



CELEBRATION *of* SCIENCE

SAC 2023



Welcome to the 73rd Meeting of the MGH Scientific Advisory Committee (SAC) on March 29 & 30 of 2023.

As in past years, we will begin our two-day SAC meeting with a Celebration of Science at MGH. Our virtual poster sessions begin at 11:00 am on Wednesday, March 29, followed by an afternoon

Research Symposium from 2:00 pm to 5:00 pm. Merit Cudkowicz MD, MSc, will begin the symposium with a report on the past year of research at MGH and then we will turn our attention to the outstanding MGH researchers who were selected as the 2023 Howard Goodman Award recipients: Gaurav Gaiha, MD, PhD and Alexandra-Chloe Villani, PhD and the 2023 Martin Research Prize recipients: Marcela Maus, MD, PhD, Russell Jenkins, MD, PhD, and Ruanne Barnabas, MBChB, MSc, DPhil.

Thursday, March 30, 2023, marks the start of our official SAC business day, and as we usually do on day two of this meeting, we will devote the day to a specific theme. The theme of SAC this year will be The Adoption of Novel Technologies in the Practice of Medicine: Digital Health and AI. The day has been divided into 3 sessions and a lunch. The first session entitled “The Power of AI to Transform Health Care”, will start at 8:35 am and will be followed by a session focusing on real world examples of how AI is already starting to transform healthcare. After this session we will break for lunch where SAC members will have the opportunity to meet and hear from MGH investigators in small, unstructured, informal conversations. After lunch we will be hearing about novel technologies that are transforming healthcare including wearables and digital therapeutics. This session will lead us into a panel discussion and closing remarks to end the meeting.

To maximize the time for discussion during the day, the annual MGH Research Institute Executive Report and financials for FY22 have been provided in these printed materials (starting on page 12) for your review in advance of the meeting. Dr. Cudkowicz will highlight some of this information in her annual ECOR Report.

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

David F. M. Brown, MD
President, Massachusetts
General Hospital

Merit E. Cudkowicz, MD, MSc
Chair, Executive Committee
on Research (ECOR)

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Agenda

Wednesday, March 29, 2023

11:00 AM – 1:00 PM **Virtual Poster Session**

2:00 – 5:00 PM **Celebration Of Science**

2:00 – 2:15 PM **Welcome and Introduction**

David F. M. Brown, MD, President, Massachusetts General Hospital

2:15 – 2:45 PM **Introduction to the Celebration of Science & Research at MGH**

Merit Cudkowicz MD, MSc, Chair of the Executive Committee on Research (ECOR)

2:45 – 3:10 PM **Howard M. Goodman Fellowship**

Protective T cell Responses and Rational T cell-based Vaccines for Infectious Diseases

Gaurav Gaiha, MD, PhD, Assistant Professor, Department of Medicine / Ragon Institute

3:10 – 3:35 PM **Howard M. Goodman Fellowship**

Deciphering the Immunologic and Antigenic Drivers of ICI-associated Myocarditis

Alexandra-Chloé Villani, PhD, Assistant Professor, Department of Medicine / Center for Immunology and Inflammatory Diseases / Cancer Center

3:35 – 3:45 PM **Break**

3:45 – 4:10 PM **Martin Prize for Fundamental Research**

Targeting TBK1 to Overcome Resistance to Cancer Immunotherapy

Russell Jenkins, MD, PhD, Assistant Professor, Department of Medicine / Hematology-Oncology / Cancer Center

4:10 – 4:35 PM **Martin Prize for Clinical Research**

Distinct Cellular Dynamics Associated with Response to CAR-T Therapy for Refractory B Cell Lymphoma

Marcela Maus, MD, PhD, Associate Professor, Department of Medicine / Cancer Center

4:35 – 5:00 PM **Martin Prize for Population Health Sciences**

Efficacy of Single-Dose Human Papillomavirus Vaccination among Young African Women

Ruanne Barnabas, MBChB, MSc, DPhil, Professor, Department of Medicine / Chief, Infectious Diseases

Thursday, March 30, 2023

The Adoption of Novel Technologies in the Practice of Medicine: Digital Health and AI

8:35 – 9:55 AM

The Power of AI to Transform Health Care

Welcome and Introduction

Merit Cudkowicz, MD, MSc, Chair of ECOR

Cancer Genomics and AI

Gaddy Getz, PhD, Pathology, Director of Bioinformatics, Massachusetts General Hospital Cancer Center

Temporal Degradation of AI Algorithms in Medicine and Other Industries

Oleg Pianykh, PhD, Director of Medical Analytics, Department of Radiology, Massachusetts General Hospital

Advancing Genomic Medicine through Global Collaboration

Heidi Rehm, PhD, Director, Genomic Medicine Unit, Center for Genomic Medicine, Chief Genomics Officer, Department of Medicine, Massachusetts General Hospital

AI Activities at the MGB Data Science Office

Keith J. Dreyer, DO, PhD, FACR, FSIM, Chief Data Science Officer, Mass General Brigham

Q and A

Moderator: Judy Hung, MD, Director, Division of Clinical Research

9:55 - 10:15 AM

Break

10:15 – 12:00 PM

How can AI transform Health Care? Real World Examples

Predicting Breast Cancer

Constance Lehman, MD, PhD, Director of Breast Imaging Research Center, Massachusetts General Hospital

Conducting Target Trials in Electronic Health Records on Two Continents: Drug Repurposing for Neurodegenerative Disease

Mark Albers, MD, PhD, Frank Wilkens Jr. and Family Endowed Scholar in Alzheimer's Disease Research, Mass General Institute of Neurodegenerative Disease

FDA Approved AI Algorithms for Diabetic Retinopathy via Color Fundus Photographs

Grayson W. Armstrong, MD, MPH, Director, Ophthalmology Emergency Services, Massachusetts Eye & Ear

AI Work in Collaboration with BWH Engineers Looking at Embryo and Gamete Selection for IVF

Irene Dimitriadis, MD, Obstetrics, Gynecology, Massachusetts General Hospital, Medical Director, Third Party Reproduction

Predicting Lung Cancer Risk with AI

Lecia V. Sequist, MD, MPH, Director, Center for Innovation in Early Cancer Detection, Massachusetts General Hospital, The Landry Family Professor of Medicine, Harvard Medical School

Q and A

Moderator: Bruce Rosen, MD, PhD, Director of Athinoula A. Martinos Center for Biomedical Imaging, Massachusetts General Hospital

Agenda

12:00 - 1:15 PM

SAC Member Lunch with MGH Faculty

1:15 – 2:45 PM

Novel Technologies

Wearables

Rosalind Picard, ScD, FIEEE, Director of Affective Computing Research, Massachusetts Institute of Technology, Faculty Chair, MIT Mind Hand Heart

Mobile Phone-based Interventions for Mental Health

Sabine Wilhelm, PhD, Director, Center for Digital Mental Health, Director, Center for OCD and Related Disorders, Massachusetts General Hospital

Legal and Ethical Issues in Medical AI

Glenn Cohen, JD, Deputy Dean and James A. Attwood and Leslie Williams Professor of Law, Harvard Law School, Faculty Director, Petrie-Flom Center for Health Law Policy, Biotechnology & Bioethics

Panel Discussion: Challenges of AI in Health Care

Rosalind Picard, ScD, FIEEE

Sabine Wilhelm, PhD

Glenn Cohen, JD

Benjamin Silverman, MD, Senior IRB Chair, Mass General Brigham

Adam Landman, MD, MS, MIS, MHS, Chief Information Officer; Digital Innovation Officer, Brigham and Women's Hospital

Moderator: Collin Stultz, MD, PhD, Co-Director, Harvard-MIT Health Sciences & Technology, Massachusetts Institute of Technology, Nina T. and Robert Rubin Professor in Medical Engineering and Science, MIT, Professor, Electrical Engineering and Computer Science, MIT

2:45 – 2:50 PM

Closing Remarks

Concluding Remarks

Merit Cudkowicz MD, MSc, Chair of ECOR

2:50 – 3:20 PM

SAC Member Session (*closed session*)

3:20 – 3:50 PM

Discussion & Debrief: Research Leadership & SAC members only (*closed session*)

Howard M. Goodman Fellowship

2023 HOWARD M. GOODMAN FELLOWSHIP

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



Gaurav Gaiha, MD, PhD
Assistant Professor of Medicine /
Ragon Institute

Protective T cell Responses and Rational T cell-based Vaccines for Infectious Diseases

A major challenge with the development of effective vaccines for viruses is their ability to mutate and escape from immune responses. This is particularly notable for HIV and more recently has been observed with SARS-CoV-2 and the COVID-19 pandemic. To overcome this challenge, I have been focused on determining the mechanisms by which certain unique individuals are able to naturally counteract this viral variation. This led to work demonstrating that a component of the immune system known as CD8 T cells play a key role in natural HIV suppression. Moreover, I found that CD8 T cells in these unique individuals specifically target parts of the virus that are unable to mutate without substantial effects on viral integrity. Identifying these mutationally constrained regions of viruses was accomplished by developing a new computational approach that integrates protein structure with network theory. This technology was subsequently applied to SARS-CoV-2 and has been able to identify viral regions that have resisted variation over the course of the pandemic. My laboratory is now actively working to generate variant-resistant T cell vaccines for HIV and SARS-CoV-2—with plans to apply this approach to other viral pathogens—in order to advance translatable entities for patients.



Alexandra-Chloe Villani, PhD
Assistant Professor of Medicine /
Center for Immunology and
Inflammatory Diseases /
Cancer Center

Deciphering the Immunologic and Antigenic Drivers of ICI-associated Myocarditis

Immune checkpoint inhibitor (ICI) immunotherapies, which harness and enhance the human body's own defense mechanisms to kill cancer cells, have revolutionized the treatment of solid cancers by changing the prognosis for many patients, improving their quality of life, and offering long-lasting remission. But beyond unleashing the immune system to attack tumors, these therapies can also spur assaults on healthy organs called "immune-related adverse events" (irAEs). To date, nearly every human organ system has been reported as affected by irAEs with a wide spectrum of severity, ranging from minor skin rashes and fevers, to severe gastrointestinal irAEs and deadly heart inflammation complications, which this proposal particularly focuses on. Our laboratory is working towards understanding why and how these irAEs occur in cancer patients by analyzing patient samples using state-of-the-art genomic technologies and integrative immunological approaches. Our goal is to identify therapeutic solutions to prevent or better clinically manage irAEs without reducing the lifesaving potential of immunotherapy, by identifying culprit cellular components that could be therapeutically targeted through 'primary prevention' screening test approach, or after the onset of irAEs. Findings from this research will be greatly beneficial in improving patient care for all cancer types that are therapeutically managed by ICI immunotherapy.

Martin Research Prizes

2023 MARTIN RESEARCH PRIZE FOR CLINICAL AND FUNDAMENTAL RESEARCH

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



MARTIN PRIZE FOR FUNDAMENTAL RESEARCH

Russell Jenkins, MD, PhD

Assistant Professor, Department of Medicine, Hematology-Oncology / Cancer Center

Targeting TBK1 to Overcome Resistance to Cancer Immunotherapy

Cancer immunotherapy has transformed the treatment of advanced melanoma, although roughly half of patients develop resistance that is ultimately fatal. Novel treatments are desperately needed for melanoma patients with resistance to cancer immunotherapy. To identify candidate therapeutic strategies for these patients, we have focused on identifying and targeting unique vulnerabilities for immunotherapy-resistant melanoma. We identified TANK-binding kinase 1 (TBK1) as a candidate immune evasion gene using unbiased genetic screens and performed validation studies using both genetic tools to delete TBK1 and drugs to inhibit the function of TBK1. These studies were performed across multiple experimental model systems including novel patient-derived tumor models from melanoma patients clinically resistant to ICB) confirming that resistant cancer cells can be sensitized to immunotherapy following TBK1 inhibition or deletion (Sun et al. Nature 2023, in press). These findings confirm that targeting TBK1 is a novel and effective strategy to overcome cancer immunotherapy resistance and provide a novel framework to evaluate other emerging immune evasion targets.



MARTIN PRIZE FOR CLINICAL RESEARCH

Marcela Maus, MD, PhD

Associate Professor, Department of Medicine / Cancer Center

Distinct cellular dynamics associated with response to CAR-T therapy for refractory B cell lymphoma

Chimeric antigen receptor modified T cells, or CAR-T, is a form of immune-cell therapy, that has transformed the treatment of large-cell lymphoma, a kind of blood cancer. About 40% of patients with lymphomas have long-term responses after treatment with CAR-T, but not all patients respond. A multi-disciplinary, multi-institution team here discovered that the presence of a certain kind of inhibitory T cell, when they are inadvertently modified with the CAR, is associated with relapse. Using single-cell RNA sequencing and deep computational analyses, the team also showed which kinds of T cells are the most effective in patients who respond to two of the CAR T cell products in clinical use. Their work sheds light on how CAR T cells work and on what strategies could be implemented to make them work in more patients.



MARTIN PRIZE FOR POPULATION HEALTH SCIENCES RESEARCH

**Ruanne Barnabas, MBChB,
MSc, DPhil**

Professor, Department of Medicine,
Chief, Infectious Diseases,
Massachusetts General Hospital

Efficacy of Single-Dose Human Papillomavirus Vaccination among Young African Women

HPV vaccination is one of three fundamental pillars of the World Health Organization's (WHO) strategy to eliminate cervical cancer. Still, HPV vaccine coverage is low—15% of eligible girls and adolescents worldwide are vaccinated despite the vaccine's high efficacy in preventing >95% of HPV infection and cervical cancer. Observational data suggested that single-dose HPV vaccination was efficacious compared to standard multi-dose regimens; however, due to concerns about clinically meaningful lower efficacy, multi-dose regimens were recommended. Also, because of concerns about exposure to HPV, the WHO recommended vaccination for 9-14-year-olds before sexual debut. However, in settings where catch-up vaccination to age 26 years was high, the clinical benefits of vaccination doubled, with Australia expecting to eliminate cervical cancer in 2024. High cost and vaccine availability also curtailed HPV vaccine coverage. Thus, a single-dose HPV vaccination strategy would be game-changing for vaccine access.

Working closely with the Kenyan Ministry of Health and Kenyan Medical Research Institute collaborators, we conducted the KENya Single-dose HPV-vaccine Efficacy (KEN SHE) Study. We enrolled 2,275 participants aged 15-20 years who were randomly assigned to receive either the bivalent HPV, nonavalent HPV, or meningococcal control vaccine. Participants were followed every six months. After 18 months of follow-up, we reported the primary outcomes. Both the bivalent and nonavalent vaccines prevented 97.5% of new, persistent HPV 16/18, the precursor of 70% of cervical cancer cases. We also found high efficacy (95%) against other HPV types that cause cancer. These results were presented to the UK Joint Committee of Vaccination and Immunization (JCVI) and the WHO. The JCVI has changed its recommendation to endorse single-dose HPV vaccination (August 2022). In April 2022, the WHO changed their recommendation for either one or two doses of the HPV vaccine for 9-20-year-olds, citing KEN SHE as a pivotal study to support that decision.

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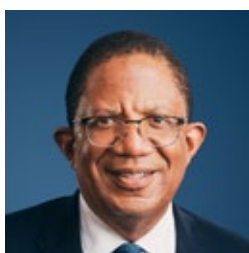
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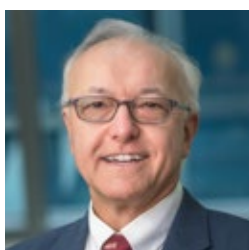
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*Chair Appointment, ‡ Chiefs Council

Massachusetts General Research Institute

Executive Report

THANK YOU, EVERYONE! IT'S BEEN AN HONOR AND A PRIVILEGE. (A LOOK BACK AT THE LAST DECADE)

We often hear one of the things that makes MGH so special is its “culture of caring.” As someone who has spent most of his career at MGH, I can assure you that this culture is very real and is at the heart of all that makes MGH so extraordinary. This is a realization you come to over time, as you interact with colleagues who, irrespective of their roles in patient care, research, or support, do their jobs day in and day out with focus and dedication. The longer you are immersed in it, the more the culture becomes a part of you, something that brings you into work each day energized and motivated to do your best and make a difference.

For me personally, this culture kept me at MGH for over 20 years and later brought me back to finish my career. I’ve had the honor and privilege to serve as the MGH Senior Vice President for Research for the last decade. But my history with MGH started some 40 years ago. In 1982, while serving as Director of Harvard’s Fairchild Biochemical Laboratories, I was hired as a consultant to help Dr. Howard Goodman design the space for the new MGH Department of Molecular Biology. At the conclusion of that job, Howard convinced me to “jump ship” from Harvard FAS to Harvard Medical School and MGH by bringing me on as Director of Molecular Biology Laboratories, where I helped establish the department’s administration and operations. For the next 20 years, I served in the department and was given an expanded hospital role as a member of ECOR to chair its facilities subcommittee by then SVP for Research Dr. Ron Newbower. It was this opportunity that exposed me to hospital and research leaders who, by example, taught me the MGH culture of caring.

Before leaving office, in one of my final interviews (for Dr. Slaugenhaupt’s “From the Lab Bench” December issue), I was asked what I thought was the best thing about MGH. Without hesitation, I said it was our people. Collectively, they *are* the culture of caring that is the main ingredient of the MGH secret sauce. When I came back to MGH in 2012 (after a year in Iraq serving in Operation Iraqi Freedom and after an eight-year “sabbatical” in Palm Beach building Scripps Florida), I asked then SVP for Human Resources Jeff Davis what I needed to do to be successful as an SVP at MGH. His answer was simple. “Surround yourself with great people and get out of their way.” Because of my tendency to get into the weeds on issues, I’m not sure how well I got out of my staff’s way. But I do know that they are, to a person, “great people”; they have been the engine to so much of what has been accomplished this past decade. Accordingly, I would be remiss to not mention them (current and past) by name—Dr. Anne Clancy, Dr. Maurizio

Fava, Michael Fisher, Trish Frederico, Wendy Hobbs, Dr. Judy Hung, Dr. Donna Jarrell, Tatiana Koretskaia, Maire Leyne, Kelley McLellan, Karen Montillo, Kele Piper, Misha Pivovarov, Dr. Sue Slaugenhaupt, Gary Smith—and thank them publicly for all they have done and continue to do every day to sustain our incredible research enterprise.

Because of their efforts, the work of their staffs, and our amazing researcher community, annual research revenues grew 67% (from \$780M to \$1.3B) from 2012 to 2022. At the start of this same period in 2012, dozens of researchers along with research and hospital leaders came together to create and then implement a Strategic Plan for MGH Research. This plan resulted in the creation of the Board-Approved Mass General Research Institute (MGRI). Other initiatives created from this plan were: 1) The position of MGRI Scientific Director (and staff) to promote research externally to the public, donors, and industry; 2) The Division of Clinical Research to promote the translation of discoveries to clinical care; 3) The Translational Research Center (TRC) and \$13M buildout of the TCRC (Translational and Clinical Research Centers) on White 12 for in- and out-patient clinical trials; 4) The Partners (now MGB) Biobank at MGH; 5) The Isuggest system for employees to suggest process improvements. To date, over 1700 suggestions have been received, over 900 implemented, and over 150 currently active.

The last decade also saw the establishment of the position of Director of Research IT Solutions, whose work subsequently led to the creation of the following tools/programs: 1) Evals (electronic employee performance evaluation system, being adopted MGB-wide); 2) Online Lab Safety Survey to document annual lab safety rounds; 3) iLog (electronic documentation and tracking system for research controlled substances); 4) Real-Time Online Space Metrics program fully integrated into the MGH Research Space Management System; 5) Research People Database, which tracks composition of our research community in real time including daily cardkey data showing who is onsite.

The MGH Research Safety Committee, which meets quarterly and has representatives from every onsite laboratory, was also established in 2012. This committee created the MGH Help & Safety smartphone app that is now available hospital-wide, established numerous task forces to address specific safety needs, and, working the MGH EH&S department, completely rewrote the MGH Research Safety Manual. During the two-year span when COVID actively constrained onsite research, the committee assembled 200+ lab managers and research staff to establish the MGH COVID Safety Officer brigade to ensure research could continue safely and in full compliance with

hospital and government policies. It created a COVID safety website and resource guide and published weekly “Tuesday Tips” to keep the research community informed of the latest COVID developments and identify resources for personal and professional help. And it helped establish the MGH/BWH Center for COVID Innovation, which created numerous tools, devices, and processes to deal with COVID across our hospitals.

Other noteworthy developments implemented by our research support staff over the last decade include: 1) Making the @mgh.harvard.edu email address available to all hospital employees by having it link to the same inbox as @partners.org. As a result, research staff can access the Harvard research libraries, obtain educational discounts on many programs from software vendors, and have their email address identify MGH as their place of employment. 2) Getting the MGH animal care program fully accredited by AAALAC (Association for Assessment and Accreditation of Laboratory Animal Care), the gold standard for animal program compliance, and maintaining full accreditation for the last ten years. 3) Creating the MGH Research Intranet — <https://mghresearch.partners.org/> with a full array of readily accessible tools and resources for the research community.

These accomplishments stand as a testament to the dedication, creativity, and perseverance of our research management support staff AND to the unwavering support provided to our research enterprise by hospital and MGB leadership, specifically, Drs. Peter Slavin, David Brown, Anne Klibanski, Ravi Thadhani, and Paul Anderson, together with Sally Mason Boemer, Greg Pauly, Shea Asfaw, and a host of other SVP and VP colleagues. And special thanks to Andrew Chase, Scott McNeal, Dee Dee Chen, Chris Clark, Tracy Sykes, and Emily Sobiecki for always taking my far-too-many phone calls and answering my far-too-many questions. As I stated earlier, these people, and so many others I have failed to personally name and thank here, *are* the culture of caring that is MGH. It has truly been an honor and a privilege to work with them to help sustain and advance our research mission.

A Year of Transitions in Research Leadership

Welcome, Bob! As of 1 January 2023, Dr. Bob Kingston succeeded me in the expanded role of MGH Chief Academic Officer and SVP for Research and Education. Bob is not only an outstanding leader (former Chair of Molecular Biology) and scientist (member of the National Academy of Sciences), he is also a caring and dedicated MGH'er. As Chair of Molecular Biology, Bob helped integrate fundamental and translational science throughout our clinical departments and elevated the caliber and

breadth of their research programs. Having known him for over 50 years (I was his chemistry TA when he was a Harvard undergraduate!), I am confident Bob will continue to promote and grow the research enterprise in the coming years.

Thank you, Ravi! Concurrent with my departure as Research SVP in January, MGB Chief Academic Officer Dr. Ravi Thadhani left us to become Emory University's Executive Vice President of Health Affairs. Ravi was a long-time MGH'er (Chief of the Renal Division in the Department of Medicine) and a tireless advocate for research across the MGB enterprise during his time as system CAO. Thank you, Ravi, for all you did for MGH and MGB and best wishes in your new position.

Thank you, Donna! After 20 years of service to MGH, initially as Associate Director for the Center for Comparative Medicine (CCM) for 10 years, and subsequently as the Attending Veterinarian and CCM Director, Dr. Donna Jarrell retired and relocated back with family to North Carolina. Under Donna's leadership, CCM grew to over 150 staff and became one of the largest and most diverse academic animal care programs in the country. She implemented lean management practices to effectively direct her large staff and became a national leader in the animal care community, serving as ACLAM President from 2020-2021. Congratulations, Donna, on an outstanding career and best wishes in your retirement.

Thank you, Chris! After over 30 years of service, Chris Clark stepped down this past summer as an attorney in the MGB Office of General Counsel and Director of the Office for Interactions with Industry. Chris, I speak for all my research colleagues when I say that we are so appreciative of your wise counsel and all you have built at OII and OGC. But, more than just legal advice, we will always remember your thoughtfulness, optimism, and ability to genuinely listen to our problems. Your can-do approach has served MGH and MGB well; you truly exemplify the best of what it means to be a lawyer. On behalf of everyone in the Mass General Research Institute, thank you for all you have done and built.

Thank you, Peggy and Ann! This past year also saw the departure of two of my closest SVP colleagues and long-time MGH'ers, Peggy Slasman (SVP for Public Affairs) and Ann Prestipino (SVP for Surgery, Anesthesia, Emergency Medicine, and Clinical Business Development). While not directly involved with the research enterprise itself, both Peggy and Ann were staunch supporters of and advocates for research. Their wise counsel and patience bringing me along as a novice SVP are greatly appreciated and warmly remembered.

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In memoriam, Dr. Jerry Austen. 2022 saw the passing of Dr. Jerry Austen after over six decades of extraordinary service to MGH. Jerry was a great supporter of research, a wise counselor to all, and truly the heart and soul of MGH. He was the founding President and CEO of the MGPO, the first physician elected to the MGH Board of Trustees, and a founder of the Partners HealthCare system. In 2020, MGH dedicated the W. Gerald Austen, MD, Building to recognize his six decades of extraordinary leadership and service. Put simply, Jerry led by example; his legacy of selfless dedication continues to inspire all who knew him and serve MGH.

Highlights of MGRI Accomplishments/Milestones in 2022

Detailed accounts of the progress of all research-related departments are given in subsequent sections of this executive report. Here, we highlight some of the more notable departmental accomplishments of 2022. These include:

- Research revenues for FY22 reached another all-time high of \$1.297B (\$1B direct costs and \$297M indirect), a \$100M (8.4%) increase from FY21. Our authorized funding dollars from the National Institutes of Health (NIH) in FY22 was \$560M which ranks us #15 in NIH funding for all institutions and #1 for independent hospital, a spot we have held for the past 20+ years. The percentage of funding awarded from the entire NIH extramural grant pool (market share) was 1.6% for MGH and 3% for MGB as a whole.
- The 2022 Warren Prize was awarded to Dr. Mary-Claire King for her significant contributions to the field of genetics.
- The committees reviewing interim and internal support provided by ECOR (the Executive Committee On Research) reviewed over 800 applications and awarded \$11.3M to 102 investigators. These included 115 interim support grants, 22 postdoc fellowships, 7 Claflin Distinguished Scholar Awards (that facilitate academic careers of women in science), and 6 MGH Physician/Scientist Development Awards (to support the development of research investigators who are considered underrepresented in medicine).
- The Office of the (MGRI) Scientific Director (OSD), working with Development, added 4 Research Scholars in 2022, bringing total to 74, and is currently preparing to announce the class of 2023, which will bring the Research Scholar total to 79. The OSD and Development also conducted a successful in-person Lab Day in October 2022. The event featured laboratory tours and scientific presentations with three MGH Research Scholars and their teams.
- The OSD made significant progress in promoting the MGRI in 2022, with over 350 high-impact papers featured in their *Snapshot of Science* publication. Their Bench Press blog entered its fifth year, with its most popular story, “Researchers Call for More Studies to Learn How our Brain Changes When We’re Awake After Midnight,” receiving over 26,000 views.
- The OSD Social media outlets—Facebook, Twitter, and Instagram—showed continued growth in posts and followers. Twitter continues to be their go-to platform for promoting research studies and has seen great engagement from the scientific community, while their Instagram and LinkedIn accounts had the most promising growth in 2022.
- The OSD Strategic Alliance group continued its highly successful Bridging Academia and Industry educational program in 2022. To date, they have organized 24 industry-focused sessions during which our investigators presented these programs to selected industry executives. This past year, they launched one collaboration with a biotech company, and they trained 26 faculty from across 13 departments and thematic research centers, with 44 faculty (24 academia, 20 industry) teaching and mentoring the project teams.
- The Division of Clinical Research (DCR) faculty provided over 480 individual consultations to Faculty and Staff from over 25 divisions and departments across MGH and MGB in 2022. Also in 2022, the DCR Center for Clinical Research Education offered 200 live and online courses with over 6,000 participants. Most recently, DCR has become the hub for all MGB services (CTO, IRB/HRA, QI, Innovation), and the Harvard Catalyst.
- As of December 2022, 140,000+ participants have consented and 95,000+ sample have been collected by the MGB BioBank. The Biobank has distributed samples and data to more than 450 studies, including 250 at MGH.
- The total number of new Translational Research Center (TRC) studies initiated in 2022 was 42 through early December 2022, in line with last year’s total of 44 initiated through the end of December in 2021. Revenues were \$5.82m in direct costs and \$1.73m of indirect costs up from 2021 revenues of \$5.16m and \$1.63m, respectively. At the close of the calendar year 2022, there were 77 active studies being conducted in the TRC, up slightly from the 74 that were active at the end of calendar 2021.

- In 2022, CCM was able to contract with Charles River Laboratories (CRL), Transnetyx and Vivalytics to offer researchers additional rodent breeding colony management services, including breeding software tools, project management expertise, genotyping, cryopreservation, and off-site housing.
- The MGH IACUC processed over 3,200 transactions in 2022. These were comprised of new protocols and triennial reviews, as well as scientific and study staff amendments. The Office of Animal Welfare Assurance (OAWA) partnered with the IACUC to meet the volume demand while maintaining turn-around-times to support research.
- In FY22, the Research Compliance Office accomplished some very important initiatives, including: 1) The implementation of iLog, MGH's Controlled Substances Database; 2) Research Misconduct Cases. In 2022, we saw 7 new cases of research misconduct and closed out 9 cases. We also received 3 notices from ORI in which they agreed with our determination officially closing the cases; 3) Transportation of Biological Specimens. In FY22, we launched BioLift, the new app to schedule and track the transport of biological samples using internal resources; 4) Minors in Laboratory and Research Spaces. Research Compliance assembled a multi-disciplinary workgroup to rewrite the policy and develop an onboarding process to include an intake form and parental consent form bringing us into compliance with state and federal laws and regulations. An APP was developed to operationalize this process which includes approvals from key stakeholders in high-risk areas and HR; 5) Research Survey. Eliminating a one-size-fits-all approach to training, the research survey is a great tool to customize training to the job and role that will be performed. At orientation, anyone in a research role is required to take the research survey. This year we moved it to the new Open Courses platform, but also made several upgrades to improve the user experience as well as make it easier to monitor for compliance. We expect the launch of the new platform in early 2023.
- As of FY2022, the MGH Committee on Awards and Honors has been chaired by Dr. Jeanine Wiener-Kronish. This past year, the committee strategically narrowed its scope and the awards and honors it tracks. Still, over 100 MGH'ers received awards and honors by national and international societies.
- Research IS Support team had a busy and very productive 2022. Progress was made in several areas under individual working groups. These include: 1) Communication; 2) COVID-19 Projects; 3) Applications

for Research Administration; 4) Applications for Research Training and Education; 5) Infrastructure Improvements. Details of specific accomplishments are given in the Research IS Support section below.

- MGH innovators had another strong year in FY22. Although slightly down in absolute numbers from last year, MGH'ers filed 1272 patents, had 496 patents issued, and brought in over \$77.5M in royalty and licensing revenues.
- The Center for Innovation in Digital Healthcare (CIDH) leadership began working in late 2022 in close partnership Adam Landman, Chief Information Officer and SVP for Mass General Brigham Digital, to more formally integrate CIDH, iHub and DHI under a newly formed program, Mass General Brigham Emerging Technologies and Solutions (MGBETS).

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.

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, 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.

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GUIDE

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

<https://ecor.mgh.harvard.edu/>

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 Merit E. Cudkowicz, MD, MSc (Chief, Neurology); the Vice Chair is Maurizio Fava, MD (Chief, Psychiatry); and the Immediate Past Chair is David E. Fisher, MD, PhD (Chief, Dermatology). Each position is a three-year term, with the Vice Chair succeeding to the role of Chair and the previous Chair remaining a part of the ECOR leadership team after their Chair term, thereby assuring continuity over a nine-year period.

ECOR Membership

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

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

ECOR's broad areas of focus include:

Meetings and Events

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

Research Council

Research Council meetings take place on the first Monday of the month. 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 ECOR evaluate our research mission and address challenges the hospital is facing. SAC membership has included Nobel laureates and leaders in science and medicine from academia, industry, and government. Current membership is listed on pages 8–9.

Warren Triennial Prize and Symposium

The Warren Triennial Prize was first given in 1871 in honor of Dr. John Collins Warren, a dedicated teacher, researcher, and a founding member of the Massachusetts General Hospital (MGH). Dr. Collins played a key role in establishing the journal now known as the New England Journal of

Medicine, which was first published in 1812, and took part in the first public demonstration of ether anesthesia in what is now known as the Ether Dome at the MGH in 1846.

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 2017, 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.

The 2022 Warren Prize was awarded to Dr. Mary-Claire King for her significant contributions to the field of genetics.



A medallion of Dr. Warren, presented to recipients.

Committees, Subcommittees, and Initiatives

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

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

The Committee on Fundamental Research (CFR) was created out of the former PhD Steering Committee to provide a forum for fundamental research investigators to actively engage in developing solutions to improve MGH/Mass General Brigham 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 pages 42–44.

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 183 members - 57 Professors, 79 Associate Professors, and 47 Assistant Professors. Approximately 60 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) Vitalization and Advocacy Committee

The CNY Quality of Life Committee was founded in 2018 with the goal of enhancing the research community located in the Navy Yard in Charlestown. The group has been recently renamed to the CNY Vitalization and Advocacy Committee (VAC) and 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 since its founding and has been able to:

- Obtain funding and successfully petitioned research leadership for financial support to enhance community building
- Improve transportation between campuses by:

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- Working with the city and Partners/MGB 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 the bridges of CNY149
- Provide bike and walking routes between campuses
- Add and improve meal options by (prior to COVID-19):
 - 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
 - Established hot meal alternatives by hosting FOODA onsite 5 days a week (3x at CNY149 and 2x at CNY114).
 - 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 (on hiatus due to COVID-19)
 - Offering Cookies, Coffee and Classical Music events several times throughout the year (on hiatus due to COVID-19)
 - Offering Ice Cream Socials in the summer
 - 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
 - Virtual Trivia night events

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
- Increase MGRI branding at CNY
- Restart many initiatives and programs that have been impacted by COVID-19

- Remain focused on rebuilding community and enhancing interactions, especially in light of lack of social interactions due to the ongoing pandemic that has lasted 2 years

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. In FY22, ECOR awarded \$11.3M to 102 investigators. ECOR also oversees the internal selection process for limited submission opportunities like the Pew Scholars Program. To meet the needs of an increasing application pool, we use an online grant management system where we manage the entire life cycle of an ECOR application from the start of an application, through the review process, and to the notification of funding.

