deficits, significant neuroimmune alterations and changes in mitochondrial energetics, all of which are precipitated by natural hormonal exposure near birth (see #1 below). Second, our ongoing work in a mouse model of combined prenatal maternal diesel exhaust exposure and maternal stress, which recapitulates two highly relevant risks factors for ASD, reveal that offspring born to exposed mothers are characterized by significant social behavior deficits, neuroimmune alterations, gastrointestinal alterations, and gut microbial changes (see #2 below), with many effects more pronounced in males. Third, as individuals with ASD are often characterized by both brain and gastrointestinal



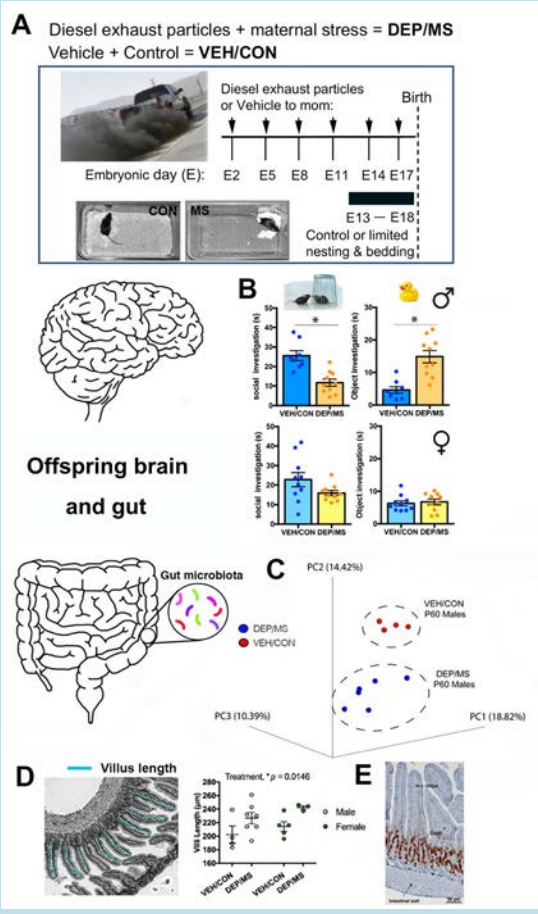
Sex hormones regulate sex-biased vulnerability to perinatal immune challenge. (A) Experimental timeline. Injection of the active form of testosterone (E2) during a perinatal critical period masculinizes female mice. The bacterial endotoxin LPS or saline vehicle are then injected on postnatal day 9 as an immune challenge. (B) Perinatal LPS induces deficits in sociability in males (blue) and masculinized female mice (F + E2, pink), but not in female mice (red). (C) Perinatal LPS induces downregulation of mitochondrial genes (blue shading) within microglia in males and masculinized female mice, but not female mice. (D) Perinatal LPS induces mitochondrial fragmentation (leftward shift of line) within microglia in males (purple vs. blue line) but not in female mice (red vs. orange line).

inflammation, we continue to investigate how the modulation of the anti-inflammatory hormone oxytocin at birth impacts the development of brain circuitry, gastrointestinal structure, gut microbiome colonization and social behavior in offspring. We have found significant sex-dependent and dose-dependent effects of oxytocin concentration at birth on the developing brain and gastrointestinal system of offspring (see #3 below). This research is funded by NIH grants, philanthropic donations and ECOR support. The pre-clinical arm of the Lurie Center and the clinical arm continue to participate in regular "think tank" meetings for the interaction and cross-fertilization of clinical and basic research concepts.

Three notable findings from this year:

1. Sex hormones may be responsible for perinatal immune challenge-induced deficits in social behavior and altered mitochondrial function in microglia.

We have demonstrated that a perinatal immune challenge (Fig. 1A) results in social deficits in male but not female mice (Fig. 1B). This perinatal challenge also induces marked downregulation of genes encoding mitochondrial bioenergetic proteins within microglia, the innate immune cells of the brain (Fig. 1C). Consistent with this downregulation of mitochondrial genes, we find an increase in microglial mitochondrial fragmentation (Fig. 1D), as well as impairment in microglial mitochondrial respiration in males only. To determine why males are particularly vulnerable to this perinatal immune challenge, we studied the male-specific surge in gonadal hormones that occurs during a critical period surrounding birth that is also responsible for masculinizing the male brain. Injection of female pups with a male sex hormone during this perinatal critical period has been shown to divert the female brain phenotype towards a masculinized male-like state (Fig. 1A). We showed that this masculinization induces vulnerability to subsequent immune challenge, as masculinized female pups subjected to perinatal immune challenge displayed deficits in social behavior (Fig 1B) and microglial mitochondrial gene downregulation (Fig. 1C), similar to normal males given an immune challenge. We believe that these data have relevance for the sex bias in ASD and may lead to drugable targets for potential treatments.

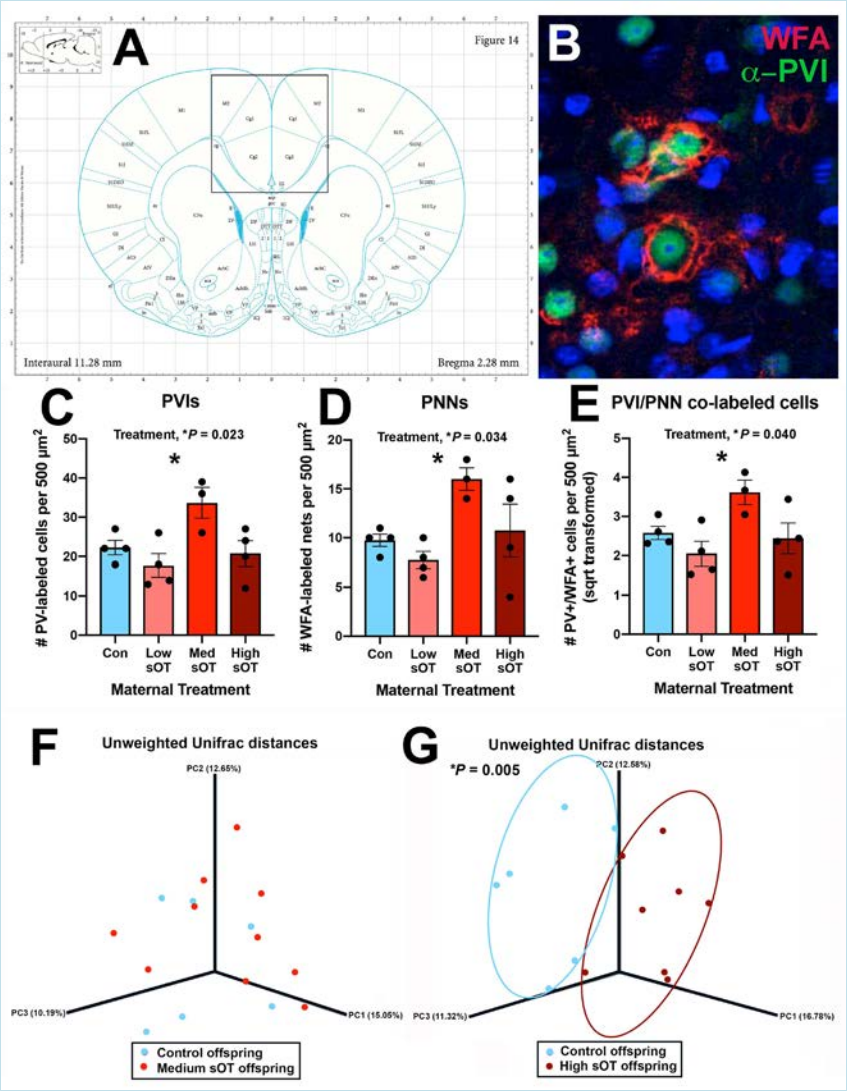


Combined prenatal exposure to diesel exhaust particles and maternal stress alters social behavior, gut microbiota and gastrointestinal structure in offspring. (A) Experimental methodology. Pregnant mice are exposed to either diesel exhaust particles (DEP) or vehicle (VEH) on embryonic day (E) 2, E5, E8, E11, E14 and E17 and either a maternal stressor of limited nesting and bedding (MS) or control bedding (CON) from E13-18. (B) Male offspring born to DEP/MS exposed mothers prefer to interact with an inanimate object (rubber duck) rather than another mouse on postnatal day (PND) 45, as compared to male control offspring born to VEH/CON dams. No social deficits were observed in female offspring from either group. (C) A principal coordinates analysis demonstrates that DEP/MS male offspring (blue circles) have a gut microbiome on PND 45 that is significantly different from VEH/CON male offspring (red circles). (D) DEP/MS males and females have significantly longer intestinal villi at PND 45 compared to VEH/CON offspring. (E) Ki67 staining (brown) identifies proliferating cells in the intestinal crypts.

2. Combined exposure to diesel exhaust particles and maternal stress during pregnancy increases the length of intestinal villi in offspring, suggesting nutrient deficiencies in adulthood.

Maternal immune activation during pregnancy is a leading theory for the etiology of ASD. We have a mouse model of maternal immune activation that involves combined prenatal maternal diesel exhaust exposure and maternal stress (DEP/MS) (Fig. 2A), two highly relevant risks factors for ASD. Within this model, we have previously shown that prenatal exposure to DEP/MS causes brain immune changes, such as hyper-ramification of microglia, as well as social behavior deficits in male offspring (Fig. 2B), consistent with the male-biased occurrence of ASD. Because children with ASD are increasingly characterized by gastrointestinal dysfunction, gut inflammation and altered gut microbial profiles, we have been actively investigating how the gastrointestinal system is impacted by our combined prenatal exposure. We have shown that DEP/MS male offspring (Fig. 2C, blue circles) have a significantly different gut microbial profile at postnatal day 45 than VEH/CON offspring (Fig. 2C, red circles). Most recently, we have found that both DEP/MS male and female offspring have significantly longer intestinal villi (Fig. 2D), possibly indicating nutrient deficiencies. We are currently assessing whether changes in cell proliferation (Fig. 2E) give rise to this structural alteration of the gastrointestinal wall. With these studies, we hope to gain insight as to how to correct gastrointestinal abnormalities for the amelioration of atypical social behaviors.

3. Maternal exogenous oxytocin exposure at birth has dose-dependent effects on the organization of brain circuits and the gut microbiome of offspring.



Dose-dependent effects of synthetic oxytocin at birth on the brain and behavior of offspring. (A) A schematic of a cross-section through a rodent brain highlighting the anterior cingulate cortex (Cg1 and Cg2)(black box), an area that is routinely implicated in ASD. (B) Co-labeling of parvalbumin interneurons (PVIs, green) and perineuronal nets (PNNs, red). (C-E) Administration of 5 International Units (IU)(red bars, medium dose) of synthetic oxytocin (sOT) at birth to pregnant dams increases the number of PVIs (C), PNNs (D) and PVIs enwrapped by PNNs (E) in the Cg2 of male offspring, as compared to untreated offspring (blue bars) and offspring in the 2.5 IU (pink bars, low dose) and 10 IU (dark red bars, high dose) sOT treatment groups. (F-G) Principal coordinates analyses show that male offspring born to mothers that were injected with a medium dose (5 IU) of sOT at birth do not have a different gut microbiome at postnatal day (PND) 45 compared to control offspring (F), while male offspring born to mothers injected with a high dose (10 IU) of sOT do have a significantly different microbiome compared to control offspring at PND 45.

Oxytocin is an adaptive and potent anti-inflammatory hormone for the developing fetal brain and gastrointestinal tract during major life stressors such as birth. Using an animal model to simulate labor induction, we continue to examine how maternal exposure to different doses of synthetic oxytocin (sOT; Pitocin) at birth impacts the development of offspring. Specifically, within the anterior cingulate cortex (Fig. 3A; Cg1 and Cg2), we have been examining the development of parvalbumin inhibitory neurons (PVIs) and the perineuronal nets (PNNs) that encase them (Fig. 3B). The development of perineuronal nets around PVIs promotes PVI maturation and provides synaptic stability and the proper balance of excitation and inhibition within cortical circuits. An alteration in PVI/PNN circuitry can shift the balance of excitation and inhibition within these circuits, contributing to behavioral deficits associated with ASD. Male offspring born to pregnant dams injected with a medium dose (5 International Units, IU) of sOT have increased PVIs (Fig. 3C), increased perineuronal nets (Fig. 3D) and a greater number of PVIs encased by PNNs (Fig. 3E), as compared to control males or those born to mothers injected with a low (2.5 IU) or high (10 IU) dose of sOT. We have also discovered that exposure to a high (10 IU; Fig. 3G), but not medium (5 IU; Fig. 3F), dose of sOT at birth significantly alters the gut microbiota of male offspring, as compared to control offspring. Many individuals with ASD are characterized by altered gut microbial profiles, gut dysbiosis, and gut inflammation, as compared to neurotypical children. Our future studies will examine how these sOT-induced changes within our animal model impact social affiliation and anxiety-like behavior. With these research, we hope to optimize the birth process for the most beneficial outcomes for offspring.

Neonatology and Newborn Medicine

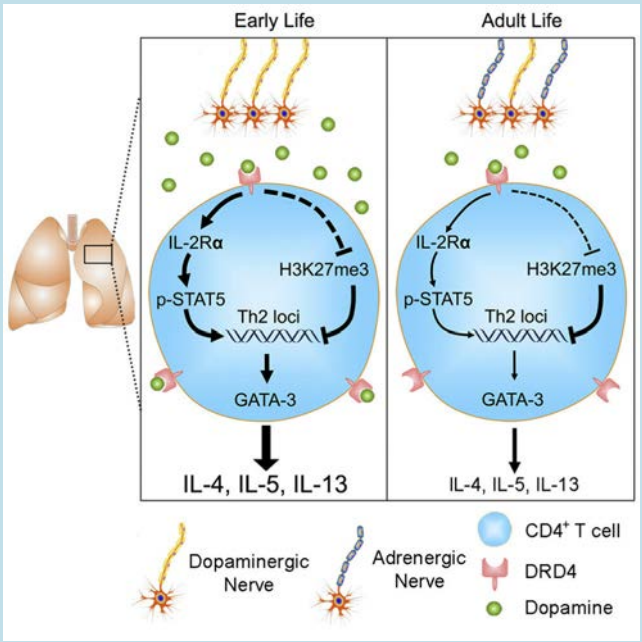
1. Age-Related Dopaminergic Innervation Augments T Helper 2-Type Allergic Inflammation in the Postnatal Lung.

Wang W, Cohen JA, Wallrapp A, Trieu KG, Barrios J, Shao F, Krishnamoorthy N, Kuchroo VK, Jones MR, Fine A, Bai Y, Ai X.
Immunity. 2019 Dec 17;51(6):1102-1118.e7. (doi: 10.1016/j.immuni.2019.10.002) Epub 2019 Nov 19.

Abstract

Young children are more susceptible to developing allergic asthma than adults. As neural innervation of the peripheral tissue continues to develop after birth, neurons may modulate tissue inflammation in an age-related manner. Here we showed that sympathetic nerves underwent

a dopaminergic-to-adrenergic transition during post-natal development of the lung in mice and humans. Dopamine signaled through a specific dopamine receptor (DRD4) to promote T helper 2 (Th2) cell differentiation. The dopamine-DRD4 pathway acted synergistically with the cytokine IL-4 by upregulating IL-2-STAT5 signaling and reducing inhibitory histone trimethylation at Th2 gene loci. In murine models of allergen exposure, the dopamine-DRD4 pathway augmented Th2 inflammation in the lungs of young mice. However, this pathway operated marginally after sympathetic nerves became adrenergic in the adult lung. Taken together, the communication between dopaminergic nerves and CD4+ T cells provides an age-related mechanism underlying the susceptibility to allergic inflammation in the early lung.



Children are more prone to developing allergic asthma than adults. Wang et al. find that sympathetic nerves undergo a dopaminergic-to-adrenergic transition during post-natal development of the lung. Dopamine signaling in CD4+ T cells promotes a Th2 phenotype, which makes young mice more susceptible to allergy. These findings provide an age-related mechanism underlying the susceptibility of the young to allergic inflammation.

2. Development of machine learning models to predict neonatal follow-up bilirubin levels and comparison with clinician performance

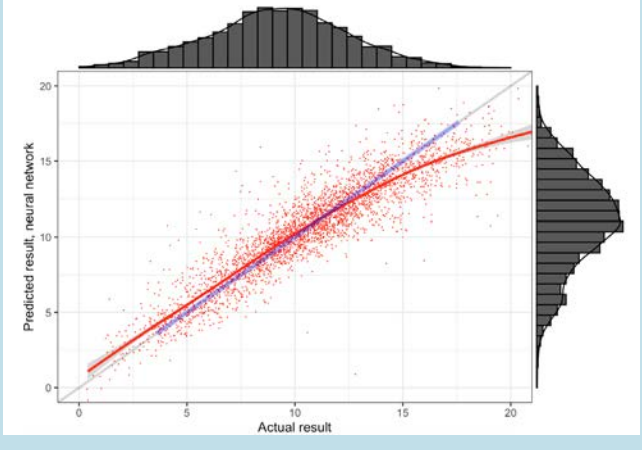
Joseph Chou
Poster for MGH Clinical Research Day 2019: Translation Science Award

OBJECTIVES. Hyperbilirubinemia affects many newborns and if not appropriately treated can result in irreversible brain injury. We sought to develop predictive models of follow-up total serum bilirubin and to compare performance with clinician predictions.