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 \$54,840. In FY22, 22 fellows received the award.

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 2022, seven women received the Claflin Award.



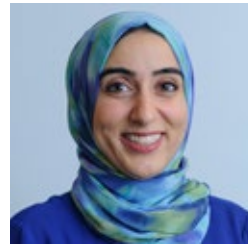
Maria Battistone, PhD
Assistant Professor
Medicine/Nephrology



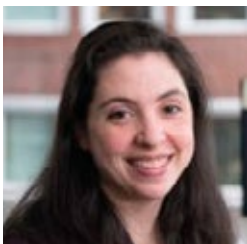
Anne Neilan, MD, MPH
Assistant Professor
Medicine/Infectious Disease



Clarissa Cooley, PhD
Instructor
Radiology/Athinoula A. Martinos
Center for Biomedical Imaging



Altaf Saadi, MD, MSc
Assistant Professor
Neurology



Rachel Jimenez, MD
Assistant Professor
Radiation Oncology



Miriam Udler, MD, PhD
Assistant Professor
Medicine/Diabetes Unit



Maureen Leonard, MD, MMSc
Assistant Professor
Pediatric Service

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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 (UiM), and thereby increase

opportunities for UiM 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 at least four awards going forward. The total amount of funding per awardee in FY22 was \$180,000 in direct costs.

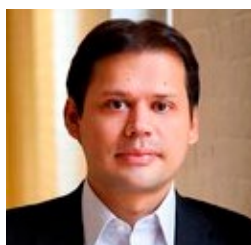
In 2022, six investigators received this award:



Veronica Clavijo Jordan, PhD
Assistant Professor
Radiology/Athinoula A. Martinos
Center for Biomedical Imaging



Asishana A. Osho, MD, MPH
Assistant Professor
Surgery



Ronald G. Garcia, MD, PhD
Assistant Professor
Psychiatry



Jacqueline A. Seiglie, MD MSc
Instructor
Medicine/Diabetes Unit
Center for Global Health at MGH



Edmarie Guzman-Velez, PhD
Assistant Professor
Psychiatry



Mabel Toribio, MD
Assistant Professor
Medicine/Metabolism Unit

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 2022,

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

The 2022 Class of Mass General Research Scholars:



Andrea Ciaranello, MD, MPH
MGH Research Scholar 2022–2027
Associate Professor
Department of Medicine



Matthew Rosen, PhD
Kiyomi and Ed Baird MGH Research Scholar 2022–2027
Assistant Professor
Radiology, Martinos Center for Biomedical Imaging



Jenna Galloway, PhD
MGH Research Scholar 2022–2027
Associate Professor
Orthopedic Surgery, Center for Regenerative Medicine



Shannon Stott, PhD
d'Arbeloff MGH Research Scholar 2022–2027
Assistant Professor
Department of Medicine, Cancer Center

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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, one to two Goodman Fellows are chosen from the MGH community to honor that legacy and to support the pursuit of excellence by young scientists of uncommon passion and ability. Each award is for two years at \$100,000 per year. Please see page 5 for more information on the 2023 recipients.

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 several \$100,000 Martin Research Prizes to recognize outstanding research papers published by MGH investigators. ECOR offers prizes in three categories: fundamental research, clinical research, and population health sciences research. Please see pages 6–7 for more information on the three 2023 recipients.

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: 84% of investigators who received funding from the Interim Support Program between 2006–2022 are still working within the institution. Since the program's inception in 2006, ECOR has awarded over \$65M of interim support funding. Our investigators have gone on to leverage these funds ten-fold, bringing in \$674M of federal funding to the institution.

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 all investigators regardless of score.

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 \$7.5M.

Awards and Honors

The summer of 2014 saw the creation of the MGH Committee on Awards and Honors. After serving for five years as chair, Dr. Samuel Thier, president of MGH from 1994–1997, stepped down and passed the baton to Dr. Jerry Rosenbaum, Psychiatrist-in-Chief Emeritus, Director, Center for Anxiety and Traumatic Stress Disorders (CATSD) and Director, Center for Neuroscience of Psychedelics, who chaired the Committee for 2 years.

As of FY2022, the MGH Committee on Awards and Honors has been chaired by Dr. Jeanine Wiener-Kronish. Dr. Wiener-Kronish is the Henry Isaiah Dorr Distinguished Professor of Research and Teaching in Anaesthetics and served as Chief of Anesthesia, Critical Care, and Pain Medicine at MGH for many years. Dr. Wiener-Kronish has devoted much of her academic career to investigating the mechanism of acute lung injury produced by *Pseudomonas aeruginosa*, a gram-negative bacterium that can infect patients in the intensive care unit. The goal of her research is to establish whether there are beneficial communities of bacteria that protect patients against asthma and infections. Dr. Wiener-Kronish has been in multiple leadership roles, which include AUA president and founding member of the Academy of Anesthesia Mentors.

Under Dr. Wiener-Kronish, the MGH Committee on Awards and Honors strategically narrowed its scope and the awards and honors it tracks. The Committee continues to focus on a limited number of distinguished honorific societies, awards and ensuring equity in its nominations.

In 2022, some of the major awards and prizes received by MGH investigators include the following:

Academy for Emergency Ultrasound Most Prolific Researcher of the Year

Andrew Liteplo, MD (Emergency Medicine)

American Academy of Nursing Academy Edge Runner

Diane Carroll, PhD, RN, FAAN, FAHA, FESC (Munn Center for Nursing Research)

Alzheimer's Association International Conference 2022 de Leon Prize in Neuroimaging

Heidi Jacobs, PhD (Radiology)

**Alzheimer's Association International Conference
Lifetime Achievement Awards in Alzheimer's Disease
Research**

Keith Johnson, MD (Radiology, Gordon Center)

**American Academy of Pediatrics 2022 Murray
Davidson Award**

Ronald Kleinman, MD (Pediatrics)

**2022 American Association for Public Opinion Research
Inclusive Voices Award**

Margarita Alegria, PhD (Mongan Institute, Disparities
Research Unit)

**American Association of Neurological Surgeons 2022
National Brain Tumor Society Award**

Priscilla Brastianos, MD (Medicine, Hematology Oncology,
Cancer Center)

**American College of Cardiology 2023 Douglas P. Zipes
Distinguished Young Scientist Award**

Michael Honigberg, MD, MPP (Medicine, Cardiology)

**American College of Cardiology and the European
Society of Cardiology Young Investigator Awards**

Shady Abohashem, MD (Radiology)

**American College of Cardiology Distinguished Scientist
Award-Clinical Domain**

Ik-Kyung Jang, MD, PhD, FACC (Medicine, Cardiology
Division)

**American Gastroenterological Association Research
Scholar Award**

Trisha S. Pasricha, MD (Medicine, Gastroenterology)

**American Heart Association Jeffrey M. Hoeg
Arteriosclerosis Thrombosis and Vascular Biology
Award for Basic Science and Clinical Research**

Pradeep Natarajan, MD (Cardiology)

American Heart Association Research Goes Red Grant

Michael Honigberg, MD, MPP (Medicine, Cardiology)

**American Institute for Medical and Biological
Engineering (AIMBE) 2022 Pierre M. Galletti Award**

Emery Brown, MD, PhD (Anesthesia, Critical Care and Pain
Medicine)

**American Physical Therapy Association's Academy of
Neurology Excellence in Neurological Research Award**

Teresa Kimberley, PhD, PT, FAPTA (Institute of Health
Professions)

**American Psychological Association Society of
Addiction Psychology (Division 50) Award for
Distinguished Scientific Contributions to the
Application of Psychology**

John Kelly, PhD, ABPP (Psychiatry)

**2022 American Public Health Association Disability
Section Lifetime Achievement Award**

Lisa Iezzoni, MD, MSc (Medicine, Mongan Institute)

American Society for Clinical Investigation

Shawn Demehri, MD, PhD (Dermatology)

Areej El-Jawahri, MD (Medicine, Hematology Oncology,
Cancer Center)

Kristopher Kahle, MD, PhD (Neurosurgery)

Pradeep Natarajan, MD, MMSc (Medicine, Cardiology)

Sara Pai, MD, PhD (Surgery)

**American Society for Laser Medicine & Surgery
Distinguished Contributor Award**

Rox Anderson, MD (Dermatology)

**American Society for Laser Medicine & Surgery Dr.
Horace Furumoto Innovations Young Investigator Award**

Lilit Garibyan, MD, PhD

**Massachusetts Life Science Center's (MLSC) Research
Infrastructure Program**

Massachusetts Cancer Center

American Society of Human Genetics Curt Stern Award

Heidi Rehm, PhD (Center for Genomic Medicine, Medicine)

**American Society of Nephrology Dr. Barbara Murphy
Trailblazer Award**

Julie Ingelfinger, MD (Pediatrics)

**Annals of Internal Medicine and the American College of
Physicians Junior Investigator Recognition Award**

Hanny Al-Samkari, MD (Medicine, Hematology Oncology)

**2022 António Champalimaud Vision Award from the
Portugal-based Champalimaud Foundation**

Claes Dohlman, MD, PhD (Ophthalmology, Mass Eye
and Ear)

**Association for Research in Vision and Ophthalmology
2022 Mildred Weisenfeld Award Lecture**

Janey L. Wiggs, MD, PhD (Ophthalmology, Mass Eye
and Ear)

**International Society for Bipolar Disorders 2022 Samuel
Gershon Junior Investigator**

Annie Kathuria, PhD (Psychiatry)

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Aziz and Nur Hamzaogullari Endowed Scholar in Hematologic Malignancies

Abner Louissaint Jr., MD, PhD (Pathology)

2022 Blavatnik National Awards for Young Scientists in Chemistry (finalist)

Jacob Hooker, PhD (Martinos Center)*

2022 Boston Chamber of Commerce Women's Network Pinnacle Awards

Marcela del Carmen, MD (Massachusetts General Physicians Organization, OBGYN)

Burroughs Wellcome Fund 2022 Next Generation Pregnancy Initiative Award

Jian Shu, PhD (Dermatology)

Chan Zuckerberg Initiative Cycle 5 Essential Open Source Software for Science Grant

Gordon Harris, PhD (Radiology)

Conquer Cancer 2022 Advanced Clinical Research Award for Diversity and Inclusion in Breast Cancer

Rachel Jimenez, MD (Radiation Oncology)

Cullen Education and Research Fund (CERF) Medical Engineering Prize

Leigh Hochberg, MD, PhD (Neurology)
Sabrina Paganoni, MD, PhD (Physical Medicine and Rehabilitation)

Cystic Fibrosis Foundation LeRoy Matthews Physician-Scientist Award

Viral Shah, MD, PhD (Center for Regenerative Medicine)

2022 Distinguished Scientist Award

Andrew Nierenberg, MD (Psychiatry)

Diversity MBA's Top 100 under 50 Emerging Leaders for 2022

Fatima Cody Stanford, MD, MPH, MPA, MBA (Medicine, Pediatrics)

2022 Doris Duke Physician Scientist Fellowships

John Chiosi, MD (Medicine)
Arnav Mehta, MD, PhD (Medicine)
Michelle Rengarajan, MD, PhD (Medicine)

Ellet H. Drake Memorial Award of American Society for Laser Medicine and Surgery

Fernanda H. Sakamoto, MD, PhD (Wellman Center)

European Society of Neuroradiology (ESNR) Honorary Member Award

Joshua A. Hirsch, MD (Radiology)

Executive Committee of the Health Sector Coordinating Council (HSCC) Cybersecurity Working Group

Julian M. Goldman, MD (Anesthesia, Critical Care and Pain Medicine)

Giants of Cancer Care Class of 2022

Jennifer Temel, MD (Cancer Center)

Glaucoma Visionary by Glaucoma Today

Janey Wiggs, MD, PhD (Ophthalmology)

Gruber Foundation Neuroscience Prize (co-recipient)

Emery N. Brown, MD, PhD (Anesthesia, Critical Care and Pain Medicine)

Interdisciplinary Association for Population Health Science 2022 Stephanie Robert Mentoring Award

Alexander Tsai, MD, PhD (Center for Global Health, Mongan Institute)

2023 Keystone Symposia Fellows Program

David Alagpulinsa, PhD (Medicine)

2022 LEO Foundation Award

Shawn Demehri, MD, PhD (Dermatology)

Melanoma Academy Melanoma Research Program Leadership Award

David Fisher, MD, PhD, (Dermatology)

MLSC Women's Health Innovation Award

Curtis Cetrulo, MD (Surgery)

Muscular Dystrophy Association Diamond Award

Sabrina Paganoni, MD, PhD (Neurology)

National Academy of Inventors

Orhun K. Muratoglu, PhD (Orthopedic Surgery)
Brett E. Bouma, PhD (Dermatology, Wellman Center)

National Academies of Sciences, Engineering and Medicine Committee on Transforming Health Care to Create Whole Health

Zirui Song, MD, PhD (Medicine)

National Academy of Medicine

Craig Blackstone, MD, PhD (Neurology)

National Academy of Medicine's Healthy Longevity Global Competition Awardee

Vanessa B. Kerry, MD MSc (Medicine, Pulmonary and Critical Care)

2022-2023 National Academy of Medicine Scholars in Diagnostic Excellence

Miriam Bredella, MD (Radiology)
Fatima Cody Stanford, MD, MPH, MPA (Medicine, Pediatrics)

National Association for Proton Therapy Lifetime Achievement Award

Jay Loeffler, MD (Radiation Oncology)

National Cancer Institute Champions and Changemakers of Cancer Prevention recognition

Andrew Chan, MD, MPH (Cancer Center)

National Council for Wellbeing's Lifetime Achievement Award

John Kelly, PhD, ABPP (Psychiatry)

National Foundation for Cancer Research 2022 Szent-Györgyi Prize for Progress in Cancer Research

Rakesh K. Jain, PhD (Radiation Oncology)

National Institute of Allergy and Infectious Diseases Human Immunology Project Consortium (U19)

Galit Alter, PhD*

Andrea Edlow, MD, MSc (OBGYN)

Boris Juelg, MD, PhD (Infectious Diseases, Ragon Institute)
Alex Shalek, PhD (Ragon Institute)

2022 National Institutes of Health Director's New Innovator Awards

Rachel Buckley, PhD (Neurology)
Ben Kleinstiver, PhD (Center for Genomic Medicine, Pathology)
Debattama Sen, PhD (Cancer Center)

National Institutes of Health New Innovator Award DP2

Jian Shu, PhD (Dermatology)

National Inventors Hall of Fame

R. Rox Anderson, MD (Dermatology)

2022 Navy SEAL Foundation (NSF) Distinguished Scientific Award

MGH Center for the Neuroscience of Psychedelics

2022 New York University McSilver Institute Champion of Mental Health Equity

Margarita Alegria, PhD (Mongan Institute, Disparities Research Unit)

Newsweek America's Best Dermatologists for 2022

R. Rox Anderson, MD (Wellman Center)

Ophthalmological Society

Ula Jurkunas, MD (Ophthalmology)

Optica Foundation 2022 class of Optica Ambassadors

Sangyeon "Fred" Cho, PhD (Dermatology)

Organization for Nurse Leaders President's Award

Gaurdia E. Banister, RN, PhD, NEA-BC, FAAN (Institute for Patient Care)

2022 Orthopaedic Research Society New Investigator Recognition Award

Alireza Borjali, PhD (Orthopaedic Surgery)

Patient-Centered Outcomes Research Institute (PCORI)

Louisa Sylvia, PhD

President of the Eastern Nursing Research Society

Jane Flanagan, PhD, RN, ANP/AHN-BC, FNI, FNAP, FAAN (Munn Center)

Research.com Best Female Scientists (Ranked No. 106 in the U.S., No. 160 in the world)

Xandra Breakefield, PhD (Neurology)

Research.com No. 82 Among the Top 1,000 Scientists in Medicine

Rakesh K. Jain, PhD (Radiation Oncology)

Research Institute of Molecular Pathology 2022 International Birnstiel Awards

Margarete Diaz Cuadros (Molecular Biology)

2022 Roberts' Prize for Best Paper in Physics in Medicine and Biology

Clemens Grassberger, PhD (Radiation Oncology)
Abdelkhalek Hammi, PhD (Radiation Oncology)
Lucas McCullum (Radiation Oncology)
Harald Paganetti, PhD (Radiation Oncology)
Jennifer Pursley, PhD (Radiation Oncology)
Jungwook Shin, PhD (Radiation Oncology)
Shu "Stella" Xing, PhD (Radiation Oncology)

Samsung Ho-Am Prize in Medicine

J. Keith Joung, MD, PhD* (Pathology)

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Scientific Research Honor Society Sigma Xi

Abder-Rahman Ali, PhD, MSc (Radiology)

Society for Academic Emergency Medicine (SAEM) 2022 Mid-Career Investigator Award

Kohei Hasegawa, MD, PhD (Emergency Medicine)

Society of Neuro-Oncology Women in Neuro-Oncology Mid-Career Exemplary Physician Award

Priscilla Brastianos, MD, (Medicine, Hematology Oncology, Cancer Center)

Society for Obstetric Anesthesia and Perinatology Vice president (president-elect)

May Pian-Smith, MD, MS (Anesthesia, Critical Care and Pain Medicine)

Stand Up To Cancer (SU2C) Health Equity Committee

Andrew T. Chan, MD, MPH* (Cancer Center)

2022 Szent-Györgyi Prize for Progress in Cancer Research from the National Foundation for Cancer Research

Rakesh K. Jain, PhD (Radiation Oncology)

Target ALS Rebecca Luker Courage Award

Merit E. Cudkowicz, MD (Neurology)

Weill Medical College of Cornell University 2022 Samuel W. Perry III, MD Distinguished Award in Psychiatric Medicine

Jill Goldstein, PhD, MPH (Psychiatry)

Women's Edge and The Boston Globe Top 100 Women-Led Businesses in Massachusetts 2022

Marcela del Carmen, MD, MPH

Paula Milone-Nuzzo, PhD, RN, FHH, FAAN (Institute of Health Professions)

Wyss Medical Foundation Jesse B. Jupiter Fund

Jesse B. Jupiter, MD (Orthopedic Surgery)

*MGH Research Scholar

PROMOTE

Office of the Scientific Director (OSD)—Susan A. Slaughaupt, PhD

<https://www.massgeneral.org/research>

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

- Communications
- Philanthropic outreach
- Building new partnerships with industry

Our communications 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 Mass General Development Office to increase philanthropic giving for research through programs such as the MGH Research Scholars and Endowed Mass General Research Institute chairs.

Finally, we are building new relationships with industry through our Strategic Alliances initiative, now named the Longfellow Project, and by working in close partnership with the Mass General Brigham Innovation office. Below, we expand on each of these initiatives and give a few highlights from the past year.

Communications

Email newsletters: We continue to create and distribute our newsletter communications to help promote the remarkable work of our research community.

- *Snapshot of Science* is a monthly newsletter sent to nearly 10,000 people that includes a monthly list of publications from high impact journals in which a Mass General investigator is a first or last author. In 2022, we featured over 350 high-impact papers in the *Snapshot of Science*.
- *From the Lab Bench* is a monthly newsletter that features stories about research at Mass General, updates on events and other research news.

Both emails continue to perform very well, averaging a 40% open rate during 2022. The industry standard open rate for emails is 17%.

The Research Institute Blog: Our blog, *Bench Press*, is in its fifth 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 two new postings each week and includes original content, recaps of news articles, awards and honors announcements, infographics, tips for communicating science and much more.

- Our most popular story this year was “Researchers Call for More Studies to Learn How our Brain Changes When We’re Awake After Midnight,” featuring Elizabeth Klerman, MD, PhD, from the Department of Neurology. The story received over 26,000 views.

Social Media: We continue to use social media as a vehicle for promoting research at Mass General hospital, keeping a close eye on how each platform performs and adjusting our strategy as needed. Twitter continues to be our go-to platform for promoting research studies and has seen great engagement from the scientific community, while our Instagram and LinkedIn accounts had the most promising growth in 2022. You can find links to all our social media accounts at <https://linktr.ee/mghresearchcommunications>

Improving Communication Processes and Efficiency:

This year the MGRI team expanded, adding a second communication specialist, and took on a new role coordinating the production, posting and promotion of research press releases when the MGH public affairs team was merged into Mass General Brigham.

- **Research Communications Intake Form:** Because of the high volume of requests for press releases that we were receiving from the MGRI community and the scattershot way in which those requests came into us, we realized that we needed a more effective system to track and manage these requests. We created a brief intake form that serves as a starting point for all new requests.

Communicating Science: The Research Institute has launched a series of initiatives designed to help our scientists better communicate the importance of their research to the public. In 2022, we hosted two Science Slams: one virtual in February (nine “slammers” and 107 attendees), and one in person with our summer students in June (nine “slammers” and 70 attendees). We also continued our online science conversation series, QUIIPS (“Quick Interviews with Interesting People”) featuring candid conversations between junior researchers and their mentors/senior leaders.

Internship Program: This year we hosted an intern from the Aspire program at Mass General, which offers opportunities for individuals on the autism spectrum to develop skills to succeed at work and in the community.

Collaborative Efforts: We continue to work closely with our colleagues in Public Affairs, Development, and Central Marketing to coordinate the promotion of our research stories across various communication outlets (including MGH Hotline, Development’s Giving website, and the main Mass General website and Facebook page). The sharing of content and ideas across these departments is a crucial component of our communications plan 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 philanthropists and prospective donors to support research and to educate individuals, foundations, and corporations about the important role that unrestricted support for research plays in driving new discoveries in medicine.

We had a successful year of fundraising, and our ability to raise unrestricted funding for research continues to grow.

In 2022, we bestowed four new MGH Research Scholar awards, bringing the total number of MGH Research Scholar \$500,000 awards granted over the past 11 years to 74. Since 2011, this remarkable program, fueled entirely by philanthropy, has had a substantial impact on the careers of the awardees and the advancement of research across Mass General, across the country and around the world.

Since 2015, we also established seven Endowed MGH Research Institute Chairs, which provide more permanent support to the chair incumbents. We continue to prioritize our goal of supporting more members of our research community with MGH Research Scholar awards and Endowed MGH Research Institute Chairs.

Our Research Institute leadership team—partnered with our Development Office colleagues to advise on and host numerous virtual and in person meetings and events with donors and prospects throughout 2022, including the popular Mass General Research Institute LAB DAY.

LAB DAY 2022 was held on October 19 in person for the first time since the pandemic at the Charlestown Navy Yard campus. The event featured laboratory tours and scientific presentations with three MGH Research Scholars and their teams.

Overall, the success of our collaboration with the Development Office can be seen in our growing engagement with the fundraising team and the introduction of new prospective donors who are passionate about the impact and value of providing unrestricted support for Mass General researchers.

Strategic Alliances (The Longfellow Project)

In 2015, we developed and launched the Strategic Alliances initiative (now titled the Longfellow Project) with the objective of helping our investigators engage in solid collaborations with the biopharma and venture industries at all stages of their work, from basic science and proof of concept to development and transfer to market and patient care.

With the incredible and sustained support of the Research Institute Advisory Council (RIAC), which includes leaders in

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the biopharma and venture industries, we have been able to push our programs forward in 2022.

The initiative is built on three pillars: Challenge-Driven Programs, Training and Education, and Research Community Building.

Challenge-Driven Programs: Our challenge-driven programs come from research “problems (biology, technology, medicine)” collected from departments and centers across Mass General and aggregated under broader “themes.”

In total, we have built eight programs around Epigenetics, Cancer Immunotherapy, Neuroinflammation in Neurodegeneration, the Microbiome, Cardiometabolics, Rare Diseases, Antimicrobial Resistance, and Sleep that bring together 223 investigators from 20 departments and centers across the institution.

We have organized 24 industry-focused sessions during which our investigators presented these programs to selected industry executives. In 2022, we launched one collaboration with a biotech company.

Our goal is to continue to build collaborations between Mass General investigators and our industry partners that improve the lives of patients both at MGH and around the world.

Training and Education: Given the vital importance of the academic-industry bond in translating exciting science into practical solutions for patients, we developed the *Bridging Academia and Industry* educational program co-directed by Gabriela Apiou, PhD, Director, Strategic Alliances, and Robert Tepper, MD, Partner, Third Rock Venture and RIAC member. The program is open to all Mass General faculty (MD and/or PhD) and aims to teach the importance of collaboration across academia and industry, the language that makes the dialogue productive and what it really takes to go from the lab to clinical practice.

The program is organized in 15 three-hour weekly sessions and includes a course on translational research strategy and tactics, and a project competition. In 2022, we trained 26 faculty from across 13 departments and thematic research centers, with 44 faculty (24 academia, 20 industry) teaching and mentoring the project teams. The winning project team received \$150K in funding to perform relevant research experiments and develop a sound go-to-market plan.

Research Community Building and Support: Rooted in a common understanding of the science being performed across the MGRI, our efforts under the Research Community Building pillar aim to help investigators at MGH

advance their research by initiating and strengthening connections between themselves, MGB Innovation, research support groups across MGH and MGB and academic and industry potential partners.

In 2022 we continued to help investigators engage in several MGB Innovation programs such as the Innovation Discovery Grants, Chiesi Neuroscience RFP, Sanofi iAwards, NIBR Global Scholars Program and the Boston Scientific Corps Translation-in-Kind program.

We continued to promote the Longfellow Project model to internal and external groups, including academic and non-profit organizations, pharmaceutical and biotechnology companies, and venture firms, nationally and internationally.

Dr. Apiou gave five invited talks, locally, nationally, and internationally, describing the Longfellow Project model of collaboration that we have taught and practiced at MGRI since 2015.

Division of Clinical Research (DCR)—Judy Hung MD, Director

<https://dcr.massgeneral.org/>

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 27th 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 patients. Last year, DCR Faculty provided over 480 individual consultations to Faculty and Staff from over 25 divisions and departments across MGH and MGB. The DCR Center for Clinical Research Education has offered 200 live and online courses with over 6,000 participants. More recently, DCR has become the hub for all MGB services (CTO, IRB/HRA, QI, Innovation), and the Harvard Catalyst.

Following DCR’s Mission as well as MGH Strategic Plan recommendations, the following DCR Centers and Units are providing support to MGH and MGB 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 and 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 and 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. (See CCRE expanded report below)

Center for Quantitative Health (CQH), Roy Perlis, MD, MSc

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 principal 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 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 Mass General Research Institute.

Yvonne L. Munn Center for Nursing Research, Gaurdia Banister, RN, PhD

The official dedication of the Munn Center in May 2008 acknowledged the hospital's commitment to nursing and interdisciplinary research collaborations that foster high quality, cost-effective, patient and family-centric care. Some of the Center's goals include accelerate research in core areas of focus 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.

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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 trials and other research results and the implementation of their advances to improve clinical practice and public health. The main activity of the CERU is research mentoring for MGH trainees and faculty at all levels and 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

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

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

The Global Health Research Unit (GHRU) offers free consultations on the conduct of global health research, as well as sponsors campus-wide seminars on general principles for global health research. The GHRU research is 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

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 MGB.

Information Technology Unit, Mikhail Pivovarov

The broad goal of the Information Technology Unit (ITU) is to support the increasing information technology needs of the MGH research community. The Unit’s specific approaches to meeting this goal are improving existing information management resources, while creating a broad, latest information management infrastructure to support the work of the research community at MGH and MGB; envisioning and creating transformative informatics and IT solutions for the clinical research community and beyond.

Mentoring Corner, Karen Miller, MD

The Mentoring Corner Unit assists mentees in identifying appropriate mentors, mentorship tools and provides advice on all aspects of K-award and RO1 applications. This Unit consistently achieves high ratings from participants.

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 MGB 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

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 and 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.

Below is the expanded report on three cornerstone initiatives: DCR Center for Clinical Research Education, The MGB Biobank at MGH and the Translational Research Center (TRC).

DCR Center for Clinical Research Education (DCR CCRE)

The DCR CCRE provides education to MGH/MGB clinical research community on research principles, design, methods, and study implementation best practices. The CCRE aims to provide an integrated, useful, scientifically accurate and comprehensive educational curriculum with course offerings that are designed to enhance the quality of clinical research and prepare for the future, as we increase the volume of translational and early phase studies. Education topics include the principles and processes of conducting clinical research. The core curriculum exposes fellows and junior faculty not only to the key tenets, issues, and techniques of clinical research but also to the multiple support and consultative services available from DCR and across the system. Other educational offerings include introductory courses in grant writing, biostatistics, data management, clinical trials, qualitative and mixed methods research, patient recruitment and retention.

The DCR CCRE builds technology solutions to support curriculum development and delivery, using online, remote, and hybrid learning models. The CCRE produces many virtual events including MGH Clinical Research Day, MGH Clinical Research Council meetings and other scientific events.

The DCR CCRE switched to virtual offerings and a fully remote virtual team in 2020. We have turned this response to the COVID-19 pandemic into our competitive advantage. With a fully remote team focusing on education, we were able to optimize our processes, attract and hire unique talent and produce quality courses for the clinical research community. With the virtual tools available to us, we continue to improve the quantity and quality of the curriculum. We continue to be the team of choice to work with on educational offerings for other research focused groups within MGH and MGB (Mass General Brigham).

The DCR CCRE work is organized into five pillars: technology, curriculum, instructional design, user experience, and analytics. We use technology to provide and support solutions for instructional design, course delivery, and scientific events. We maintain a comprehensive curriculum for clinical research which includes engaging courses and well-defined curriculum pathways. We design our educational offerings with the latest understanding of learning theory, adult learning principles, and innovative instructional strategies. We keep our users at the center of everything we do. We build in metrics, analytics, and user feedback into all our systems.

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ACCOMPLISHMENTS IN 2022

Curriculum

Overall course and learner metrics in 2022

In 2022, we continued to offer our curriculum through OpenCourses in collaboration with many DCR units and centers as well as other groups across the system. We have the largest curriculum in clinical research education among MGB and HMS. This year, we offered 68 unique Live courses, 65 unique On Demand courses, and 332 courses total (Figure 1) with just under 20,000 total enrollments representing almost 6,000 unique learners (Figure 2). Please note that all data in this report are annualized and represent November 2021 through October 2022.

We have seen growth in both our offerings and audience in the past five years. Figure 3 compares learner enrollments and total courses from 2018-2022. Despite a brief dip in the number of courses in 2020 due to the pandemic and a slight reduction in on-demand enrollments in 2021 due to a staged transition to OpenCourses. We have seen a steady trend of growth in interest in our live offerings, our on-demand offerings, and in our total courses offered.

Figure 1. DCR Courses in 2022

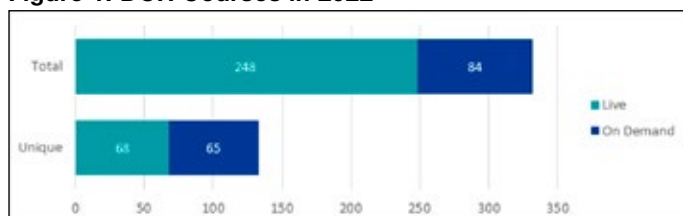
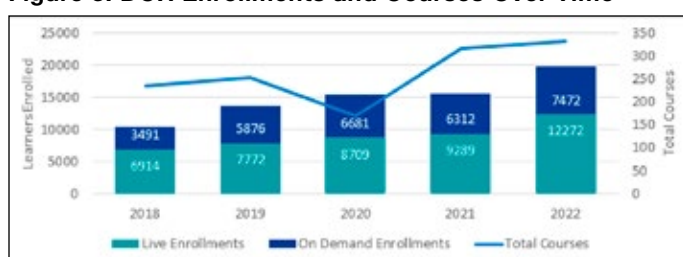


Figure 2. Learner Enrollments in DCR Courses in 2022



Figure 3. DCR Enrollments and Courses Over Time



Specific Course Highlights

Learn Something New Program

Learn Something New is our summer program for clinical research study staff. We involve experienced clinical research study staff and other MGB staff to educate clinical research study staff. This is an important program to share expertise with beginner and junior study staff and give presentation and public speaker experience for more experienced study staff.

Table 1. Summary Metrics for 2022 Learn Something New Program

	Total Courses	Total Enrolled
Live Courses	16	1528
On Demand Courses	23	177
Grand Total	39	1705

Clinical Skills for Research Study Staff

We offer several courses for research study staff who need to learn clinical skills such as peripheral blood draw, ECG, and vital signs collection for their research studies. We have long offered courses teaching these skills, and in the past few years have updated our curriculum to meet the scheduling needs of both our learners and our peer instructors. For each of the clinical skills we offer training for, we have divided the curriculum into two parts: didactic content that is available on demand and hands-on content that is available in person for small groups. Our hands-on courses, particularly for blood draw, are very popular and are offered throughout the year. We have an excellent cohort of peer instructors who are instrumental in sharing their clinical skills in our hands on courses.