METHODS. Subjects were babies of any gestation born between June 2015 and June 2019 at four hospitals. The prediction target was a follow-up bilirubin obtained < 72 hours after a prior measurement. Birth before versus after February 2019 was used to generate a training set (27,428 target measurements) and held-out test set (3,320 measurements) respectively. Multiple supervised learning models were trained. To assess model performance, predictions on the held-out test set were also compared with corresponding predictions from clinicians.

RESULTS. The best predictive performance on the held-out test set was obtained with the neural network (mean absolute error, MAE 1.04 mg/dL) and Xgboost (MAE 1.03 mg/dL) models. A limited number of predictors was sufficient for best performance and avoiding overfitting. Clinicians made a total of 210 prospective predictions. The neural network model performance on this subset of predictions had a MAE of 1.05 mg/dL, compared to clinician predictions with MAE 1.36 mg/dL ($p < 0.0001$).

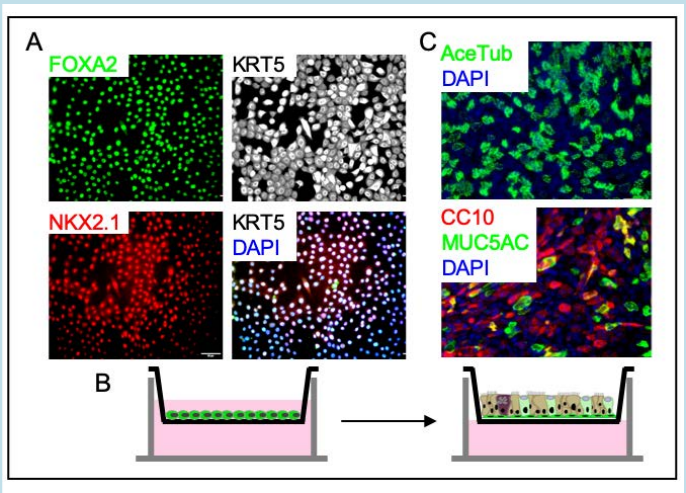
CONCLUSIONS. We have developed predictive models for newborn follow-up bilirubin which outperform clinicians. This may be the first report of total serum bilirubin predictive models that are not limited to late preterm and older newborns and which takes into account the effect of phototherapy.



Neural network predictions versus actual values (n=3,320). The red curve is smoothed through all the points, each of which represents a single predicted value. The bar plots show the distributions of the predicted and actual values. The gray line represents idealized perfectly accurate predictions with the blue segment showing the range of 95% of the actual values, with range from 3.6 (2.5%) to 17.6 (97.5%) and a median of 10.6 mg/dL.

3. Rho/SMAD/mTOR Triple Inhibition Enables Long-Term Expansion of Human Neonatal Tracheal Aspirate-Derived Airway Basal Stem Cells
Junjie Lu, Xiaobo Zhu, Jessica E Shui, Linjie Xiong, Todd Gierahn, Cheng Zhang, Michael Wood, Suzanne Hally, J. Christopher Love, Hu Li, Benjamin C Crawford, Hongmei Mou, Paul H Lerou. Pediatric Research, in press

Abstract
Background: Bronchopulmonary dysplasia remains one of the most common complication of prematurity, despite significant improvements in perinatal care. Functional modeling of human lung development and disease, like BPD, is limited by our ability to access the lung and to maintain relevant stem cell populations in culture.
Methods: We supplemented Rho/SMAD signaling inhibition with mTOR inhibition to generate epithelial basal cell lines from tracheal aspirates of neonates.
Results: Single cell RNA-sequencing confirmed the presence of epithelial cells in tracheal aspirates obtained from intubated neonates. Using Rho/SMAD/mTOR triple signaling inhibition, neonatal tracheal aspirate-derived (nTAD) basal stem cells can be expanded long-term and retain the ability to differentiate into pseudo-stratified airway epithelium.
Conclusions: Our data demonstrate that neonatal tracheal aspirate-derived epithelial cells can provide a novel ex vivo human cellular model to study neonatal lung development and disease.



(A) Basal cell markers in undifferentiated tracheal aspirate-derived BSCs. (B) ALI differentiation results in (C) ciliated (ActTub) and secretory cells: club (CC10) and goblet (MUC5AC).

Nephrology
Steroid-resistant nephrotic syndrome (SRNS) is a common cause of ESRD in patients presenting under 25 years of age. We performed mutation analysis in 24 single-gene causes of SRNS in a cohort of 72 families, who presented with SRNS before the age of 25 years. Within an 18-month interval, we obtained DNA samples, pedigree information, and clinical information from 77 consecutive children with SRNS seen at Boston Children's Hospital (BCH). Mutation analysis was completed by combining high-throughput multiplex PCR with next-generation sequencing. We analyzed the sequences of 18 recessive and 6 dominant genes of SRNS in all 72 families for disease-causing variants. We identified the disease-causing mutation in 8 out of 72 (11.1%) families. Mutations were detected in the six genes: NPHS1 (2 out of 72), WT1 (2 out of 72), NPHS2, MYO1E, TRPC6, and INF2. As our cohort was mostly non-consanguineous patients, our identification rate of 11.1% reflects that of other groups where the population studied was non-consanguineous in nature. This study demonstrates that understanding the molecular diagnosis may have important consequences for the management and treatment of those patients with steroid-resistant nephrotic syndrome. This study helped pave the way for future exome studies once WES technology became cheaper and more feasible.

Tan W, Lovric S, Ashraf S, Rao J, Schapiro D, Airik M, Shril S, Gee HY, Baum M, Daouk G, Ferguson MA, Rodig N, Somers M, Stein D, Vivante A, Warejko JK, Widmeier E, Hildebrandt F. Analysis of 24 genes reveals a monogenic cause in 11.1% of cases with steroid resistant nephrotic syndrome at a single center, Pediatric Nephrology, 2018; 33(2):305-314. PMID: 28921387

Jansen metaphyseal chondrodysplasia (JMC) is caused by heterozygous activating PTH/PTHrP receptor mutations that lead to severe mineral ion abnormalities, delayed chondrocyte differentiation, and short stature. We have now collected clinical and laboratory data for a large cohort of JMC patients and showed all PTHR1 mutations, except for the T410R mutation, were associated with indistinguishable mineral ion abnormalities and similarly severe growth impairment. Hypercalciuria persisted into adulthood. An inverse agonist ligand effectively reduced in vitro PTH-independent cAMP formation at all five PTHR1 mutants, suggesting a potential path towards therapy.

Saito H, Noda H, Gatault P, Böckenhauer D, Loke KY, Hiort O, Silve C, Sharwood E, Matsunaga Martin R, Dillon MJ, Gillis D, Harris M, Rao SD, Pauli RM, Gardella TJ, Jüppner H. Progression of Mineral Ion Abnormalities in Patients with Jansen's Metaphyseal Chondrodysplasia. J Clin Endocrinol Metab. 2018;103:2660–2669. PMID: 29788189

The alpha-subunit of the stimulatory G-protein (Gαs) links numerous receptors to adenylyl cyclase. Gαs, encoded by GNAS, is expressed predominantly from the maternal allele in certain tissues. Thus, maternal heterozygous loss-of-function mutations cause hormonal resistance, as in pseudohypoparathyroidism type Ia, while somatic gain-of-function mutations cause hormone-independent endocrine stimulation, as in McCune-Albright Syndrome. We now identified two unrelated boys presenting with a new combination of clinical findings that suggest both gain and loss of Gαs function, which resulted in the identification of the same novel Gαs mutation (c.1136T>G; p.F376V). Both unrelated patients

presented with unexplained hyponatremia in infancy, followed by severe early-onset gonadotrophin-independent precocious puberty, skeletal abnormalities, and evidence for PTH-resistance in the proximal renal tubules. In vitro studies demonstrated that Gαs-F376V enhanced ligand-independent signaling at the PTH1R, LHCGR and V2R and, at the same time, blunted ligand-dependent responses. The Gαs p.F376V mutation causes a previously unrecognized multi-system disorder.

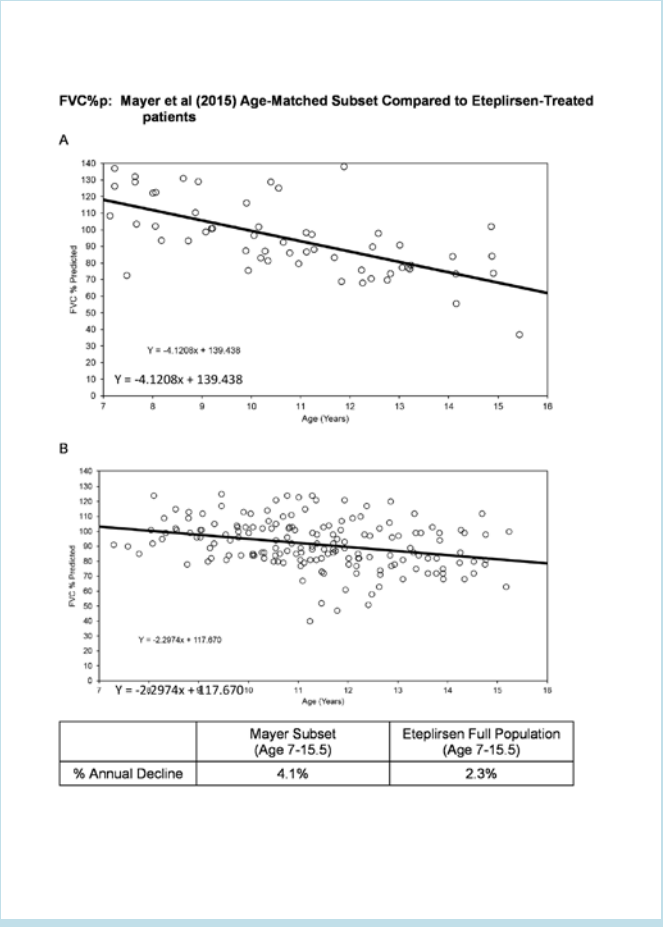
Biebermann H, Kleinau G, Schnabel D, Bockenhauer D, Wilson LC, Tully I, Kiff S, Scheerer P, Reyes M, Paisdzior S, Gregory JW, Allgrove J, Krude H, Mannstadt M, Gardella TJ, Dattani M, Jüppner H, Grüters A. A new multi-system disorder caused by the Gαs mutation p. F376V. J Clin Endocrinol Metab. 2019; 104:1079-1089. PMID: 30312418; PMCID: PMC6380466.

Shortening of metacarpals and/or -tarsals is typically observed in pseudohypoparathyroidism (PHP) type Ia (PHP1A) or pseudo-PHP (PPHP), related disorders that are caused by GNAS mutations involving those exons that encode the α-subunit of the stimulatory G protein (Gαs). We now investigated a large Caucasian family with shortened metacarpals and -tarsals, as well as reduced adult height, but no hormonal abnormalities. Whole exome sequencing of the proband's genomic DNA revealed a heterozygous A>G change at nucleotide -3 of PTHLH exon 3 that encodes the last two amino acids of the Pre-Pro sequence and the secreted PTHrP(1-139); the same nucleotide change was also found in the other available family members. RT-PCR experiments revealed that the splice-side mutation causes the insertion of two genomic nucleotides, which leads to a frame-shift after residue 34 of the PrePro sequence thus encoding 29 novel amino acids that share no homology with PTHrP or any other protein. Our findings extend previous reports indicating that PTHrP haploinsufficiency causes of AHO-like features, which are similar to those observed with GNAS mutations, but do not affect the regulation of mineral ion homeostasis.

Reyes M, Bravenboer B, Jüppner H. A heterozygous splice-site mutation in PTHLH causes autosomal dominant shortening of metacarpals and -tarsals. J Bone Mineral Res. 2019; 34:482-489. PMID: 30458061; PMCID: PMC6637419

Pediatric Palliative Care

We have received funding to determine feasibility of potential outcome measures, from the Lynch Foundation and from MGH ACO funds. We are working in collaboration with Dr. Perrin's research group in this endeavor. No publications have resulted from this effort as yet. We have collaborated with the Pediatric CF group in the past, resulting in two publications, and we are in the early stages of collaborating with them to examine the palliative care needs of children and young adults hospitalized with CF. We also are taking the lead on the pediatric component of a hospital-wide effort to enhance skills with conversations about serious illness with patients and families. We have modified the adult Serious Illness Conversation and the training module, which has been used to train two subsequent years of junior residents, all the PICU attendings and fellows, and all of the pediatric hospitalists. No publications have resulted from this effort, however presentations have been made in the past year both to the New England Pediatric Hospitalist conference in Boston, and the National Pediatric Hospitalist conference in Seattle.



	Mayer Subset (Age 7-15.5)	Eteplirsen Full Population (Age 7-15.5)
% Annual Decline	4.1%	2.3%

Pulmonary

Duchenne muscular dystrophy (DMD) is a rare, degenerative, X-linked genetic disease that results in progressive muscle loss and premature death, most commonly from respiratory or cardiac failure. DMD is primarily caused by whole exon deletions, resulting in a shift of the dystrophin mRNA reading frame that prevents the production of functional dystrophin protein. Eteplirsen, a phosphorodiamidate morpholino oligomer (PMO), is designed to skip exon 51, restore the reading frame, and induce production of internally shortened dystrophin in patients with mutations amenable to

such treatment. 12 patients were treated with eteplirsen for over 5 years. Pulmonary function tests included forced vital capacity (FVC), maximum expiratory pressure (MEP), and maximum inspiratory pressure (MIP) were measured.

Results: Age-adjusted mixed-model repeated-measures analysis showed decreases of 2.3% and 2.6% annually for FVC%p (FVC percentage of predicted) and MEP%p, and an annual increase of 0.6% for MIP%p for the eteplirsen-treated cohort. The expected decline in FVC%p is a 4.1% decline. The published natural history reports annual declines of at least 2.7% and 3.8% for MEP%p and MIP%p, respectively, in patients with DMD.

Conclusions: With eteplirsen treatment, deterioration of respiratory muscle function based on FVC%p was half of expected rate; MEP%p and MIP%p compared favorably with natural history.

Kinane TB, Mayer OH, Duda PW, Lowes LP, Moody SL, Mendell JR. Long-Term Pulmonary Function in Duchenne Muscular Dystrophy: Comparison of Eteplirsen-Treated Patients to Natural History. J Neuromuscul Dis. 2018;5(1):47-58. doi: 10.3233/JND-170272. PubMed PMID: 29278896

Khan N, Eliopoulos H, Han L, Kinane TB, Lowes LP, Mendell JR, Gordish-DressmanH, Henricson EK, McDonald CM; Eteplirsen Investigators and the CINRG DNHSInvestigators. Eteplirsen Treatment Attenuates Respiratory Decline in Ambulatory and Non-Ambulatory Patients with Duchenne Muscular Dystrophy. J Neuromuscul Dis. 2019;6(2):213-225. doi: 10.3233/JND-180351. PubMed PMID: 30856119

Psychiatry

Department Report

Maurizio Fava, 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. For its exceptional results in patient care, the MGH Department of Psychiatry has been rated the #1 department of psychiatry in 20 of the past 24 years (during all of which we have been in the top three) in the annual "America's Best Hospitals" survey by US News & World Report.

Research Innovation: The Department's vast array of clinical, translational and basic research programs is dedicated to pioneering advances in neuroscience, genetics, therapeutics and the prevention of psychiatric disorders. The Department has one of the three largest clinical research programs in the hospital. Using cutting-edge tools such as neuroimaging, genetics and genomics, and experimental animal and cellular models, Department of Psychiatry researchers are beginning to map the pathways through which brain biology interacts with life circumstances and events to produce psychiatric illnesses. This research is making it possible to pinpoint affected areas of the brain; understand inherited risk factors and the role of environmental stress; develop more effective psychotherapies, medications, and neurotherapeutic treatments; and ultimately to prevent these illnesses from occurring by intervening early. In FY19, Department faculty had more than $80 million in research support, continuing its record of successful funding despite a challenging funding environment. In addition, our faculty authored over 1,000 publications in academic journals.

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 mental health care. Each year, we train 100 adult and child/adolescent psychiatry residents, psychology interns and clinical fellows to be leaders in their areas of specialization. Further, dozens or more of postdoctoral fellows across neuroscience, research psychology, and a variety of other fields train here and the Department provides provide research placements for local and national/international visiting fellows, medical and graduate students, and other types of trainees.