Design and Conduct of Clinical Trials

Design and Conduct of Clinical Trials (DCCT) is one of our most popular courses. It is our introductory course for junior investigators who are new to clinical research. Offered every fall, it is a 15-session course lasting about 2 months and culminating in the learners drafting and presenting their own clinical trial ideas. In 2022, we had 100 learners apply and 64 applicants were approved to enroll. We used the new Application Enrollment plugin on OpenCourses to manage the learner application process for this course and received positive feedback from the course directors on the features and usability of this new plugin. Learners and instructors had the following to say about their experience with the course:

“As I had mentioned before to Teresa, I really enjoyed using the platform you have chosen. I found it the easiest

Table 2. Clinical Skills Program in 2022

Format	Clinical Skills Courses	Total Courses	Total Enrolled
Live	Phlebotomy for Clinical Research Staff (Hands-On)	34	313
	Vital Signs for Clinical Research Staff (Hands-On)	9	93
	ECG for Clinical Research Study Staff (Hands-On)	9	64
	Subtotal	52	470
On Demand	ECG for Research Staff (Didactic)	1	194
	Phlebotomy for Research Staff (Didactic)	1	340
	Vital Signs for Research Staff (Didactic)	1	167
	Subtotal	3	701
	Grand Total	55	1171

Table 3. Human Research Affairs, Compliance and Education Office Courses and Enrollments in 2022

Format	C&E Course Titles	Total Courses	Total Enrollments
Live	Clinical Research Bootcamp	19	1526
	ClinicalTrials.gov	12	523
	Study Team Data Management and Internal QA Monitoring Plans	12	917
	IND and IDE Responsibilities for Sponsor-Investigators and Study Staff	6	174
	Informed Consent Including eConsent	12	703
	Clinical Research Inspections and Audits	2	157
	Human Subjects Research Recordkeeping and Record Retention	12	1044
	Virtual Visits	6	192
	Writing a Clinical Research Protocol	12	681
	Grand Totals	93	5917

and most intuitive of the several different platforms I have used.”

“I like the ability to learn something relevant to my career goals without having to pay an arm and a leg for a degree.”

“Great feedback from the professors.”

“I had loads of questions, which were answered by the speakers, so very helpful, wish I could have accessed a talk like this sooner as research faculty.”

Expanded Recruitment Course from DCR's CARE Research Center

We collaborated with the Community Access, Recruitment, and Engagement Research Center to expand their previous educational offerings into a new course, *Recruitment, Engagement, and Retention Strategies to Improve Diversity in Clinical Research Studies*. This updated course expanded their previous single session course into a 3-session course. Each session included a breakout room activity to encourage learners to engage with the material and apply it

to their current studies. 203 learners enrolled in this course and 116 attended at least one session. We received positive feedback from the learners on the breakout room activities and overall usefulness of the course.

New Digital Health Research Program

We collaborated with members from the Center for Innovation in Digital Healthcare (CIDH) to create a series of courses geared toward helping researchers and research teams interested in digital health research navigate the various groups and tools available within the MGB system. Another course in this series focused on the research administration process is planned for early 2023. In 2022, we had 279 learners enroll in 4 courses in this new series.

Existing Collaborations

We collaborate with many groups to host their courses on our platforms. We have hosted the MGH seminars for the Responsible Conduct of Research program since 2019. We have collaborated to host what is now the Human Research

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Table 4. Research, Information, Science, and Computing Courses and Enrollments in 2022

Format	RISC Course Titles	Total Courses	Total Enrollments
Live	Biobank Portal	10	225
	REDCap eConsent Functionality	2	206
	REDCap: Getting Started	2	214
	REDCap Survey Features and Functionality	2	151
	REDCap User Group Meeting	3	71
	Introduction to RPDR	9	473
	Subtotal	28	1340
On Demand	Guide to the Research Patient Data Registry (RPDR) Simulation	1	331
	REDCap: Getting Started Recording	1	31
	REDCap eConsent Functionality Recording	2	13
	REDCap User Group Meeting Recording	1	3
	Biobank Portal Recording	2	7
	Introduction to RPDR Recording	2	21
	RPDR Advanced Course Recording	1	16
	Subtotal	10	422
	Grand Totals	38	1762

Table 5. Responsible Conduct of Research Program Courses and Enrollments in 2022

Format	RCR Program Course Titles	Total Courses	Total Enrollments
Live	Clinical Research Bootcamp	19	1526
	ClinicalTrials.gov	12	523
	Good Clinical Practice in Research at an Academic Research Institute	2	263
	Clinical Research Inspections and Audits	2	157
	Responsible Data Management	2	100
	Research Integrity	1	44
	The Lab—Avoiding Scientific Misconduct	1	40
	Responsible Authorship and Publication	1	40
	Managing Conflicts of Interest	1	37
	Mentor-Mentee Relationships and Responsibilities	1	54
	Responsible Authorship	1	28
	Responsibilities of Scientific Peer Reviews	1	62
	Writing a Clinical Research Protocol	12	681
	Grand Totals	56	3555

Affairs Compliance and Education Office's courses MGB wide since 2020. We have collaborated with Research Information, Science, and Computing to offer their courses for several years. As you can see in tables 3-5 below, these collaborations offer many valuable and popular courses to our research audiences.

In addition to these programs, we host the research safety training with MGH Research Compliance Office.

New Collaborations in 2022

In addition to the existing collaborations outlined above, we initiated collaborations with three new groups in 2022. We started to work with the **MGH Cancer Center Protocol Office (CCPO)** to host their new hire trainings early in 2022. Since starting this collaboration, we have hosted 2 courses with **485** enrollments.

We worked with the **Center for Innovation in Digital Healthcare (CIDH)** and helped produce 4 courses in 2022 with 3 more planned for 2023. These 4 courses enrolled 279 learners. The CIDH team had the following to say about their experience working with us:

"We had a wonderful experience working with Jamie and the DCR team over the past year. Since it was our first time launching this type of live online curriculum, we were not clear on how to get started and what details we needed to be aware of. Jamie provided step-by-step instruction and met with us as needed to support us along the way. Some elements included building the course page, drafting course advertisements, best practice presentation methodology and tips, and technical assistance. Jamie even gave us constructive criticism on the presentation in advance and after our session, further improving the class dynamics, and Jamie provided detailed edits on our first course's resource document. The DCR team demonstrated professionalism and in-depth knowledge of their work and helped us with three extraordinarily successful live online classes, launched over the last few months. We are confident that the DCR team members will continue their outstanding work on nurturing the MGB research community in the future."

We also started collaborating with the **MGH Center for Comparative Medicine (CCM)** in October 2022. So far, we have posted 3 on demand courses and set up 2 live courses for them, but given the infancy of this collaboration, we do not yet have enrollment metrics to report.

Instructional Design

In 2022, we articulated that instructional design was a pillar of the work that we do, and we focused much of our attention on building up this aspect of our center.

We believe learning experience design starts with a multidisciplinary and methodical approach that draws on best practices of learning theories, adult learning principles, teaching strategies, and cognitive science. We take the time to ensure there is alignment between assessments, objectives, instructional strategies, and organizational goals. All learning assets are architected with the learner and organizational goals in mind. Some of the accomplishments in this area are described below.

Instructional Design Curriculum

In addition to our research audiences, we endeavored to share our knowledge of instructional design with educational and training professionals within the system. Teresa La, our senior instructional designer, created the first of a series of courses on principles and pragmatic practices trainers can use to improve their teaching and courses. This course, *Instructional Design: Tips and Strategies to Boost Learner Engagement*, opened in August 2022, and so far, has enrolled **96** learners. This course has been well received, and several learners have expressed interest in further courses in this area.

Additional Instructional Design Resources

We also hired per diem instructional designers to expand our capacity to improve existing courses and develop new ones. This is a particular area where we feel we can bring our in-house expertise and connections to the national instructional designer community to the system.

Instructional Design Projects

We have several ongoing instructional design projects to improve and add to our curriculum. These include:

- **Performing Effective Literature Searches.** This project consists of 3 modules and is being done in collaboration with the Treadwell Library. This course follows a game-based learning approach. Games and simulations allow learners to learn while having fun. Learners are allowed to practice tasks, apply knowledge, and infer principles.
- **Natural Language Processing in Clinical Research.** This technical and pragmatic course is being developed in collaboration with an investigator from BWH and consists of 3 modules. The first 2 modules will be built using a classic tutorial structure in order to best reflect the needs of learners and the nature of the subject matter. Learners begin with an introduction to the lesson and then proceed through a series of topics teaching progressively more advanced concepts. The 3rd module will be a simulation-based training, which involves the use of a specific natural language processing tool and guided-practical activities.

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- **Applying for PCORI Funding.** This is a collaboration between the CCRE, the DCR PCORI unit, and Harvard Catalyst and consists of 6 modules. The aim is to highlight how PCORI is different from other funding sources and to give applicants the tools they need to write responsive and competitive applications.
- **MGH Clinical Research Nurse Orientation.** This is a collaboration with the MGH CRN Collaborative and consists of 6 modules. This course follows a classic tutorial structure, which best reflects the needs of learners and the nature of the subject matter. Learners begin with an introduction to the lesson and then proceed through a series of topics teaching progressively more advanced concepts. Practical activities and knowledge check questions are added throughout the course to increase learner engagement and knowledge retention.
- **Phlebotomy for Clinical Research Study Staff.** This is a revision of the existing didactic phlebotomy training. The aim is to increase learning effectiveness by incorporating more interactivity and practical activities.
- **Creating Effective Scientific Posters.** This is a revision of an existing course in the Communicating Science Program. The aim is to provide practical steps and design principles to create effective scientific posters.
- **New Research Staff Training: Conducting Clinical Research.** This is a major overhaul of the existing onboarding training for new hire coordinators. This aim is to provide a practical high-level overview of clinical research and a document of resources new hires can use after the completion of the course.
- **Guide to the Research Patient Data Registry.** This is a collaboration with Stacey Duey from RISC and will be an updated version of the current RPDR simulation course. This is a simulation-based training, which involves the use of RPDR Query Tool to model real-world scenarios.
- **Pragmatic Courses in Clinical Research Operations.** We are collaborating with senior and experienced clinical research project managers at MGH to develop additional pragmatic on demand courses for junior clinical research study staff.

Our collaborators have the following to say about their experience working with us:

“Teresa has made the idea become reality! She has gone beyond our expectations! We thought we would make a PowerPoint module, but Teresa took our ideas to new heights! Now our project is interactive and full of life and personality which will keep participants engaged in the learning! One of many examples of her passion for the material is she looked up academic journals discussing

what makes an effective online learning modules within nursing! She has thought about each critical detail in the design which has made this an outstanding module and we cannot wait to share it! Thank you, Teresa, for your hard-work, commitment, organization, and innovative ideas!”

Technology

OpenCourses Metrics and Improvements

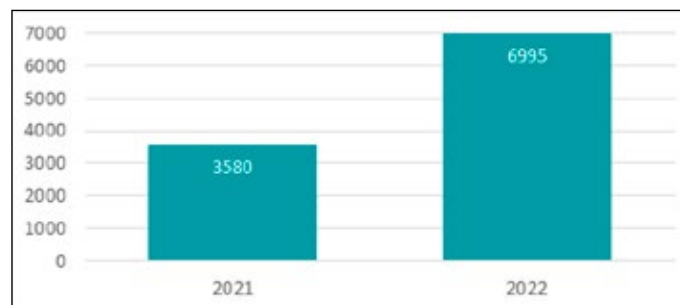
[OpenCourses](#) is our learning management system (LMS) which went live in July 2021 and is built on the open-source software, Moodle. OpenCourses allows us to host on-demand courses, course registrations, and course materials and content for learners to access directly. OpenCourses has well-established APIs to allow us fully integration with the MGB Digital ecosystem. As an open-source solution, OpenCourses is customizable to suit our needs.

User Metrics 2022

With OpenCourses and the [People DB](#) (a database of MGB employees managed by the DCR which pulls role information from Active Directory), we can assess our audience more accurately and with more depth. Since 2020 and our switch to virtual, our courses are available MGB-wide.

Our active users on OpenCourses grew from **3,580** in 2021 to **6,995** users in 2022 (Figure 4). Active users are defined as those who registered for an account or enrolled in a course during the specified timeframe. These data are not directly comparable as the data for 2021 represent new or active users from June 2021 through October 2021 and the 2022 data represent new or active users for November 2021 through October 2022.

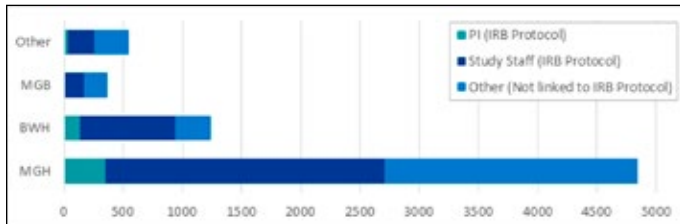
Figure 4. Active Users in 2021 and 2022



In addition to MGH community, our users include employees across the system from BWH, McLean, Mass Eye and Ear, Dana Farber, Newton-Wellesley, Salem Hospital, and North Shore (Figure 5). The largest role cohort we serve are clinical research study staff (on IRB protocols).

We have also seen an increase in other (not clinical research) user groups.

Figure 5. Active Users in 2022 by Institution and Role



Improvements to User Experience

After launching OpenCourses in 2021, we spent 2022 creating plugins to improve the user experience. Several of these plugins are described below:

- **Course Application Plugin.** This plugin created a mechanism for learners to apply for a specific course, and instructors to approve or deny enrollment of learners based on their applications. This plugin was first implemented in May 2022. It was successfully utilized to manage enrollment into one of our flagship courses, Design and Conduct of Clinical Trials. We are currently designing an update to this plugin based on feedback from the instructors of that course.
- **Add to Calendar Plugin.** This plugin was created to automate the creation of .ics files on the course page of live courses and allow users to navigate directly to live session links from their calendars.
- **Star Rating Plugin.** This plugin was created to allow learners to leave star ratings and course reviews on courses in a familiar manner to other star rating and review websites. This plugin also improved how star rating and review data are managed in the backend compared to the prior star rating plugin.
- **Improvements to Self-Enrollment Experience.** There were a few related plugins that were created to improve the user experience during self-enrollment. Some of the features added or updated were: 1) an updated enrollment page which displays learner star ratings and reviews, 2) an enrollment success popup with the option to download an .ics file for Live courses, and 3) an updated enrollment success email which linked directly to the course page and included an email for questions.
- **Updated Course Catalog.** We iterated on the course catalog with the goal of making it easy for learners to find courses relevant to them. Our latest iteration went live in November 2022.

• Session Attendance Evaluation Reminder Plugin.

This plugin was created to automate the process of sending reminder emails to learners to complete course evaluations.

New Integrations with OpenCourses

In addition to the user facing improvements on OpenCourses, we have also implemented features to improve the backend. Some of these features are described here:

- **API with People DB.** In 2021, we implemented an API between OpenCourses and People DB to transfer enrollment and completion records. In 2022, we implemented a method for People DB to automatically create OpenCourses accounts for new employees and enroll them on job-specific courses within a chief code or employment group.
- **Google Analytics.** We installed Google Analytics to both OpenCourses and DCR website to track user activity and to improve user experience. We used the insights gained from this plugin to design the latest iteration of our Course Catalog which went live in November 2022.
- **API with DCR website.** We linked our upcoming live courses on OpenCourses course catalog for display on the DCR website.
- **Weekly Metrics Dashboard.** We developed and implemented a weekly analytics dashboard to monitor new user activity, course enrollments, completions, and learner feedback.

Clinical Research Day 2022

[Clinical Research Day](#) is an annual celebration of clinical and translational research at MGH.

The theme for Clinical Research Day 2022 was “*New Technologies and Novel Opportunities: Clinical Research and Patient Care*”. The keynote address entitled “*The Digital Reconstruction of Healthcare*” was given by Dr. John Halamka, President, Mayo Clinic Platform. Our panel discussion, moderated by DCR Director Dr. Judy Hung, included the following panelists: Drs. John Halamka, Adam Landman, Chief Information Officer and Sr. VP of Digital, MGB, Anthony Philippakis, Chief Data Officer, Broad Institute of MIT and Harvard, Randy Gollub, Associate Director for Translational Research, Psychiatric Neuroimaging Program, MGH, and Shawn Murphy, Chief Research Information Officer, MGB. We had **243** attendees at the keynote, **132** attendees at the panel discussion, and **558** attendees at the poster session. We saw an increase

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in abstract and poster submissions in 2022 compared to 2021, with **275** abstracts and **319** posters submitted.

Since 2020, we have used an in-house built scientific event [portal](#) to host all Clinical Research Day activities virtually, including:

- Abstract and poster submissions, review, and selection
- Award nomination submissions, review, and selection
- Interactive abstract and poster galleries including highlights for award winning abstracts and posters
- Event management includes award announcements, schedule announcements with direct links to virtual events, and event recordings.

Our scientific event portal is modular and modifiable, and instances of our portal are currently in use by other departments and centers.

Course Management Application

We started to develop the [Course Management Application \(CMA\)](#) in 2021 to help us collaborate with other teams on course development, management, and evaluation. In 2022 the CMA underwent a redesign to accommodate our evolving needs. While the implementation of that redesign is currently in progress, we anticipate the updated version to go live by the end of the calendar year.

DCR website

In 2022, we implemented some new integrations to DCR [website](#). In collaboration with MGB Research Computing Core Information Systems (RCIS), we created a QA site to test API integrations and site improvements. One new integration we have tested is the previously mentioned API with [OpenCourses](#) to display a calendar of upcoming Live Courses on our public site.

We are working on updating the design and content of our website. In addition, we have implemented a testimonial plugin to automate the collection and publication of testimonials.

Communication

In 2022 we expanded our email communication to all employees involved in human subject's research across the system. Our listserv of employees involved in clinical research includes **13,989** unique emails, and this listserv is updated regularly. We also maintain an MS Teams group to facilitate a community of practice for clinical research coordinators.

Future Focus

Curriculum

In 2023, we plan to shape our clinical research curriculum with the help of senior staff and other experts in clinical research. We plan to focus on pragmatic and case-based content and provide our learners with hands on learning activities like breakout rooms with scenario discussions and role play courses to practice interpersonal skills.

Instructional Design

We plan to continue expanding our capacity and reach regarding instructional design in 2023. We hope to have at least one more course in our instructional design series, continue to develop new and revamp existing on demand courses, and coach our instructors on best practices for instruction, course material development, and learner engagement.

Technology

We have made great strides in creating technology to support how we work with subject matter experts and stakeholders this year. Next year, we plan to implement these new technologies within the team and to support our collaborations with individuals across the system. We also plan to go live with our website redesign which includes both improvements to design and content for our users as well as backend improvements to user behavior data collection, automated calendar publishing of upcoming courses, and automated collection and publishing of user testimonials.

The Mass General Brigham Biobank at MGH—Susan A. Slaugenhaupt, PhD and Jordan Smoller, MD, ScD

The Mass General Brigham Biobank at MGH, under the direction of Susan Slaugenhaupt and Jordan Smoller, is a research infrastructure that provides biospecimens and genomic data to Mass General Brigham investigators, including MGH investigators. The samples and data are linked to electronic health record data and survey data and may be queried via self-service tools. The Biobank includes samples and data from across Mass General Brigham hospitals and community health centers. As of December 2022, 140,000+ participants have consented and 95,000+ sample have been collected. The Biobank has distributed samples and data to more than 450 studies, including 250 at MGH.

The key value/services provided to Mass General Brigham investigators are:

- Access to DNA, serum, plasma, and PBMCs (for COVID-19 patients only). Since 2020 the Biobank collaborated with studies at MGH and BWH to recruit COVID-19 patients and collect, process, and distribute 17,000+ samples to Mass General Brigham investigators and, under the auspices of the Massachusetts Consortium on Pathogen Readiness (Mass CPR) consortium, to non-Mass General Brigham investigators.
- Access to a large cohort of patients who are consented for broad-based research and recontact. This includes a repository of COVID-19 patients and their phenotypic data.
- 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., lifestyle, family history surveys).
- Sample management services.
- Support recontact of Biobank consented participants for additional sample collection.
- GWAS data, exome sequence data, and imputed genomic data (65,000+ subjects).
- Support inventory, storage, and distribution of COVID-19 vaccines for Mass General Brigham hospitals and non-Mass General Brigham affiliated physicians.
- Support COVID-19 serologic studies across Mass General Brigham hospitals in recruitment and scheduling, sample processing and management, and data and sample distribution.
- Support COVID-19 vaccine clinical trials at Mass General Brigham in the form of reassignment of large numbers of trained staff.
- Participation in a NIH-funded longitudinal research cohort, the *All of Us Research Program*, which aims to consent over 60,000 participants in New England (as part of the larger goal of 1M+ participants) via a \$56.5M 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 10 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. The grant is for \$6.7M over 5 years plus \$1.3M in two supplements.
- Participation in a NIH-funded program to address Post-Acute Sequelae of SARS-Cov-2 infection (PASC) Data Resource Core (DRC), which create a robust Central Data Enclave with 40,000+ post-COVID RECOVER cohort participants, generate robust and scalable embedded analytic tools, and support investigators on application "of rigorous biostatistical methods for principled design and analysis of RECOVER adult, pregnancy, pediatric and autopsy cohort studies. The grant is for \$41M over 4 years.

Translational Research Center (TRC)—Mason W. Freeman, MD

Goals

The TRC's overall goal is to facilitate the movement of basic science discoveries, made both at the MGH and in the larger biopharma community, into the clinic in order to improve patient care via the generation of better diagnostics and therapeutics. 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 project to be advanced;
- Providing an assessment of the feasibility and cost of pre-clinical studies, including pharmacology, manufacturing, and toxicology;
- Preparing electronic submissions to the FDA that enable programs to obtain an IND
- Preparing investigators to conducting successful 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.

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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 move forward. In 2022, the focus on new trials shifted away from the COVID trial work that had driven much of the activity in the TCRC since mid-2020.

Accomplishments

The total number of new TRC studies initiated in 2022 was 42 through early December 2022, in line with last year's total of 44 initiated through the end of December in 2021. Revenues coming into funds whose studies are utilizing the TRC component of the TCRC were \$5.82m in direct costs and \$1.73m of indirect costs up from 2021 revenues of \$5.16m and \$1.63m, respectively. At the close of the calendar year 2022, there were 77 active studies being conducted in the TRC, up slightly from the 74 that were active at the end of calendar 2021.

The COVID-19 vaccine studies initiated in late 2020 and thereafter in adults are now coming to a close and should officially end by mid-2023. One pediatric study of a COVID-19 vaccine remains active. The pace of overall activity in the TCRC continues to remain high with 2558 patient visits, down slightly from the 2788 in 2021 when a large number of follow-up vaccine visits were required and the TRC reached its highest visit number since opening the renovated trial facility on White 12 in 2016.

Only one of this year's new TRC studies approved for conduct in the TCRC was COVID-related. The remainder of the trials, as usual, explore therapies for a multitude of human diseases, including conditions such as familial adenomatous polyposis (PI, Daniel Chung, GI Unit), systemic sclerosis (PI, Flavio Castellino, Rheumatology Division), Non-Alcoholic Fatty Liver Disease (PI, Laura Dichtel, Endocrine Division), and Pediatric Acute-Onset Neuropsychiatric syndrome (PI, Kyle Williams, Psychiatry Dept). Many of our long-standing programs highlighted in previous SAC reports continued their quest for improved therapies with newer approaches for treating ALS, Schizophrenia, Parkinson's, and food allergies. The versatility of the research staff in the TCRC is evident in the wide array of disorders that are intensively studied on White 12. Their commitment to compassionate and quality patient care while performing exacting human clinical research is the hallmark of what the TCRC provides to the MGH's clinical research community.

Adaptations Planned

In the spring of 2022, Dr. Rick Mofsen retired after his very successful role running COVID-19 vaccine trials at MGH for over two years. Part of the transition plan he helped put in place included the hiring of several part-time young investigators to take over and divide up his responsibilities as the TCRC's first full-time investigator. These individuals are being supervised by more senior investigators this year with the goal of training them to assume PI roles in 2023. The concept of having part-time faculty PIs employed by the TRC who also maintain their departmental affiliations in providing clinical care, serving in teaching roles, or potentially performing their own independent research projects is being evaluated as a future model for recruiting PIs to the TRC to perform industry studies. It is asking a great deal of our young faculty to take on this challenge and it will take a year or two to determine whether the model can succeed given all the demands on young faculty members' time today. The acute shortage of qualified PIs for industry studies at MGH demands we continue to explore different models for filling this need.

SUPPORT

MGH Research Institute—FY 22 By the Number\$— Gary J. Smith, MPA, Executive Director, Administration and Finance, MGH Research Management

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

Research revenues for FY22 reached another all-time high of \$1.297B (\$1B direct costs and \$297M indirect), a \$100M (8.4%) increase from FY21. Our authorized funding dollars from the National Institutes of Health (NIH) in FY22 was \$560M which ranks us #15 in NIH funding for all institutions and #1 for independent hospital, a spot we have held for the past 20+ years. The percentage of funding awarded from the entire NIH extramural grant pool (market share) was 1.6% for MGH and 3% for MGB as a whole.

MGH FY22 proposal submissions fell to 4,746 for all sponsors from our COVID related peak activity in FY20 and FY21, a decrease of 4% from the prior fiscal year. FY22 research proposal submissions were slightly higher than our pre-COVID activity. DHHS success rates for MGH proposals is an impressive 27%, which is higher than the NIH FY21 national average of 21%.

Research expenditures from direct DHHS funding (which consists mostly of NIH funding and excludes incoming subcontracts), accounts for 42% of MGH research.

These DHHS-sponsored research expenditures increased significantly from \$524M to \$547M in FY22. Federal Subcontract (predominately NIH) expenditures were \$145M (11% of total research) in FY22, increasing from \$139M in the previous year.

Research expenditures for all our other non-NIH sponsor types in FY22 totaled \$603M which was a 13% increase from FY21. All Other Sponsor (+12%), Non-Profit (+13%), Foundations (+8%) and Industry (+25%) categories saw significant increases from FY21. Our research activity type is 52% clinical (clinical trials and other clinical research) and 43% basic/fundamental research of the total research portfolio. This trend towards clinical research has occurred over the past few years. In past years, the split has been close to 50/50 between clinical and basic research. Training activities make up the remaining 5%.

In aggregate, research activity (direct + indirect dollars) continues to comprise slightly under one quarter (24%) of the total MGH annual operating budget and is distributed across more than 30 departments and centers.

Our financial outlook for FY23 remains strong. Early results show our overall research expenditures running ahead of budget and are expected to exceed FY22 results. Our current FY23 budget performance and the high volume of grant applications submitted points to another strong financial year and beyond for the MGH Research Institute.

Congratulations and thank you to our investigators, research administrators, postdocs, and other support staff that are the catalysts for our strong financial results.

Research Space—Oversight and Analytics—Wendy Hobbs, Director, Research Space Management Group

The Research Space Management Group (RSMG) functions under the organizational sponsorship of the Research Institute and is responsible to the Executive Committee on Research (ECOR). 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 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 goals is to support the Research Institute's Prime Directive by creating an environment where scientists can concentrate on their research without worrying about their physical workspace. 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 its responsibility seriously to analyze research space utilization using sophisticated metrics to ensure that all research space is used effectively.

MGH currently owns or leases approximately 1.31M net assignable square feet (nasf) of space, essentially no net increase from last year. Research sites now exist in forty-two buildings across seven campuses in four cities. The percentage allocations amongst the campuses are similar to the previous year, with 42% in the Charlestown Navy Yard campus, 21% on the Main Campus, 21% in Charles River Park, 8% 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 of \$209 per square foot in the Fiscal Year 2022 to \$222 per square foot. The Research Portfolio has continued to perform well and consistently over the past two years. Of the major campuses listed above, the Boston Campus has the highest IDC density, \$363. Major research groups contributing to the high IDC density have research sites at Building 149, 101 Merrimac St., 125 Nashua St., 165 and 175 Cambridge, 5 Longfellow, Bartlett Extension, and Thier.

Fulfilling outstanding space requests remains one of RSMG's most complex challenges, particularly when there are few 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 ECOR, RISC, and the research community to understand the true space requirements and promote space adjacency amongst collaborative groups. Outstanding space requests from departments with valid funded grants averaged 97,963 nasf over the past five years. In September of this year, space requests increased to 46,825 nasf for wet space and 34,770 nasf for dry space, a total of 81,595 nasf. Never static, the current space request total in December 2022 is approximately 83,195 nasf, reflecting new Institution and Department initiatives.

Constantly updating and analyzing data in the Research Space Management System (RSMS), RSMG utilizes this one-of-a-kind relational database to identify opportunities for optimized space use and improved densities. Coupling RSMS data analysis with space subsidy metrics and site surveys, analysts identify underutilized 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 valuable and much-needed underutilized space into active revenue-generating research space.

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In Fiscal Year 2022, the Research community had a productive year of renovations. Forty-five renovation projects were underway with a total budget of \$55,057,483. RSMG completed twenty-three projects this year, including the multi-phased I3/IBC program that expands over two floors at CNY-149. The completed projects had a total budget of \$29,491,019. Multiple projects are expected to be completed in 2023.

Fiscal year 2022 brought the third annual online certification of space, agreements, and people electronically in Insight. The 2021 asset tracking upgrades allowed for the 2022 certification of assets via Insight. This enhancement is critical to satisfying compliance with tracking capital equipment purchased with research funds. Since the inception of the original Research Space Management Data Base at MGH, RSMG has always kept an inventory of capital equipment purchases subject to frequent audits. The addition of Asset Certification to Insight brings complete transparency to the audit process and facilitates input from the Principal Investigator upon whom the responsibility for tracking capital equipment ultimately rests.

Research Building Management, led by Patricia Frederico, is a division of Research Space Management that oversees research building operations and is the primary contact for all research facility issues. Research Building Management operates a centralized glass washing core that serves over 75 Units and oversees developer rooms, CO2 tank farms, electronic bulletin boards, shared copy machines, and AV support for all research conference rooms. Monthly safety surveillance rounds are organized and conducted with other key support departments. Collaborative applications such as Zoom and Teams were completed in the Richard B. Simches research building. Further enhancements for the Charlestown Navy Yard are underway. New additions for 2023 include working with the Boston Fire department to improve lab safety and cleanliness and continued monthly training for new employees in the proper procedures for using research autoclaves.

Animal Care and Compliance—Donna Matthews 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-1/BL-2/

BL-3 rodent facility that supports the Ragon Institute in Cambridge, MA, and a rodent facility at 65 Landsdowne Street. The MGRI animal program maintains a contractual agreement with Tufts University College of Veterinary Medicine, North Grafton location, to offer relief housing for livestock. In collaboration with our MGB partners, MGH is working with McLean Hospital and Boston University for additional NHP housing space and CRL for rodent breeding space.

The Center for Comparative Medicine (CCM) is the central laboratory animal care service for MGRI investigators and is led by Donna Matthews Jarrell, DVM, DACLAM, who also serves as the MGH Attending Veterinarian. CCM facilities are located on the Charles River Plaza campus, the Charlestown Navy Yard Campus, and the Cambridge Campus. Its activities include husbandry, animal procurement, importing and exporting mouse lines from other academic institutions, inter-institutional transportation, preventive and clinical veterinary care, training in animal manipulative techniques, surgery and post-operative support, mouse breeding and colony preservation, and consultation in animal modeling and protocol design. There are approximately 130 employees, currently including four staff veterinarians (all of whom are board-certified in laboratory animal medicine) and a leadership team of 27 mid- and director-level managers, who provide these services throughout the MGRI. CCM also supports the development of laboratory animal veterinary specialists through their Laboratory Animal Medicine and Management (LAMM) residency, the first residency with an equal focus on clinical medicine and program management in the country. This residency is recognized by the American College of Laboratory Animal Medicine (ACLAM) as well as MGH's Graduate Medical Education (GME) Program.

Specific CCM efforts taken in 2022 are noted below:

Over the last 3 years during the COVID pandemic, CCM in partnership with the MGH IACUC has continued to ensure high quality animal care and validated regulatory compliance despite significant staffing challenges. Census management, especially related to the rodent population, were heavily managed against the personnel resources available. CCM and IACUC Leadership met a minimum of weekly throughout the pandemic and CCM senior leadership met 3 times a week to prioritize how all resources and operations would be utilized. Over the past year, CCM was able to manage demand and supply in a manner that research was not halted.

In partnership with the Executive Committee of Research's (ECOR) Subcommittee on Animal Resources (SAR) and MGB's Chief Academic Officer (CAO), CCM was

able to contract with Charles River Laboratories (CRL), Transnetyx and Vivalytics to offer researchers additional rodent breeding colony management services including breeding software tools, project management expertise, genotyping, cryopreservation, and off-site housing. It was CCM's intention, along with the other MGB animal care and use programs, to provide researchers with the necessary resources to manage their census and thus their costs during these challenging times.

CCM's financial performance was impacted by unexpected escalating supply costs at the beginning of the year but was able to recover at the end of the year through a robust vendor management program. Additional costs controls were instituted through the Center's lean/agile culture of continuous improvement and reduction of waste. The utilization of a more efficient "spot-changing" rodent cage change program helped to balance the workload of each frontline veterinary care staff employee. This new Guide-related performance standard was published in the peer-reviewed Journal of the American Association of Laboratory Animal Science (JAALAS) in November 2022 (<https://www.aalas.org/publications/jaalas/digital-editions>). Elimination of non-valued added activities and process improvements over the past 5+ years stabilized the Center's financial performance so that no additional Hospital subsidy was necessary.

CCM also prioritized Diversity, Equity, and Inclusion (DEI) initiatives through the CCM Be Better Program first launched in 2020. Systemic investigation into policies, practices and behavioral expectations were evaluated through a DEI lens. Several initiatives were completed that provided a positive impact included a career ladder expansion for the frontline care staff; revision to the Center's attendance policy; qualitative and quantitative assessment survey—provided in 5 different languages - of all CCM staff measuring their opinions on inclusivity, belonging and safety during the last year; and the hosting of administrators, faculty and program managers from four historically black colleges and universities (HBCUs) with biomedical research programs and/or biomedical career undergraduate degree programs, providing both management support and lean belt certification educational materials for biomedical science undergrads. The latter initiative was provided in partnership with the Vivarium Operations Excellence Network (<http://www.voenetwork.com>) which MGH served as an organizational founding member.

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 over 30 members including veterinary staff, IACUC administrators, research investigators from many departments and research centers throughout the MGH Research Institute, and four community/non-scientist representatives. Dr. James S. Allan, Associate Professor of Surgery, assumed the role of IACUC Chair this year (formerly IACUC Associate Vice-Chair) following the passing of beloved Dr. Zapol. Jim is supported by Mark Randolph MASc, Director, Plastic Surgery Research Laboratory, IACUC Vice Chair (formerly IACUC Assistant Vice Chair). The professional staff office supporting the IACUC is the Office of Animal Welfare Assurance (OAWA) and is led by Anne Clancy, PhD. The office welcomed a new member this year, Carolyn Fader, BS, CPIA, IACUC Regulatory Compliance Specialist. Carolyn partners with Dr. Adria Colletti, IACUC Compliance Lead for the compliance arm of the IACUC office.

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. Annual Reports to all regulatory agencies were accepted without concern and we also successfully renegotiated our Assurance with OLAW this year, which is required every 4 years. A new Commissioner was appointed in the City of Cambridge this year. Dr. Bryant Hall met with the IACUC leadership to help establish a successful partnership for our facilities located in Cambridge.

Specific IACUC Efforts in 2022

A primary role of the IACUC is the review and approval of IACUC applications. Currently, there are over 900 active protocols being performed by over 370 Principal Investigators. The number of transactions approved by the IACUC continues to increase each year, a trend that continued this year. Over 3,200 transactions were processed by the MGH IACUC in the past fiscal year, comprised of new protocols, triennial reviews, as well as scientific and study staff amendments. The OAWA partnered with the IACUC to meet the volume demand while maintaining turn-around-times to support research. Complete metrics data for the MGH IACUC are available on the Partners Research Navigator website, Research-Analytics-Reporting.

OAWA participated in a number of process improvement initiatives to increase efficiency to meet workload demands

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and to promote collaboration throughout the MGB community including: (1) implementation of an animal laboratory space request process to improve transparency and standardize the request & review procedure; (2) distributed a protocol preparation guideline document at the time of protocol submission to promote successful submissions and faster reviews; (3) collaborated with Occupational Health Services to improve the documentation process for animal research clearances; and (4) improved communications to streamline the Facility access process.

Also, of note for 2022, the OAWA published four editions of the quarterly IACUC newsletter as part of our outreach efforts to partner with the research community, and OAWA, with CCM and the research community, met quarterly as the Animal Research Community (ARC) group to review animal research best practices, discuss new tools and resources and review non-compliance examples. The end of this year saw a significant reduction in the number of non-compliance incidents reported to the Federal agencies.

Research IS Support—Misha Pivovarov, Director, Research IT Solutions

In FY22, the Research Institute continued to support IS needs of project teams across MGH and MGB. Misha Pivovarov, Director of Research IT Solutions, continued to coordinate IS activity between MGH researchers and MGB IS. Much of the work is done by IS working groups involved in numerous tactical projects (e.g., web support, software selection, software development, policy/procedural issues, etc.) as well as major strategic initiatives. These working groups are now interacting with research leadership to identify and implement solutions and infrastructure to best support the research community's cutting-edge and dynamic technical needs.

COVID-19-related projects continued to dominate in research IS during FY22. With remote work becoming a new normal, Research Institute supported departmental IS teams that worked very hard to enable and optimize remote work by providing hardware and software support. New online systems were developed and implemented to support a hybrid workforce that helped COVID Safety Officers, and departmental managers achieve >95% compliance with policies.

In FY22, progress was made in several areas under the individual working groups.

- **Communication:** Two streams of communication have been established: a) departmental IT administrators are organized in a user group that provides feedback from departments to define requirements, propose solutions,

and implement policies; b) regular communication channel with MGB IS leadership serves as a venue for forming a unified approach on strategic initiatives as well as on day-to-day operations.

- **COVID-19 Projects:** (a) developed several online modules for managing access to research space, monitoring COVIDPass compliance; (b) added additional data feeds to a comprehensive database of people with training information loaded from multiple MGB systems; (c) built online information gathering module to facilitate CCM processes during new COVID-19 surge.
- **Applications for Research Administration:** (a) developed a new web-based system to track and monitor intra-hospital shipments of biological samples for research; (b) continued enhancement of the HR online evaluations and continued to roll out across all MGB institutions (c) deployed MGH Help and Safety App for mobile phones and made it available to the entire MGH community
- **Work on Applications for Research Training and Education:** (a) established an electronic interface (API) with the new learning management system managed DCR (Open Courses); (b) started working on the project to redesign new-hire orientation questionnaire and required courses assignment.
- **Infrastructure Improvements:** (a) continues to work with MGB IS to enhance infrastructure platforms such as email, computing, and storage options for researchers (b) working with MGB information security and network security teams to develop and implement policies, standards, and procedures for enabling secure and friendly computing environment (c) negotiated an agreement with AWS and NIH (via Four Points Technology, LLC) that covers all MGB research projects under NIH STRIDES initiative.

Research Compliance—Kelé Piper, Director, Research Compliance

Research Compliance operates under the NIH compliance model of the Seven Elements of an Effective Compliance Program with a focused approach to compliance rather than operations. A key component of this approach is to have a strong partnership with the research community which has been a concerted focus of our program. I believe this type of relationship is key to our success in getting a compliant outcome.

This year, we conducted our second research risk assessment which demonstrated significant improvements in areas that had been identified as high-risk areas in 2020 now being identified as areas of low risk in 2022. The risk

assessment allows us to work from a risk-based workplan proactively addressing issues that pose the greatest risk to the institution.

In FY22, we have been able to accomplish some very important initiatives. A few examples are described below:

- With the implementation of **iLog, MGH's Controlled Substances Database**, we have been able to complete approximately 60 proactive audits to assist labs with their controlled substance compliance in preparation for DEA audits that we have been told are going to start randomly occurring. We continue to make progress on Phase II of this project as we collaborate with Workday developers to place better controls for purchasing, receipt, and delivery of controlled substances. iLog builds have been completed and tools have been modified to expand the MGH controlled substances infrastructure to four MGB hospitals. We hope to have this implemented in early 2023. Both the DEA and Massachusetts Department of Public Health (MA DPH) consider us the gold standard.
- **Research Misconduct:** In 2022, we saw 7 new cases of research misconduct and closed out 9 cases. Cases with federal funding are then forwarded to ORI where they review our findings. They have the option of agreeing with our determination, opening their own investigation, or declining to do anything. These cases remain active until we have an ORI determination. Once they close the record, we maintain the documentation for 7 years. In 2022, we received 3 notices from ORI in which they agreed with our determination officially closing the cases.
- **Transportation of Biological Specimens:** In FY22, we launched BioLift, a new app to schedule and track the transport of biological samples using internal resources. Currently, we have routes between main campus and CNY and main campus and Ragon Institute; however, we will be continuing to monitor this process to determine expansion needs. For the most part, this solution was implemented with existing resources outside of purchasing the incoming and outgoing boxes and the development of the BioLift app. The link can be found on the Help and Safety APP.
- **Minors in Laboratory and Research Spaces:** Research Compliance assembled a multi-disciplinary workgroup to rewrite the policy and develop an onboarding process to include an intake form and parental consent form bringing us into compliance with state and federal laws and regulations. An app was developed to operationalize this process which includes approvals from key stakeholders in high-risk areas and HR. We will now be able to track and account for all minors on our campus.

- **Research Survey:** Eliminating a one-size fits all approach to training, the research survey is a great tool to customize training to the job and role that will be performed. At orientation, anyone in a research role is required to take the research survey. This year we moved it to the new Open Courses platform, but also made a number of upgrades and improvements to improve the user experience as well as make it easier to monitor for compliance. We expect the launch of the new platform in early 2023.
- **Exit Out Packet.... coming soon!** Again, we worked with groups from around the system to update and create what is now a paper process into an electronic format in Insight. While still with the developers, we are hoping for the build to be complete in the first quarter of 2023. This new process will allow for a consolidated approach when researchers leave the institution. The new modules will identify the areas in which the research has an interest or activities to allow for transition or closure of those activities prior to the researcher leaving the institution. This electronic process will allow for approvals to occur simultaneously with final reviews by the Department Administrator, Chief and the Sr. VP.

For FY23, we are looking forward to making improvement in the onboarding and offboarding of non-employees, data storage and security, and the ordering, receipt, and delivery of controlled substances.

Center for Innovation in Digital HealthCare (CIDH)—Sara Silacci; Shawn Murphy, MD, PhD; David Y. Ting, MD, FACP, FAAP

In FY22, the MGH Center for Innovation in Digital HealthCare continued to serve the MGH digital health innovation and research communities along four missional themes of **guidance, support, advocacy, and promotion**. Ms. Sara Silacci continued in her role serving as Chief Strategy Officer and Senior Managing Director for CIDH, and David Louis, MD, MGH Chief of Pathology, continued to serve as the Executive Sponsor, and was joined by Harry Orf, PhD, Senior Vice President for Research at MGH, whose call to action in this report in 2018 led to the formation of CIDH in early 2018. The number of CIDH staff remained flat for the first time since launching. CIDH also retained operational oversight in support of the academic mission for MGH's Health Data Initiative (led by Tom McCoy, MD) and Medical Device Plug'N'Play lab (led by Julian Goldman, MD).

With faculty Co-Directors, David Ting, MD, Chief Digital Health Officer for MGH and Shawn Murphy, MD, PhD, Chief Research Information Officer at Mass General Brigham

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(MGB), along with Keith Jennings, Chief Information Officer for MGH/MGPO and Ye Chin Lee, Vice President, Strategic Research Operations at MGB, CIDH, has begun to informally expand its service capabilities across the Mass General Brigham research community, supporting investigators from Brigham and Women's Hospital, Mass Eye and Ear, and Spaulding Rehabilitation Hospital. In partnership with the Brigham Health Digital Innovation Hub (iHub), Mass General Brigham Digital Health Innovation (DHI), and MGH innovation labs such as the Healthcare Transformation Lab, Center for Innovations in Care Delivery, Springboard Studio, and the MESH Incubator provided support for members of the MGH and MGB research community seeking to align their research and innovation portfolios with System strategy.

At the time of this report, CIDH leadership is working in close partnership Adam Landman, Chief Information Officer and SVP for Mass General Brigham Digital, to more formally integrate CIDH, iHub and DHI under a newly formed program, Mass General Brigham Emerging Technologies, and Solutions (MGBETS). MGBETS stemmed from a call to action from leaders across MGB and the AMCs to better coordinate and scale the unique services currently offered by the three founding teams and create more streamlined processes and governance to increase revenue and throughput for the MGB research and innovation community, as well as the external partners looking to engage with MGB. CIDH will lead "Research Acceleration," one of three primary domains within MGBETS. The other two domains are "Clinical Operations Acceleration" and "Emerging Technologies and Custom Solutions."

Since launching in FY19, CIDH has facilitated over \$45M for industry sponsored research collaborations, as well as government and philanthropic grants. CIDH's transactions also include five royalty-bearing licenses and equity positions (projected revenue is not included in the total above). Importantly, CIDH's has now served 1,800 clinician-researchers and staff from over 90 departments, centers, programs, and labs from across Enterprise.

Furthermore, in FY22, CIDH accomplishments may be further detailed along its four missional themes and overarching goals:

CIDH guides MGH innovators around how to develop, safely experiment, implement, operationalize, and commercialize validated digital health solutions.

Leverage MGB's investments in Digital Health, and technology advances to help MGH achieve its mission.

- CIDH's Research and Innovation Acceleration team (RIAT) restructured CIDH's internal consultation service to provide concrete structured guidance within a set time-frame to researchers and innovators in need of long-term or more complex "hands-on" guidance and support
 - 48 innovators, from 16 unique clinical divisions, participated in this service, and rated it 5-stars.
- CIDH launched a monthly Digital Health Journal Club in September 2021 to MGH "friends and family"
 - Formed to discuss the latest DH scientific literature
 - 26 active members, 15 articles reviewed in four major topic areas including Operations, Behavioral Health Modification, Clinical Decision Support Tools, and Data Platforms
 - In FY23, the Club will now be opened up to the entire MGB research community.

CIDH supports MGH innovators seeking resources to enable and accelerate digital health experimentation or solution implementation within MGH, and at scale across the Enterprise.

Maintain MGH's position as a leader in healthcare innovation by facilitating complex collaborations across the MGB and greater healthcare and academic ecosystem.

- The Smart and Autonomous Medical Systems CORE within CIDH, led by Dr. Julian Goldman. SaAMs is also a designated Massachusetts eHealth Institute "Sandbox," was awarded two State-sponsored awards to provide an environment for cybersecurity and interoperability innovation for two MA-based start-ups.
- The CIDH Strategic Alliances project execution team drove project engagements for clinical-researcher faculty across multiple departments:
 - Becton Dickinson's "Intelliport" device validation (Anesthesia)
 - Fern Health-MGH co-development of pain management apps (Anesthesia, Neurology, Patient Care Services, and Psychiatry)
 - US Health and Human Services sponsored study to evaluate barriers to market-entry for Israeli and US healthcare startups
- In support of testing and selecting new technologies for MGH's physical sites and the new building, in partnership with MGH Planning, CIDH's Cambridge Street Project team launched three pilots to evaluate technologies relative to wayfinding, real-time location tracking, and inpatient entertainment/education.

CIDH advocates for MGH innovators and MGH-led digital health initiatives, collaborations, and innovations within MGH and at the Enterprise level.

Create academic and educational programs that promote MGH and MGB digital healthcare and prioritize improving equity in clinical outcomes.

- CIDH's Research and Innovation Acceleration Team (RIAT) launched the first and second class in of a three-part curriculum
 - Initiated in response to an education and training “gap” identified by research leaders within the MGHRI
 - 81 research and study staff have participated in the course which was rated 4.9 overall by attendees
 - Given the program has been successful at MGH and we are expanding the offering to the Enterprise (will need to be adapted based on the site-based support teams and policies).

Newsletter:

- Published 12 issues of the CIDH Digital Health Digest
- Maintained open rate at the healthcare industry average, 35% or above, using Constant Contact reporting.

LinkedIn:

- Promote Innovator Spotlight Series, digital health research and thought leadership, relevant events
- Grew following and maintained CIDH as the most followed LinkedIn page at MGH after MGH
- Gained 1,508 new followers, 3,724 page views, and 134 new posts.

CIDH promotes new and existing strategic digital health initiatives, collaborations, and innovations led by MGH innovators both within MGH, and externally.

Organize collaborations that **connect MGH digital innovators and researchers** with industry, **while diversifying revenue streams** through industry-sponsored research and commercialization.

The CIDH Strategic Alliances team facilitated a number of engagements between MGH researchers and external sponsors:

- The Ether Dome Group for Entrepreneurship (EDGE) Corporate Member pipeline expanded to 10+ large pharma and med device prospects; managed opportunities from introduction through program scoping with AstraZeneca, Takeda, Boehringer Ingelheim, and Boston Scientific

- Engaged with Health2047, AMA's Silicon-Valley-based Venture Studio, to partner on co-development projects
- Launched the Hospital Integrated Research Organization (HIRO) to better enable patient clinical drug trials with Clinical Research Services and Clinical Trials Agreements in place to support Industry-initiated drug trial pipeline. Supporting cohort feasibility studies and prospective trial design to optimize enrollment
- Conducted ~80 intakes with early-stage companies to evaluate emerging technologies and to support MGH faculty with vetting industry opportunities
- As part of MGB's commitment to MassChallenge Health Tech (MCHT), coordinated with iHub, DHI, and other MGH/MGB innovation groups to evaluate startups; engaged as advisor to Delfina, a pregnancy care management platform.

Mass General Brigham Research Departments

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

Ravi Thadhani, MD, MPH, the Chief Academic Officer (CAO) for Mass General Brigham and Merranda Logan, MD, MPH, the Associate CAO, work closely with senior research leadership across the Mass General Brigham 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, Ross Zafonte, DO, President and former Senior Vice President of Medical Affairs Research and Education at Spaulding, Michael Gilmore, PhD, Chief Scientific Officer at Massachusetts Eye and Ear, and Nara Gavini, PhD, MPhil, Associate Provost for Research at the MGH Institute of Health Professions, 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 Mass General Brigham CAO works closely with the MGHRI and its scientific director, Sue Slaughaupt, PhD and ECOR leadership. The office of the Mass General Brigham CAO directly oversees several departments that support a ~\$2 billion research enterprise including the IRB, Research Management, Research IS & Computing, the Clinical Trials Office, and Personalized Medicine (Mass General Brigham Biobank and associated research cores). Together, these offices provide critical infrastructure that enables an efficient and innovative research enterprise. Research infrastructure at Mass General Brigham also includes Research Compliance and the Biosafety Office to

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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 five areas: (1) the Institutional Review Boards (IRBs); (2) the IRB Office supporting the IRB operations; (3) the Compliance and Education Office (C&E Office), (4) the Research Navigator Office (RNO), and (5) the Human Embryonic Stem Cell Research Oversight Committee (ESCRO).

The HRA provides oversight of all research involving humans conducted by Mass General Brigham employees and oversees the Human Research Protection Program (HRPP) that is accredited by the Association for the Accreditation of Human Research Protection Programs (AAHRPP).

As HRA supports the large and complex Mass General Brigham research portfolio, it constantly encounters advances in science and research that present new ethical and regulatory challenges. New challenges of risk/benefit analysis that must be addressed include research in genetics, big data, data sharing, mobile apps, artificial intelligence, and gene therapy. The COVID-19 pandemic has given rise to new approaches to research review and flexibility in the conduct of research including expansion of research conducted virtually or remotely and a new recognition of the importance of efforts to diversify research populations, the research community and to prioritize inclusion and equity in research. 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 subject 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), unanticipated problems, and noncompliance with the approved protocol. Details of each of these reviews are mandated and informed by federal regulations and policies, state laws, and in some cases the conditions of grant awards. IRB review requires close coordination and communication with Research Management, the Clinical Trials Office, Office of General Counsel, Office of Interaction with Industry as well as Mass General Brigham- and institution-level sign-offs and ancillary reviews.

IRB Office: The IRB 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 determinations under the federal regulations for research that is exempt from IRB review and research that falls outside of the definition of human subject research. The IRB Office also provides education and support to the research community, maintains policies and procedures, and documentation required by the federal regulations.

HRA IRB and HRO Activity 10/1/21 - 9/30/22 (FY22) (Includes Initial Review, Continuing Review and Amendments)

Full Board Review	1,871
Expedited Review	23,724
Cede Review to a Non-MGB IRB (Does not include ceded protocols to Dana Farber Cancer Center)	304
Administrative Action	1,834
Total	27,733

*Does not include an additional 19,259 Staff Amendments that are auto approved by the Insight system on submission.

C&E Office: The C&E Office 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 C&E staff work 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; support sites through external audits (e.g., FDA inspection); provide specific training for holders of investigational drug and device applications from the FDA; support study teams with educational activities including study specific consultations, provide Regulatory Binder consultations, and present at numerous department and institution educational sessions. In addition, the C&E Office administers the ClinicalTrials.gov program required for compliance with federal law.

HRA C&E Office Activity 10/1/2021-9/30/2022 (FY22)

Type of Activity	Number
Audits	102
Targeted Audits	82
Study Start Up Assessments	7
Consultations	280
Presentations/education	120

RNO: Initiated in July 2021, the RNO staff, called “Research Navigators” provide support to patients and community members who call into the live help line with questions about research in general or specific research studies. The RNO Research Navigators are also available to Mass General Brigham clinical staff and outside physicians who are working with patients who wish to know about research, to enroll in our research studies, or who have patients to refer for recruitment in research studies. The contact information for the Research Navigators is provided on all Mass General Brigham research invitations that are distributed through Patient Gateway or via mail services. The RNO is also a resource available to our researchers and their staff through the help line or email.

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.

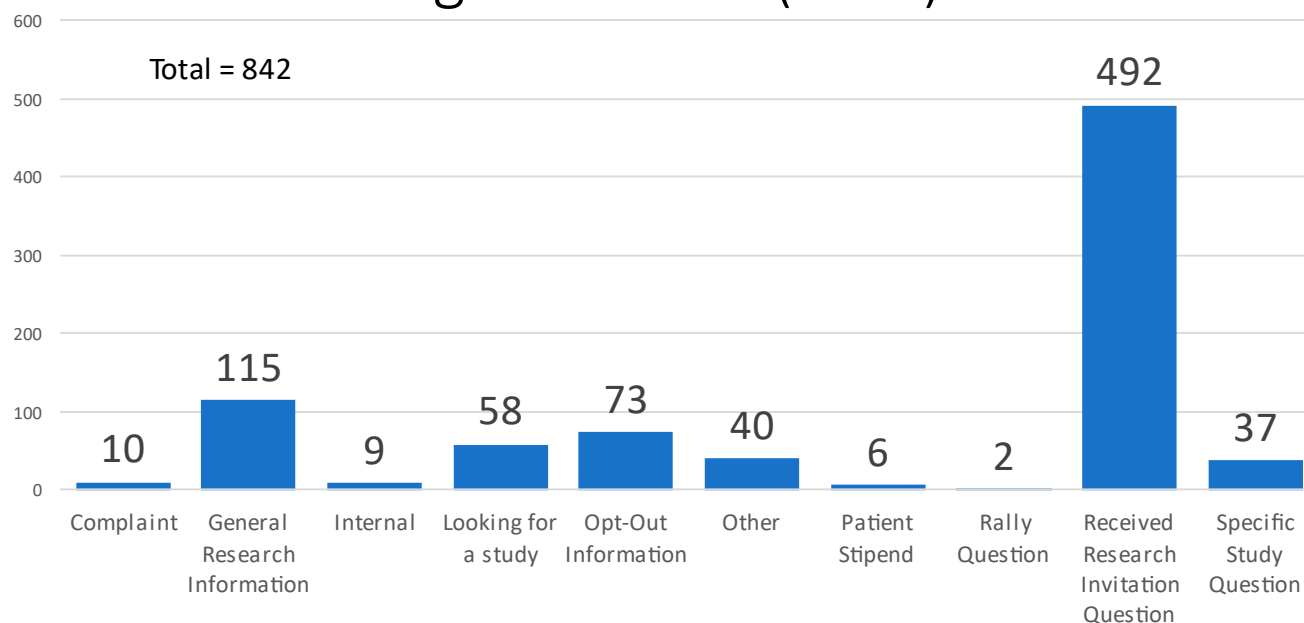
In summary, the health of the Mass General Brigham research enterprise relies on our ability to conduct safe, ethical, compliant, and leading research. The entities within the HRA are critical to support these areas in collaboration with the research community.

Clinical Trials Office—Stephen D. Wiviott, MD, Vice President, Clinical Trials Research and Administration

The Mass General Brigham (MGB) Clinical Trials Office (CTO) serves to facilitate, support, and expand the conduct of clinical trials at MGB through service excellence and effective collaboration between investigators and industry sponsors. The CTO is responsible for services to the MGB research community including contracting and budget development/negotiation for clinical trials sponsored and/or funded by industry, billing, and a clinical trials management system (OnCore). 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, MGB provides 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 MGB hospitals’ scientific mission.

The Clinical Trials Office had a highly productive year in support of MGB investigators again this year. Overall volume of executed agreements remained steady between FY21 and 22; an 18% increase from 2020 (Table). The CTO formally launched the Clinical Trials Central Billing Office (CBO) with two FTEs initiating this effort. To date we have 6 Principal Investigators participating in this program with 38 trials.

Research Navigator Office (RNO) Calls



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CTMS/ OnCore utilization continues to be an opportunity for improvement with focus on retraining staff on efficient usage by study teams. OnCore will be upgraded to V2021R3 in Q2 which will include fixes and enhancements ensuring the stability and improving application functionality. The CTMS team is updating the format and content of our monthly reports to provide additional clarity around clinical trials activity and finances. The integration of OnCore and PeopleSoft improved reconciliation of payments for clinical trial funds, however, industry sponsor automatic payments continue to present challenges for study teams. MGB adopted an automatic reconciliation process for FY23 where any available sponsor payments will be automatically reconciled to invoices that are older than 180 days.

The MGB research community utilization of Advarra Payments continues to grow—increasing nearly 10-fold since 2019. Advarra Payments in FY22 had a significant increase in payments made to study subjects. There has been a great demand in both the industry sponsored and non-industry sponsored clinical trials to use Advarra Payments.

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

Mass General Brigham Research Compliance Office

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 Mass General Brigham. 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 and machine learning on MGB-supported, privacy-aware, processing platforms at-scale. More information can be found on our website, <https://rc.partners.org>.

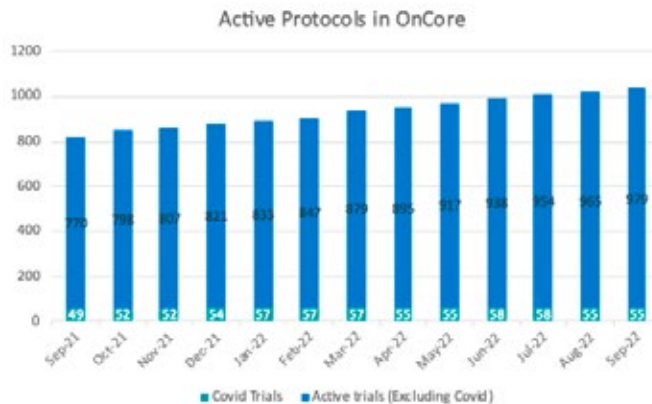
Queries against integrated healthcare data can be initiated through the **Research Patient Data Registry (RPDR)**, a centralized clinical data registry that gathers electronic healthcare data from across all Mass General Brigham institutions. With a self-serve query tool, researchers can define patient 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 almost 1840 scientists in a year, obtaining over 5,400 sets of EHR data in 2022. Calculated over 4 years the total agreement amounts attached to projects obtaining sets of data from the RPDR were \$2.27 Billion. 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 **MGB 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 MGB Biobank Portal,

CTO Executed Agreements Volume (all-MGB)

Agreement Type	FY22	% Change FY22-21	FY21	% Change FY21-20	FY20
Clinical Trial Agreements	375	-5%	396	8%	365
Amendments	794	20%	664	15%	579
Support & Other* Agreements	356	-13%	407	33%	306
Confidentiality Disclosure Agreements	672	-3%	695	-5%	731
Subcontracts	238	-17%	288	182%	102
Total	2435	-1%	2450	18%	2083

OnCore CTMS FY22 Status



857
Active
Users



259
Users
Trained

1335
Invoices
Created

1635
Payments
recorded

259
Protocols
Open to
Accrual

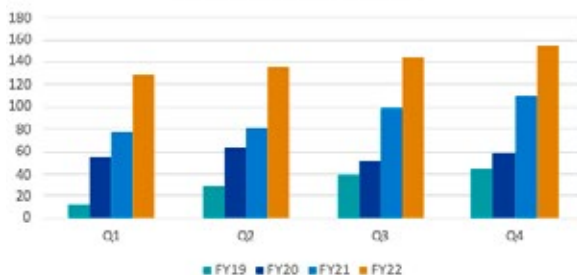


Advarra Participant Payments FY22 Q4 Status

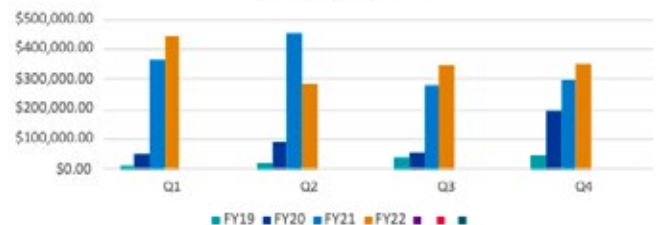
Active Protocols



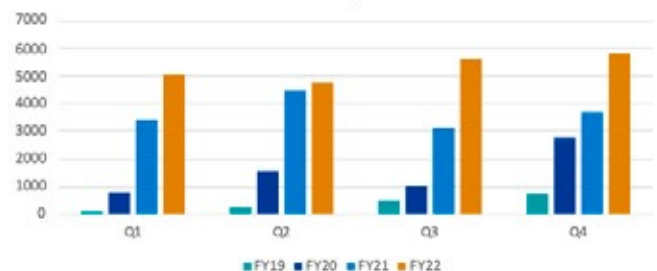
Protocols with Payments



Total Stipends Paid



Individual Payments Paid



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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 139,000 consented Biobank subjects. Another component of the Big Data Commons, the Clinical Image Bank, enables investigators to obtain DICOM images from Mass General Brigham PACS clinical image repositories for research and has served over 3 million images to hundreds of research projects. This year, the Big Data Commons also incorporated new device data; over 11 million EKGs are now available to the research community.

RISC's patient recruitment strategy continues to encompass several pathways to optimize the number of patients involved in research. Patients of the Mass General Brigham have the opportunity to learn about ongoing research that may be a good fit for them through invitations delivered by Patient Gateway. Since the start of this initiative, over 600,000 patients for 200+ studies have been identified and invited. Members of the public can search for studies and volunteer through **Rally with Mass General Brigham** (rally.massgeneralbrigham.org), a research portal for the lay public that presents studies in an attractive, lay-friendly, and informative format. In 2022, the site experienced over 90,000 visitors per quarter; since Rally's inception, over 120,000 people have identified themselves to over 1,600 studies using this system. Over 5,000 volunteers have taken the additional step of creating Rally profiles and present an ongoing opportunity for deeper engagement with our research volunteer community.

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 3000 scientists, \$295M in grants and 2000+ 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 MGB IS. We provide advocacy and guidance on behalf of research to the many enterprise projects that involve MGB Information Security, ITS, Network Engineering, Security, and other corporate departments.

The MGB Data Enclave provides secure collaborative workspaces within a secure environment with a shared set of computational resources. It provides access and tools for researchers to work on complex data analysis and machine learning, while adhering to policies for research and auditability for ~400 research access requests. Tools are preloaded for data analysis/ML including SAS, Rstudio, Excel, R, and others. This environment also allows for industry and 3rd party partners to work collaboratively on data behind institutional firewalls with the appropriate IRB approval and POI registration.

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), REDCap eConsent, LabArchives, and GitLab. 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. The team and tools support many researchers and projects including 19,500 active REDCap users; over 1,500 active GitLab users; and 14,000 LabArchives accounts. RISC REDCap supports over 6,000 MGB IRB protocols and 1,100 eConsent projects. The institution-wide Electronic Lab Notebook initiative maintained its 98% PI account activation rate, with the focus on onboarding new PIs into the system.

RECOVER (Researching COVID to Enhance Recovery), a research initiative from the National Institutes of Health (NIH) seeks to understand, prevent, and treat PASC, including Long COVID. Mass General Brigham researchers were selected to serve as the PASC Data Resource Core to support and contribute to the collection, coordination, and analysis of data collected on PASC patients, including COVID-19 "long-haulers," throughout the nation. The PASC Data Resource Core provides expertise on study design and facilitates the collection and analysis of standardized data across different cohort studies. The team is led by Andrea Foulkes, ScD, Chief of Biostatistics at Massachusetts General Hospital, Elizabeth Karlson, MD, MS Director of Mass General Brigham Personalized Medicine, and Shawn Murphy, MD, PhD, Chief Research Information Officer at Mass General Brigham.

Mass General Brigham Personalized Medicine (MGBPM)—Elizabeth W. Karlson, MD, MS, Scientific Director

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

1. Mass General Brigham Biobank
2. Biobank Genomics Core (BGC)
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.

Mass General Brigham Biobank: The Mass General Brigham Biobank (Biobank) is research infrastructure that provides biospecimens and genomic data to Mass General Brigham investigators. Patients are consented to join the Biobank across Mass General Brigham hospitals and community health centers. Their blood is collected and processed to DNA, serum, and plasma and the DNA is further processed to genomic data. The resulting biospecimens and genomic data are linked to a common electronic health record which spans all of Mass General Brigham. As of December 2022, 140,000+ participants have consented and 95,000+ samples have been collected. In addition, the Biobank has supported over \$633M in research activities through the distribution of Biobank samples and data as well as through sample management services, such as DNA extraction services.

The key value/services provided to Mass General Brigham investigators are:

- Access to a large cohort of patients who are consented for broad-based research and recontact. This includes a repository of COVID-19 patients and their phenotypic data.
- Access to DNA, serum, plasma, and PBMCS (for COVID-19 patients only). Since 2020 the Biobank collaborated with studies at MGH and BWH to recruit COVID-19 patients and collect, process, and distribute 17,000+ samples to Mass General Brigham investigators and, under the auspices of the Massachusetts Consortium on Pathogen Readiness (Mass CPR) consortium, to non-Mass General Brigham investigators.

- 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., lifestyle, family history surveys).
- Sample management services.
- Support recontact of Biobank consented participants for additional sample collection.
- GWAS data, exome sequence data, and imputed genomic data (65,000+ subjects).
- Support inventory, storage, and distribution of COVID-19 vaccines for Mass General Brigham hospitals and non-Mass General Brigham affiliated physicians.
- Support COVID-19 serologic studies across Mass General Brigham hospitals in recruitment and scheduling, sample processing and management, and data and sample distribution.
- Support COVID-19 vaccine clinical trials at Mass General Brigham in the form of reassignment of large numbers of trained staff.
- Participation in a NIH-funded longitudinal research cohort, the *All of Us Research Program*, which aims to consent over 60,000 participants in New England (as part of the larger goal of 1M+ participants) via a \$56.5M grant at MGH that includes BWH, Faulkner Hospital, Newton Wellesley Hospital and Community Health Centers, MGH Chelsea, MGH Revere, and BWH Brookside, along with Boston Medical Center.
- Participation in a NIH-funded research network, eMERGE IV, that aims to develop polygenic risk scores for 10 medical conditions and disseminate those risk scores in clinical practice at 10 academic medical centers and assess the impact of this genetic information on health care. The grant is for \$6.0M over 5 years plus \$1.3M in two supplements.
- Participation in a NIH-funded program to address Post-Acute Sequelae of SARS-Cov-2 infection (PASC) Data Resource Core (DRC), which create a robust Central Data Enclave with 40,000+ RECOVER cohort participants, generate robust and scalable embedded analytic tools, and support investigators on application of rigorous biostatistical methods for principled design and analysis of RECOVER adult, pregnancy, pediatric and autopsy cohort studies. The grant is for \$41M over 4 years.