In addition, our educational efforts reach tens of thousands of psychiatrists, non-psychiatric physicians and other health professionals through the Psychiatry Academy and its dozens of webinars, simulations, online courses, live conferences and more.

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. 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. Since 2013 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.

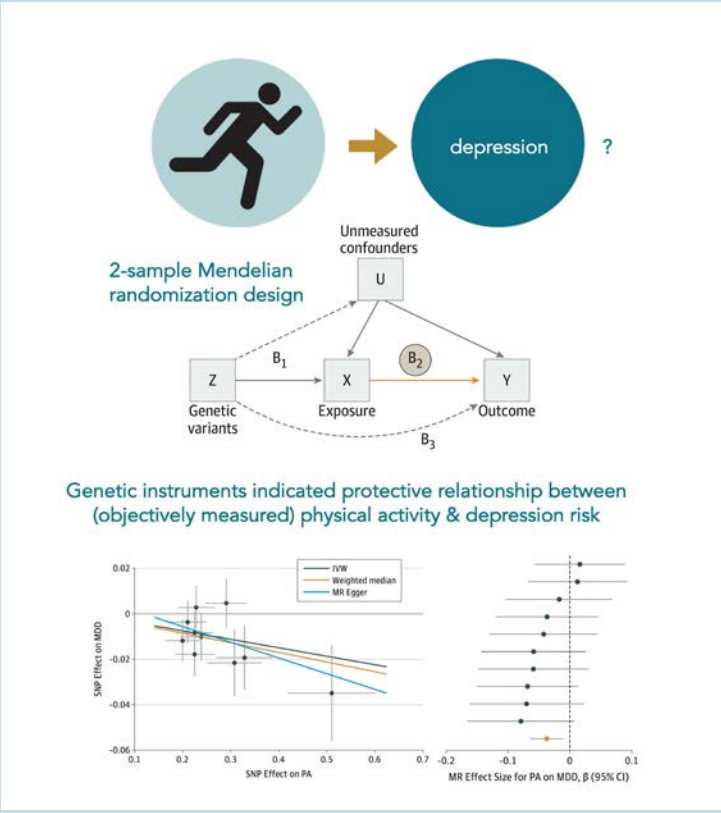
New Initiative: This year, among other exciting initiative, the Department is launching the Precision Psychiatry/Learning Health System, the goals of which are to:

1. Establish the MGH Department of Psychiatry as national leader in the emerging paradigm of "precision psychiatry", the application of precision medicine to the diagnosis, treatment, and prevention of mental illness; and

2. Establish the MGH Department of Psychiatry as a national leader in research, training, and clinical aspects of suicide, including the prediction and prevention of suicidal behavioral and the care of patients across all areas of medicine who are affected by this growing public health crisis.

Achievements

Choi KW et al, 2019. Assessment of Bidirectional Relationships Between Physical Activity and Depression Among Adults: A 2-Sample Mendelian Randomization Study.

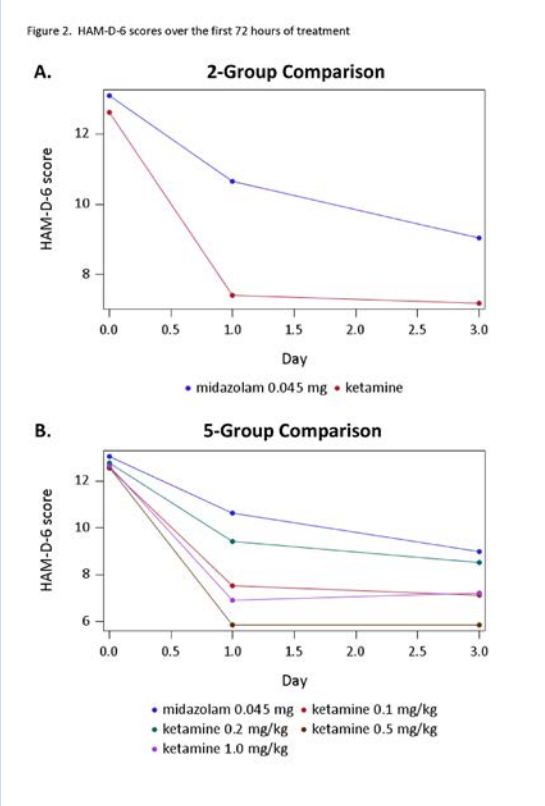


Increasing evidence shows that physical activity is associated with reduced risk for depression, pointing to a potential modifiable target for prevention. However, the causality and direction of this association are not clear; physical activity may protect against depression, and/or depression may result in decreased physical activity. To answer these questions, Choi and colleagues used a novel analytic strategy—two-sample Mendelian randomization—that harnesses genetic variation as a natural experiment, to test potential causal relationships between physical activity and depression. The genetic variants used as instruments in this study were identified from prior large-scale genome-wide association studies of physical activity (discovery n=91,084 to 377,234) and depression (discovery n=143,265). Mendelian randomization analyses indicated that physical activity (measured using wrist-worn activity trackers, but not with self-report) showed a protective effect on depression, with limited evidence in the other direction. Overall, this study supports the hypothesis that enhancing physical activity is an effective prevention strategy for depression.

Choi KW, Chen CY, Stein MB, Klimentidis YC, Wang MJ, Koenen KC, Smoller JW. Assessment of Bidirectional Relationships Between Physical Activity and Depression Among Adults: A 2-Sample Mendelian Randomization Study. JAMA Psychiatry. 2019 Apr 01; 76(4):399-408.

Fava M et al, 2018. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD).

Numerous placebo-controlled studies have demonstrated the ability of ketamine, an NMDA receptor antagonist, to induce rapid (within hours), transient antidepressant effects when administered intravenously (IV) at subanesthetic doses (0.5 mg/kg over 40 min). However, the optimal antidepressant dose remains unknown. We aimed to compare to active placebo the rapid acting antidepressant properties of a broad range of subanesthetic doses of IV ketamine among outpatients with treatment-resistant depression (TRD). A range of IV ketamine doses were compared to active placebo in the treatment of adult TRD over a 3-day period following a single infusion over 40 min. This was an outpatient study conducted across six US academic sites. Outpatients were 18-70 years old with TRD, defined as failure to achieve a satisfactory response (e.g., less than 50% improvement of depression symptoms) to at least two adequate treatment courses during the current depressive episode. Following a washout period, 99 eligible subjects were randomly assigned to one of the five arms in a 1:1:1:1:1 fashion: a single intravenous dose of ketamine 0.1 mg/kg (n = 18), a single dose of ketamine 0.2 mg/kg (n = 20), a single dose of ketamine 0.5 mg/kg (n = 22), a single dose of ketamine 1.0 mg/kg (n = 20), and a single dose of midazolam 0.045 mg/kg (active placebo) (n = 19). The study assessments (HAM-D-6, MADRS, SDQ, PAS, CGI-S, and CGI-I) were performed at days 0, 1, 3 (endpoint), 5, 7, 14, and 30 to assess the safety and efficacy. The overall group × time interaction effect was significant for the primary outcome measure, the HAM-D-6. In post hoc pairwise comparisons controlling for multiple comparisons, standard dose (0.5 mg/kg) and high dose (1 mg/kg) of intravenous ketamine were superior to active placebo; a low dose (0.1 mg/kg) was significant only prior to adjustment (p = 0.02, p-adj = 0.14, d = -0.82 at day 1). Most of the interaction effect was due to differences at day 1, with no significant adjusted pairwise differences at day 3. This pattern generally held for secondary outcomes. The infusions of ketamine were relatively

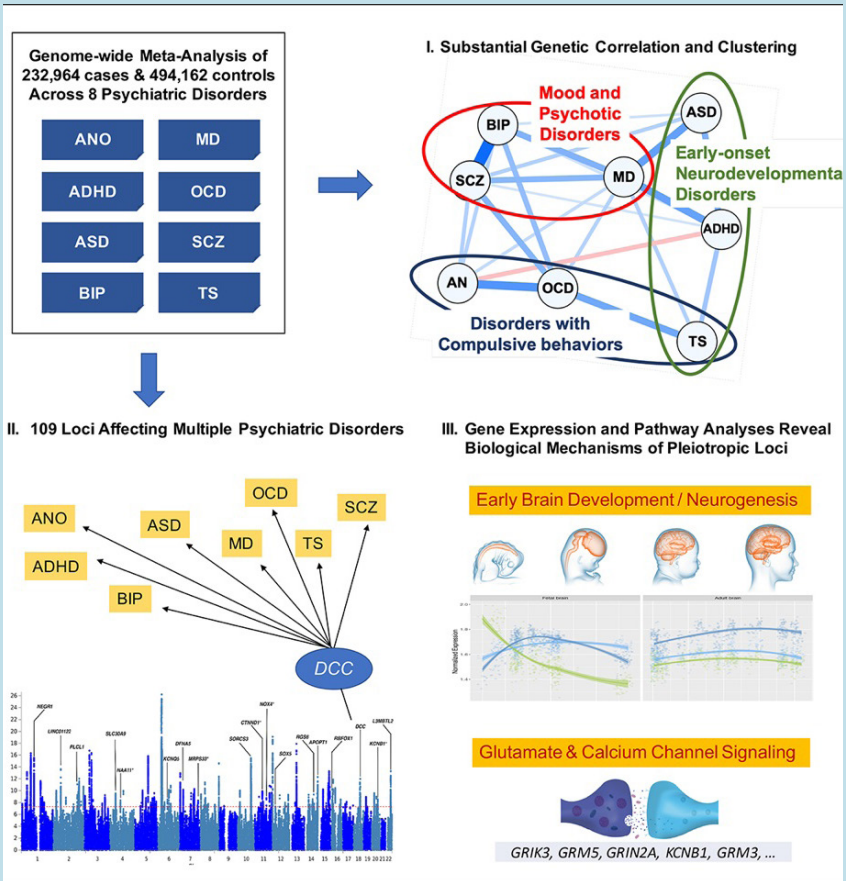


well tolerated compared to active placebo, except for greater dissociative symptoms and transient blood pressure elevations with the higher doses. Our results suggest that there is evidence for the efficacy of the 0.5 mg/kg and 1.0 mg/kg subanesthetic doses of IV ketamine and no clear or consistent evidence for clinically meaningful efficacy of lower doses of IV ketamine.

Fava M, Freeman MP, Flynn M, Judge H, Hoeppner BB, Cusin C, Ionescu DF, Mathew SJ, Chang LC, Iosifescu DV, Murrough J, Debattista C, Schatzberg AF, Trivedi MH, Jha MK, Sanacora G, Wilkinson ST, Papakostas GI. Double-blind, placebo-controlled, dose-ranging trial of intravenous ketamine as adjunctive therapy in treatment-resistant depression (TRD). Mol Psychiatry. 2018 Oct 3.

Lee, Phil H et al, 2019. Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders.

The current classification of psychiatric disorders is based on clinically-defined syndromes established by consensus of experts, and the boundaries between them are often fuzzy. Psychiatric disorders are known to be heritable and prior evidence suggests the existence of shared genetic influences. In the largest study of its kind, led by Phil Hyoun Lee, PhD and Jordan W. Smoller, MD, ScD of MGH Psychiatry and their colleagues in the MGH Center for Genomic Medicine as well as an international team of investigators, genome-wide genetic data for more than 727,000 individuals were examined to dissect the cross-disorder genetic relationships among spanning eight major neuropsychiatric disorders. The authors identified 109 genetic loci that affect the risk for more than one psychiatric disorder, including 23 loci associated with 4 or more disorders and 11 loci with opposite effects on multiple disorders. Based on patterns of genomic relationships, they identified three groups of genetically-related conditions: disorders characterized by compulsive behaviors (anorexia nervosa, obsessive-compulsive disorder and, to a lesser extent, Tourette syndrome); mood and psychotic disorders (bipolar disorder, major depression and schizophrenia); and early-onset neurodevelopmental disorders (autism spectrum disorder, ADHD and Tourette syndrome). The researchers also found evidence that genes associated with multiple disorders show increased expression beginning in the second trimester of pregnancy and appear to play an important role in brain development as well as the biology of glutamatergic and calcium channel signaling. These results provide new insights into the underlying biological basis and of psychiatric disorders and have implications for the classification of psychiatric disorders as well as potential targets for developing new treatments that might benefit multiple conditions.



Lee, Phil, Anttila, Verneri, Won, Hyejung, Feng, Yen-Chen, Rosenthal, Jacob, Zhu, Zhaozhong, Tucker-Drob, Elliot, Nivard, Michel, Grotzinger, Andrew, Posthuma, Danielle, Wang, Meg, Yu, Dongmei, Rujescu, Dan, Tooney,

Paul, Grünblatt, Edna, Falkai, Peter, Gelernter, Joel, Mathews, Carol, Smoller, Jordan. (2019). Genomic Relationships, Novel Loci, and Pleiotropic Mechanisms across Eight Psychiatric Disorders. Cell. 179. 1469-1482. 10.1016/j.cell.2019.11.020.

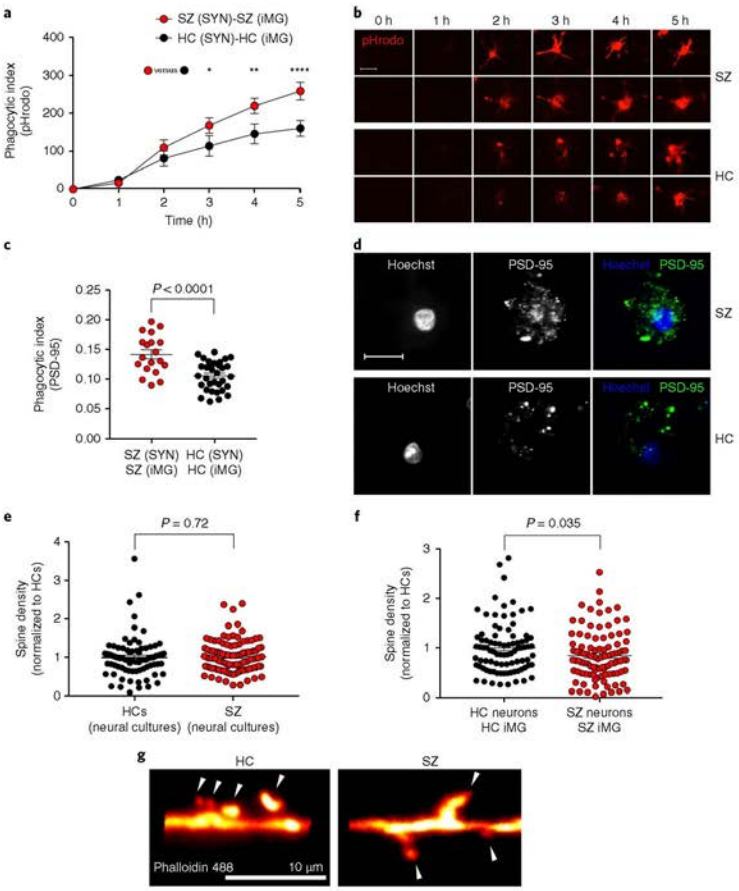


Fig. 3 | Increased engulfment of synaptic structures in schizophrenia-derived models. a, Quantification of pHrodo (red)-labeled SYN uptake in iMG cells during live imaging. The phagocytic index represents the mean pHrodo$^+$ area per iMG cell. SZ-derived models were designed by using iMG cells derived from 13 patients and SYNs derived from 3 patients (combined to form $n = 13$ SZ (SYN)-SZ (iMG) models), while HC models were derived from 9 HCs and SYN from 3 HCs (both groups matched with correspondent SZ patients); $n = 13$ HC (SYN)-HC (iMG) models. Nine images (20×) per well were automatically acquired every hour and the means were then extracted and analyzed using a two-way repeated ANOVA. There was a significant interaction between the effects of time and group on phagocytic index ($F(5,60) = 4.84$; $P = 0.0009$). Šidák's multiple comparison tests gave an adjusted P value of 0.035 at 3 h, 0.002 at 4 h, and < 0.0001 at 5 h. All other comparisons were non-significant. **b**, The first two rows display representative images from the SZ models in **a**; the last two rows represent images from the HC models in **a**. Scale bar, 25 µm. **c**, Quantification of phagocytic inclusions (PSD-95$^+$ inclusions, 0.5–1.5 µm) using confocal microscopy in a sample containing SYNs derived from a total of 4 SZ patients and 4 matched HCs, combined in different combinations with iMG cells from 13 SZ patients and 18 matched HCs ($n = 19$ SZ (SYN)-SZ (iMG) models and $n = 33$ HC (SYN)-HC(iMG) models). The phagocytic index represents the number of PSD-95$^+$ particles (0.5–1.5 µm) per iMG cytoplasm area. Twenty randomly selected confocal images were taken per well and the means were analyzed using a t test (equal variance); $t(50) = 4.55$, $P < 0.0001$ (two-sided). **d**, Representative confocal images for the two groups in **c**. Scale bar, 30 µm. **e**, Quantification of spine density (spines per 10-µm dendrite) in neural lines derived from 3 SZ patients versus 2 HCs ($n = 80$ randomly selected dendrites examined in the SZ group and $n = 100$ randomly selected dendrites examined in the HC group); Welch-corrected t test; $t(148) = 0.35$, $P = 0.72$ (two-sided). **f**, Quantification of spine density in the same neural lines but cocultured with iMG cells (derived from 3 SZ patients or 2 HCs; $n = 88$ randomly selected dendrites examined in HC group and $n = 99$ randomly selected dendrites examined in the SZ group) as indicated; t test (equal variance); $t(185) = 2.1$, $P = 0.035$ (two-sided). Data in both graphs are normalized to the HC group. **g**, Representative images of phalloidin 488-stained high-magnification confocal images of dendritic spines (indicated by the arrowheads) in HC and SZ neural cultures described in **f**. The mean number of spines per 10-µm dendrite was 4.5 (s.e.m. = 0.25) for HC cultures and 3.8 (s.e.m. = 0.23) in SZ cultures. All reported P values are two-sided; the mean ± s.e.m. is indicated for each group in all graphs. *$P < 0.05$, **$P < 0.01$, ****$P < 0.0001$.

Sellgren CM et al, 2019. Increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning.

a. Summary in layman's terms

The manuscript utilizes a patient-derived cellular model created by the authors to examine synaptic pruning, the process by which connections between brain cells are shaped. It relies on a patient-derived stem cell biobank developed by the authors over nearly 10 years, one of the largest of its kind for brain diseases in the world. Using blood and stem cells from people with schizophrenia, and healthy individuals, they demonstrate for the first time that the process of synaptic pruning is abnormal in people with schizophrenia, testing a hypothesis based on genomewide association studies. They further show that antibodies or small molecules, including the FDA-approved antibiotic minocycline,

can be effective in normalizing synaptic pruning. This suggests an opportunity for preventing rather than solely treating schizophrenia. Finally, they turn to electronic health records from more than 15,000 adolescents in the Partners HealthCare system followed for up to 8 years. They show that exposure to minocycline, compared to other antibiotics, as treatment for acne is associated with a significant decrease in subsequent schizophrenia risk.

b. Specific biological innovation of the study
The authors present the first human cellular model of synaptic pruning, and adapt it to allow high-throughput screening for novel therapeutics that modulate pruning (and impact microglia function more generally). They apply this model to demonstrate the first robust cellular phenotype associated with schizophrenia. Further, for the first time in human models, they demonstrate a mechanism by which a schizophrenia risk locus (complement factor 4) contributes to disease risk.

c. Potential impact on patient care and/or how the findings contributed to an improved understanding in their chosen field.
Schizophrenia has a lifetime prevalence of 1%, and existing therapeutics are based on understandings of the brain more than 5 decades old; they have substantial limitations in terms of efficacy as well as tolerability, such that schizophrenia remains a chronic and disabling disease, particularly as its onset is typically in adolescence or early adulthood. Development of novel therapeutics in psychiatry has been inhibited by a lack of treatment targets, and a lack of biological understanding of pathophysiology. This paper validates a new treatment target, identifies an existing FDA-approved medication that modulates that target, and suggests a potential disease biomarker (since the cells are readily generated from patient samples). More generally it suggests the real possibility of interventions aimed at prevention of an incredibly disabling and chronic disease.

Sellgren CM, Gracias J, Watmuff B, Biag JD, Thanos JM, Whittredge PB, Fu T, Worringer K, Brown HE, Wang J, Kaykas A, Karmacharya R, Goold CP, Sheridan SD, Perlis RH. Increased synapse elimination by microglia in schizophrenia patient-derived models of synaptic pruning. Nat Neurosci. 2019 03; 22(3):374-385.

Jay S. Loeffler, MD, Chief

Research Overview:

The Mass General Department of Radiation Oncology had approximately $27M in research expenditures in 2019. Nearly 32% of this research funding originated from NIH/NCI support. The department continues to have an impressive record as a highly collaborative research team, reflected in the rich publication record of our faculty with over 268 publications in 2019. Additionally, in 2019, the Department of Radiation Oncology maintained 32 active clinical trials, with an additional 1 that was completed, and 336 clinical trial accruals.

Presently, the main areas of research focus within the department include clinical trials, proton research, pediatric research, physics research, translational research, and laboratory-based basic research. The department boasts an extensive physics research program including efforts in bio-mathematical modeling, outcome modeling, Monte Carlo simulations, and optimization of intensity-modulated photon and proton therapy. Mass General Radiation Oncology also has an active tumor and radiation biology program with major interests in tumor microenvironment, DNA repair, and precision radiation medicine. It is anticipated that research conducted in the Department of Radiation Oncology will lead to improved approaches to radiation therapy in cancer treatment and will help further understanding of mechanisms of radiation-induced toxicities, leading to development of novel targets for cancer therapy as well as new preventative approaches.

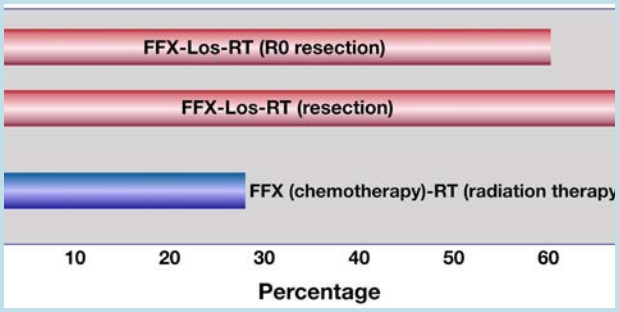
1) Department General Achievements:

- The 2019 Radiation Oncology Research Retreat, entitled "Reaching Out: Opportunities for Interdisciplinary Physics Research," was held on September 26, 2019 with the goal of demonstrating success stories of interdisciplinary collaborations in physics research as well as outlining opportunities and challenges moving forward. Participants joined in a panel discussion and a brainstorming session in addition to hearing from several speakers including keynote speaker, Joseph Deasy, PhD, Medical Physics Department Chair at the Memorial Sloan Kettering Cancer Institute in New York. Presentations focused on the interaction between physics research and clinical practice in both directions, such as how physics research strives to impact patient treatment and how clinical practice defines research needs and provides data for research. Helen Shih, MD, Harald Paganetti, PhD, and Lance Munn, PhD were able to speak from the clinical, physics, and Steele Lab perspectives.
- The Department of Radiation Oncology was awarded Research Grants from the National Cancer Institute (NCI/ NIH) outlined below:
    1. R01 Harald Paganetti, PhD, for "Fast Individualized Delivery Adaptation in Proton Therapy." The goal of this research is to predict the dose distribution in the patient immediately prior to treatment delivery and correct for any discrepancies between the measured and intended dose while the patient is in the room for on-line adaptation.
    2. R01 grant Jan Schuemann, PhD, for "TOPAS – nBio, a Monte Carlo tool for radiation biology research." The goal of this research is to customize Monte Ccarlo for simulations of sub-cellular radiation biology and radiation chemistry.
    3. R21 grant to study the interaction between radiation therapy and checkpoint inhibitors in hepatocellular carcinoma patients. Harald Paganetti, PhD, Theodore Hong, MD, and Clemens Grassberger, PhD will investigate how different treatment regimens could affect such combinations. If successful, these studies could enable patient stratification and lead to new therapeutic approaches, improving outcomes for patients.
- Theodore Hong, MD, Jennifer Wo, MD, Lorraine Drapek, DNP, Thomas DeLaney, MD, Rakesh Jain, PhD, Dan Duda, PhD, Yves Boucher, PhD and MGH Cancer Center colleagues reported the findings of a Phase 2 Clinical trial in "Total Neoadjuvant Therapy With FOLFIRINOX in Combination With Losartan Followed by Chemoradiotherapy for Locally Advanced Pancreatic Cancer," published in the July 1, 2019 edition of JAMA Oncology. These findings were picked up by news outlets including HealthDay News and the Boston Herald.
- Torunn Yock, MD, and Helen Shih, MD MPH, were inducted as Fellows of the American Society for Radiation Oncology (ASTRO) for their contributions to the field of radiation oncology in research, clinical service, and education.

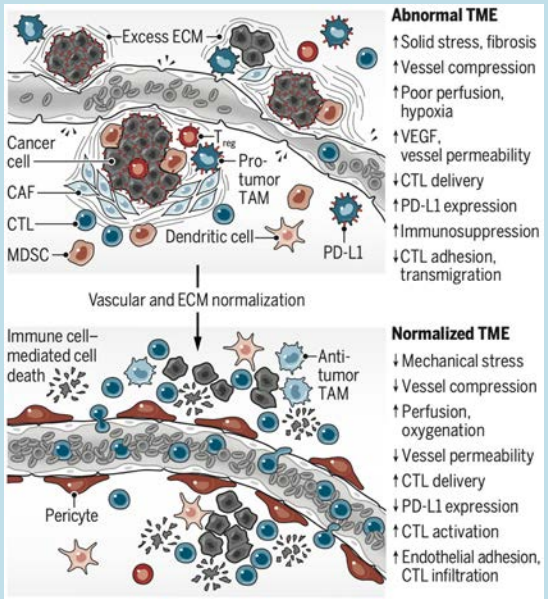
2) Physics Achievements:

- Thomas Bortfeld, PhD, was selected to deliver keynote addresses at the Engineering & Physical Sciences in Medicine (EPSM) Conference in October 2019 in Perth, Australia, and at the Swiss Society of Radiobiology and Medical Physics in November 2019 in Villigen, Switzerland.
- Harald Paganetti, PhD, delivered a keynote address at the International Conference GRK 1739 - DNA DAMAGE AND BEYOND: From molecular mechanisms to innovative concepts in the treatment of cancer, from 25-26 October 2019, Essen "Generic and personalized biological treatment optimization in proton therapy"

- Research fellow Abdel Hammi, PhD's, abstract "Modeling the Radiation Dose to Circulating Lymphocytes for Different Radiotherapy Modalities and Delivery Parameters," was awarded second place in the American Association of Physicists in Medicine (AAPM) Young Investigators' Competition. Dr Hammi was recognized at the Awards and Honors Ceremony at the AAPM Annual Meeting in July 2019 in San Antonio, Texas.
- Jan Schuemann, PhD, received the Expanding Theories Award from the Brain Tumor Charity. This award supports studies that explore and develop novel concepts that may lead to significant improvements in clinical outcomes. Dr. Schuemann's research explores if extreme dose rate (EDR) proton therapy, also called FLASH therapy, can be used to spare healthy brain tissue while treating tumors.
- Jan Schuemann, PhD, was also selected to deliver a keynote address at the second International Conference on Monte Carlo Techniques for Medical Applications (MCMA) held in June 2019 in Montreal, Canada. His talk, "Multi-scale Monte Carlo Simulations and Applications in Treatment Planning," presented his lab's work in extending Monte Carlo modeling of radiation damage to the sub-cellular level, with the goal of improving treatment planning by understanding the biological effects of dose.
- At the 58th Particle Therapy Co-operative Group (PTCOG) meeting in Manchester, UK in June 2019, Joost Verburg, PhD, won the Michael Goitein Best Abstract Award in the Physics category for his abstract on the prompt gamma-ray spectroscopy system for proton range verification. More than 720 abstracts were submitted.
- At the AAPM Annual Meeting in July 2019 in San Antonio, Texas, Joost Verburg, PhD, Fernando Hueso-Gonzalez, PhD, Thomas Ruggieri and Thomas Bortfeld, PhD, received the "Best in Physics" designation for their abstract titled "Initial Experience with a Robotically Positioned Clinical Prototype Prompt Gamma-Ray Spectroscopy System for in Vivo Proton Range Verification."
- The American Physical Society (APS) held its Annual Meeting focusing on applied and materials physics in Boston in March 2019. As part of its efforts to promote the knowledge and understanding of the use of physics in medicine among its members, Jennifer Pursley, PhD, and Thomas Bortfeld, PhD, organized a tour of the MGH Department of Radiation Oncology for meeting attendees. Dr. Pursley, Susu Yan, PhD, Joost Verburg, PhD, Hyeri Lee, PhD, and Yiwen Xu, PhD, served as tour guides, leading 50 physicists on a tour of Cox Lower Level, Lunder LL3 and the Francis H. Burr Proton Therapy Center.
- Wonmo Sung, PhD, was recognized as a 2019 Annual Meeting Abstract Award Recipient at the 2019 ASTRO Annual Meeting in Chicago in September 2019. Dr. Sung was one of four recipients of the Basic/Translational Science Award in the Radiation Physics category. The award included a $1,000 honorarium, a certificate of recognition and a complimentary registration to the Annual Meeting.



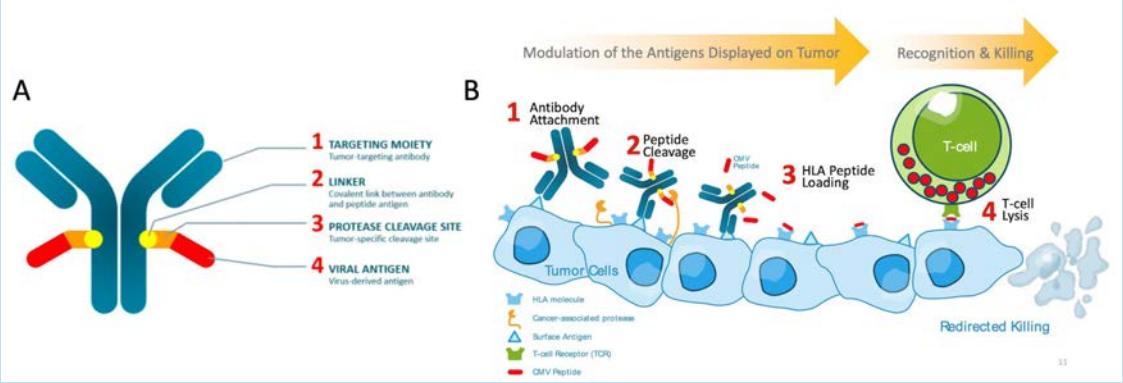
Unprecedented increase in R0 (complete) resection rate in locally-advanced pancreatic ductal adenocarcinoma patients treated with losartan and chemoradiation prior to surgery. This combination therapy trial stemmed from a pre-clinical study published in 2013 by Dr. Jain and colleagues in the Steele Laboratories, and is now being tested in a randomized study with immunotherapy with support from the StandUp2Cancer (SU-2-C) initiative. (From: Murphy J, et al. A phase II study of neoadjuvant FOLFIRINOX in combination with losartan followed by chemoradiotherapy in locally advanced pancreatic cancer: R0 resection rate and clinical outcomes. JAMA Oncology 5: 1020-7, 2019.)



Normalizing the tumor microenvironment (TME) to improve immunotherapy. Excess extracellular matrix (ECM) can cause vessel compression. Excess angiogenic molecules produced by cancer or stromal cells also make tumor vasculature dys-functional. ECM-normalizing drugs can decompress the blood vessels, and anti-angiogenesis therapies can reverse many of the TME abnormalities, resulting in improved perfusion and immune cell infiltration and creation of an immunostimulatory microenvironment – leading to improved treatment outcome. US-FDA approval of five different combinations of anti-VEGF/R drugs with immune-checkpoint blockers for four different indications in the past 12 months is supportive of this concept. CAF, cancer-associated fibroblast; CTL, cytotoxic T lymphocyte; ECM, extracellular matrix; MDSC, myeloid-derived suppressor cell; PD-L1, programmed cell death protein ligand 1; TAM, tumor-associated macrophage; TME, tumor microenvironment; T , regulatory T cell; VEGF, vascular endothelial growth factor. (Munn LL, Jain RK. Vascular regulation of anti-tumor immunity. Science 365: 544-545, 2019.)