Biobank Genomics Core: The Biobank Genomics Core (BGC) supports research groups (\$105M in grants annually)

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as well as system-wide Mass General Brigham initiatives such as the Biobank with the following cost-effective services:

- Next Gen Sequencing services using NovaSeq including whole genome sequencing, exome sequencing, targeted sequencing/amplicon-seq, RNAseq, and miRNAseq.
- Genotyping services including high density genotyping arrays on Illumina's Infinium platform (Global Diversity Array, Global Screening Array), genome wide methylation profiling (MethylationEPIC Array), and TaqMan single SNP genotyping.
- Additional NGS services include SARS-CoV-2 whole genome sequencing from nasopharyngeal swabs, 16S rRNA gene microbial profiling from blood, stool, and other sources, targeted methyl-seq.
- Sequencing and genotyping workflows optimized for MGB Biobank samples including DNA analysis and miRNA analysis from serum/plasma.
- Basic and advanced analysis options for genomic and expression analysis, in partnership with the Personalized Medicine Bioinformatics team.
- Integration with the LMM enables "clinical-grade" laboratory processes and procedures, such as nucleic acid extraction, genotyping, and sequencing.

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:

- Developing innovative clinical genetic and genomic testing for both clinical use and for genomic medicine programs including but not limited to genome and exome interpretation for indication testing or screening, pharmacogenomics (PGx), risk assessments, secondary findings, and polygenic risk scores.
- Participation in translational and clinical research grants, including leading laboratory and interpretation aims across multiple projects. High-profile current projects include eMERGE IV, BabySeq2, PopSeq, GenoVA, RADIANT, and the *All of Us Research Program*, where we lead the Variant Adjudication Committee. The LMM also supports multiple smaller translational and clinical grants.
- Managing MGB Biobank Return of Research Result (RoR) program, including identification and interpretation of actionable variants, coordinating with participants and clinicians, and clinical confirmation of results.
- Providing clinical confirmation testing for research studies

- Clinical interpretation services that advance MGB research activities and findings, including collaborations with BWH investigators (Bahrain Genome Project) and MGH investigators (MGH cardiology)
- Offering diagnostic and screening germline assays for internal and external ordering providers, including some that are not offered at other CLIA laboratories

Personalized Medicine IT and Bioinformatics:

Personalized Medicine IT and Bioinformatics teams supplies IT and computing support for the Biobank, LMM, BGC 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 MGB Biobank, LMM and BGC
- Develop functionality required to maintain near real-time programmatic access to patient genetic data for the LMM and MGB Biobank
- Advance the system needs for broad incorporation of genomic data into clinical and research activities.
- Develop and validate novel assays, pipelines, and interpretation infrastructure for the LMM and BGC. Recent activity includes launching one of the first clinical polygenic risk score assays to support the GenoVA Study
- Offer custom analysis for NGS data to MGB Investigators through the BGC, such as: genome/exome/panel variant calling and filtration
- Support data processing, analysis, storage, and dissemination of genomic data for MGB Biobank participants
- Support eMERGE development of processes for returning new types of clinical genetic results such as polygenic risk scores to study participants and providers

The movement towards whole genome sequencing (WGS) identifies and generates data on 3-5 million genetic variants per patient. New forms of IT support are required to effectively manage and process this increase in data velocity as research and clinical care use of WGS scales. Personalized Medicine has begun creating the support required to meet this need. We are migrating key bioinformatics pipelines to the cloud, designing for the latest database technology and preparing to support genome build 38.

Mass General Brigham Innovation—Chris Coburn, Chief Innovation Officer

Mass General Brigham Innovation is the business development unit responsible for advancing compelling new assets created by system faculty and accelerating their path to market through a set of services that drive commercialization, support innovators, increase asset value, and bring new revenue to the system all ultimately for the benefit of patients. Recent actions are designed to accelerate and grow commercial impact. Mass General Brigham Innovation is the largest academic organization of its kind with 130 staff that includes 2 MDs, 32 PhDs, 2 PharmDs, 20 JDs, and 29 MBA/MS/MAs. Its responsibilities include company creation, translational funding, venture investing, licensing, strategic alliances, and other research collaborations, and managing intellectual property including patent prosecution.

Investing for Growth

In the last decade, more than 300 companies have been established based in whole or in part on the work of Mass General Brigham investigators, with two-thirds of those tied to MGH. Founded in 2008, Mass General Brigham Ventures (MGBV) has more than \$450 million in capital under management. The venture capital team has invested in 55 companies, realized 15 successful exits, and produced top quartile venture returns. In 2021, MGBV closed on \$251 million for its third venture capital fund, including strategic investments from Eli Lilly and Fosun Pharma among others. The exclusive investment focus is on companies using technologies developed by MGH and other MGB faculty. Notable Mass General Brigham Ventures successes include CoStim, a pioneer in next generation immuno-oncology

drugs (acquired by Novartis), Editas Medicine, a market leader in CRISPR genome editing technology (NASDAQ: EDIT), and Keros Therapeutics, a leader in TGF- β directed therapeutics (NASDAQ: KROS).

Commercialization and business development involving digital technologies and corporate partners is a key strategic priority. As part of that, the Artificial Intelligence and Digital Innovation Fund (AIDIF), has made multiple investments in emerging digital companies bringing solutions such as data extraction and patient access that are being implemented at MGH and elsewhere in the system. A recent example is DexCare, a digital optimization platform that allows patients to access healthcare based on individual health needs, preferences, location, and schedule.

A system wide Gene and Cell Therapy Institute (GCTI) was launched in 2022 to maximize the extensive platform of basic research, translational science, and world class clinical care. The Institute positions Mass General Brigham to become the pre-eminent academic institution to discover, translate, and apply gene and cell therapies to improve the lives of patients.

Highlighting research and innovation from throughout the system and connecting Mass General Brigham faculty with industry leaders and top investors are the goals of the annual World Medical Innovation Forum (WMIF) June 12-14, 2023, now in partnership with Bank of America. This year's Forum agenda will cover oncology, CNS/brain health, and immunology and inflammation and include a broad view of innovation in these segments, showcasing MGB faculty and Bank of America's investment leaders.

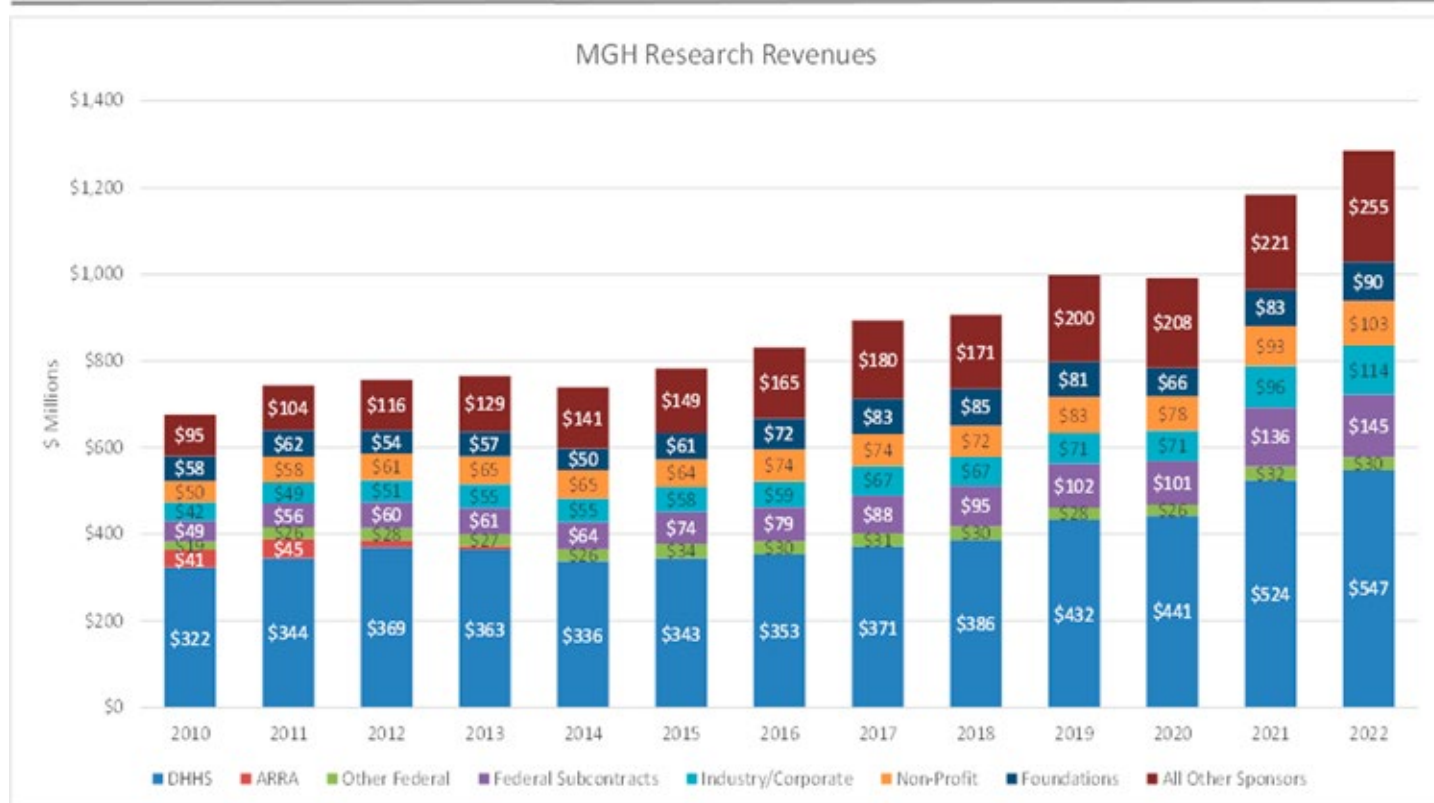
MGH Results

MGH Commercialization Outcomes	FY16	FY17	FY18	FY19	FY20	FY21	FY22
License transactions	130	133	198	197	145	191	160
Material Transfer	1,067	1,360	1,374	1,537	1,256	1,452	1,263
Inventions	365	311	366	355	384	362	373
Patents Filed (US & Intl)	910	1,091	1,643	1,593	1,483	1,325	1,272
Patents Issued (US)	126	136	150	165	149	162	128
Patents Issued (Intl)*	311	421	317	464	335	403	368
Commercialization Income	\$77M	\$87.7M	\$94.6M	\$298M	\$143M	\$84.9M	\$77.5M

Totals include the favorable impact of a pathology royalty buyout.

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

MGH Research Revenue Trends



Total MGH research revenues of \$1.28B represent an increase of 8% from FY21, driven by increases across DHHS, Federal Subcontract, and especially Industry and Internal sponsors.

Growing the Community of Innovators

Expanding the number and diversity of MGH innovators is a major priority. The Innovator Community Expansion Initiative (ICEI), was established to increase the output of commercially viable innovation to benefit patients and build an inclusive innovation community representing our entire workforce. It focuses on clinicians, early career researchers, women, and other under-represented groups. During the past year, dozens of MGH senior diverse faculty participated in development and networking sessions with senior industry leaders and investors to gain direct insights into company operations and governance.

As part of building the pipeline of innovators, the Commercialization, and Inclusive Leadership (CILP) program launched this year for new and potential innovators. MESH, originally launched at MGH, continues to expand as an innovation and entrepreneurship platform for MGB systemwide. The platform has more than 2000

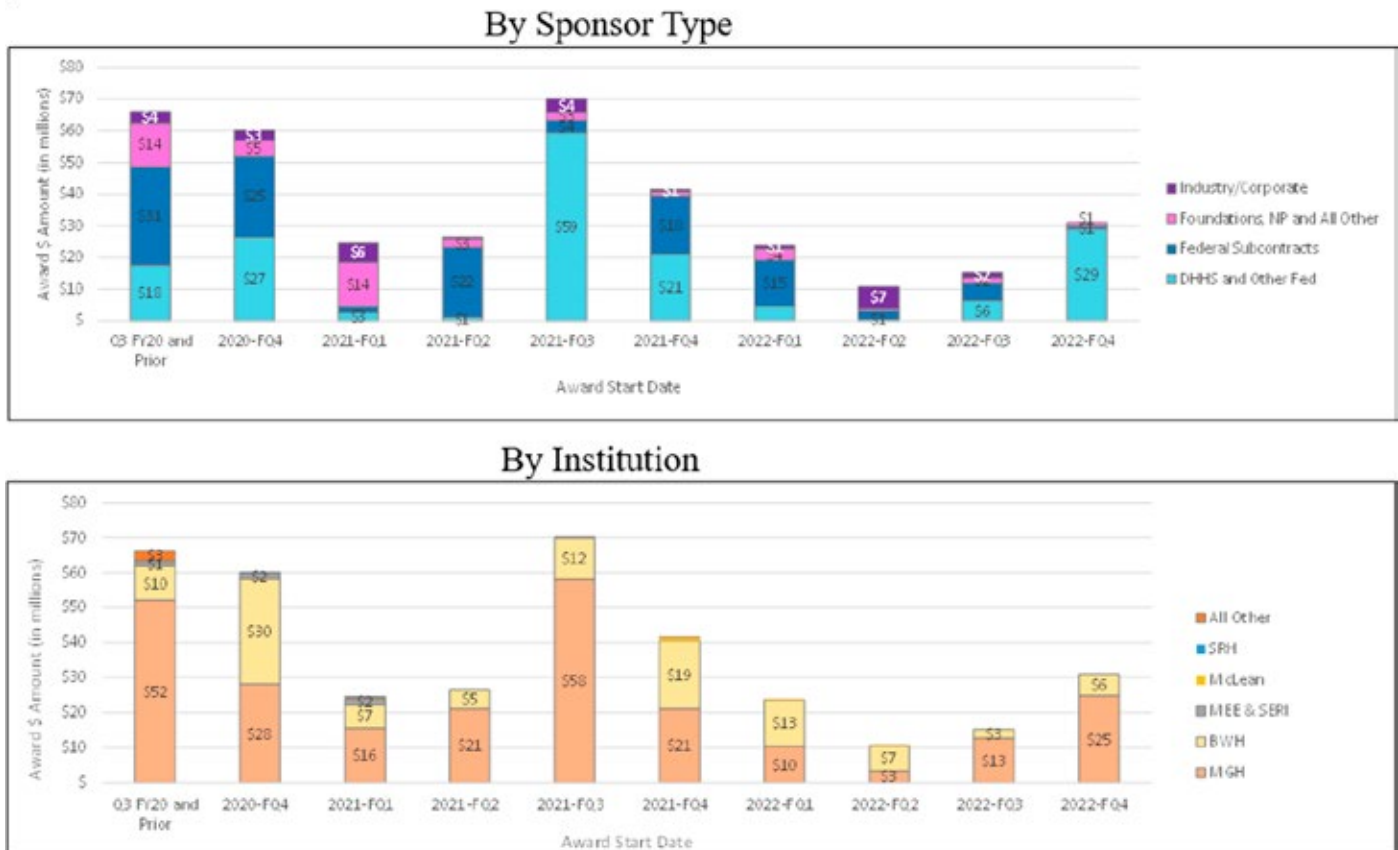
faculty/trainees registered, with nearly half from MGH. Its Innovation Bootcamp, a custom learning and networking system, has been viewed by over 2,500 users since its inception in 2021.

Mass General Brigham Research Management— Andrew Chase, Vice President of Research Management and Research Finance

MGB Research Management supports the MGH 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 oversight 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.

COVID-19 New Awards

by Sponsor Type, Institution and Quarter through October 18, 2022



New Covid-19 awards increased from \$15M in Q3 FY22 to \$31M in Q4 FY22. MGH and BWH continue to account for the vast majority of new COVID

As highlighted across all sections of this report, the MGH research community continued its success with another year of growth. MGH was the primary driver for the increase in overall MGB Research Revenue to \$2.2B, accounting for \$1.28B, an 8% increase from last year. MGH now represents 58% of the research activity across the Mass General Brigham system.

The significant growth in activity was seen across all sponsor types and occurred despite decreasing COVID related funding activity, which is now concentrated on a smaller number of larger projects.

The overall outlook for research remains very positive for MGH. MGH submitted 4,746 proposals in FY22. Although proposal submission volume was down 4% compared to last year, with NIH proposals down 4%, this was expected as it follows a 2-year stretch of significant growth in

FY20 (+9%) and FY21 (+5%) fueled by COVID related submissions.

Compliance with Federal regulations continues to require time and energy. Research Management's goal remains to minimize the administrative burden on the MGH Investigator community while promoting compliance with the NIH requirements. Last year attention was focused on operationalizing and monitoring compliance with the NIH Other Support disclosure requirements for domestic and foreign research activities. The significant efforts and investments made in education, tools, and Insight functionality helped prepare MGH and other MGB hospitals for the rollout of this new federal requirement. The investment in the insight system to prepopulate the NIH's other support form and allow for an electronic PI signature to document attestation to the accuracy of the

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information, have helped to reduce the administrative burden associated with the Other Support requirements.

In FY22 we had to also begin preparations for the New NIH Data Management and Sharing policy that will be in effect on January 25, 2023. All research that results in the generation of scientific data, and is funded or conducted, in whole or in part by NIH, must now include a Data Management and Sharing plan that includes sharing the data generated in a public repository. This new requirement represents a significant logistical challenge and cultural change for the research community. Working with MGB Human Research Affairs and MGB Research Compliance Teams, Research Management has been conducting outreach to the MGH research community to get perspective and recommendations on how to define the institutional approach to help investigators be compliant with the Data Management and Sharing requirements.

Research Management continues to think innovatively to address the increased workload and the ever-expanding federal compliance requirements as the research enterprise grows. Although this combination of increased volume and complexity has strained core operations, we continue to work collaboratively with hospital departments to develop tools that can help mitigate the increased workload. Last year we rolled out a new pending worklist for Hospital Departments that provides full transparency on the current status of any work item across Research Management in one dashboard. This includes the status of proposal applications and all the agreements and contracts that are in negotiation with sponsors and collaborators. Investigators no longer need to reach out to ask for the status of a contract negotiation as the information is

available to them in three clicks from the home page in Insight.

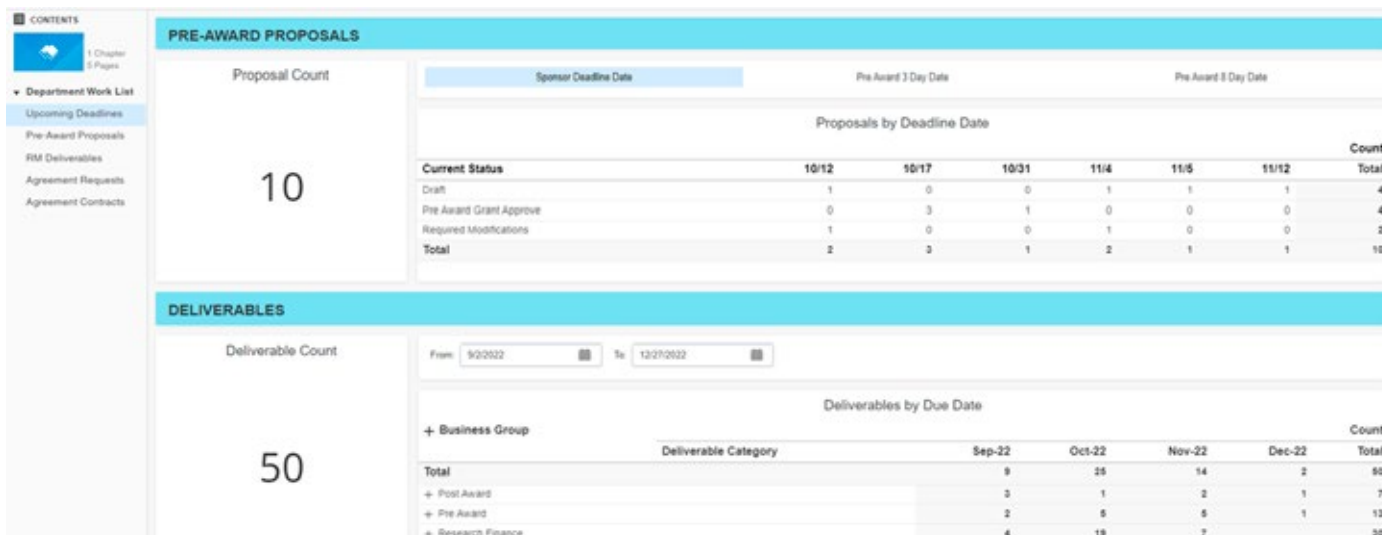
Research Leadership and Research Management have been heavily involved over the past year in the preparation for the implementation of Workday as MGB transitions from PeopleSoft to Workday as the core system for HR, Finance and Supply Chain functions. As research administrative and financial processes are embedded within all of three of these core functional areas, it is critical to address the unique needs of research and ensure that the functionality that has been built through PeopleSoft customizations or Insight functionality over the past 15 years is not lost when we move to the new system. This major project will become the primary focus for Research Management and most of the enterprise service functions over the next year and a half as we get closer to the targeted implementation in the summer of 2024.

Mass General Brigham Office for Interactions with Industry—Emily Sobiecki, Esq., Director

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

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

Sample Department Worklist Dashboard



- The **Professional and Institutional Conflicts Committee (PICC)**, a subcommittee of the MGB 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 most live cases that raise conflict of interest issues for MGB 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 MGB 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 MGB. 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 MGB fellowship programs or other MGB 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 MGB and Harvard Medical School conflict of interest policies. As part of its normal workflow, the Research Activities Section processes over 17,000 financial interest disclosures per year needed for compliance with the federal regulations and institutional COI 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 MGB policy and is responsible for obtaining COA and PICC review of outside activities of senior institutional officials. As part of its normal workflow, the Outside Activities section handles between 2300 and 2700 consulting and related agreements each year.
- The **Educational Grants** section oversees the receipt of industry funding in support of MGB educational activities, to ensure compliance with MGB policy. This section also has responsibility for handling gifts from industry to support research activities. As part of the normal workflow, the Educational Grants section handles between 150 and 200 grants, bringing in between \$5M and \$6M in funding, each year and collaborates with the

hospital Development Offices on the review of incoming gifts from companies to support research project. Over the past year, this section worked with the Development Offices on the review of 30-40 gifts constituting >\$10M.

- The **Systems and Education** section works with MGB 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 MGB community; maintains the OII web site; and coordinates the distribution of educational materials to the MGB community. As part of the normal workflow, the Systems and Education section handles the distribution and completion of annual disclosure forms to over 15,000 Mass General Brigham staff, and also facilitates the Conflicts of Interest in Research online training course for, on average, approximately 1500 faculty per year.

In addition to the activities detailed above, other key OII responsibilities include the review of conflicts arising in purchasing, procurement, and similar types of transactions; working with Departmental leadership on the review and management of complicated conflict scenarios involving MGB personnel taking on part-time employment with for-profit entities; and, coordinating with the IRB and COA on the identification, review, and management of institutional conflicts of interest.

OII continues to focus on integration amongst the four substantive sections of the office detailed above 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.

The fourth consecutive \$1 billion research revenue landmark reached in 2022 is a testament to the extraordinary group of leaders, faculty, and staff whose dedication has been so vital to maintaining our position as a preeminent biomedical research institution. Collectively, they are the culture of caring at MGH, they are responsible for all the progress documented in this report, and they will continue to rise to the challenges the hospital faces in the coming year. As I transition out of my position as SVP for Research, I want to again say that it has been an honor and a privilege to serve the hospital in this capacity.

Respectfully submitted,

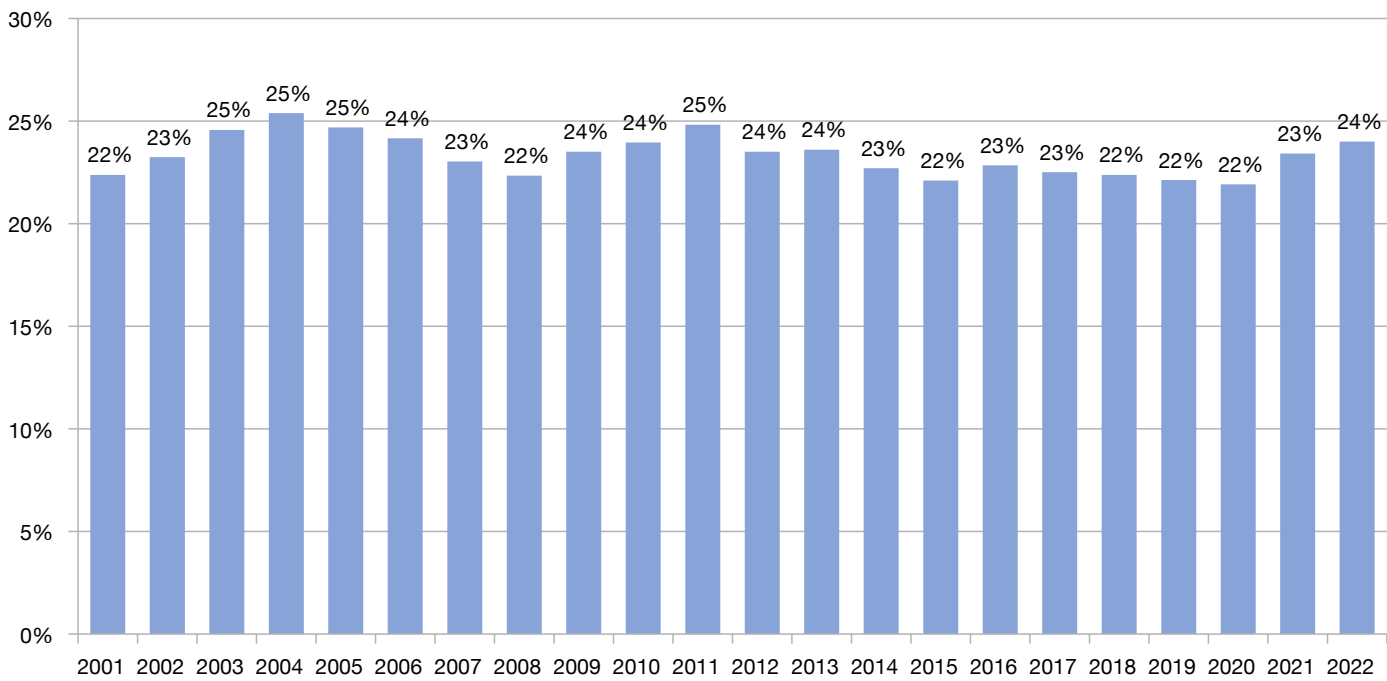


Harry W. Orf, PhD
Senior Vice President for Research
Massachusetts General Hospital

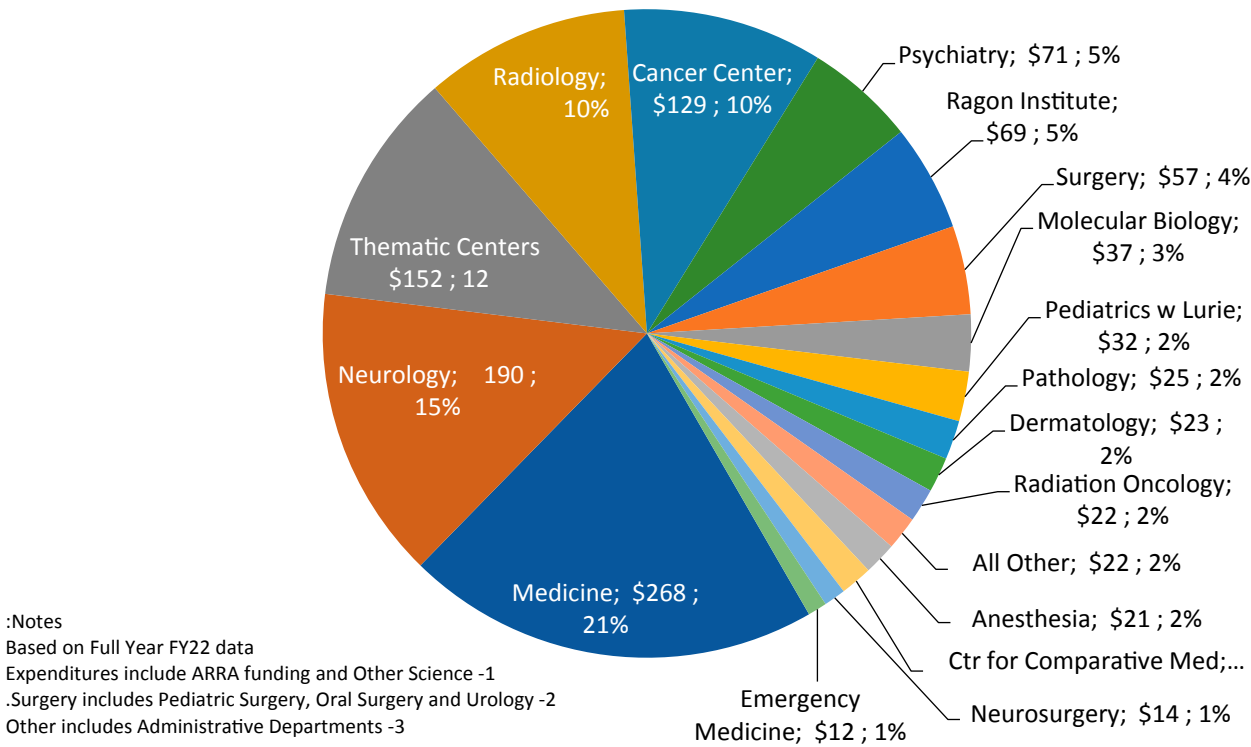
Massachusetts General Research Institute

Executive Report

MGH Research Revenue as a Percentage of Total MGH Operating Revenue
FY2001– FY2022 Actual



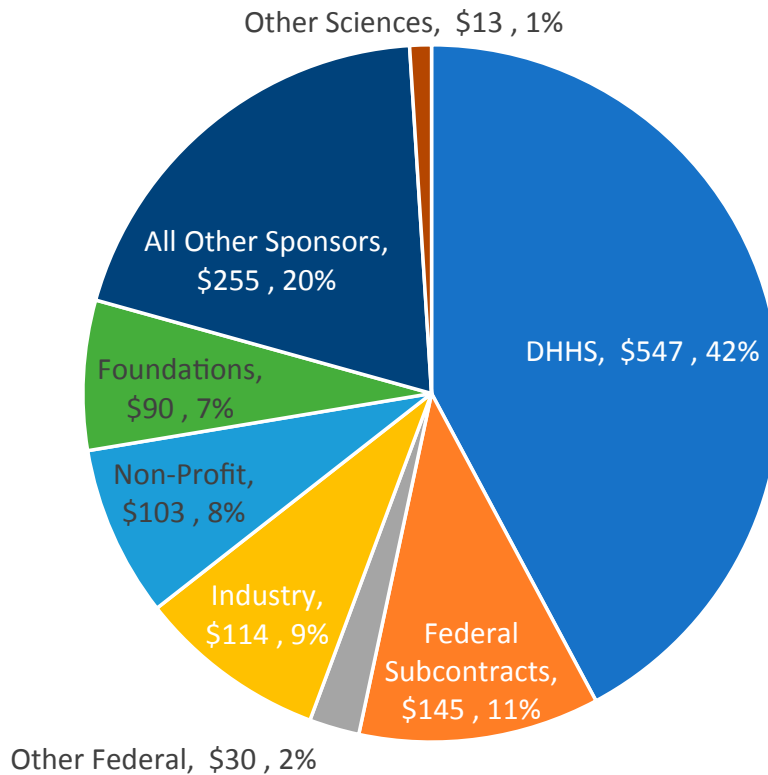
FY 2022 MGH Research Expenditures by Department Direct & Indirect Expenditures \$1,297M (\$ Millions)



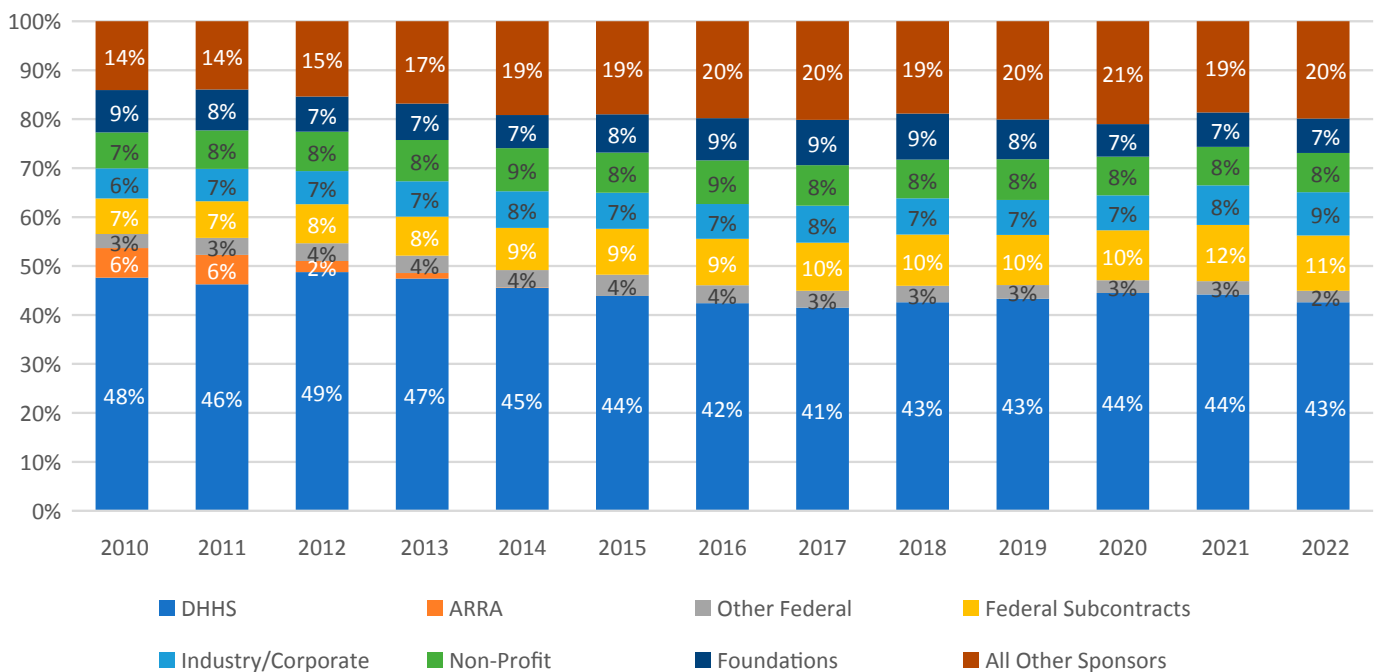
Massachusetts General Research Institute

Executive Report

FY22 MGH Total Research Revenue by Sponsor = \$1,297 M (in millions)



MGH Research Revenue Sponsor Mix



Massachusetts General Research Institute

Executive Report

MASSACHUSETTS GENERAL HOSPITAL Science Activity by Sponsor			
Type of Activity	'Fiscal Year 10/01/21-09/30/22		
	Direct	Indirect	Total
Federal & State	424,768,923	164,175,293	588,944,216
Non-Federal	574,942,073	133,097,083	708,039,156
Total Expenses FY 21	999,710,996	297,272,376	1,296,983,372
Analysis of:			
Federal Activity by Sponsor			
NIH	394,834,748	152,576,864	547,411,612
DOD	15,497,835	9,155,490	24,653,325
DARPA	1,514,180	329,694	1,843,874
NASA	632,219	252,848	885,067
NSF	407,165	181,364	588,529
Other Federal	1,632,659	534,064	2,166,723
Total Other Federal Activity	19,684,058	10,453,460	30,137,518
Subtotal Federal	414,518,806	163,030,324	577,549,130
State	10,250,117	1,144,969	11,395,086
Total State Activity	10,250,117	1,144,969	11,395,086
Total Federal and State	424,768,923	164,175,293	588,944,216
Non-Federal Activity by Sponsor			
Industry	86,732,116	32,677,076	119,409,192
Foundations	79,597,316	11,160,365	90,757,681
Subcontracts/Other Nonprofit	162,448,533	54,797,137	217,245,670
MGH Endowment & Gifts	229,353,061	29,589,281	258,942,342
Total Non-Federal Activity	558,131,026	128,223,859	686,354,885
Total Expenses	982,899,949	292,399,152	1,275,299,101
Harvard College	16,811,047	4,873,224	21,684,271
Grand Total	999,710,996	297,272,376	1,296,983,372



Image Award Finalist
The Art of Retroviral Insertional Mutagenesis
David Sykes, MD, PhD
Center for Regenerative Medicine

Center for Diversity and Inclusion (CDI)

Programmatic Report

ELENA OLSON, JD, EXECUTIVE DIRECTOR

<https://www.massgeneral.org/cdi>

MISSION

The Center for Diversity and Inclusion promotes the recruitment and advancement of physicians, scientists, and nursing and patient care services staff underrepresented in medicine (UiM); and seeks to develop an inclusive and engaged workforce at Mass General where all can experience a genuine and sustained sense of belonging.