3) Clinical/Biology Research Achievements:

- The BOTSOGO (Botswana Oncology Global Outreach) Collaboration, co-directed by Jason Efstathiou, MD, DPhil, MGH, and Scott Dryden-Peterson, MD, BWH, helped pilot a novel lymphoma diagnostic device in parts of Botswana. The



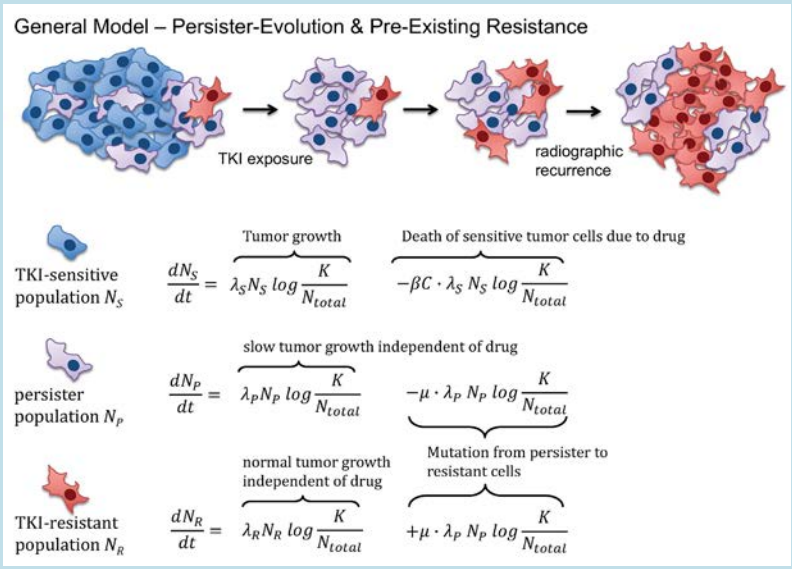
Novel immunotherapy approach to increase tumor antigenicity using Antibody Peptide Epitope Constructs (APECs). (A) Schematic of the APEC structure. (B) Sequence of binding and antibody activation events leading to passive loading on empty HLA molecules with viral peptides and subsequent detection by anti-viral T-cells. (From: Millar et al., Nature Biotechnology, in press.)

contrast-enhanced microhalography (CEM) device, developed by the MGH Center for Systems Biology, may enable a specific diagnosis of lymphoma and breast cancer in large clinics and primary hospitals. Additionally, a large NCI-supported trial named Potlako, designed to test whether a package of primary provider education and patient navigation support implemented in Botswana can reduce time to entry into oncology care and cancer stage, concluded with 970 cancer suspects enrolled and 275 cancers diagnosed, with patients starting cancer treatment 2.4 months earlier on average.

- Paul Busse, MD, PhD, Clinical Director of MGH Radiation Oncology, was honored as the inaugural incumbent of the Joseph W. Cotchett Endowed Chair in Radiation Oncology, made possible through the generosity of Joseph W. Cotchett, Esq. This chair will advance research, care and education in Radiation Oncology. This is the first MGH Endowed Chair for the Department of Radiation Oncology.
- Sophia Kamran, MD, was one of five 2019 recipients of the MGH Center for Diversity and Inclusion Physician/Scientist Development Awards in recognition of her excellence in scientific investigation at MGH. The award is funded by the Mass General Executive Committee on Research.
- Damilola Oladeru, MD, was awarded a grant from the Center of Expertise in Health Policy and Management for her research project, "National Survey of Stakeholders' Attitudes, Knowledge and Practice Behavior About Incarcerated Patients With Cancer and Fragmented Prison Health Care System."
- Sophia Kamran, MD, and Anthony Zietman, MD, played key roles in the newly redesigned ASTRO 2019 Presidential Symposium, held at the ASTRO 2019 Annual Meeting in September. Drs. Kamran and Zietman were selected to argue the "con" side of the question "Can stereotactic ablative radiotherapy (SABR) cure metastatic disease on a large scale, and should it be the new standard of care for treating metastatic cancers?"
- David Miyamoto, MD, PhD, was awarded funding from the MGH Center for Innovation in Early Cancer Detection (CIECD) to support his work on Molecular Signatures of Circulating Tumor Cells for Early Detection of Aggressive Prostate Cancer.
- Sujith Baliga, MD, Pediatric Proton Clinical Research fellow in the 2018-2019 academic year, attended the ASCO/AACR Methods in Clinical Cancer Research Workshop in Vail, Colorado in July-August 2019 and won the Daniel D. Von Hoff Award for the most innovative protocol.
- David Konieczkowski, MD, PhD, received a grant from the RSNA Research & Education Foundation Board of Trustees to fund his research "Impact of Androgen Receptor Splice Variant Expression on Outcomes of Post-prostatectomy Therapy" with mentors David Miyamoto, MD, PhD, and Jason Efstathiou, MD, DPhil.
- Anthony Zietman, MD, received the 2019 Harvard Global Health Catalyst (GHC) Distinguished Leader Award. Awardees are nominated and voted for by the Harvard GHC organizing committee and past award winners. Dr. Zietman and fellow GHC award winners were recognized at the Global Health Catalyst Summit at Harvard Medical School in May 2019.
- William Hwang, MD, PhD, received the Conquer Cancer Foundation of ASCO/Sherwin Family Young Investigator Award for his work on "Radiotherapy-Mediated Reprogramming of the Immune Ecosystem in Pancreatic Ductal Adenocarcinoma at Single-Cell Resolution." His mentors on this research are Theodore Hong, MD, as well as Tyler Jacks, PhD of MIT.
- Henning Willers, MD, Lead PI of the Laboratory of Cellular & Molecular Radiation Oncology and his research team were awarded a $2.8 million grant from the NCI to develop new and effective combinations of radiation with biological drugs by focusing on inter-tumoral genomic heterogeneity. His collaborators in this multi-phase effort include co-principal investigators Cyril Benes, PhD, Director of the MGH Center for Molecular Therapeutics (CMT); Mechthild Krause, MD, Director of OncoRay, Dresden, Germany; and Michael Baumann,

MD, Director of the German Cancer Research Center (DKFZ); as well as Nils Cordes, MD, OncoRay; Theodore Hong, MD; Lori Wirth, MD, MGH Head and Neck Medical Oncology; and others.

- Chirayu Patel, MD received the International Lymphoma Radiation Oncology Group (ILROG) ISRT Case Presentation award at the ASTRO Modern Radiotherapy for Hematologic Malignancies Conference at the University of California, San Diego in February 2019 for his presentation of a challenging case of a post-operative head and neck high grade lymphoma patient he treated at MGH. This interactive presentation encompassed real-time audience participation as Dr. Patel explained the reasoning behind his treatment plan contouring decisions and taught the audience about this difficult case.
- In December 2019, the Pediatric Proton/Photon Consortium Registry (PPCR), a consented, multi-center registry established and headed by Torunn Yock, MD, MCH to expedite outcomes research on proton radiotherapy and to better define the role of proton radiation in treating pediatric cancers, celebrated the milestone of having enrolled its 3000th patient.
- A new intra-departmental seed grant program was implemented, the Loeffler Team Science Seed Funding Program (LTSFP), to foster interdisciplinary team science and support early career investigators in Radiation Oncology. Sophia Kamran, MD, and Chirayu Patel, MD, were the inaugural recipients for their respective projects Adaptive immune response evolution after radiation therapy for oligometastatic prostate cancer and Harvesting Radiation Therapy To Enhance CAR T Efficacy Early in Post-CAR T Cell Therapy Refractory Lymphoma: A Pilot Study.



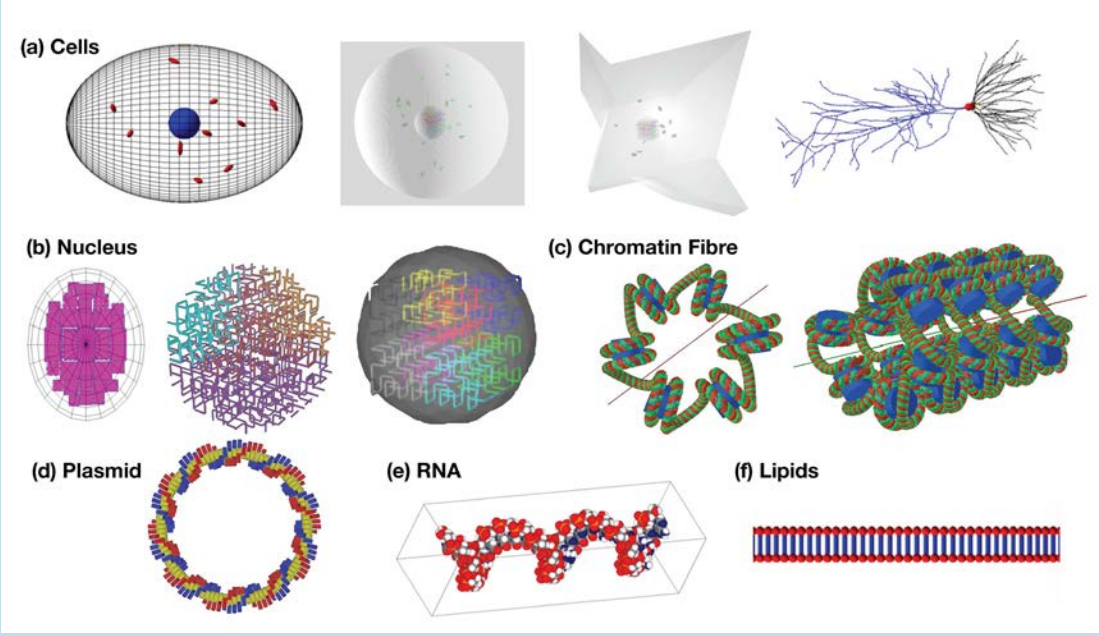
General Model and system of differential equations describing the temporal evolution of all cancer cell subpopulations, including both persister-evolution and pre-existing resistance. From: Cancer Res. 2019 79(14):3776-3788 "Patient-Specific Tumor Growth Trajectories Determine Persistent and Resistant Cancer Cell Populations during Treatment with Targeted Therapies." Grassberger et al.

4) Biology: Edwin Steele Laboratories Achievements:

- Rakesh K. Jain, PhD, gave the 2019 Judah Folkman Lecture at Harvard Medical School/Boston Children's Hospital and the 2019 Jeffrey H. Isner Memorial Lecture at Tufts University School of Medicine
- Rakesh K. Jain, PhD, received grants from the Advanced Medical Research Foundation and the Jane's Trust Foundation as well as a $ 100,000 gift from Dr. Herman and Joan Suit to support the Steele Labs
- Rakesh K. Jain, PhD, was named as a "Highly Cited Researchers 2019" by Clarivate Analytics/Web of Science for the sixth year in a row. His publications have been cited >100,000
- Rakesh K. Jain, PhD, delivered the Plenary Lecture: "Reengineering the Tumor Microenvironment to Enhance Cancer Treatment: Bench to Bedside", 17th International Photodynamic Association World Congress, Cambridge, MA (July 1, 2019)
- Rakesh K. Jain, PhD, gave the Keynote Lecture: "Reprogramming the Tumor Microenvironment to Enhance Cancer Treatment: Bench to Bedside", Gordon Research Conference on Angiogenesis, Salve Regina, Newport, RI (August 4-9, 2019)
- Dai Fukumura, MD, PhD, Deputy Director of the Steele Laboratories and head of the Fukumura Lab in the Steele Laboratory was also named as a "Highly Cited Researchers 2019" by Clarivate Analytics/Web of Science. This list "recognizes world-class researchers selected for their exceptional research performance, demonstrated by production of multiple highly cited papers that rank in the top 1% by citations for field and year in Web of Science.
- Igor Garkvstev, MD, PhD and Rakesh K. Jain, PhD, were chosen as the second runner up in the National Foundation for Cancer Research's Salisbury Venture Competition for Translational Research for their project on improving cancer treatment by co-targeting cancer stem cells and immunosuppression
- Timothy Padera, PhD, head of the Padera Lab of the Steele Laboratories for Tumor Biology and Associate Professor in Radiation Oncology at Harvard Medical School, was elected to the American Institute for Medical and Biological Engineering (AIMBE) College of Fellows in the Class of 2019. This peer-nominated recognition is designated for the most accomplished and distinguished scientists,

academic researchers, and clinical practitioners in the fields of medical and biological engineering

- Yves Boucher, PhD, head of the Boucher Lab of the Steele Laboratories, received a Department of Defense Breast Cancer Research Program Breakthrough Award
- Dan G. Duda, DMD, PhD, director of Translational Research in GI Radiation Oncology and head of the Duda Lab of the Steele Laboratories, received a Department of Defense Peer Reviewed Cancer Research Program Impact Award
- Lei Xu, MD, PhD, head of the Xu Lab of the Steele Laboratories, received a Department of Defense Neurofibromatosis Research Program Impact Award
- Zohreh Amoozgar, PhD, post-doctoral fellow, received MGH Cancer Center Excellence Award
- Patrik Andersson, PhD, post-doctoral fellow, received a Swedish Brain Tumor Foundation Fellowship
- Gustavo Cruzeiro, PhD, post-doctoral fellow, received a Tosteson and Fund for Medical Discovery (FMD) Postdoctoral Fellowship
- Meenal Datta, PhD, post-doctoral fellow, received the AACR-Loxo Oncology Pediatric Cancer Research Fellowship and the AACR Scholar-in-Training Award
- Shan Krishnan, PhD, post-doctoral fellow, received a Department of Defense Peer Reviewed Cancer Research Program Horizon Award
- Pragya Kumar, MS, research fellow, received Research Proposal Award from the University of Chicago for her MS Thesis Research in the Steele Labs
- Franz Pruefer, MD, PhD, post-doctoral fellow, received fellowships from the Mexican National Science Commission and the Mexico City Science Commission
- Jun Ren, PhD, post-doctoral fellow, received the Cancer Research Institute (CRI) Irvington Post-Doctoral Fellowship, the Tosteson and Fund for Medical Discovery (FMD) Postdoctoral Fellowship and the American Brain Tumor Association (ABTA) Basic Research Fellowship. [Declined ABTA Fellowship due to overlap with the CRI Fellowship]
- Kangsan Roh, PhD, post-doctoral fellow, received Best Oral Presentation Award at the Korean Society of Lymphedema Conference



Geometries available in TOPAS-nBio. (a) An ellipsoid cell shown with a nucleus (blue) and mitochondria (red), a spherical and a fibroblast cell with nucleus and mitochondria. Also shown is a hippocampal neuron with a soma (red) and dendrites (black and blue). (b) Three full nucleus models, one based on the Geant4-DNA example (left) and two different fractal models (center and right). (c) A chromatin fiber consisting of nucleosomes each composed of histone proteins (blue) wrapped by two turns of a double helix DNA (green and red). (d) A circular plasmid consisting of 100 basepairs. (e) RNA strand recreated using the TOPAS-nBio interface to the protein database. (f) A lipid (membrane) layer.
From: Radiat Res. 2019 191(2):125-138 "TOPAS-nBio: An Extension to the TOPAS Simulation Toolkit for Cellular and Sub-cellular Radiobiology" Schuemann et al.

James A. Brink, MD, Chief

Radiology Research at Massachusetts General Hospital has had another excellent year, with continued growth and ever-greater impact. By far the largest radiology department in the world, MGH Radiology reported total research activity of $125M for the 2019 fiscal year (FY2019), a 19% increase over the year before. In fact, FY2019 was the first year that the department's research revenues exceeded its professional clinical revenues.

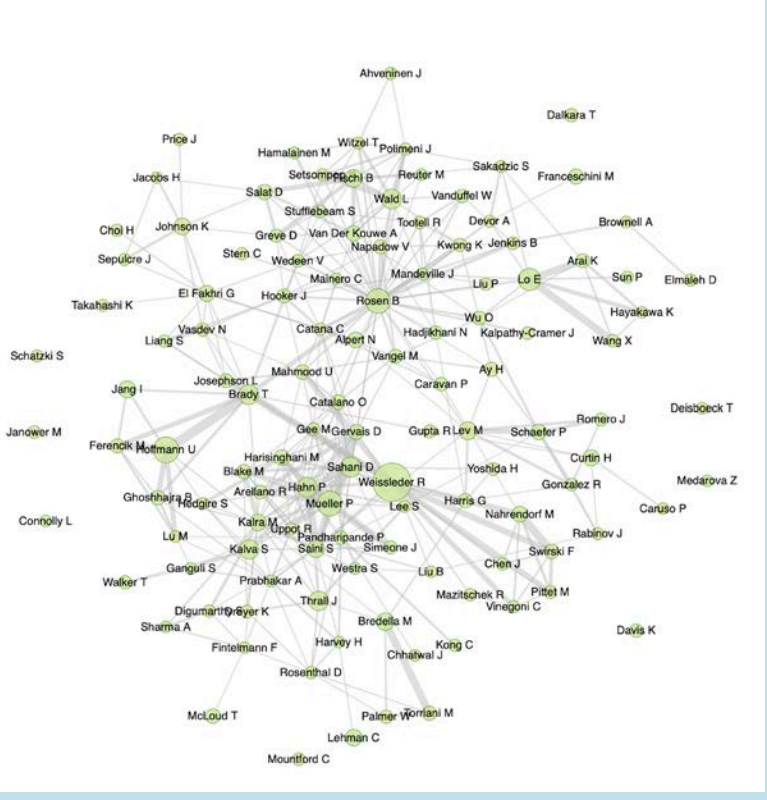
The third-largest department at Mass General, behind only Neurology and Medicine, Radiology accounted for 10% of the hospital's total research revenue in FY2019. The percentage is substantially higher, approximately 15% or more, if you factor in the research from other departments within the hospital, including Neurology, Psychiatry, Anesthesiology and Cardiology, that depend on Radiology's unique and world leading imaging resources and technology.