FOCUS

CDI accomplishes its mission through three focus areas:

- Promoting the recruitment and professional development—at all career stages—of UiM physicians and scientists from student to trainee to faculty
- Developing diversity, equity and inclusion education and learning for physicians and scientists.
- Supporting research in equity, diversity, and inclusion

STRATEGIC PRIORITIES

As a central resource for diversity and inclusion at Mass General Hospital, the goals of CDI are to work with all departments, as well as many local and national strategic partners, focusing on three strategic priority areas:

- Exposing UiM students to academic medicine through flagship programs such as the Summer Research Trainee Program (SRTP) and the Visiting Clerkship Program
- Advancing careers and building community amongst UiM physicians, researchers, and trainees
- Championing health equity and addressing bias and racism through education, policy, and advocacy

In 2021, to continue the increasing success of CDI's efforts and to support the burgeoning initiatives affecting the MGH research workforce, CDI hired additional staff, including a new Student Program Coordinator, an Administrative Director for Research and two Faculty Co-Directors for Research: Drs. Cesar Castro, Associate Professor of Medicine and Julie Price, Professor of Radiology both at Harvard Medical School.

Building CDI Research Strategic Plan

Drs. Castro and Price developed and communicated their strategic plan, "Propelling and Sustaining Underrepresented Investigator Careers at MGH" to MGH research leaders in November 2021 and have been ambitiously executing

their strategy, gathering information, and identifying key resources along with CDI staff.

HIGHLIGHTED ACCOMPLISHMENTS OVER THE PAST YEAR:

Implementing the strategic plan included the creation of a CDI Research Advisory Committee. This small but accomplished group is tasked with guiding CDI expansion to the research workforce and building a diverse community of physicians and scientists at MGH. The advisory committee membership is nearly fully established.

Cultivating collaborations with HBCUs, MGH postdoctoral research fellows and post baccalaureates, Center for Collaborative Medicine, department chairs and centers. Here, CDI seeks to leverage existing and new levers to meet the needs of UiM researchers across MGH and to ensure their success. Over the past year, the Co-Directors met with leaders across MGH, BWH and HBCU's.

In collaboration with the Mass General Post-Baccalaureate Association and Mass General Postdoctoral Associations the following events occurred, and programs established:

- International Medical Graduate (IMG) panel discussions to provide tips on applying for residency as an IMG
- Pathways to Science and Medicine (PSM) Workshops and Mentoring Program Meet and Greet and two PSM Workshops with Bunker Hill Community College to help expose and introduce a wider range of career options to students interested in science and medicine

The Physician/Scientist Development Awards (PSDA) and the Clinician-Teacher Development Awards (CTDA) continue to **support the research and career development of UiM** faculty across MGH. Six PSDA awards were granted in 2022, See page 20. More UiM researchers will now be able to take advantage of these PSDA funds to help them build a successful research program at MGH and alleviate debt burden. This award continues to provide funding to promising UiM faculty and plays a key role in the path to independence in their research careers.

In addition, Drs. Castro and Price have been meeting with K-award and PSDA/CTDA recipients, to learn from their experiences and offer advice and available resources to these early careerists. The meetings are an ongoing effort to support UiM faculty with their transition to research independence and to further UiM community building.

The **Chester Pierce Research Society (CPRS)** is a speaker series named in honor of MGH's late Professor Emeritus in Psychiatry, Chester Pierce, MD. Dr. Pierce was the first

and once most senior African-American physician-scientist at MGH. CPRS is designed to promote diversity and health equity by featuring the novel basic, translational, clinical, and health services and disparities research of investigators in the MGH and CDI UiM community.

Since its inception in 2004, the CPRS has sponsored over 50 talks by MGH UiM physicians and scientists and attended by numerous faculty and staff across the MGH ecosystem. The CPRS is an opportunity for CDI to recognize and promote UiM faculty, particularly the robust research of previous PSDA and CTDA recipients. While the series was on hiatus due to COVID, the program was reinstated in 2021. 2022 speakers included Drs. Jocelyn Carter, Cesar Castro, David Perez, Julie Price, and Oladapo O. Yeku.

The **UiM Faculty Retention and Recruitment Fund** has also made a significant impact. The Fund was created as part of the structural equity plan at the end of 2020. In FY 2022, the Fund helped retain and recruit 13 faculty, of which 7 were researchers. CDI also created a Fund Collaborative of all recipients allowing for internetworking and collaboration.

External funding: CDI has enhanced its website to include information on applying for NIH diversity supplements and diversity-focused funding applications. Plans for a panel discussion specifically focused on NIH Diversity supplements are underway and will include strategizing to establish candidate pools and ensuring identification of “Diversity Supplements” in Insight. Additional initiatives include identifying funding opportunities that require UiM status, assembling a T32 Principal Investigator Subcommittee, and supporting DEI-related requirements for funding opportunities.

To create a sense of **community among MGH UiM researchers and research staff**, the CDI Faculty Co-Directors of Research and the Administrative Director for Research created the Research Recharge forum. Research Recharge will be held multiple times throughout the year at various research locations across MGH. The CDI’s first Research Recharge occurred November 2, 2022. The CDI looks forward to the new opportunities and friendships that will result from these events.

Provided virtual and onsite experience for SRTP students and increased the number of participants. The [SRTP](#) was established to build a pipeline of UiM students committed to academic medicine. Since 1992, SRTP has brought talented UiM college, graduate, and medical students from across the country to engage in a novel research

project with an MGH investigator. To date, 428 students have completed the program with over 164 colleges and universities represented with the help of 214 preceptors in 34 MGH Departments, Divisions and Centers. This year, because of our commitment to increasing the diversity of trainees, SRTP was able to host 30 students for the Summer of 2022, making it one of the largest SRTP cohort to date, compared to the average cohort of 20 students in past years.

The program, which ran from June 2022 to August 2022, allowed UiM undergraduate, medical, graduate, and post-baccalaureate students to complete research with MGH faculty preceptors within science labs, clinical sites, health policy and health services settings across 15 departments and centers at MGH.

Each student was matched with a research project and preceptor, with thoughtful consideration given to the student’s research interests and long-term professional goals. In addition to one-on-one mentorship, students were introduced to virtual networking events with key hospital leadership, career workshops, and research development seminars along with social events, in accordance with COVID-19 protocol.

Center for Faculty Development (CFD)

Programmatic Report

MIRIAM BREDELLA, MD, MBA, DIRECTOR

<https://www.massgeneral.org/faculty-development>

Mission/Focus

The Center for Faculty Development (CFD) aims to serve as a center of excellence on the career development of our diverse clinical and research faculty and trainees by sharing best practices on mentoring, well-being, and promotion. The CFD is the umbrella organization geared broadly for all faculty and includes four distinct branches, the Office for Clinical Careers (OCC), the Office for Research Careers (ORC), the Office for Well-Being (OWB), and the Office for Women's Careers (OWC), which address specific concerns for each respective constituency. In addition, a Graduate Student Division (GSD) and Postdoctoral Division (PDD) are housed within the ORC branch to address the needs of the graduate student and postdoctoral communities.

Achievements

Dr. Miriam A. Bredella has been leading the CFD for almost 3 years as Director. She is a Professor of Radiology and Vice Chair for Faculty Affairs and Clinical Operations in the Department of Radiology. She is also an NIH-funded clinical-translational researcher and directs the Harvard-wide KL2 program, where she oversees the training of the next generation of clinical translational investigators across all Harvard-affiliated hospitals and medical specialties. Executive Director, Maire Leyne, MS, MBA, has been working beside Dr. Bredella in leading the CFD. Maire is also the Director of the Executive Committee on Research (ECOR) within the Mass General Research Institute (MGRI).

In 2022, the CFD and its offices saw continued success in the integrated approach to providing services and resources to our faculty and trainees. The CFD continues to integrate new resources into the CFD website in addition to the pages on promotion, mentoring, and well-being. Dr. Anne Levy, Senior Program Manager, has assisted with ongoing and new initiatives to ensure the implementation of best practices in providing faculty support in the areas of teaching and learning; mentoring; research; writing; promotions and leadership development. All programs continued to be offered virtually via Zoom which allowed the CFD to extend the invitations to all MGB employees and outside institutions; because the COVID-19 pandemic became less severe, the CFD was also able to offer in-person events to bring people together, including a celebration of TEDxMGH talk participants and a working meeting for wellness leaders across MGH departments. The CFD also expanded its library of recorded webinars and podcasts available to faculty and trainees.

Over the past 12 months, the CFD created and/or developed several programs, including:

- The new Office for Senior Faculty Transitions (OSFT)
 - Offered a 9-session course by Drs. Stephanie and Russ Eisenstat, “Re-imagine, Re-Energize and Re-invent: Crafting the Next Stage of Your Work and Life”
 - Offered a 4-session Faculty Transition Series focused on topics to help faculty transitioning to retirement.
 - Includes videos of faculty who have successfully retired and maintained connections to MGH.
- A 4-session Career Development panel series that addresses specific aspects of academic career development, whether to build toward promotion consideration or to enrich professional knowledge and experience.
- A 7-session Social Media Series to help faculty and trainees build their brand and impact, bookended with presentations by Amy Oxentencko, MD, and Rupa Wong MD, and include sessions led by MGH-internal experts on the strategic use of LinkedIn and Twitter.
- A 2-session Time Management series focused on learning time management tips to make life easier and more efficient.
- The “Leadership Development Program for Researchers,” now in its third year, aims to prepare investigators for the challenges inherent in establishing and maintaining a successful research program. This 9-month program features didactic and interactive sessions, with tracks for faculty, post-doctoral fellows and graduate students. The second iteration also includes peer group meetings between each session to deepen the learning and build peer networks across departments.
- The “Anne Klibanski Visiting Scholars Awards” is also in its third year, as well as the complementary ‘Anne Klibanski Visiting Scholar Lecture Series’ which brings together faculty from institutions that have hosted Anne Klibanski Scholars with MGH scholars, on topics that overlap both research areas, thereby increasing networking and national exposure for women faculty.
- The CFD was again very much involved in putting together the 2022 virtual CHADD Mentoring Course, “Mentoring in a Hybrid World,” which showcased three MGH-based programs, two of which are CFD-initiated: the Anne Klibanski Visiting Scholar Award and the Men Allies in Action. The third, the MGH Department of Medicine Parental Wellness Program, is currently being expanded to other departments with the support of the CFD.

- In the context of institution-wide efforts to build capacity for high-quality mentorship, Dr. Bredella completed CIMER (Center for the Improvement in the Mentored Experiences in Research) facilitator training, and the plan is for Dr. Levy also to be trained, after which the CFD will be able to train MGH faculty in best mentoring practices. Dr. Levy presented a workshop on mentoring to volunteer mentors in the MGPA mentoring program.
- The launch of the Men Allies in Action program with training by Brad Johnson and Dave Smith for the 30+ designated faculty; the cohort now includes over 40 men faculty. Post-training meetings and ongoing communications serve to build awareness of the crucial importance of men allyship for the success of women faculty.
- New peer mentoring program for parents of young children. The women peer mentoring cohorts have continued to meet, both in person and via Zoom, and included guest men allies in action leaders.
- Grant Writing Course, an 8-session series created by the MGH Science Writing Group and open to all MGH faculty and trainees, is being offered a second time, given its success. This course spanned the entire process, including information on the different NIH funding mechanisms and on when a program officer should be contacted.
- New Writing Course offering, Basics of Science Writing for English Language Learner (ELL) Investigators and a new 3-session Manuscript-Writing Workshop for English Language Learners (ELL).
- The CFD Writing Support service continues, in which MGH science writers provide freelance writing and editing services for MGH faculty and trainees, fully subsidized by the CFD, for up to 5 hours, limited to once annually.
- Promotion support expanded to direct work with departments and divisions, including the Department of Surgery, the Division of Pulmonary and Critical Care, and the NORCH Associate Members Symposium.
- Ongoing detailed CV and Chief's letter review for faculty being considered for promotion.
- Created the "Chiefs Corner", a short monthly email, highlighting key initiatives from the CFD of interest to the Chiefs at MGH.

Strategic Priorities for the Coming Year

- Grow the Office for Senior Faculty Transitions, including ways for faculty who are retired to mentor current faculty in various areas from general career advice to writing support.
- Develop ways to support and celebrate the work of community physicians.
- Continue expanding and deepening the men allies in action mentorship culture at MGH with a poster campaign to increase awareness and encourage best practices in supporting women.
- Continue to collaborate with departments to identify faculty development liaisons to leverage best practices and resources and to serve on CFD working groups
- Provide professional development programs and workshops that meet the needs of our faculty and trainees. Series include:
 - Anne Klibanski Visiting Scholar Monthly Lecture Series
 - Financial Planning workshops
 - Marcela Del Carmen Lecture Series for the Advancement of Women and Diverse Faculty
 - Maurizio Fava Lecture Series on Well-Being
 - Meditation Series
 - Nancy J. Tarbell, MD, Faculty Development Lecture Serie
 - Parenting Series
 - Stress-Resiliency Series
 - Women in Medicine Month lecture
 - Writing Workshops
 - Speed Mentoring sessions
- Recognize and further celebrate outstanding mentorship by continuing to sponsor the new annual CFD Excellence in Mentoring Awards.
- Offer individual consultations to help faculty, research fellows and graduate students with advice and guidance.
- Implement a new online system for the annual career conferences (ACC) that is searchable and that can provide important metrics on many important factors, such as equity and diversity. The system will be implemented MGB-wide.
- Continue to automate CFD processes where practical to enhance efficiencies.

Center for Faculty Development (CFD)

Programmatic Report

- Continue to collaborate with the Mass General Physician's Organization and Mass General Research Institute on gender parity, equity and respect as well as burnout issues.
- Continue collaboration 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.

Office for Research Careers (ORC) – Marcia B. Goldberg, MD, Director; Graduate Student Division (GSD) – Mary Boussein, PhD, Director; Postdoctoral Division (PDD) – Bakhos A. Tannous, PhD, Director

The Office for Research Careers (ORC) is one of the four branches of the Center for Faculty Development. ORC is home to both the Graduate Student Division and Postdoctoral Division. The Office for Research Careers is directed by Dr. Marcia Goldberg, Professor of Medicine and Microbiology. Dr. Bakhos Tannous, Professor of Neurology, leads the Postdoctoral Division, among which the Mass General Postdoc Association (MGPA) falls. Dr. Mary Boussein, Professor of Orthopedic Surgery at HMS, spearheads the Graduate Student Division.

ORC, GSD and PDD Achievements

- Increased coordination and communication with other MGH departments (i.e., MGPA, GPS, HR, DCR, CDI, etc.) to support the research faculty at MGH through a more systems-wide approach. This has led to many co-sponsored initiatives and programs that have greatly benefited the faculty and trainees at the institution.
- Expanded the Leadership Development Program for Researchers to include not only a didactic component but also a peer mentoring component. This provided participants with additional opportunities to network and constantly grow as leaders during the program.
- Implemented and updated two onboarding checklists for postdocs and graduate students that will assist them in navigating MGH and the resources available to them.
- Created a short email every two weeks that advertised PDD, GSD, CFD and hospital-wide events of interest to the postdocs and graduate students at MGH.
- Promoted a Postdoctoral Fellowship Certificate that postdocs can utilize as confirmation of their postdoctoral training at MGH. This has helped many MGH postdocs in applying for full-time positions.
- Continued to collect sample grant applications for early career investigators to utilize as a resource when submitting their first grants.
- Worked with MGH Human Resources to:
 - Collect important demographic information on clinicians, researchers, and trainees at MGH, which the CFD can use to better plan initiatives and programs.
 - Update the onboarding process for trainees to collect important info during the onboarding phase of hiring.
 - Rethink the off-boarding process of trainees to capture their departure promptly.
- Created an internal job database platform that principal investigators and postdocs can utilize to post and seek employment opportunities. It was updated to show opportunities not only internally but externally to attract more trainees to the institution in a tough job market.
- Processed 55 extension requests for post docs whose research might have been impacted by the ongoing pandemic.
- The PDD organized a Postdoc Retreat centered around our postdoctoral fellows' well-being and career development. More than 200 postdocs attended a two-day retreat to network with fellow postdocs and learn more about the resources available to them at MGH.
- Provided "Improve your English Pronunciation" and "English for Speakers of Other Language (ESOL)" classes specifically designed for researchers. A 12-week semester of ESOL is divided into four class levels based on their English skill level.
- Supported the MGPA during the restructuring of their association to better represent the diverse postdoctoral community at MGH. MGPA expanded the number of postdocs in each committee and is working on increasing its social media presence.
 - Frequent communication with the MGPA has allowed the PDD to get valuable feedback on initiatives and projects discussed and created.
- Continued to offer seminars and workshops targeted specifically to faculty, postdocs, and graduate students (e.g., an overview of careers in the life sciences industry, identifying funding opportunities, tips for writing fellowship applications), including the following:
 - 8-week Grant Writing Course
 - Scientific Writing Group Grants
 - Postdoc Retreat
 - Stress Resiliency Program for Trainees

- Grad Student Monthly Networking Event
- Grad Student Monthly Career Development Seminar Series

Strategic Priorities - ORC

- Continue to facilitate collaborations among the ORC, the GSD, and the PDD to create programs that serve some of the overlapping needs of the research community.
- 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.
- Continue to collaborate and contribute to efforts that assist researchers in transition due to funding issues, the shrinking faculty job market, and the current pandemic including:
 - Advising research faculty on ways of identifying grant opportunities and on grant-writing strategies.
 - 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.
- Organize an in-depth grant management series that provides early and mid-career PIs with practical tips on efficiently managing their lab and grant funding:
 - Manage spending on grants (Insight, MicroStrategy, and Budget Documents)
 - Distribution of % effort of lab members and PIs on grants
 - Managing changes in science
 - Creating and leading a diverse lab
- Present the unique research landscape of MGH and the various opportunities offered to PIs to increase their research portfolio at MGH and elsewhere in their specific areas of expertise
- Create templates of common administrative documents that can help early-stage PIs and trainees apply for their first grants.

Strategic Priorities - GSD

- Better identify graduate students conducting research at MGH and ways to support their career advancement and research goals.
- Rethink the off-boarding process of MGH graduate students to better capture in real-time the number of graduate students at the institution.
- Recreate the graduate student community, which was hit hard due to the COVID-19 pandemic. Utilize social events and monthly seminars to connect graduate students at MGH with one another.
- Increase the number of graduate students in research labs at MGH. Develop creative ways to recruit trainees to the institution.
- Enhance communication with graduate students and PIs through more prevalent digital platforms and website resources other than conventional email.
- Host programs and events in areas and topics that graduate students highlighted as areas for improvement.
- Provide examples of successful fellowship applications and provide writing workshops for graduate funding opportunities.
- Survey graduate students regarding well-being, as well as career development needs.

Strategic Priorities - PDD

- Rebuild the postdoc community that was hit hard during the COVID-19 pandemic:
 - Increase awareness of the MGPA and its many committees
 - Resources available to them through the PDD, CFD, and other MGH departments
- Help and support the MGPA in the revamping of their website and social media platforms (LinkedIn, Twitter, Instagram, etc.)
- Utilize feedback and results from the Postdoc Retreat and Postdoc Well-Being Survey to tackle issues and difficulties faced by the postdoctoral community at MGH, ultimately improving well-being among this population of researchers.
- Establish an online appointment platform for postdoctoral fellows to enable improved tracking of annual career meetings, secondary mentors, promotions, and salaries.
- Create an alumni database that gathers information on the outcomes and career pathways of former MGH postdoctoral fellows.

Center for Faculty Development (CFD)

Programmatic Report

- Continue to offer programs through more convenient and accessible means that will encourage greater participation, including offering programs at different locations and making resources available online and/or on demand.
 - Utilize video-conferencing programs like Zoom and Microsoft Teams to record and live-stream events across the organization and at affiliated institutions.
- Increase programming in career exploration, to assist postdocs in achieving a better understanding of the various career paths available to them.
- Build relationships with alumni to help foster a community and create an accessible resource for our current postdoctoral research fellows.
- Continue to enhance and streamline communication through more convenient and prevalent digital platforms in addition to email.
- Collaborate with internationally trained MDs 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.
- Continued the “Parenting Series” focused on well-being and work-life balance for MGH faculty and trainee parents, bringing together panels to discuss complex and difficult issues including navigating social media with teens, parenting older children, parenting through and beyond divorce, and parenting children with medical/physical disabilities.
- Expanded and continued to meet with the OWC Advisory Board to oversee and advise the OWC strategic mission and priorities.
- Implemented three cohorts of a 10-week Financial Planning course for various levels of faculty and trainees.
- Provided an opportunity for MGH women clinical faculty to connect with peers in a safe space and improve work-life balance through a 5-week “Setting a Course for Better Work-Life Balance” Coaching Workshop series.
- Engaged male leaders at MGH in a training to become better allies for women.
- Implemented a new group coaching series with the Mass General Research Institute for research-focused women investigators, to create connections among faculty by bringing them together informally to address specific topics of interest and concern.
- Held the second annual “Marcela Del Carmen, MD Lecture Series for the Advancement of Women and Diverse Faculty” to promote and support women in academic medicine as well as faculty from diverse backgrounds. This year’s lecture was with Boris Groysberg and Colleen Ammerman, Professors at Harvard Business School and Co-authors of “Glass Half-Broken: Shattering the Barriers that Still Hold Women Back at Work.”
- Collaborated with the Brigham and Women’s Hospital Office for Women’s Careers for the 2022 Women in Medicine and Science Symposium. The symposium featured a keynote by Dr. Nawal Nour and highlighted research from 12 women faculty across BWH and MGH.
- Revived the Caring for Dependent(s) Travel Awards program, which are grants for faculty and trainees intended to help defray additional care expenses that go above and beyond care needs, (e.g., extended day care, extended elder care, caregiver travel) while the faculty member is traveling to an academic meeting or conference. The CFD granted a total of \$16,500 among 33 award recipients in 2022.

Office for Women’s Careers (OWC)—Louisa G. Sylvia, PhD, Director

Dr. Louisa G. Sylvia is the Director of the Office for Women’s Careers. Dr. Sylvia is an Associate Professor of Psychiatry at Harvard Medical School and a staff psychologist and Associate Director at Dauten Family Center for Bipolar Treatment Innovation at MGH.

OWC Mission

To promote equity and advancement for women faculty and trainees by cultivating awareness, advocating for change, and empowering women faculty and trainees to achieve personal and professional fulfillment.

Achievements

- The OWC continued efforts to support and advance the careers of women faculty in 2022.

- Created a Lactation Space Task Force to increase the number of lactation rooms at MGH (Main campus, CNY, etc.) and also improve the quality and comfort of the lactation rooms. The task force is comprised of women in positions of leadership at MGH/MGB, such as from the Employee Assistance Program, Buildings and Grounds, etc.
- Brought a group of MGH women faculty to the MA Conference for Women to generate new ideas for the OWC and enhance networking for these faculty and staff.

Strategic Priorities

- 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 will include negotiation training and leadership skill building for women, supporting rising women leaders to take advantage of outside resources such as the Executive Leadership in Academic Medicine (ELAM) program, and advocating for parental leave, lactation, and childcare initiatives.
- Increase engagement with, and awareness of, the OWC across MGH.
- Improve recognition of women faculty and encourage their support and mentoring across MGH.
- Improve networking and peer support for women faculty and trainees.
- Improve mentoring and sponsorship for women across MGH.
- Create scholarship opportunities for women faculty and trainees.
- 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.
- 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.
- Increase women faculty members' retention and job satisfaction.
- Provide individual counseling, advice and support.

- Meet with OWC Advisory Board bi-monthly to maintain project alignment.
- Provide updates on key initiatives and outcomes quarterly.

Office for Clinical Careers (OCC)—Cristina R. Ferrone, MD, Director

Dr. Cristina Ferrone is the Director of the Office for Clinical Careers (OCC). Dr. Ferrone is a Professor of Surgery and the Director of the Surgical Liver Program. She is currently the principal investigator of a large national clinical trial for pancreatic cancer and has obtained NIH funding for her translational research effort. She has been an active member of the Frigoletto Committee on Physician Well-Being since its inception. As part of the Frigoletto Committee she started the women in surgery connectivity series. Dr. Ferrone has been the Associate Program Director for the General Surgery Residency since 2006. She has mentored many junior faculty, residents, research fellows, medical and high school students. She is currently an elected physician member of the MGPO Board of Trustees.

OCC Mission

The OCC supports faculty and the advancement of their careers (through one-on-one meetings, CV reviews, skill-building seminars, and mentorship).

Achievements

- Developed an online ACC platform for all Departments. Met with all MGH departments to create the workflow for faculty. Launched the online platform in over half of all MGH departments. Advised other MGB institutions, including BWH, MEE, and Spaulding, on the process of developing their own electronic ACC forms.
- Collaborated with other MGH clinicians on the “Magic Wand Initiative”, a pilot program to empower and educate clinicians to become leaders in biomedical innovation around the world. Program pilot in Surgery, Orthopedics and Anesthesia. Hosted an event for program awardees to update each other on their projects' progress and collaborate with other clinicians for problem-solving.
- Continued the lecture series in collaboration with Springboard Studio and the Magic Wand Initiative. The “Virtual Water Cooler Series: Demystifying Innovation” is meant to create a collaborative space for clinical faculty looking to bridge into innovation.

Center for Faculty Development (CFD)

Programmatic Report

- Advised faculty and trainees from different departments regarding career advice, CV/cover letter critique, mentorship, and promotion.

Strategic Priorities

- Onboard new Director of the Office for Clinical Careers

Office for Well-Being (OWB)—Darshan H. Mehta, MD, MPH, Director

Dr. Darshan H. Mehta is the Director of the Office for Well-Being. Dr. Mehta is an Assistant Professor of Medicine and Psychiatry at HMS, the Medical Director of the Benson-Henry Institute for Mind Body Medicine at MGH (BHI-MGH), and the Education Director of the Osher Center for Integrative Medicine at Brigham & Women's Hospital and HMS. At HMS, he leads a well-being curriculum required for all 1st-year HMS/HSDM students. He is also the MGH Site Director for the Practice of Medicine curriculum. This longitudinal year-long course focuses on the fundamentals of doctoring—from interviewing and communication skills to physical exam and clinical diagnosis—and is required of all 1st-year HMS/HSDM students.

OWB Mission

The OWB aims to improve the well-being of our faculty and trainees across the career span through designing initiatives to improve resilience and to create a positive work culture.

Achievements

- Continued the TEDxMGH talk series. This monthly series shares inspirational stories from the hospital community and how those in the community have handled challenges, through innovation, resilience, vulnerability and connection. Hosted an in-person reception to celebrate our TEDxMGH speakers and thank them for sharing their stories.
- Participated in the Well-Being Integration Working Group for NIH CLIC-CTSA. Based upon the work at BHI-MGH, this curriculum has been presented and discussed at the CLIC Working Group. If successful, this will serve as a model for NIH-funded trainees.
- Led twice-weekly meditation series for the MGH community. The OWB, in collaboration with the MGPO Frigoletto committee, began a weekly guided meditation series on Mondays led by the director, Dr. Darshan Mehta, in 2020. In 2021 this was expanded to include Wednesdays with guest meditation leaders from across MGB and both have continued throughout 2022.

- Implemented the Maurizio Fava Lecture Series on Well-Being, which was created to honor Dr. Fava's vision and advocacy for the well-being of the MGH community. The OWB hosted one installment of the series in 2022 with Dr. Victor Dzau, President of the National Academy of Medicine.
- Created the Well-Being Education Grants program, which are grants for clinicians and investigators (graduate students, post-docs, residents, fellows, and faculty) to help defray the cost of professional training around resilience and well-being. The OWB granted a total of \$35,134 spread among 73 award recipients.
- The OWB Director, Dr. Darshan Mehta, offered the Stress Resiliency Program to three different cohorts throughout the year. This program aims to address the increasing pressures of work and life balances that can be caused by a wide range of factors (professional and personal lifestyle changes) and is designed to help participants regain control and build resilience through a variety of mind-body strategies and self-care interventions.
- Continued the 'Fun Fridays' program, which offers a refreshing mid-day break from work to indulge in physical, mental, or creative activity with a different session leader each week.
- Met with all appointed wellness champions within departments at MGH. Hosted an in-person reception to discuss their key values and goals for well-being in our institution.
- Coordinated two new group coaching programs: "Group Coaching for a Healthy Lifestyle" with facilitator Elizabeth Pegg Frates, MD, FACLM, DipABLM, is a 6-session workshop series created to help participants identify ways to grow in health and happiness. "What's Next? It's Your Time." with facilitator Elise Tofias Phillips, MD, is a 5-session course intended for participants to set the stage for exploration, discovery, and planning for the next stage of their life.

Strategic Priorities

- Improve the well-being of the faculty and trainees at MGH through initiatives designed to increase resilience and create a positive work culture
- Provide individual counseling, advice and support to members of the MGH community.
- Develop a comprehensive, easy-to-navigate website that can promote resources and guide faculty to their respective departmental/divisional well-being champions

- To have well-being as a routine institutional performance metric with targeted interventions, tailored coaching and incorporating discussions of well-being in professional contexts (e.g., annual career conference).
- To provide resources to promote self-care, working in collaboration with resources across Mass General/ Mass General Brigham including, but not limited to, the Employee Assistance Program, the Benson-Henry Institute for Mind Body Medicine at Mass General, the Frigoletto Committee on Physician Well-Being/Mass General Physicians Organization and the Center for Physician Well-Being in the Mass General Department of Medicine.

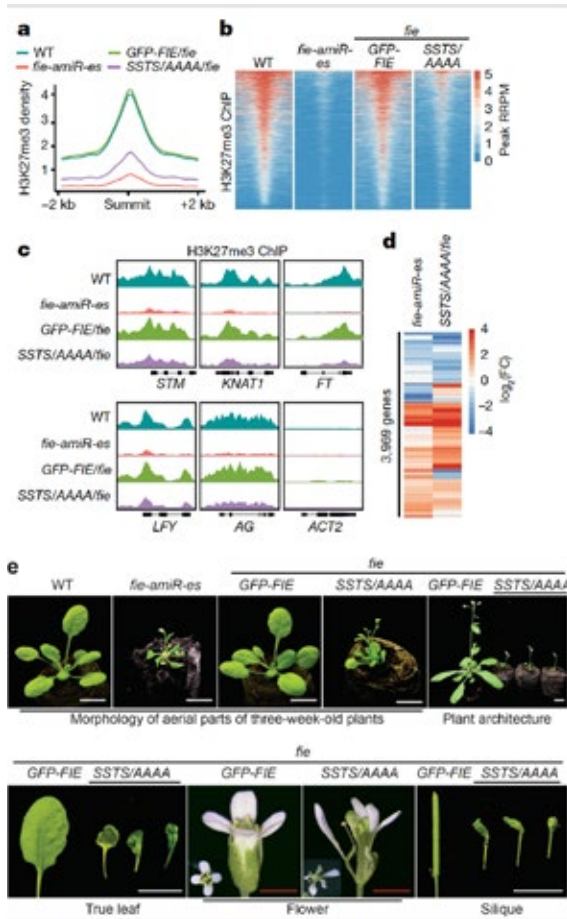


Figure 1. Targeted FIE mutation alters the global H3K27me3 landscape to reprogram the transcriptome and disrupt organogenesis. a. Reduction of global H3K27me3 levels in *fe* mutants. b. Depletion of H3K27me3 in *fe* mutants. Heat map of H3K27me3 enrichment. c. IGV browser view of H3K27me3 occupancy at PRC2 target genes with key developmental roles. ACT2, a non-PRC2-target gene, serves as a negative control. d. Transcriptome reprogramming in *fe* mutants. e. Developmental defects in the *fe* mutant lacking TOR phosphorylation.

RAMNIK XAVIER, MD, PHD, DIRECTOR

Overview:

Faculty in the Center for Computational and Integrative Biology (CCIB) apply interdisciplinary approaches and new technologies to answer enduring biological questions and provide insights into human disease. Novel chemical, genomics and computational tools are developed to probe signaling pathways, identify mediators of host-microbe interactions, and design therapeutic disease interventions. Center investigators also conduct translational research to explore the potential utility of early-stage drug candidates in phase 1 studies carried out in small populations of individuals with the target disease indication. The drug candidates are developed either in the local academic community or presented to the Translational Medicine Group from the biopharmaceutical industry.

Below, we highlight a landmark study in plants linking nutrient signaling and developmental programs; the identification of a conserved DNA helicase that links mitochondrial surveillance with detoxification, antimicrobial and aging pathways; a method that captures the transcriptional landscape in bacteria at the single cell level; and two studies that probe gene function and microbiome contribution to immune homeostasis in health and disease.

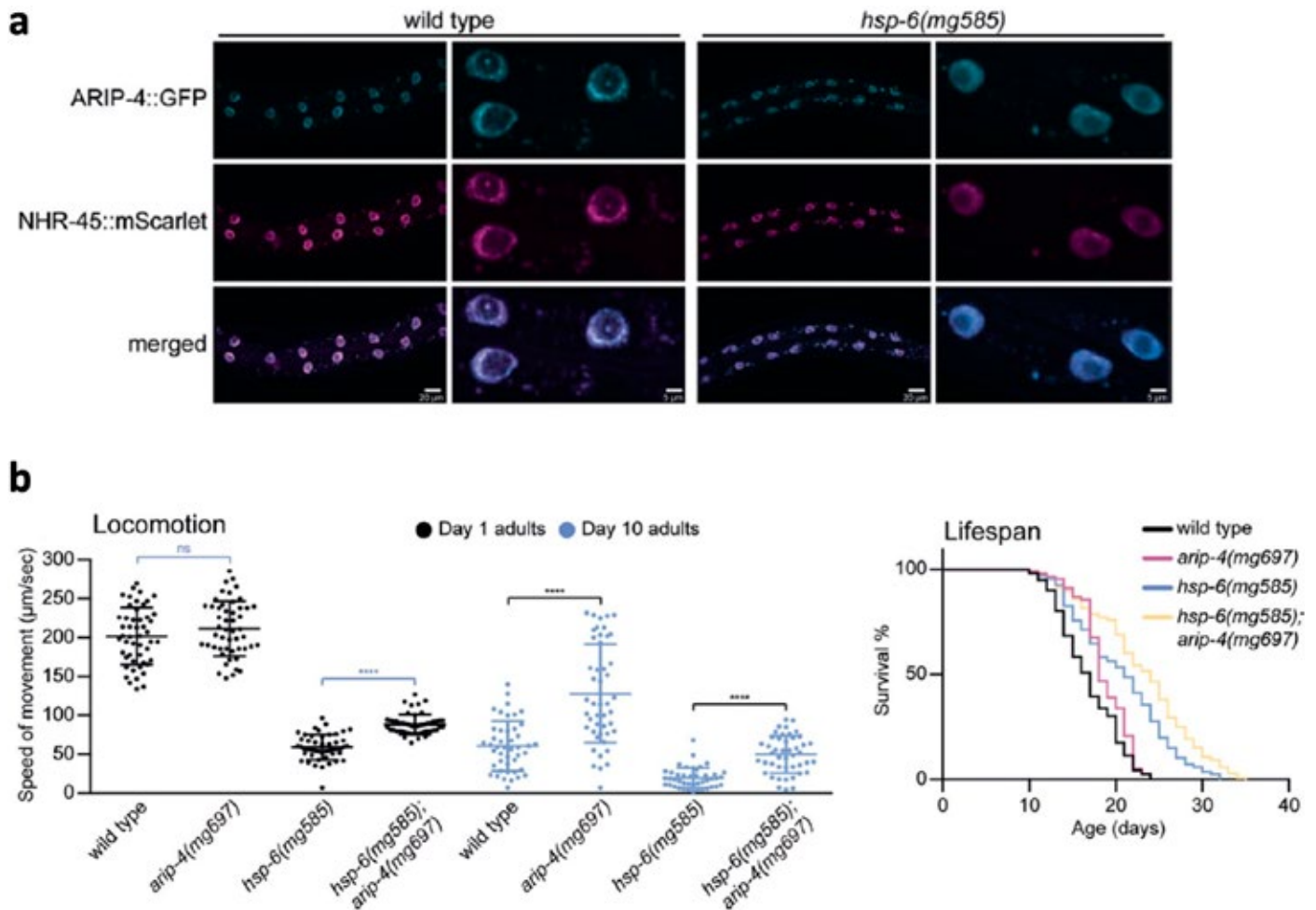
Achievements

A fundamental mechanism controlling development. The target of rapamycin (TOR) kinase is a master regulator of nutrient and energy signaling that controls growth and development, but how TOR impacts cell fate decisions and differentiation is poorly understood. In a study recently published in *Nature*, **Jen Sheen** and colleagues dissected the molecular mechanisms of a glucose-TOR-FIE-PRC2 signaling axis that regulates epigenetic modification of key developmental transcription factors in *Arabidopsis thaliana*. In contrast to the conventional view of a preformed nuclear PRC2 containing FIE as a key static component interacting with other complex components, their findings revealed that FIE serves as a molecular bridge, directly linking glucose-TOR signaling with PRC2-regulated H3K27me3 dynamics and gene silencing (Fig. 1). The authors propose that this signaling axis serves as a nutritional checkpoint for regulating PRC2 activity throughout key differentiation phases and processes during postembryonic development. This study has broad relevance for developmental control of multicellular organisms, advancing our conceptual understanding of how systemic nutrient information can be transmitted to remodel the transcriptional landscape central to cell fate regulation in diverse developmental programs.

Reference — <https://doi.org/10.1038/s41586-022-05171-5>

Activating detoxification pathways can be deleterious to health.

Disturbance of mitochondrial function by toxins, pathogens, or mutations triggers drug detoxification and immune responses through MDT-15- and NHR-45-mediated transcriptional regulation. In a genetic screen for mutants that fail to activate the detoxification response to



mitochondrial dysfunction in *Caenorhabditis elegans*, the **Ruvkun lab** identified the conserved DNA helicase RAD-26/ARIP-4 ([PNAS](#)). In the context of *hsp-6(mg585)*, a hypomorphic mutation in the mitochondrial chaperone HSP-6/mtHSP70 that activates detoxification and RNA interference defense pathways, the lab showed that ARIP-4 acts as a transcriptional coactivator for NHR-45. They showed that ARIP-4 and NHR-45 physically interact, colocalize in the nucleus (Fig. 2a), and co-regulate genes involved in drug detoxification, antibacterial immunity, and antiviral RNAi response. Previous studies had shown that loss of *nhr-45* is beneficial for health and life span of worms also harboring the *hsp-6(mg585)* mutation. Therefore, the authors tested whether decoupling mitochondrial response pathways with an *arip-4* mutation might increase healthy life span. The results, shown in Fig. 2b, confirm their hypothesis and emphasize the deleterious effects of defense responses triggered by mutations that cannot be detoxified.

Reference: <https://doi.org/10.1073/pnas.2215966119>

Capturing the transcriptional landscape of bacterial populations.

Single-cell RNA-sequencing has led to important discoveries in mammalian systems, but technical challenges have hindered similar progress in microbial populations. **Chris Smillie, Deb Hung, and**

Figure 2. Decoupling mitochondrial response pathways with an *arip-4* mutation increases healthy life span. a. ARIP-4 protein colocalizes and associates with NHR-45 protein for transcriptional regulation in response to mitochondrial dysfunction. b. *arip-4* mutant shows an extended healthy life span.

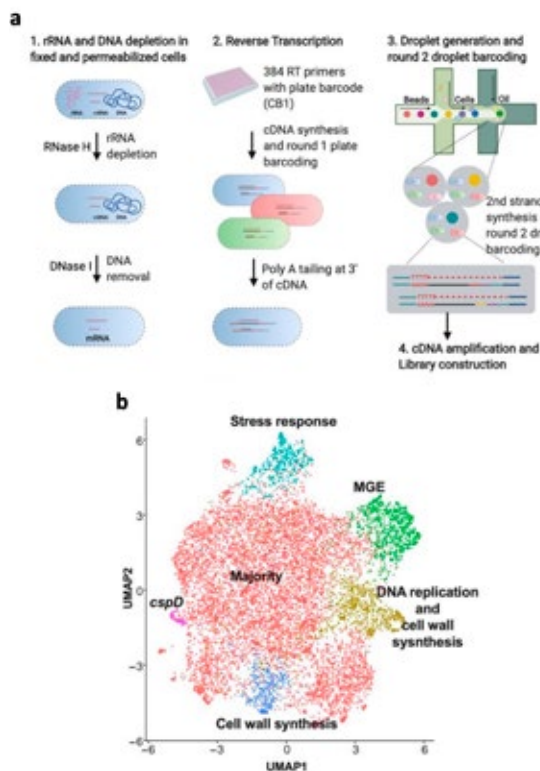


Figure 3. BacDrop enables single-cell RNAseq in bacteria. a. BacDrop workflow. b. BacDrop reveals heterogeneous responses to antibiotic exposure.

colleagues report in *Cell*, the development of a highly scalable, droplet-based method for bacterial single-cell RNA-sequencing called BacDrop (Fig. 3a). They demonstrated that BacDrop can reveal transcriptional heterogeneity both in stable populations and in response to perturbations such as antibiotic treatment. In a model of *Klebsiella pneumoniae* response to antibiotics, they used BacDrop to discover rare subpopulations of *K. pneumoniae* that were all but invisible to past work, including cells that express mobile genetic elements that help promote antibiotic resistance, and elusive “persister” cells that are metabolically shielded from multiple forms of antibiotics (Fig. 3b). This new technology will enable greater understanding of bacterial survival, adaptation, and evolution within complex communities.

Reference - <https://doi.org/10.1016/j.cell.2023.01.002>

A delicate balance between microbes, immunity, and the human host.

A major challenge in the study of inflammatory disease is to determine how disease genes and their corresponding alleles exert their influence on the biology of health and disease, as well as how the microbiome contributes to disease onset, progression, and recurrence. Tissue acidification occurs during inflammation and tumorigenesis. To learn how pH sensing affects tissue homeostasis, the **Xavier lab** and colleagues studied the pH sensor GPR65 and one of its coding variants, Ile231Leu, which is associated with risk in inflammatory bowel disease (*Nature Immunology*). They found that mice with this variant had impaired antibacterial defenses in an infection model and heightened inflammation in a colitis model. GPR65 Ile231Leu led to cytokine imbalance, altered metabolism and increased release of IL12 and IL23 in dendritic cells at acidic pH, leading to enhanced antigen presentation (Fig. 4). This study identifies a mechanism by which pH sensing regulates inflammatory circuits to maintain homeostasis and offers an example of critical variant-to-function efforts. Turning their attention to the microbiome and its role in shaping immune responses, the Xavier lab tracked the co-development of microbiomes and metabolomes in a cohort of 70 mother–infant pairs from late pregnancy to 1 year of age (*Cell*). The investigators uncovered an additional mode of vertical transmission, where maternal gut bacteria share genes with infant gut strains in the absence of stable engraftment of the maternal bacteria themselves. The genes were frequently involved in functions related to metabolism of infant dietary substrates. Further, metagenomic and metabolomic analyses revealed hundreds of metabolites as well as microbe–metabolite associations that were unique to infants. Metabolomic and cytokine profiles were distinct in infants who received regular—but not extensively hydrolyzed—formula compared to exclusively breastfed infants. Together, the study expands our understanding of maternal influences on the infant gut microbiome, with potentially profound implications for immune and neurodevelopment early in life (Fig. 5).

References - <https://doi.org/10.1038/s41590-022-01231-0> and <https://doi.org/10.1016/j.cell.2022.11.023>

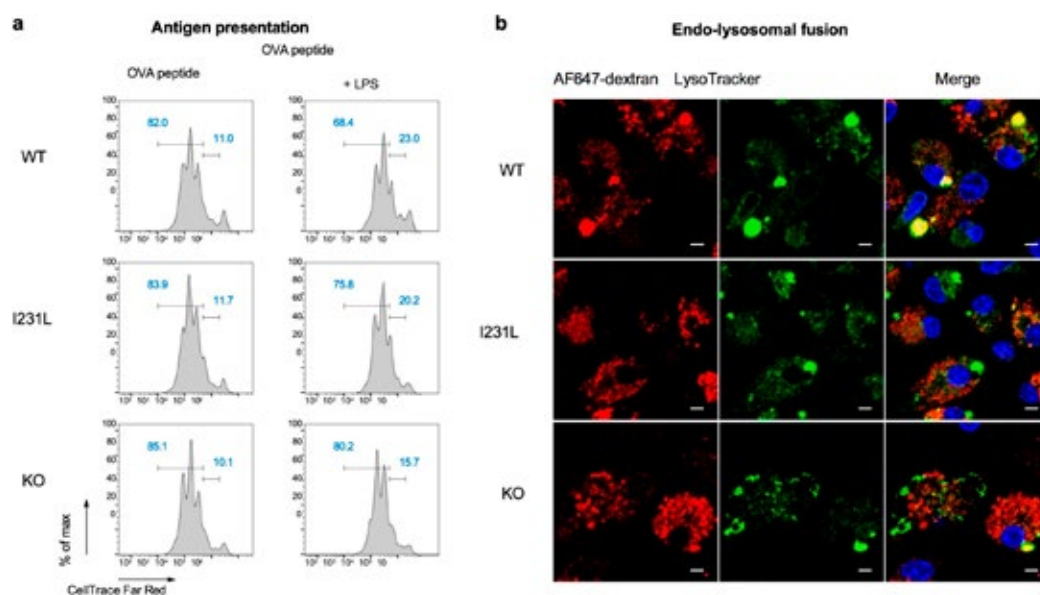


Figure 4. GPR65 Ile231Leu enhances antigen presentation in dendritic cells by influencing endo-lysosomal fusion and degradation capacity. a. Representative profiles of divided OT-II T cells in a BMDC:OT-II T cell co-culturing-based antigen presentation assay. b. Endo-lysosome fusion in BMDCs detected by microscopy.

Developmental Origins of Health and Disease

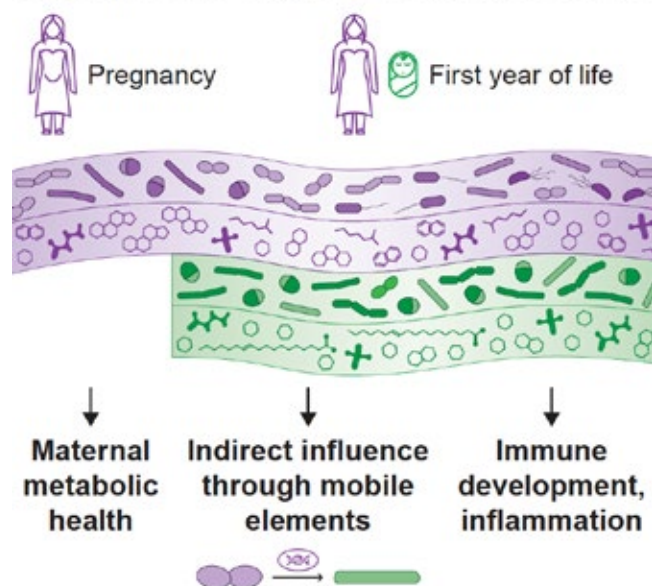


Figure 5. Maternal influences on the infant gut microbiome.

Center for Genomic Medicine

Thematic Center Report

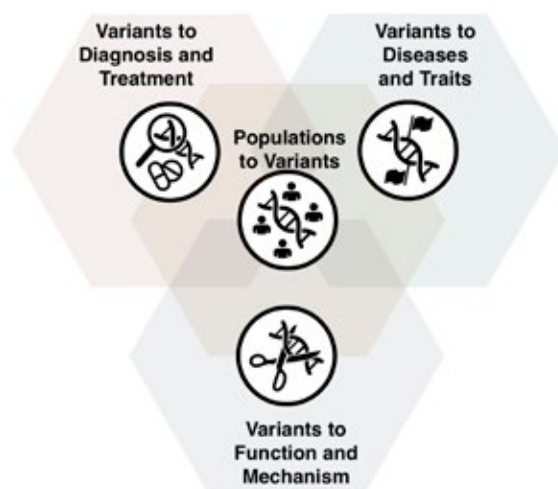


Figure 1.

MICHAEL TALKOWSKI, PHD, DIRECTOR

Mission

The MGH Center for Genomic Medicine (CGM) represents one of the largest and most vibrant hubs of genomic medicine research in the world. We are a diverse and cross-disciplinary genomics environment with 50 faculty drawn from MGH Departments, Centers, and Units. The CGM envisages a community of faculty and scientists collaborating across MGH departments to define the '**Genomic Medicine Cycle**' (Figure 1). The cycle is a research paradigm that begins with mapping genetic variation across global populations, followed by defining phenotypes and traits associated with differences between individuals. It progresses to characterizing the mechanisms by which DNA changes lead to disease and is completed when the knowledge gained delivers benefit back to individuals in the form of diagnosis and treatment. Our long-term vision is to serve as the genomic medicine and analytic hub for clinical genomics and biobank research across MGH departments and programs.

Scientific Leadership

Dr. Michael Talkowski is the Director of the CGM. Dr. Talkowski is the Desmond and Ann Heathwood MGH Research Scholar in the Department of Neurology, with cross-appointments in MGH Psychiatry and Pathology, and an Institute Member of the Broad Institute. Dr. Talkowski succeeded Dr. Sakar Kathiresan and Dr. James Gusella in this role. Dr. Alex Soukas is the Associate Director of the CGM. Dr. Soukas is an Associate Professor of Medicine and the Weissman Family MGH Research Scholar. Dr. Monica Salani is the CGM and Talkowski lab program manager.

Overview

The CGM is a diverse thematic Center comprised of 50 faculty engaged in all facets of genomic medicine. Our programs cut across **seven MGH departments** and include over 500 scientists at all career stages. The CGM encompasses four mission driven Units (Director/Chief) - the Psychiatric and Neurodevelopmental Genetics Unit (**PNGU**; Dr. Jordan Smoller), the Analytical and Translational Genetics Unit (**ATGU**; Dr. Mark Daly), the Molecular Neurogenetics Unit (**MNU**; Dr. James Gusella), and the Genomic Medicine Unit (**GMU**; Dr. Heidi Rehm) that was established with our recruitment of Dr. Rehm to the CGM.

Discoveries

In 2022, despite ongoing challenges presented by the pandemic, the CGM continued to be one of the most dynamic foci of genomic medicine research in the world. The scientific excellence of CGM faculty is emphasized in its remarkable publication record, acquisition of competitive funding, and the stellar track record of CGM trainees in competing for fellowships and faculty positions. The CGM PIs

published an astonishing **646** papers in 2022, a large fraction of which were published in the highest impact journals in the field. Our faculty filed numerous patents, started companies, brought new FDA approved therapeutics to rare disease patients, and were recognized with national and international awards of excellence by the genomic medicine community, as described below. Our faculty include 8 MGH Research Scholars, 6 MGH Martin Prize awardees, 3 Goodman Fellows, numerous Claflin, Fund for Medical Discovery, and other MGH research awards, and in 2022 five CGM Faculty recognized in the 2022 Clarivate Analytics' Highly Cited Researchers List for producing papers that rank in the top 1% of citations for the field in the Web of Science.

Resources

Overall expenditures for CGM faculty exceeded \$70M for the second consecutive year. Current CGM faculty are appointed in Neurology, Psychiatry, Medicine, Pediatrics, Anesthesia, Critical Care and Pain Medicine, and Surgery, with Neurology faculty being the largest representation. Almost all faculty conduct the entirety of their MGH funded research in CGM space, and the CGM has been among the four highest IDC density at MGH in the last two years based on data provided by MGH RSMG.

Organization and Administration

Over the last two years the CGM has undergone a complete reorganization of its administration and support for its long-term strategic plan. The CGM has organized a complete turnover of its senior administrative leadership, as well as its project and administrative support teams. We conducted an open search for a new Administrative Director that resulted in the hiring of **Harsha Radhakrishnan, MS**, who brings over 20 years of experience in academic science research and previously managed a group of 70 faculty and 200 researchers at MEEI. Another search introduced a new leader for CGM financial management from Columbia University, **Dananjali Ratnayaka, MBA**, who brings experience in grants management from international genomic medicine research programs. We have also hired a new program manager for media relations and development, **Piper McCabe, BS** and a new grants and finance manager **Kailah McCray, BS**, as well as an administrative coordinator Caitlin Ellis. We organized several core faculty committees that spearheaded **major infrastructure investments** and search committees that led to our hiring of **five new Assistant Professors in the CGM in 2020-2021 followed by three new Assistant Professors and an Associate Professor in 2022 (see below)**. Our faculty searches were conducted with input from the MGH Center for Diversity and Inclusion, and these new hires represent major steps forward in advancing our **scientific mission** and fulfilling our goals to **improve the diversity of scientific portfolios, career stages, gender inequities, and culture** in our CGM community.

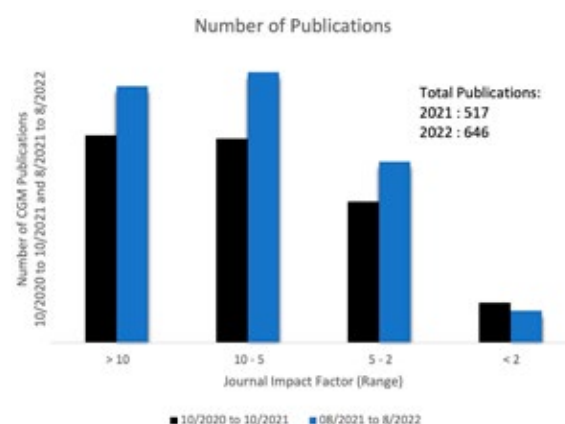


Figure 2. Publication update from CGM faculty in 2022.

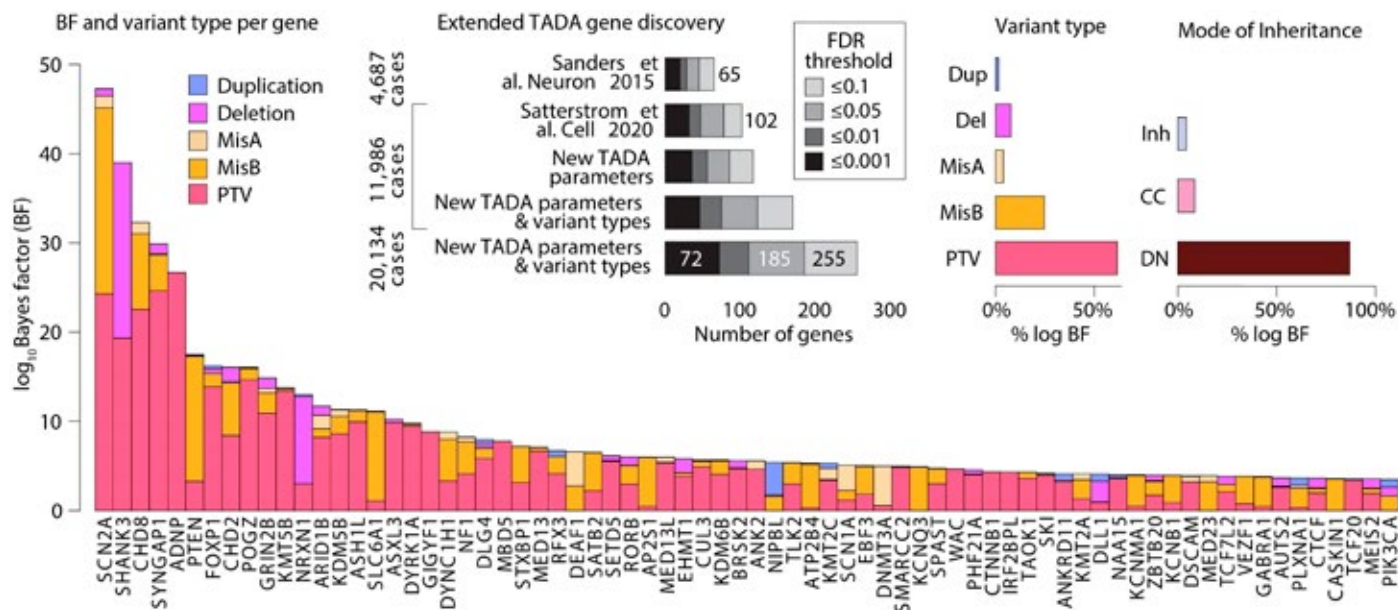


Figure 3. 72 genes associated with ASD at $FDR \leq 0.001$.

i. Achievements: A Few Vignettes of Discoveries in Genomic Medicine from Around the CGM

The Genetic Architecture of Neuropsychiatric Disorders

Rare coding variation provides insight into the genetic architecture and phenotypic context of Autism.

Fu JM et al. (2022), *Nature Genetics*; 54:1320-1331.

Mapping genomic loci implicates genes and synaptic biology in schizophrenia.

Trubetsky V et al. (2022) *Nature*; 604:502-508.

Rare coding variants in ten genes confer substantial risk for schizophrenia.

Singh T, et al. (2022), *Nature*; 604:509-516.

A series of landmark study led by CGM faculty members and many colleagues from across our ATGU, PNGU, and MNU units have begun to redefine the rare and common variant contributions to the genetic architecture of neuropsychiatric disorders. A study of over 150,000 people uncovered more than 72 genes strongly associated with autism—several for the first time—and over 350 genes linked to diverse neurodevelopmental conditions (**Figure 3**). Appearing in *Nature Genetics*, the work was led by CGM postdoctoral fellow and Autism Speaks fellowship awardee Jack Fu, ATGU member Kyle Satterstrom, and CGM associate member Harrison Brand, all affiliated with the Talkowski and Daly labs. The results reveal diverse forms of protein-coding variation in Autism and inform the molecular roots of brain development and neurodiversity.

Two of the largest studies of their kind in schizophrenia research were published in *Nature* in 2022. An exome sequencing study led by ATGU trainee Tarjinder Singh in the Daly and Neale laboratories from

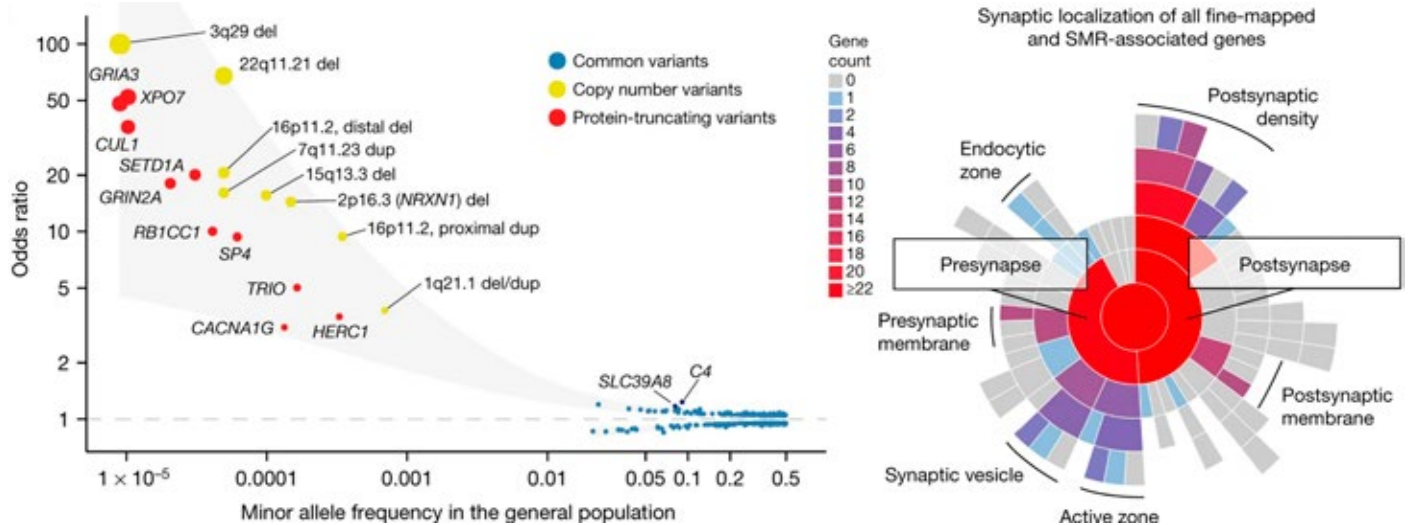


Figure 4.

121,000 subjects was published in *Nature* and identified ultra-rare protein-disrupting mutations in 10 genes that strongly increase an individual's risk of developing schizophrenia (**Figure 4**). The findings complement those of a 320,000-person genome-wide association study from the Psychiatric Genomics Consortium, also published in *Nature*, and underscore an emerging view of schizophrenia as a breakdown in communication at the synapse.

Improving polygenic prediction in ancestrally diverse populations.

Ruan Y et al. (2022). *Nature Genetics*; 54:573-580.

Polygenic risk scores (PRS) use genetic information to predict individuals' disease risk, but their accuracy is limited in non-European populations. Using genomic data from underrepresented populations, CGM faculty Tian Ge, Hailiang Huang, and colleagues developed a new method, PRSCSx, that predicts disease risk across populations. They used computational methods that maximize the value of non-European data and improve prediction accuracy in ancestrally diverse individuals. The method could help reduce health disparities when using PRS in the clinic, and support studies on genetic risk for disease.

New Therapy for Cerebral Adrenoleukodystrophy (CALD)

The US Food and Drug Administration's (FDA) Cellular, Tissue, and Gene Therapies Advisory Committee (CTGTAC) unanimously endorsed a new therapy for CALD developed by CGM and Department of Neurology faculty member Florian Eichler and a team of MGH scientists. The team collaborated with transplant experts at Boston Children's Hospital and Bluebird Bio to design a trial using an ex vivo lentiviral gene therapy approach. This therapy uses autologous cells—that is, the patient's own cells—that have undergone gene correction. Using autologous cells avoids the risks of transplants from other people and could be valuable for patients who do not have a close sibling donor match. CALD is the most severe form of

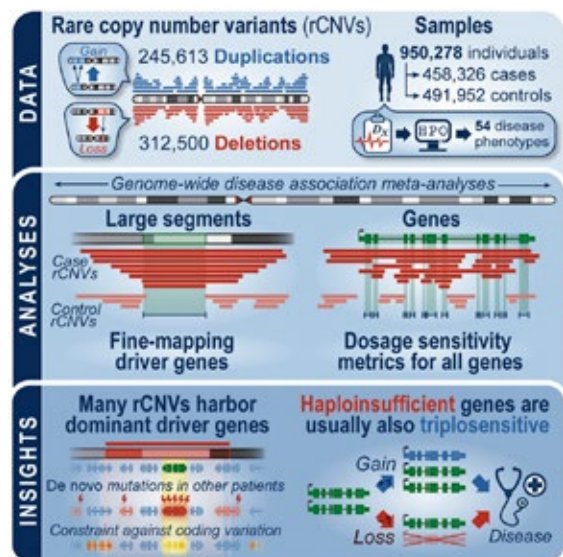


Figure 5. A cross-disorder dosage sensitivity map of the human genome from Collins et al., 2022, *Cell*.

adrenoleukodystrophy, a rare neurodegenerative disease that primarily affects boys.

Allele-specific silencing of the gain-of-function mutation in Huntington's disease using CRISPR.

Shin JW et al. (2022). *JCI Insight*. 30:e141042

Huntington's disease is caused by dominant, gain-of-function mechanisms, suggesting that allele-specific silencing of mutant Huntingtin (HTT) may have therapeutic benefit. In this study by CGM faculty members Ben Kleinstiver, Jong-Min Lee, Ihn Sik Seong and colleagues, the group capitalizes on PAM-Altering SNP (PAS) to develop an allele-specific CRISPR-Cas9 strategy to permanently inactivate mutant HTT through nonsense-mediated decay (NMD). The group developed a strategy to spare the wild type allele, while permitting mutant-specific CRISPR-Cas9 therapeutics in a predicted ~20% of HD subjects with European ancestry. GUIDE-seq analysis and subsequent validation experiments supported high levels of on-target gene specificity. This strategy proves the concept of PAS-based allele-specific NMD-CRISPR-Cas9 and supports its therapeutic potential in HD.