Radiology Research encompasses eight centers and institutes. Following are brief descriptions of the accomplishments reported by each of these in FY2019, with a particular focus on the growth each experienced during the year.

Below is a brief synopsis of the Radiology Departments Centers, their mission and recent accomplishments:

Cardiovascular Imaging Research Center
The Cardiovascular Imaging Research Center (CIRC) brings together researchers seeking to improve patient health using advanced cardiovascular imaging. The Center develops and leverages both imaging and artificial intelligence to address several broad aims. These include biomarker discovery and improvements in population health, multisystem imaging to unlock the secrets of how external stress leads to brain activation that advances atherosclerosis and addressing the excess risk of cardiovascular disease among patients with cancer.

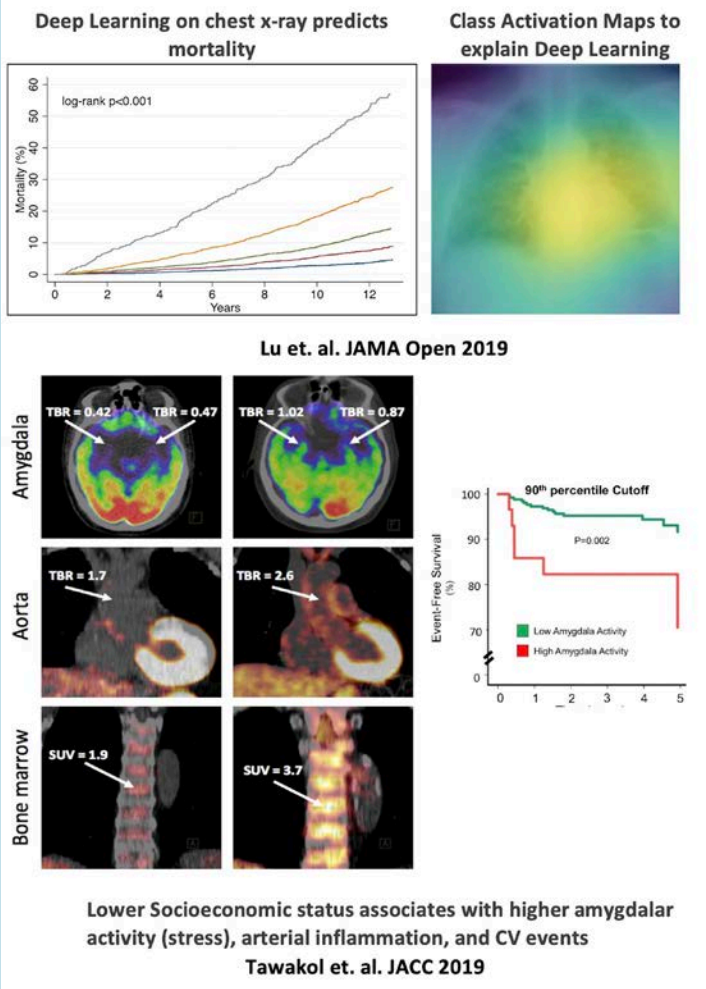
In FY2019, the CIRC added three principal investigators to its ranks, for a total of eight. The investigators were engaged in 24 projects with $5M in funding, including funding from seven R01 or equivalent grants. The Center also had a productive year in terms of disseminating its findings. CIRC researchers published roughly 75 peer-reviewed papers during the twelve-month period.



Radiology research is, by its nature, multi-disciplinary and collaborative. Studies typically involve investigators with expertise in technology development, biomedical physics and the disease areas or interventions in question.

Within Radiology, the above image shows coauthor relationships among nearly 800 members of the MGH Radiology community, many of them between researchers from different corners of the department. Here, the size of a circle is proportional to the number of publications that author has, while the thickness of the line connecting two authors' names is proportional to the number of publications they share.

Though not as easily visualized, collaborations very commonly cross departmental and even institutional lines, where Radiology department researchers regularly work with leading experts from across the institution, region, and globe. Indeed, many of the program's researchers can claim dozens of collaborators and coauthors from both within and outside the hospital.



Center for Clinical Data Science

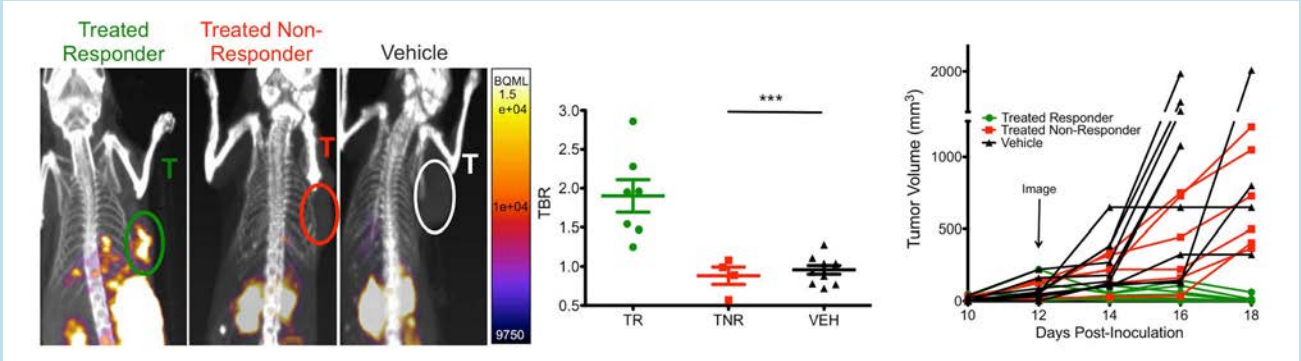
The Center for Clinical Data Science is introducing machine learning to healthcare by combining computational resources, technical expertise and the full breadth of data contained within the Partners HealthCare ecosystem. CCDS has built a high-performance GPU cluster and is using subsets of the Partners HealthCare data to develop a range of artificial intelligence algorithms that result in improved care for our patients.

The Center's achievements in FY2019 included development of an artificial intelligence 'platform' with a compute cluster and an inference system for scalable machine learning development and deployment for both clinical and research applications; the latter is a focus of attention for the coming year. Server-side development of the inference system was completed in August 2019; the software for the cluster was test-run in September 2019 and launched in November. Also in FY2019, CCDS continued executing its 'first wave' of commercial portfolio commitments: a spectrum of projects that will play an integral role in advancing the use of machine learning in healthcare, within and beyond the MGH.

Center for Precision Imaging

The Center for Precision Imaging focuses on designing, creating, and testing new methods for imaging and therapeutic targeting of important biological pathways in disease. The Center is driving the next wave of Molecular Imaging to improve patient care. Its efforts spans imaging probe development, creation of appropriate cell-based and animal models of pathology, imaging device development, and the clinical translation of the optimized concepts to help detect disease and therapeutic response in people.

In FY2019, the Center made important strides in expanding the impact of precision imaging, through an array of efforts. For example, in March 2019 the Center hosted the Frontiers in Imaging Symposium, which played an important role in educating radiologists at MGH about the many benefits of precision imaging. In addition, Center researchers collaborated with colleagues in the Institute for Innovations in Imaging (i3) to increase clinical translation of novel imaging biomarkers. They also worked closely with the Termeer Center to apply imaging to early phase cancer trials.



MGH-CPI-developed PET tracer to a novel imaging target, Granzyme B, predicts response to immunotherapy prior to tumor volume changes. MGH Cancer Center trial for first-in-human study in coming year

Radiology

Department Report

Center for Ultrasound Research and Translation

The Center for Ultrasound Research & Translation (CURT) focuses on clinical translational research and engineering innovation in the field of medical ultrasound. Through the integration of engineering and iterative translational refinement in the care environment, the Center is developing high-yield technologies targeted at key clinical problems. Areas of expertise at CURT include quantitative imaging biomarker development and validation, clinical trials and data analytics.

In FY2019, the Center succeeded in building out cutting-edge research programs and securing long-term funding to support those programs. The Clinical Translation Program was funded by creation of a pharma-funded liver disease research consortium (NIMBLE); the Machine Learning Program was funded by NIH R01, industry and DoD funding; and the Acoustic Signal Processing Program was funded by DoD and industry contracts. Efforts are now under way to develop a Chemistry Program focusing on drug delivery and contrast agents and an Industry Liaison Program, which will work to deepen engagement with industry partners and secure discretionary funding.

Gordon Center for Medical Imaging

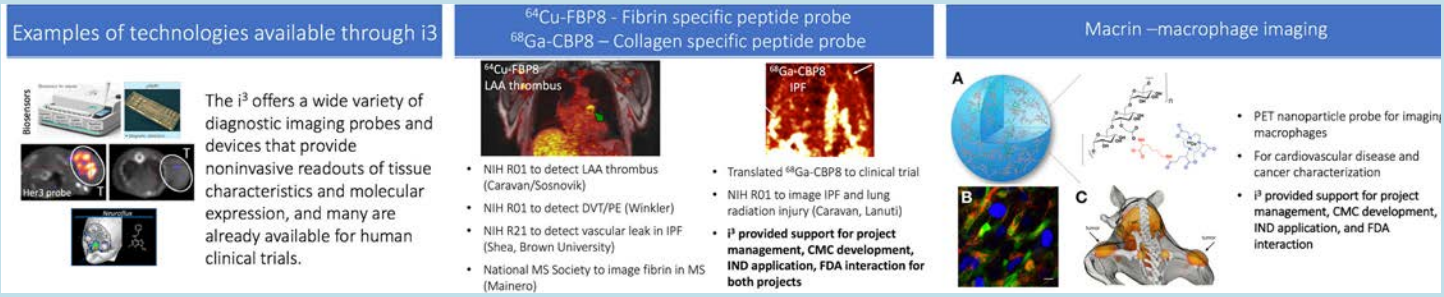
The Gordon Center for Medical Imaging is dedicated to improving patient care by developing and promoting new biomedical imaging technologies used in both diagnosis and therapy. Its investigators are engaged in research, training and translation of innovative research into clinical applications. Also, the Center offers use of its equipment and clinical research facilities to the academic community, research laboratories and industry through the Gordon PET Core.

With 19 labs (including two new labs: the Liu Lab in AI and the Lee Lab in Radiochemistry), 47 faculty and 145 members, and programs including a P41 PET/MR National Center for Biomedical Imaging and Bioengineering (NCBIB), the Gordon Center continued to serve the medical imaging community in FY2019. In addition, the Gordon PET Core performed 1,500 research studies for ten institutions in five states. On the funding front, the Center sustained its annual growth of 22% since 2016, with an estimated $26M projected by the end of FY2019.

Institute for Innovations in Imaging (i³)

The Institute for Innovations in Imaging (i³) was established to facilitate translation of basic discoveries to the bedside for diagnostic probes and devices. The i³ team leverages its extensive expertise in the biology and pathophysiology of common diseases, technology development, clinical trials and more in partnering with researchers and industry partners to develop, clinically deploy, and commercialize novel diagnostic and therapeutic tools.

FY2019 was a significant year for the Institute for Innovations in Imaging. In addition to moving into its new, CNY-10 office space, furthering its synergy with the IBC (the Interdepartmental Brain Center), the Institute hired an associate director and a radiochemist. All of this helped the i³ advance its goals of accelerating translation of new tools to detect disease and monitor treatment. In FY2019, the Institute prepared three investigative new drug (IND) applications for PET and MR imaging of cancer and cardiovascular diseases, neuro-inflammation, and to replace Gd-based MRI contrast agents while its existing technologies supported more than 30 clinical trials at MGH. At the same time, it raised more than $8M in external funding, from NIH as well as from industry. Looking forward, i³ is planning to supplement these efforts with efforts to lower the barriers for clinical translation of new diagnostic technologies, and will complete its planning and buildout of new laboratories focused on the development and production of long-lived radioisotopes for a broad range of translational applications.



Institute for Technology Assessment
The mission of the Institute for Technology Assessment is to conduct health outcomes research to guide the development, evaluation and utilization of medical technologies that improve the quality and cost-effectiveness of medical care.

The ITA accomplished a number of goals in FY2019. Among them: it worked to increase policy collaborations at the national and international levels. For example, through WHO and CDC collaborations, its members built interactive, web-based interfaces that provide outcomes projections for Hepatitis C interventions in different countries and different states. The projections draw from the ITA's population model of Hepatitis C. The Institute has also introduced initiatives to optimize population-level cancer control interventions using simulation modeling. It received new funding awards for three cancer sites in 2019: Thyroid (NIH R01), Pancreas (NIH R01) and Hepatocellular (DoD).

Athinoula A. Martinos Center for Biomedical Imaging
The Athinoula A. Martinos Center for Biomedical Imaging is one of the world's premier research centers devoted to development and application of advanced biomedical imaging technologies. Housed within the Department of Radiology at Massachusetts General Hospital and affiliated with both Harvard Medical School and MIT, the Center is developing first-of-a-kind tools and applying them to solve challenges in neuroscience, oncology, cardiology and other clinical domains.

Center researchers had a number of research accomplishments in the past year, reported in over 500 peer-reviewed journal papers in 2019. Topics studied include the development of novel human molecular imaging probes of fibrin and collagen, a study finding a new mechanism for brain waste removal during sleep studied with ultra-high field MRI, and translation of AI tools for treatment monitoring of GMBs. In addition to its research accomplishments, the Center reported progress in a number of capital projects in FY2019. Installation of a new 7T Terra MRI scanner is now complete, as is installation of a first-of-its-kind combined TMS/MEG system, which uses new optically pumped magnetometer (OPM) technology. The Center also launched a new optical microscopy core as part of the $17 million Imaging Scientists program sponsored by the Chan Zuckerberg Initiative. Finally, planning is now complete for a new Clinical Translational Research Unit (CTRU).

Ragon Institute of MGH, MIT and Harvard

Department Report

Bruce D. Walker, MD, Director
Facundo Batista, PhD, Associate Director

The evolution of the Ragon institute is driven by the evolution of human immunology knowledge. Founded initially as an HIV/AIDS research institute with the mandate of developing a vaccine, Ragon scientists have gone on to expand our understanding of human immunity from HIV/AIDS to other infectious disease, with a current focus on tuberculosis and influenza, among others. The Ragon Institute is the organizational embodiment of the scientific progression from HIV/AIDS to human immunology to human health, drawing from our unique 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.

Ultimately, the Ragon Institute is harnessing the immune system to prevent and cure human disease.

Plaque commemorating the Ragon's 10-year anniversary award

Key achievements in 2019

1. Establishment of an endowment for the Ragon Institute:
In February of 2019 Phillip T. and Susan M. Ragon made an additional $200M donation to the Ragon Institute to expand an existing $50M endowment, providing long-term sustainability to the Institute. The gift was made to MGH, which is the administrative home of the Institute. This gift coincided with plans to make the Ragon Institute a separate Department at MGH, which is currently pending final board approval.

2. Computational design of an HIV vaccine to induce broadly neutralizing antibodies: Dr. Facundo Batista, Associate Director of the Ragon Institute, led a study published in Science in which they present a generalized strategy for vaccine-mediated induction of broadly neutralizing antibodies to HIV, a critical component for an effective HIV vaccine that remains a major hurdle in the field. This was achieved by exploiting ultradeep human antibody sequencing data to identify a diverse set of potential antibody germline precursors for a bnAb with dominant HCDR3 contacts. They then developed immunogens that primed responses from these rare bnAb-precursor B cells in a mouse model, showing that they bound a multiple potential bnAb-precursor human naive B cells in ex vivo screens. This repertoire-guided germline-targeting approach provides a major step forward in establishing a framework for induction of diverse HIV bnAbs; moreover, this approach can likely be applied to antibodies from other pathogens.

Steichen JM, Lin YC, Havenar-Daughton C, Pecetta S, Ozorowski G, Willis JR, Toy L, Sok D, Liguori A, Kratochvil S, Torres JL, Kalyuzhniy O, Melzi E, Kulp DW, Raemisch S, Hu X, Bernard SM, Georgeson E, Phelps N, Adachi Y, Kubitz M, Landais E, Umotoy J, Robinson A, Briney B, Wilson IA, Burton DR, Ward AB, Crotty S, Batista FD, Schief WR. A generalized HIV vaccine design strategy for priming of broadly neutralizing antibody responses. Science. 2019;366(6470).

3. Regulation of placental transfer of antibodies from mother to child:
Ragon Member Dr. Galit Alter used her systems serology approach to define the mechanism by which mothers pass on vaccine-mediated immunity to unborn fetuses. By comparing pertussis antibodies in the mother to umbilical cord samples, Alter's group discovered that the placenta preferentially transfers maternal antibodies that activate natural killer (NK) cells to the infants. NK cells are abundant and functional

Faculty, students, postdocs, and employees at the 2019 Ragon Institute Annual Retreat

in the days following birth. This allows for activation of the innate immune system in the infant, whose adaptive immune system is not fully developed. Similar findings were seen when looking at influenza and respiratory syncytial virus. These findings hold important implicants for the development of future vaccines targeted towards pregnant women and aimed at protecting infants from infectious disease.

Jennewein MF, Goldfarb I, Dolatshahi S, Cosgrove C, Noelette FJ, Krykbaeva M, Das J, Sarkar A, Gorman MJ, Fischinger S, Boudreau CM, Brown J, Cooperrider JH, Aneja J, Suscovich TJ, Graham BS, Lauer GM, Goetghebuer T, Marchant A, Lauffenburger D, Kim AY, Riley LE, Alter G. Fc Glycan-Mediated Regulation of Placental Antibody Transfer. Cell. 2019;178(1):202-15

4. Ragon Institute receives major funding for TB vaccine work:

The Ragon Institute was established to harness the immune system to prevent and cure human disease, and although the initial goal was to develop at HIV vaccine (currently in efficacy trials in Africa), the focus expanded early on to TB, a major co-morbidity in HIV infected persons due to impaird immune function. Ragon Associate Member Dr. Sarah Fortune, in collaboration with JoAnne Flynn, professor at the University of Pittsburgh, and Henry Boom, professor at Case Western Reserve, has recently received one of three grants from the National Institute of Allergy and Infectious Diseases to create an Immune Mechanisms of Protection Against Myobacterium tuberculosis (IMPAc-TB) Center. This collaborative effort involving mulitple Ragon investigators seeks to understand the immune responses that provide protection against TB infection and disease. The seven-year contract can receive up to $58 million in funding. The highly multidisciplinary and technologically diverse research team will comprise the Ragon Institute, HSPH, Massachusetts Institute of Technology, University of Massachusetts Medical School, Boston University, University of Washington, Imperial College London, University of Cape Town, and Makerere University in Uganda. The Center will use cutting edge technologies to understand the immune responses that provide protection against TB infection and disease in humans that are infected with TB but do not develop active disease, with the intention of translating the findings into experimental models for rapid advancement into clinically relevant work. Critical focus will be on immune responses that prevent initial infection, responses elicited by promising vaccines, and understanding the implications of TB co-infections, such as HIV, on immune responses. The work builds on Dr. Alter's identification of a unique antibody response associated with resistance to TB infection.

Attendees at the Ragon Institute endowment signing ceremony. Attendees include Terry and Susan Ragon; the provost of MIT; the former president of MIT; current presidents of MGH, MIT, and Harvard; MGH board members; and the director and associate director of the Ragon Institute.

Lu LL, Smith MT, Yu KKQ, Luedemann C, Suscovich TJ, Grace PS, Cain A, Yu WH, McKitrick TR, Lauffenburger D, Cummings RD, Mayanja-Kizza H, Hawn TR, Boom WH, Stein CM, Fortune SM, Seshadri C, Alter G. IFN-gamma-independent immune markers of Mycobacterium tuberculosis exposure. Nat Med. 2019;25(6):977-8

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 and the Surgical Artificial Intelligence and Innovation Laboratory that are designed to enhance the research environment, foster collaboration, and leverage expertise and resources to expand the productivity and output in areas of interest.

Center for Transplantation Sciences (CTS)

The CTS at Massachusetts General Hospital is a multidisciplinary research center working at the interface between basic science and clinical applications in transplantation immunology and related fields. It was established in 2015 by merging the Transplantation Unit Surgery Research Laboratory and the Transplantation Biology Research Center, with Joren C. Madsen, MD, DPhil and James F. Markmann MD, PhD serving as co-directors, with newly recruited, Richard N. Pierson III, MD serving as scientific director. The position of scientific advisor is held by David H. Sachs, MD.

The mission of the Center for Transplantation Sciences (CTS) at Massachusetts General Hospital is to improve the number and the lives of recipients with organ, tissue and cell transplants by:

- Better understanding the mechanisms underlying the immune response
- Developing novel means of inducing immune tolerance
- Finding creative ways of increasing the supply of donor organs

Center for Engineering in Medicine (CEM)

The Center for Engineering in Medicine (CEM) engages in the basic sciences, clinical medicine and engineering to solve every day biomedical challenges for patients. Our team of clinically-inspired engineers, physicians and biologists, among others, use creative scientific approaches to improve health care delivery and further the use of personalized medicine, minimally invasive therapies and new technologies for today's and tomorrow's diagnostics and treatments.

The Center's position within the MGH clinical and research environments enables not only the traditional academic triad of sciences, technology, and clinical medicine, but its position also enables a fourth dimension – innovation. Serving as co-directors; Ronald Tompkins, MD, ScD, Mehmet Toner, PhD, and Martin Yarmush, MD, PhD.

Center for Organ Engineering at MGH

In the Center for Organ Engineering, Harald Ott, MD, is currently integrating stem cell biology, developmental biology, tissue engineering, and transplantation science to develop novel solutions for end organ failure. The Center is linked to the Harvard Stem Cell Institute, MIT, Harvard Medical School, the New England Organ Bank, and various clinical departments of MGH. The research has a high potential clinical impact and may help develop new forms of treatment for diseases such as heart failure, end stage lung disease, renal failure, and diabetes. Their research projects are highly innovative and give us the unique opportunity to maintain a clear translational focus in a multidisciplinary team.

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.

Spotlight on Research: The Surgical Artificial Intelligence and Innovation Laboratory (SAIIL)
SAIIL is a multidisciplinary group composed of surgeons, engineers and data scientists who are passionate about redesigning the delivery of surgical care. The team, led by Ozanan Meireles, MD and Daniel Hashimoto, MD is comprised of surgeons in Mass General's Department of Surgery, scientists from the Massachusetts Institute of Technology Computer Science and Artificial Intelligence Laboratory (CSAIL), and students from Harvard University. SAIIL's primary research goals focus on utilizing computer vision to investigate the intraoperative phase of care through real-time, automated analysis of operative video for laparoscopic, robotic, and endoscopic procedures. Other research efforts include investigating quantitative signal from the electronic medical record associated with the surgical video data and their correlation with clinical outcomes, investigation of the value of robotic kinematics in minimally invasive surgery, and co-development of video annotation software.

In 2019, SAIIL presented results of its computer vision system's automated analysis of laparoscopic sleeve gastrectomy videos at the 139th meeting of the American Surgical Association and subsequently published in Annals of Surgery. SAIIL members were also invited lecturers at several other meetings last year, including the Intelligent Health Summit (Basel, Switzerland); European Association of Endoscopic Surgeons (Seville, Spain). SAIIL's research was also covered by the media, including the Financial Times, PBS News, Harvard Medicine Magazine, and TED.

Furthermore, SAIIL has partnered with the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) to lead an international, multi-institutional collaboration among surgeons and engineers from academia and industry, with 60+ invited participants from North America, Asia, and Europe to create a consensus surgical video annotation framework to allow for international collaboration in surgical AI research (aka, surgical data science).

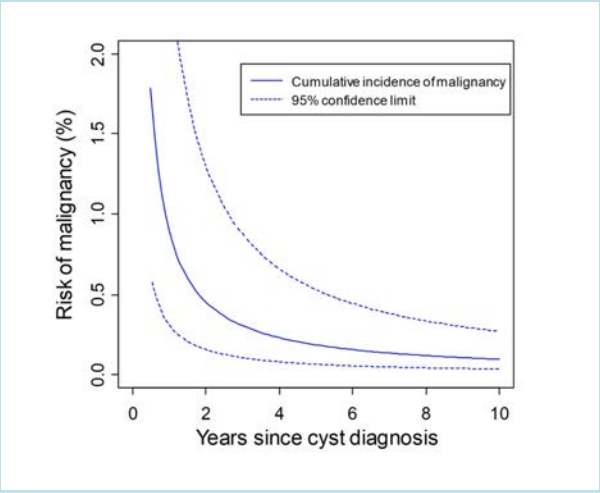
Human liver being preconditioned with the preservative cocktail during machine perfusion

Supercooling extends preservation time of human livers
Investigators from the MGH Center for Engineering in Medicine (CEM), lead by Korkut Uygen, PhD, and his team, have developed a new method for supercooling human donor livers to subzero temperatures without freezing. This technique could triple the time that a donor organ stays safe and viable during transportation from the donor to the recipient.

Currently, a donor human liver is kept only about nine hours outside the body – stored on ice in a preservative solution at temperatures ranging from 4 to 8 degrees Celsius – before the tissues become irreparably damaged and the organ has to be discarded. At colder, subzero temperatures the organ would survive longer, however, freezing causes serious injury that would make the organ not transplantable. With supercooling, the water inside the organ can be prevented form freezing as the research team previously demonstrated by tripling the preservation time of rat livers with ice-free subzero storage, and was noted as "one of the 7 awesome technologies funded by your taxes" on NIH Director's blog. Despite this success in rat livers, the likelihood of ice formation exponentially increases with volume, preventing scale up to human livers which are 200 times larger in size. In addition, for successful supercooling preservation, livers must be homogeneously preconditioned with agents that protect it from the cold which is much harder to achieve in large sized organs.

In a series of experiments, bioengineering and cryopreservation approaches were combined to develop a preservative cocktail that counters ice formation during supercooled storage. Additionally, machine perfusion technology was adapted to homogeneously precondition human livers with the cocktail. At the same time, investigators at the CEM discovered the importance of eliminating air-water interfaces to stabilize the supercooled state. Together this technical tour de force resulted in successful supercooling of the human liver at -4°C without any ice formation. With the new supercooling protocol human livers were preserved for 27 hours and it was shown that the livers retained their viability despite this substantial increase preservation duration. This is the first time that the feasibility of subzero human organ preservation has been shown. The manuscript (Nat Biotechnol 37(10):1131-1136, 2019. PMC6776681) was the issue cover. The paper was covered by the BBC, The Atlantic, New Scientist and others, and tweeted by NIH Director Francis Collins.

A leap forward in the early detection of pancreatic cancer



Carlos Fernandez-del Castillo, MD, and his team continue their research on pancreatic cancer which is now funded by 3 NIH grants. Pancreatic cancer is one of the most lethal human cancers and despite recent advances in chemotherapy, surgical resection remains the only cure. A major impediment to improving outcomes of patients is that 80% of patients are diagnosed with advanced disease and are not eligible for surgery. Pancreatic cancer arises from a variety of precancerous lesions, including intraductal papillary mucinous neoplasms (IPMNs), which provide an opportunity to treat patients before they develop cancer.

IPMNs are cystic lesions that are increasingly being detected in the pancreas during routine abdominal imaging. These cysts are biologically heterogenous and only a subset will progress to invasive disease. We performed a retrospective study focusing on small pancreatic cysts (i.e. < 15 mm) and found that if no change is seen over 3 years of follow up, the likelihood of developing pancreatic malignancy is no different than in the general population. To identify biomarkers that will distinguish low grade from high grade IPMNs we examined the extracellular vesicles (i.e. exosomes) in the blood of patients. Here we found a signature that allows us to use a simple blood draw to detect with high accuracy patients with cysts that harbor invasive cancer. This is a major breakthrough, and the first step in looking for other markers and signatures that will identify the non-invasive high-grade lesions.

Breathing New Life into Old Cell Lines for Hepatic Drug Metabolism and Drug-Drug Interaction Studies

Investigators from the Center for Engineering in Medicine (CEM) have developed a simple and rapid maturation technique for hepatic cell lines to enable their practical use in drug metabolism and drug-drug interaction studies.

The liver is the primary organ responsible for the metabolism and detoxification of most xenobiotics, including pharmaceuticals. CYP3A4, a cytochrome P450 enzyme regulated by the nuclear receptor PXR, is involved in most of the drug-metabolizing pathways in the liver. The regulation/induction of CYP3A4 and PXR is critical in toxicology and drug-drug interaction (DDI) studies which are mandated by the FDA. Hepatic cell lines, such as Huh7, could provide a cost-effective alternative to human primary hepatocytes for this use, however, they express negligible amounts of CYP450s and PXR.

CEM investigators have shown that this low PXR and CYP3A4 expression in Huh7s can be dramatically increased by culturing them super-confluently for 4 weeks. While this is a substantial improvement for the use of Huh7s in drug metabolism studies, the 4-week time period is not well suited to many industrial and research and development work-flows. In a recent publication entitled "Rapid maturation of the hepatic cell line Huh7 via CDK inhibition for PXR dependent CYP450 metabolism and induction" (Nature Scientific Reports, 2019, 9: 15848) by a research group led by Drs. O. Berk Usta and Martin L. Yarmush, CEM investigators have shown that this timeline can be dramatically accelerated. By using Dinaciclib, a potent cyclin-dependent kinase inhibitor, the investigators significantly increased basal CYP3A4 and PXR levels in as soon as 24 hours. The paper further demonstrates that Dinaciclib-matured Huh7s can be used for many drug induction studies, where CYP3A4, CYP1A2, CYP2C9, and CYP2C19 inductions were achieved following rifampicin treatment. Equally important, through a direct demonstration using amiodarone and rifampicin as model drugs, the studies showed that matured Huh7s are also a strong platform for DDI studies.

First administration of donor antigen specific regulatory T cells (Tregs) with goal of eliminating immunosuppression in liver transplant recipients
Tregs are lymphocytes that are critical in preventing autoimmunity (maintaining self tolerance) and in controlling immune responses. Experimental studies over the past two decades have established that Tregs can be used to prolong allograft survival. Recently, studies have begun to explore use of Tregs as a therapeutic in humans to facilitate bone marrow transplantation, to prevent autoimmunity, and to prevent allograft rejection. Tregs that are polyclonal and those that are antigen specific are being explored; the latter carry the theoretical advantage that they do not cause global suppression of immunity.

James Markmann, MD, and his team recently initiated the first study using donor antigen specific Tregs as a means to gain tolerance with immunosuppression elimination post solid organ transplantation. In collaboration with Eva Guinan at DFCI, we first conducted a phase I pilot in renal transplant recipients as part of an international trial of regulatory cells at 6 sites (2 in US and 4 in EU). Three patients were enrolled and successfully weaned off 2 of 3 immunosuppressive agents and we found evidence of homing of the Tregs to the kidney allograft. His team have now extended this work to a full immunosuppression withdrawal trial in liver transplant recipients, sponsored by the NIAID-Immune Tolerance Network. In November 2019, the first liver recipient received donor specific Tregs and is currently weaning immunosuppression. We anticipate enrolling a total of 9 patients over the next 1.5 years.

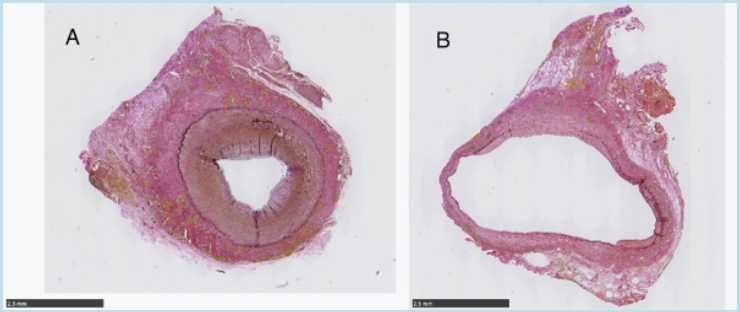
Completion of largest randomized trial of ex vivio liver perfusion (EVLP)
Ex vivo organ perfusion has the potential to radically alter the field of transplantation. In contrast to the existing standard of static cold storage in which organs are preserved in a box on ice, EVLP placed to organ on a perfusion device at the donor hospital and maintains it in physiological condition by perfusion with oxygenated blood and nutrients at body temperature. This not only permits assessment of organ quality, but also may improve the function of damaged organs, and potentially mot impactful is that EVLP will permit assessment of currently discarded organs to determine which are suitable for transplant.

In 2018, James Markmann, MD, and his team was the first in the US to perfuse and transplant a human liver using this novel technology, as part of a phase III registration trial being conducted by a local start-up company (Transmedics). Trial enrollment just completed by 21 US sites. Of 300 patients enrolled, 70 patients were enrolled at MGH. The MGH site data clearly indicate improved function of pumped livers compared to those stored using the traditional cold storage method, likely due to mitigation of ischemia and thus IR injury upon reperfusion in the recipient. Additional follow-up trials are planned to assess organs currently being discarded.

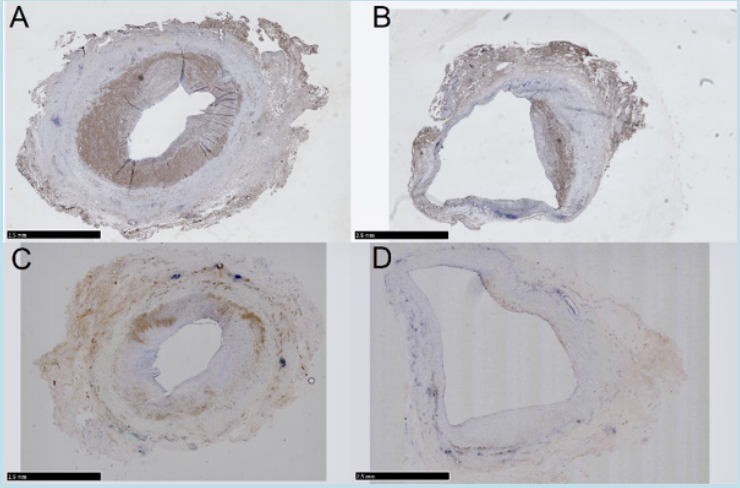
Mass General performs first application of genetically modified, live-cell, pig skin to a human wound
MGH Burn Surgeons successfully used live-cell, genetically engineered pig skin (xenograft) for the temporary closure of a burn wound through an FDA-cleared phase one clinical trial, which marks the first-time pig tissue derived from an animal with gene edits has been transplanted directly onto a human wound. MGH collaborated with Boston-based XenoTherapeutics, which designed and implemented the safety protocols for the special live pig tissue graft, known as xenoskin. The genetic modifications of these particular swine – developed in the 1990's at MGH by David Sachs, MD, removes a gene specific to pigs and not present in humans, allowing the pig skin to appear less foreign to the human immune system.

During the procedure, a 5-by-5-centimeter piece of genetically engineered pig skin was placed on the recipient's burn wound after it had been cleared of necrotic tissue. The pig skin graft was placed next to a much larger piece of cadaveric skin and both were secured with surgical staples and gauze bandages. Five days later, surgeons removed the temporary cadaveric skin and xenograft. Both skin grafts were adherent to the underlying wound bed and appeared indistinguishable from each other. No adverse events were further observed or reported and the wound was then treated further with a skin graft harvested from the patient's own thigh. Healing has progressed as anticipated and the patient will soon return to work. Analysis from the trial's Safety Review Committee show no transmission of porcine endogenous retroviruses, or PERVs, which have always posed a theoretical road block for the transplantation of pig tissues or organs transplanted into human recipients.

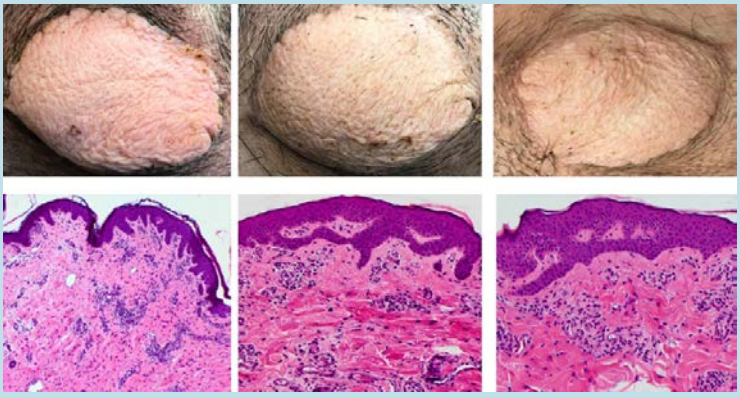
Photochemical Tissue Passivation of Arteriovenous Bypass Grafts Prevents Long-Term Development of Intimal Hyperplasia
Cardiovascular disease continues to carry a significant burden in the United States, affecting 92.1 million Americans. This includes 5.6% of Americans with coronary artery disease (CAD) and 4.3% with peripheral arterial disease (PAD). Autologous vein remains the standard conduit for lower extremity and coronary artery bypass grafting despite a 30-50% five-year failure rate, primarily attributable to intimal hyperplasia (IH) that develops in the midterm period (3-24 months) of graft maturation. Structurally, veins are not designed to withstand arterial pressure. When



Histological cross-sections of control (A) and PTP-treated (B) grafts (H&E-stained) showing increased overall wall thickness along with thickening of the media and intima and narrowing of the lumen in the control graft. Scale bar = 2.5 mm.



Immunohistochemical sections of control graft, staining for smooth muscle actin (A) and PCNA (C), along with corresponding PTP-treated graft sections for SMA (B) and PCNA (D). Heavier staining is seen for both cases in the control graft. Scale bar = 2.5 mm.



Clinical VCA pictures of successful attainment of tolerance (representative, R5) at POD 50 (top, left), POD 100 (top, middle), and 250 (top, right) with corresponding histology (bottom; left, middle, right) demonstrating absence of rejection (Banff 2007, Grade 0). POD = post-operative day; VCA = vascularized composite allograft.

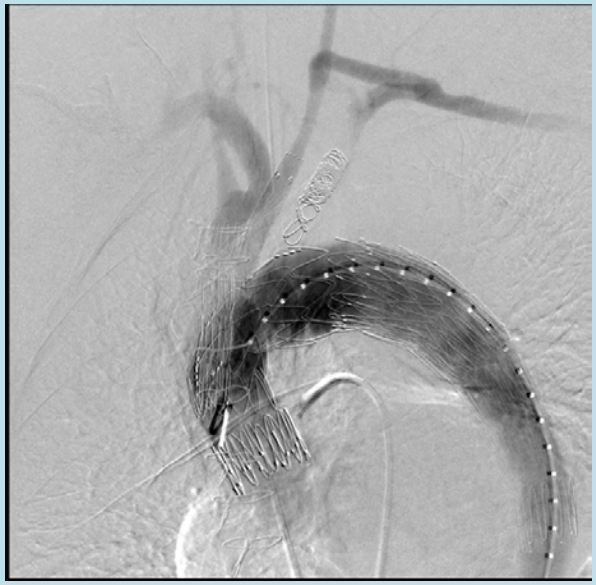
exposed to the arterial circulation, veins are unable to contract like an artery and experience a ~7-fold increase in shear stress and wall tension, which is beyond their elastic capabilities. This initial burst of shear stress creates an endothelial stretch injury, which ultimately leads to IH.

Jay Austen Jr, MD, and his team, in collaboration with Dr. Robert Redmond, in the Wellman Center for Photomedicine, discovered that by applying a light sensitive dye (Rose Bengal) to collagen rich tissues and illuminating the dyed surface with the appropriate wavelength of light (green light in this case) can strengthen the tissue through a process known as Photochemical Tissue Passivation (PTP). The team has discovered that application of PTP to vein grafts placed in arterial systems reduces intimal hyperplasia at 3-months through a process associated with downregulation of smooth muscle cell activation and proliferation. PTP also helped prevent the development of critical stenoses that were seen in untreated control grafts and was also associated with decreased mural thickness and increased luminal diameter. These findings at the midterm point of graft remodeling may predict that PTP treatment will improve long-term patency and success of vein grafts. This data was submitted for publication in 2020. This novel therapy has been spun out of the MGH and is being commercialized by a start-up company.

Developing a Strategy to Generate Immune Tolerance to Vascularized Composite Allotransplants

Through the use of modern immunosuppression regimens commonly used for successful solid organ allotransplantation, the first successful hand transplant was performed in France in 1998. Since then, the field of vascularized composite allotransplantation (VCA) has progressed to a collective, worldwide experience of more than 120 hand transplants, 44 face transplants, and a myriad of other VCAs including lower limb, abdominal wall, penis, laryngeal, scalp and even uterine transplants. Compared to solid organ transplantation such as kidney, lung, heart, pancreas etc., which are life-saving, VCAs are performed not only to improve one's quality of life, as demonstrated in longitudinal functional outcome studies (5–7), but also, to restore the patient's dignity, independence, and social confidence. However, as with any form of transplant, lifelong immunosuppression is currently required, imparting increased risk of systemic side-effects including metabolic, infectious, reno-vascular and neoplastic complications. Interestingly, despite the use of standard immunosuppression, up to 90% of VCA patients still develop at least one acute rejection episode in the first year post-transplantation, and almost 60% experience multiple rejection episodes. Of utmost concern is the looming specter of chronic rejection now that the field has accumulated more than 20 years of clinical experience in VCA. Despite the incredible clinical successes of clinical VCA, the field has reached a crossroads with an urgent need to develop strategies to minimization systemic immunosuppression or generate a state of immune tolerance to mitigate the deleterious sequelae of life-long immunosuppression.

Curtis Cetrulo, MD, is head of the clinical hand and face transplantation program in the Division of Plastic and Reconstructive Surgery. He led the team that performed the first hand transplant at the MGH and the team that performed the first penile transplant in the United States. These patients have successfully retained their transplants because they on standard immunosuppression regimens, despite some rejection episodes. Dr. Cetrulo's team has been focused on generating immune tolerance to VCAs. Particularly challenging has been achieving tolerance to the skin and epidermal elements of VCAs that are strongly immunogenic. His group has developed a novel means to generate a state of immune tolerance to VCAs including the skin across a class I MHC barrier in a swine model where the recipient is treated with nonmyeloblative irradiation, a co-stimulatory blockade agent (Belatacept), and a short postoperative course of tacrolimus. All immunosuppression was ceased at day 45 and the VCAs were completely viable and without any signs of rejection until the end of study a year and a half later (Figure 1). If these results could be translated to human VCA, patients could accept VCAs without requiring life-long immunosuppression and change the paradigm of musculoskeletal reconstruction.



Completion aortogram from a patient that underwent endovascular exclusion of an aortic arch aneurysm. The custom-made device provided two branches: one for the innominate artery and one for the left carotid artery – allowing for continued perfusion of the arch vessels with exclusion of the aneurysm. This procedure was performed through a small groin incision and a small left arm incision.

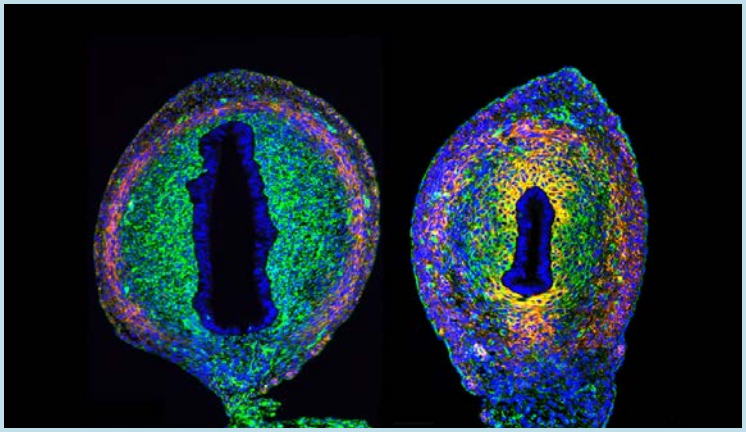
Endovascular Therapy for Complex Aortic Disease

The Division of Vascular and Endovascular Surgery has developed a program for the endovascular treatment of complex aortic disease. The program is a compilation of several early phase and physician-sponsored investigational device exemption (PS-IDE) trials. Within the Division, two PS-IDE trials exist to design custom-made devices to treat patients with thoracoabdominal aortic aneurysms. Through these programs, 50 patients from around the country have been successfully treated to date. It is anticipated that this program will continue to grow with the recruitment of additional patients.

In addition, these research programs offer the ability for collaborative teams (from vascular surgery and cardiac surgery) to begin to offer treatment to patients with aortic arch disease. The programs offer the opportunity for custom-made devices to treat aortic arch aneurysms (Figure) with and without aortic dissection. The team is also underway in expanding the program to include treatment of patients with ascending aortic disease. These advancements will offer alternate treatment for patients that currently require an invasive procedure.

New endometrial progenitor cell identified by single-cell sequencing of developing uterus reveals critical pathways underlying uterine hypoplasia and infertility

In mammals the early embryo is bipotential, possessing both the Wolffian ducts, and the Mullerian ducts. In males, secretion of Mullerian inhibiting substance (MIS) by the testis activates a "gatekeeper" cell surrounding the Mullerian duct to trigger its regression, preventing the development of the fallopian tube, uterus, cervix, and vagina. In this study Patricia Donahoe, MD, and her team, found that in the absence of MIS these gatekeeper cells persist in females, and give rise to the uterine endometrial stroma. Blocking the development of these progenitors with MIS leads to uterine hypoplasia and infertility. This study may help shed some light into how this progenitor cell, also conserved in humans, might contribute to uterine infertilities and pathologies.



Cross section and gross morphology of mouse uterus following postnatal exposure to recombinant MIS.

The Gut and the Aging Process

Gut barrier dysfunction and gut-derived chronic inflammation play a crucial role in human aging and various age-related diseases. The gut brush border enzyme intestinal alkaline phosphatase (IAP) functions to inhibit lipopolysaccharides (LPS) and other inflammatory mediators responsible for endotoxemia and also appears to be an important positive regulator of gut barrier function and microbial homeostasis. Furthermore, endogenous IAP levels decrease with age. Based upon the functional roles for IAP, Richard Hodin, MD, and his team hypothesized that this enzyme could play a critical role in regulating the aging process. We have discovered an age-related increase in gut permeability and this is accompanied by increases in gut-derived portal-venous and systemic endotoxemia and inflammation, alterations that were significantly more pronounced in IAP-deficient animals and were associated with an aggravated frailty and a shortened life span. In turn, oral supplementation with exogenous IAP significantly decreased age-related gut permeability and gut-derived systemic inflammation, resulted in significantly less frailty, and produced an extended life span. These effects of IAP were also evident in a second model system, Drosophilae melanogaster. Furthermore, IAP-supplementation in mice was associated with preserving the homeostasis of gut microbiota during aging. Based on these data, we believe oral IAP supplementation may represent a novel therapy to counteract the chronic inflammatory state leading to frailty and age-related diseases in humans.

Biofabrication of a vascularized islet organ (VIO) for type 1 diabetes

Islet transplantation is superior to extrinsic insulin supplementation in the treating severe Type 1 diabetes. However, its efficiency and longevity are limited by substantial islet loss post-transplantation due to lack of engraftment and vascular supply. To overcome these limitations, Harald Ott, MD, and his team, together with a team at the San Raffaele Diabetes Research Institute in Milan developed a novel approach to bio-fabricate functional, vascularized islet organs (VIOs) ex vivo.

They endothelialized acellular native matrixes to provide a biocompatible multicompartment scaffold with an intact hierarchical vascular tree as a backbone for islet engraftment. Over seven days of culture, islets anatomically and functionally integrated into the surrounding bio-engineered vasculature, generating a functional perfusable endocrine organ. When exposed to supra-physiologic arterial glucose levels in vivo and ex vivo, mature VIOs responded with a physiologic insulin release from the vein and provided more efficient reduction of hyperglycemia compared to conventionally transplanted fresh islets. In long-term transplants in diabetic mice, subcutaneously implanted VIOs achieved normoglycemia significantly faster and more efficiently compared to islets that were transplanted in deviceless fashion. They conclude that ex vivo bio-fabrication of VIOs enables islet engraftment and vascularization before transplantation, and thereby helps to overcome limited islet survival and function observed in conventional islet transplantation. Given recent progress in stem cells, this technology may enable assembly of functional personalized endocrine organs.

Michael L. Blute, Sr., MD, Chief

The Department of Urology has been expanding clinically and continues to develop its research infrastructure and endeavors. The department is committed to advancing urologic research through impactful clinical and translational research in urologic oncology, nephrolithiasis, pediatric urology and benign lower urinary tract dysfunction. The department supports research efforts that focus on health sciences and patient outcomes, advances in surgical technique and translational medicine. Supported by a talented faculty, the department is prominently featured nationally in leadership roles in professional and sub-specialty societies and is supported by extramural funding from the NIH, Department of Defense and industry sponsored research grants.

The department has had $7.1 million in grant funding since 2007 and continues to grow. We are adding faculty with a focus and commitment to research and continuing to build our research infrastructure with clinical databases and administrative support so that faculty can be more productive in their scholarly activity. Our collaborative relationship with Pathology, Radiology, Medical Oncology and Radiation Oncology helps to facilitate our team approach to urologic research. Our residents and Urologic Oncology fellows are actively involved in our research endeavors with dedicated research time during their training.

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Cover Image: This image depicts a white blood cell (green) recognizing and attacking a fungus called Candida albicans. Studying white blood cells and how they recognize and respond to fungal pathogens can aid in the development of novel cellular diagnostics and therapies for invasive fungal infections. This image was provided for our use by Adam Viens and Michael Mansour, MD, PhD, from the Mansour Lab in the Division of Infectious Diseases.

Back Cover Image: "Brain Structure and Function". This image depicts a medulla oblongata imaged by optical coherent tomography at the micron resolution superimposed over a photo of paint chips from old graffiti. This image was provided for our use by Caroline Magnain, PhD in the Martinos Center.

In the fall of 2019, the Research Institute held its second-annual image contest to showcase various perspectives on research at Mass General. We received 46 images from researchers of all disciplines with creative takes on what research means to them—from artistic shots of research spaces, to mixed medium images of the hippocampus and thoughtful photos conveying the humanity of our scientists. Several of the submissions from the contest can be found on page 8. To learn more about these images, check out the blog post announcing the winner and finalists.
massgeneral.link/2019-contest-winner