Sequencing identifies multiple genes and rare variants associated with Crohn's disease susceptibility.

Sazonovs A, et al. (2022), *Nature Genetics*; 54(9):1275-1283.

Genome-wide association studies (GWAS) have identified hundreds of loci associated with Crohn's disease. However, as with all complex diseases, robust identification of the genes regulated by noncoding variants has been challenging. This study by CGM investigators Mark Daly, Hailing Huang, Arno Palotie, and colleagues defines actionable biological targets in Crohn's by analyzing sequence data from more than 30,000 patients and 80,000 controls. Ten genes were identified where coding variation was associated with general onset Crohn's disease and serve to identify important therapeutic targets and a paradigm by which data emerging from large scale sequencing efforts can inform GWAS associations with far greater granularity than previously possible.

A cross-disorder dosage sensitivity map of the human genome.

Collins R, et al. (2022). *Cell*; 85(16):3041-3055.

Rare copy number variants (rCNVs)—deletions and duplications of large stretches of DNA—affect disease risk through numerous mechanisms, many of which remain unknown. A massive-scale study from the lab of CGM director Michael Talkowski and colleagues integrated rCNV data from nearly one million individuals to generate a new map that charts dosage sensitivity (genomic segments' tolerance to deletion or duplication) across the entire genome. Their findings reveal relationships between the dosage sensitivity of specific genomic regions and 54 different disorders. They also developed a machine learning model that flagged 2,987 genes as deletion-sensitive, and a surprisingly large number—1,559—as

potentially duplication-sensitive. Notably, these triplosensitive genes were strongly enriched for *de novo* missense variation from studies of neurodevelopmental disorder cases after controlling for known genes, suggesting that triplosensitive loci may represent a reservoir of novel gene discoveries in human disease. These metrics and methods provide an openly accessible new resource that will support all disease association and clinical interpretation frameworks for CNVs.

Statistical and functional convergence of genetic influences on autism at chromosome 16p.

Weiner D, et al. (2022). *Nat Genet*; 54(11):1630-1639.

The canonical paradigm for converting genetic association to mechanism involves iteratively mapping individual associations to the proximal genes through which they act. In this study from CGM (PNGU) and Department of Psychiatry faculty member Elise Robinson's laboratory - led by Harvard MD/PhD student Daniel Weiner - demonstrates the feasibility of extracting biological insights from a very large region of the genome and leverage this strategy to study the genetic influences on autism. Using a new statistical approach, they identified the 33Mb p-arm of chromosome 16 that includes the autism-associated 16p11.2 CNV as harboring the greatest excess of autism's common polygenic influences. Analysis of RNA-sequencing data revealed that both the common polygenic influences within 16p and the 16p11.2 deletion were associated with decreased average gene expression across 16p. The transcriptional effects of the rare deletion and diffuse common variation were correlated at the level of individual genes and analysis of Hi-C data revealed patterns of chromatin contact that may explain this transcriptional convergence. These results reflect a new approach for extracting biological insight from genetic association data and suggest convergence of common and rare genetic influences on autism at 16p.

II. Awards

Heidi Rehm: 2022 American Society of Human Genetics Curt Stern Award

At the annual American Society of Human Genetics (ASHG), CGM faculty member Heidi Rehm was announced as the 2022 Curt Stern Award winner. The Stern award is among the most prestigious given by ASHG and recognizes remarkable scientific achievements in human genetics that have occurred during the last 10 years. Nobody is more deserving of this award than Heidi. The breadth of her impact on clinical genetics and genomics is immeasurable. She has engaged in virtually all of the major international consortia related to variant interpretation and the open sharing of genomic information for the benefit of patients and the community. Heidi's leadership has been vital to the launch and sustained success of major international initiatives in genomic medicine, such as the All of Us Research program, the Clinical Genome Resource (ClinGen), gnomAD, GA4GH, the Centers for Mendelian Genetics (GREGoR consortium), and many others. She also has served in the field through her numerous roles

in the American College of Medical Genetics and Genomics (ACMG), including as a current member of the Board of Directors and VP of Laboratory Genetics. Heidi also serves many layers of leadership in our local genomic medicine community. She is the Chief Genomics Officer in the DOM and Director of the GMU in the CGM at MGH, she is the Medical Director of the Clinical Research Sequencing Platform and Co-Director of the Program in Medical and Population Genetics at the Broad, and she is spearheading the development of a cohesive plan to implement clinical genomics across the MGH, MGB, and Broad Institute communities. She is also co-lead of our T32 MGB Training Program in Precision Medicine and Genomic Medicine.

Alicia Martin: 2022 Sklar Innovation Award in Psychiatric Genetics

As the legacy of Pamela Sklar continues to influence our psychiatric genetics initiatives across the CGM, and particularly within our PNGU and ATGU communities, a special announcement at the World Congress for Psychiatric Genetics touched many in our community as one of our newest faculty members, Alicia Martin, PhD, was announced as the recipient of the 2022 Pamela Sklar Innovation Award. The Sklar Innovation Award honors the memory of Pamela and recognizes people and groups for innovation in Psychiatric Genetics. Alicia was recognized for her instrumental role in developing analytic tools and population genetic resources to determine polygenic risk and interpret its impact across multi-ethnic and underrepresented populations. Her work in Africa and other populations underserved in the genomics community has shed light on the major voids in current international biobank efforts in human genetics and she has been a strong advocate for the community to begin to address this considerable void in our field.

Benjamin Neale: Blavatnik Award for Young Scientists Finalist

Ben Neale, PhD, CGM faculty member in the ATGU was named a finalist for the Blavatnik Award for Young Scientists. Overall, 31 finalists were chosen from a highly competitive pool of 309 nominees across the United States. As a world leader in psychiatric genetics, Ben has advanced our understanding of the genes underlying neuropsychiatric disorders and the methods he has developed are some of the most widely used analytic tools to understand complex genetic traits. His research in the CGM, ATGU, and Stanley Center has transformed our understanding of how genetics shape disease risk.

Christiano Alves named an MGH Transformative Scholar

Christiano Alves, PhD, received one of four MGH Transformative Scholar Awards in 2022. Christiano is an Instructor in Neurology in the CGM and a member of the Kleinstiver laboratory. His proposal in spinal muscular atrophy (SMA) research is an outgrowth of his work with Kathy Swoboda and Ben to develop CRISPR-based therapeutic approaches to SMA. We are highly enthusiastic about Christiano's award and his trajectory as an emerging leader in Neurogenetics and therapeutic development.

Pradeep Natarajan, MD, MMSc: 2022 Anne Klibanski Excellence in Mentoring Award

Dr. Natarajan, of the CGM and the Department of Medicine (cardiology), was the winner of the 2022 Anne Klibanski Award for Excellence in Mentoring, which is awarded to an exceptional research mentor whose first faculty appointment occurred no more than 10 years ago. This award is named in honor of Anne Klibanski, President and CEO of MGB, founder and former Chief of the MGH Neuroendocrine Unit. She has mentored hundreds of trainees and faculty at MGH, many of whom have gone on to become leaders in academic medicine. Dr. Natarajan exemplifies the spirit of the award given to an outstanding mentor.

Kathryn Gray, MD, PhD: Harvard Medical School Young Mentorship Award

The Excellence in Mentoring Awards were established to recognize the value of quality mentoring relationships and the impact they have on professional development and career advancement in basic/clinical medicine, research, teaching, and administration. Dr. Kathryn Gray, a CGM instructor and member of the BWH Department of Obstetrics and Gynecology, was recognized for excellence in mentoring with the Harvard Medical School Young Mentorship Award.

Dr. Ben Kleinstiver: 2022 NIH Director's New Innovator Award

The [NIH Director's New Innovator Award Program](#) supports early stage investigators of exceptional creativity who propose highly innovative research projects with the potential to produce a major impact on broad, important areas relevant to the mission of NIH. CGM and Department of Pathology faculty member Dr. Ben Kleinstiver received a 2022 Innovator award to optimize and apply new protein engineering methods to accelerate the development of improved CRISPR technologies, to develop new capabilities for editing genomes, and to transform these tools into safe and effective genetic therapies.

2021 MGH Martin Prize Recognition Awards

Each year ECOR selects one fundamental and one clinical research paper as the most outstanding to emerge from MGH investigators for the Martin Prize. In 2022, ECOR provided Celebration of Science Recognition Awards for the most competitive nominations that were not selected. The awards were announced at the 2022 SAC meeting, and including CGM (ATGU) faculty member Mark Daly and CGM (PNGU) faculty member Erin Dunn for the following publications:

COVID-19 Host Genetics Initiative, Mapping the human genetic architecture of COVID-19. *Nature*. July 8, 2021. Nature doi: 10.1038/s41586-021-03767

Mark Daly on behalf of the Host Genetics Initiative

Association of Maternal Stress and Social Support During Pregnancy with Growth Marks in Children's Primary Tooth Enamel. JAMA Netw Open. 2021 Nov 1;4(11): e2129129.

Erin Dunn, ScD, MPH

III. Community

During the 2021-2022 academic year, the CGM launched an internal MGB faculty search in genomic medicine. Our search produced outstanding candidates, and four new faculty were ultimately selected. These candidates included Dr. Raghu Chivukula of the Department of Medicine, Pulmonary and Critical Care Medicine Division. Dr. Chivukula leads an innovative rare genetic diseases program with a true bedside to bench theme. Dr. Pradeep Natarajan, Associate Professor of Medicine, and Director of Preventative Cardiology at MGH was selected to join the CGM and to spearhead a world-leading program of cardiovascular genetics. Dr. Tian Ge, Assistant Professor of Psychiatry, has led innovative work in statistical genetics and polygenic risk scores, was selected to join the CGM faculty, and Dr. Konrad Karczewski, one of the leads on the Genome Aggregation Database (gnomAD) project, joins the CGM faculty in ATGU to continue his innovative work on analysis of human genetic variation and its impact.

The CGM also held its first call for associate members, who are fully integrated into CGM science and community but retain their departmental space assignment and principal appointment. Nine associate members across multiple departments and divisions including those not previously represented at CGM, including surgery, urology, obstetrics and gynecology, reproductive endocrinology, gastroenterology, and ophthalmology, were appointed, along with three senior associate members, Dr. Stephanie Seminara (Chief, Reproductive Endocrinology), Dr. Patrick Ellinor (Interim Chief of Cardiology), and Dr. Rudolph Tanzi (Director of the Genetics and Aging Research Unit).

All CGM affiliated faculty and their laboratories were invited to attend the 2022 CGM Retreat hosted at the Broad Institute, where over 200 CGM'ers engaged in scientific talks in genomic medicine from CGM and MGB (Elizabeth Karlson, MD, MS, Director of MGB Personalized Medicine), soft skills training in negotiating differences among stakeholders (Rachel Viscomi, JD, Director of Harvard Negotiation and Mediation and Clinic), the use of pronouns and language to promote diversity and inclusion (Carl Streed Jr., MD, MPH, Center for Transgender Medicine and Surgery, Boston Medical Center), and exchanging scientific ideas in a poster session and across seminars throughout the day in November 2022.

IV. Training

The primary training initiative in the CGM has been an NHGRI Institutional Research Training Grant (T32) program: **“MGB Training Program in Precision and Genomic Medicine”**, co-led by CGM faculty Drs. Heidi Rehm (GMU) and Jordan Smoller (PNGU). This T32 initiative has engaged 43 faculty within its program from throughout the MGB community and is in its **fifth** annual call for new trainees in Precision and Genomic Medicine. The **CGM Genomic Medicine Seminar** returned to hybrid with person/remote capabilities in the Simches main conference room and increased in frequency to a weekly seminar to promote greater interaction and engagement. The seminar hosted local, national, and international speakers in genomic medicine. In the Spring of 2023, we will host NHGRI Director Dr. Eric Green in the CGM Seminar Series and welcome the broader MGH and MGB genomics community to our seminar and soft skills sessions.

DAVID SCADDEN, MD, DIRECTOR

Overview:

The Center for Regenerative Medicine focuses on stem cell biology to develop novel therapies. Scientists and physician/surgeon-scientists from Medicine, Surgery, Orthopedics and Psychiatry use the principles of how stem cells create and maintain normal organ function to gain insight into diseases from tendon injury, to memory loss, to cancer, to cystic fibrosis. Using these we seek to develop drug and cell therapies.

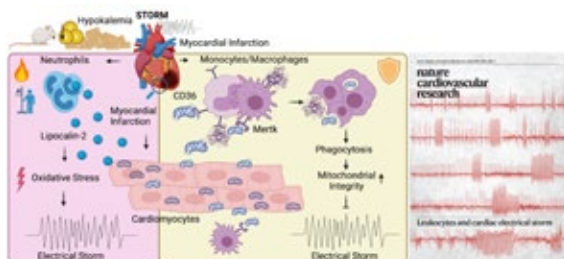
Achievements:

The Center for Regenerative Medicine in 2022:

1. Discovered a new mechanism that expands neural stem cells in the adult brain. The laboratory of Amar Sahay, PhD demonstrated that the molecule, Klf9, can increase the number of stem cells in the adult hippocampus, a region of the brain critical for memory (eLife).
2. Defined the basis for blood abnormalities in the genetic disease, Barth Syndrom. David Sykes MD, PhD and colleagues showed that mutations in TFAZZIN, which cause the syndrome, lead to endoplasmic reticulum stress in neutrophils and their enhanced cell death (Blood Advances).
3. Demonstrated that proton pumps on cell membranes change the intracellular pH and thereby enhance enzyme activities favoring macromolecule generation and cell proliferation. The lab of David Scadden, MD showed that hematopoietic cells gain a competitive advantage in vivo with proton pump activation, a process leukemic cells coopt and become dependent upon. By impeding proton pump activity in leukemia, the cells die including leukemic stem cells in animal models (Blood).



Image Award Finalist
Frozen Potential
Emma Yvanovich, BA
CRM



Sudden cardiac death occurs frequently in patients with myocardial infarction (MI). We created a mouse model in which hypokalemia combined with MI triggered spontaneous ventricular tachycardia in ambulatory mice, and showed that major leukocyte subsets have opposing effects on cardiac conduction. Neutrophils increased ventricular tachycardia via lipocalin-2 in mice, while neutrophilia associated with ventricular tachycardia in patients. In contrast, macrophages protected against arrhythmia. Higher arrhythmia burden and mortality in *Cd36*^{-/-} and *Mertk*^{-/-} mice, viewed together with reduced mitochondrial integrity and accelerated cardiomyocyte death in the absence of macrophages, indicated that receptor-mediated phagocytosis protects against lethal electrical storm. Thus, modulation of leukocyte function provides a potential therapeutic pathway for reducing the risk of sudden cardiac death.

RALPH WEISSLEDER, MD, PHD, DIRECTOR

Overview:

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, Castro, Garriss, Higgins, Hwang, Lee, Lin, Im, Miller, Nahrendorf, Naxerova, Pai and Weissleder), Core Platforms (Mouse imaging Nahrendorf; Chemistry Carlson; Biocomputing Pivovarov) and several thematic research programs. The CSB is located within the Simches and CNY Research buildings. There are currently 162 full time employees, including 32 faculty.

Achievements:

Novel bioorthogonal probe platform for highly multiplexed in vivo imaging

This year's Nobel prize in Chemistry was awarded to Bertozzi, Meldal and Sharpless for bioorthogonal chemistries to decipher biological function. Members of CSB have a long history of developing novel bioorthogonal compounds for imaging dating back nearly 15 years. In this study we describe the first platform to enable highly multiplexed imaging in live cells, tissues and mouse models. This technology will find broad utility for investigating physiologic dynamics in living systems. Specifically, the new method is based on scission-accelerated fluorophore exchange (SAFE). SAFE uses a rapid bioorthogonal click chemistry to remove immunofluorescent signals from the surface of labeled cells, cycling the nanomolar-concentration reagents in seconds and enabling multiple rounds of staining of the same samples. It is non-toxic and functional in both dispersed cells and intact living tissues. We demonstrate multiparameter ($n \geq 14$), non-disruptive imaging of murine peripheral blood mononuclear and bone marrow cells to profile cellular differentiation. We also show longitudinal multiplexed imaging of bone marrow progenitor cells as they develop into neutrophils over 6 days and real-time multiplexed cycling of living mouse hepatic tissues. We anticipate that SAFE will find broad utility for investigating physiologic dynamics in living systems.

Ko, J.; Wilkovitsch, M.; Oh, J.; Kohler, R. H.; Bolli, E.; Pittet, M. J.; Vinegoni, C.; Sykes, D. B.; Mikula, H.; Weissleder, R.; Carlson, J. C. T. Spatiotemporal multiplexed immunofluorescence imaging of living cells and tissues with bioorthogonal cycling of fluorescent probes. *Nature Biotechnol.* 2022, Jun 2. doi: 10.1038/s41587-022-01339-6.

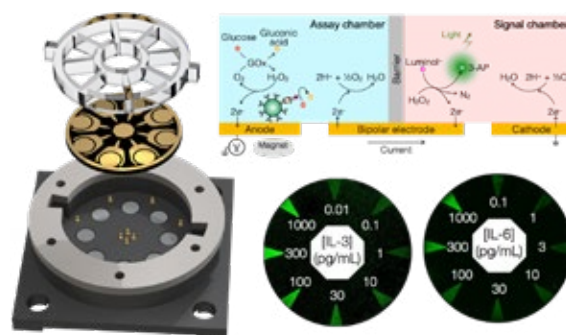
Brain motor and fear circuits regulate leukocytes during acute stress.

The nervous and immune systems are intricately linked. Although psychological stress is known to modulate immune function, mechanistic pathways linking stress networks in the brain to peripheral leukocytes remain poorly understood. Here we show that distinct brain regions shape leukocyte distribution and function throughout the body during acute stress in mice. Using optogenetics and chemogenetics, we demonstrate that motor circuits induce rapid neutrophil mobilization from the bone marrow to peripheral tissues through skeletal-muscle-derived neutrophil-attracting chemokines. Conversely, the paraventricular hypothalamus controls monocyte and lymphocyte egress from secondary lymphoid organs and blood to the bone marrow through direct, cell-intrinsic glucocorticoid signalling. These stress-induced, counter-directional, population-wide leukocyte shifts are associated with altered disease susceptibility. On the one hand, acute stress changes innate immunity by reprogramming neutrophils and directing their recruitment to sites of injury. On the other hand, corticotropin-releasing hormone neuron-mediated leukocyte shifts protect against the acquisition of autoimmunity, but impair immunity to SARS-CoV-2 and influenza infection. Collectively, these data show that distinct brain regions differentially and rapidly tailor the leukocyte landscape during psychological stress, therefore calibrating the ability of the immune system to respond to physical threats.

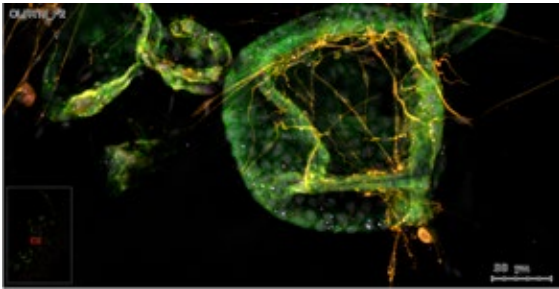
Poller, W. C.; Downey, J.; Mooslechner, A. A.; Khan, N.; Li, L.; Chan, C. T.; McAlpine, C. S.; Xu, C.; Kahles, F.; He, S.; Janssen, H.; Mindur, J. E.; Singh, S.; Kiss, M. G.; Alonso-Herranz, L.; Iwamoto, Y.; Kohler, R. H.; Wong, L. P.; Chetal, K.; Russo, S. J.; Sadreyev, R. I.; Weissleder, R.; Nahrendorf, M.; Frenette, P. S.; Divangahi, M.; Swirski, F. K. Brain motor and fear circuits regulate leukocytes during acute stress. *Nature.* 2022, 607, 578-584.

Pulmonary manifestations of chronic HPV infection in patients with recurrent respiratory papillomatosis.

Human papillomavirus (HPV) types 6 and 11 can infect the squamous epithelium of the respiratory tract. Up to 9% of patients with HPV-associated recurrent respiratory papillomatosis (RRP) have pulmonary involvement. Pulmonary manifestations of HPV infection are associated with considerable morbidity, in part because treatment options and management guidelines are lacking. Patients with pulmonary RRP have a 32-times increased lifetime risk of malignant transformation compared with the overall RRP population, highlighting the importance of routine screening for pulmonary involvement in the high risk patient populations. We describe the clinical and radiographic presentation, histopathological features, and genetics of pulmonary RRP. In addition, we provide surveillance and management



Electrochemiluminescence (ECL) in paired signal electrode (ECLipse) enables modular and scalable biosensing. ECL has an inherently low background and enables precise chemical reactions through electrical control. ECLipse is an advanced, compartment ECL system. We physically separated ECL generation from target detection. These two processes were carried out in isolated chambers and coupled through an electrode. The strategy allowed us to minimize cross-chemical reactions, design electrodes for high ECL signals, and integrate multiple sensors in a chip. As a proof of concept, we implemented an eight-plex ECLipse and applied it to detect host factors in human plasma. ECLipse achieved a higher signal-to-noise ratio than conventional ECL assays and was >7000-fold more sensitive than enzyme-linked immunosorbent assay. In a pilot clinical study, we could detect septic conditions by measuring host factors [i.e., interleukin-3 (IL-3), IL-6, and procalcitonin (PCT)]. Lee et al. *Science Advances* 8, eabq4022 (2022)



With increasing attention on the essential roles of the tumour microenvironment in recent years, the nervous system has emerged as a novel and crucial facilitator of cancer growth. In ongoing research, the Hwang lab studies how nerves contribute to tumor proliferation, stress adaptation, immunomodulation, metastasis, electrical hyperactivity and seizures, and neuropathic pain. The expanding knowledge base reveals multiple therapeutic avenues for cancer neuroscience that warrant further exploration in clinical studies. This image shows multiplexed immunofluorescence projection image (20x, spinning disk confocal) of murine pancreatic cancer organoids co-cultured with DRG sensory neurons in a Matrigel dome. Gray = nuclei; green = EpCAM; orange = beta-3-tubulin; magenta = SV2a; cyan = PSD-95. Scale bar 50 μ m. **Hwang et al. *Lancet Oncol.* 2022, 23, e62-e74**

algorithms based on our clinical experience with this complex patient population. Large cohort studies are needed to understand the natural clinical course of pulmonary RRP in order to develop guidelines for optimal and standardized surveillance. With increased awareness and understanding of this disease entity, the field can begin to develop and explore effective treatment strategies for this patient population.

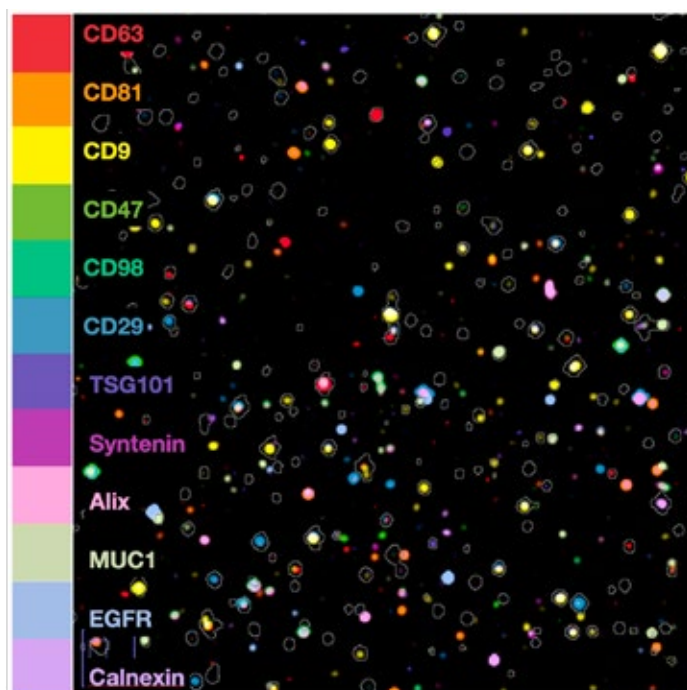
Pai, S. I.; Wasserman, I.; Ji, Y. D.; Gilman, M.; Hung, Y. P.; Faquin, W. C.; Mino-Kenudson, M.; Muniappan, A. Pulmonary manifestations of chronic HPV infection in patients with recurrent respiratory papillomatosis. *Lancet Respir Med.* 2022, 10, 997-1008.

Single-nucleus and spatial transcriptome profiling of pancreatic cancer

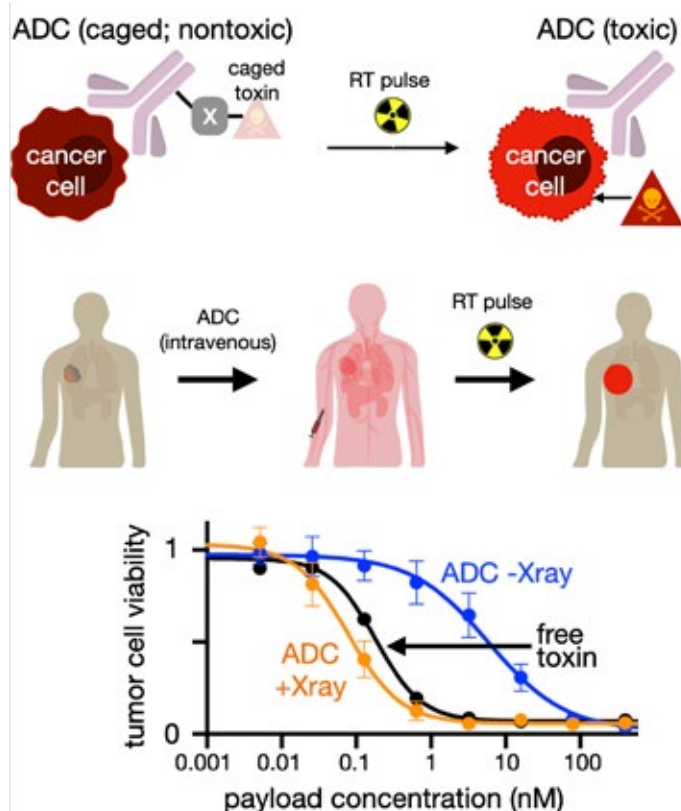
Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal and treatment-refractory cancer. Molecular stratification in pancreatic cancer remains rudimentary and does not yet inform clinical management or therapeutic development. Here, we construct a high-resolution molecular landscape of the cellular subtypes and spatial communities that compose PDAC using single-nucleus RNA sequencing and whole-transcriptome digital spatial profiling (DSP) of 43 primary PDAC tumor specimens that either received neoadjuvant therapy or were treatment naive. We uncovered recurrent expression programs across malignant cells and fibroblasts, including a newly identified neural-like progenitor malignant cell program that was enriched after chemotherapy and radiotherapy and associated with poor prognosis in independent cohorts. Integrating spatial and cellular profiles revealed three multicellular communities with distinct contributions from malignant, fibroblast and immune subtypes: classical, squamoid-basaloid and treatment enriched. Our refined molecular and cellular taxonomy can provide a framework for stratification in clinical trials and serve as a roadmap for therapeutic targeting of specific cellular phenotypes and multicellular interactions.

Hwang WL, Jagadeesh KA, Guo JA et al. Single-nucleus and spatial transcriptome profiling of pancreatic cancer identifies multicellular dynamics associated with neoadjuvant treatment. *Nat Genet.* 2022; 54(8) 1178-1191. doi:10.1038/s41588-022-01134-8. PubMed PMID: 35902743.

For a complete list of 2022 publications, please see here:
<https://csb.mgh.harvard.edu/publications?year=2022>



Exosomes and extracellular vesicles (EV) are increasingly being explored as circulating biomarkers, but their heterogeneous composition will likely mandate the development of single EV technologies. Highly multiplexed analyses of single EVs have been challenging to implement beyond a few colors during spectral sensing. Here we developed a multiplexed analysis of the single EV technique (MASEV) to interrogate thousands of individual EVs during 5 cycles of multi-channel fluorescence staining for 15 EV biomarkers. Contrary to the common belief, we show that i) several “ubiquitous” markers are much less common than believed; ii) that multiple biomarkers concur in single vesicles but only in small fractions, iii) that affinity purification can lead to loss of rare EV subtypes, and iv) that deep profiling allows detailed analysis of EV, potentially improving the diagnostic content. These findings establish the potential of MASEV for uncovering fundamental EV biology and increasing diagnostic accuracy for early cancer detection. **Spitzberg et al. *Nature Communications* 2022, in review**



Turning on antibody-drug-conjugate (ADC) payloads with local radiation therapy (RT). Tumor-targeted ADCs are used clinically to deliver toxic drug payloads to cancer cells, but off-target ADC accumulation leads to severe dose-limiting toxicities in patients. To overcome this issue, we have developed a new class of ADC that is selectively activated upon exposure to local RT. Tumor-targeted ADCs carry chemically caged toxins to cancer cells, and RT triggers local toxin release and activation (top). This strategy maximizes local cytotoxicity in tumor tissue while avoiding off-target sites of toxicity where ADCs may otherwise accumulate in the body (middle). RT enhances ADC cytotoxicity by a factor of >50-2,000 in some cases (bottom). **Miller et al. *Bioconjug Chem.* 2022 Aug 17;33(8):1474-1484**

Wellman Center for Photomedicine

Thematic Center Report

R. ROX ANDERSON, MD, DIRECTOR

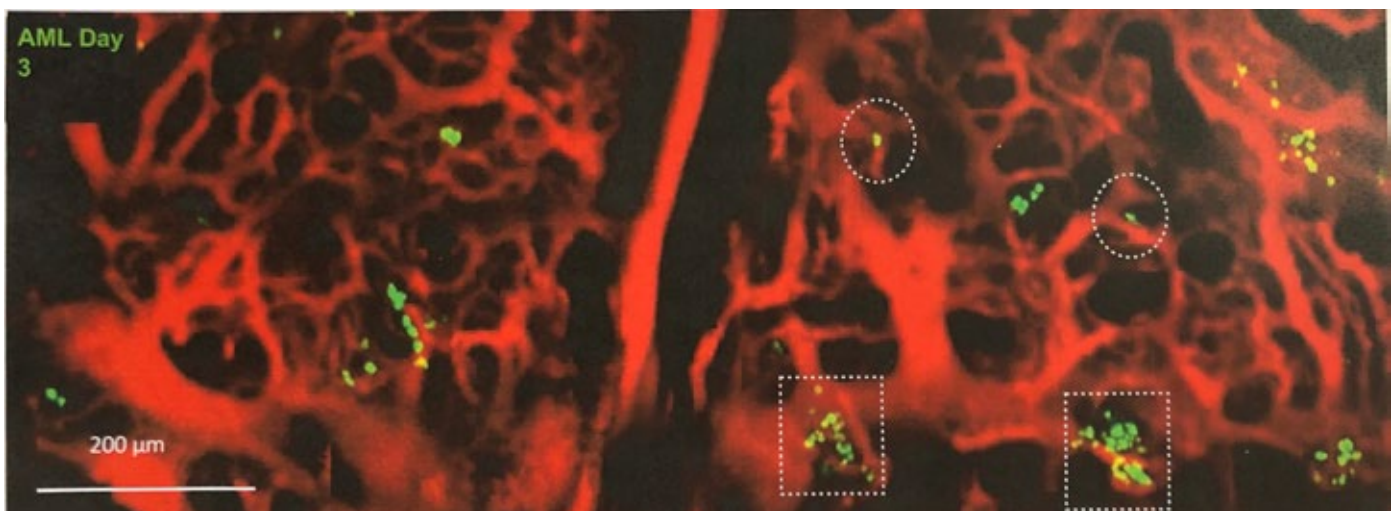
Overview

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. Major research themes include: advanced live microscopy, point-of-care optical diagnostics, light-activated treatments, wound repair and healing, trauma interventions, photobiomodulation (light-stimulated metabolic changes), melanoma genetics and treatment strategies, bio-inspired optical technologies, new medical laser technologies, and dozens of problem-driven projects.

Strategic priorities

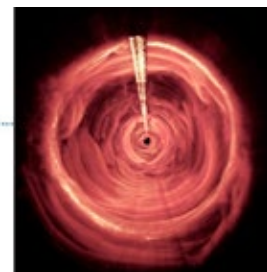
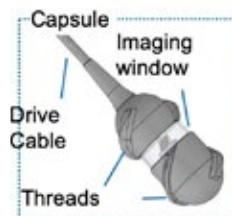
- *Leadership and excellence.* We are the world's largest research center in a rapidly expanding field, with 254 full time personnel. Our core strength is 30 excellent faculty (6 professors, 6 associate prof, 7 assistant prof, 10 instructors, 1 lecturer) plus 10 affiliated faculty. Our center includes 59 postdocs, 38 engineers, 20 graduate students, plus research, technical and clinical studies staff.

Wellman Center spent \$38M on research during FY 2022 coming from DOD, NIH, industry, foundations and donations respectively. We received 39 new research grant awards.



"Image-seq" technology was made by Charles Lin and colleagues, in order to find single cells in vivo, capture them, and discover their RNA expression. They discovered that bone marrow micro-environment, specifically the cavities where bone is either forming or being resorbed, determine whether acute myelogenous leukemia (AML) cancer cells can proliferate. In this image of live bone marrow, fluorescent AML cells are seen singly (circles) or in clusters (proliferating). The group discovered that expression of DPP4 (CD26), a transmembrane serine protease, is highly correlated with proliferation of AML cells and may be a target for AML treatment. [Haase, C., Gustafsson, K., Mei, S. *et al.* Image-seq: spatially resolved single-cell sequencing guided by in situ and in vivo imaging. *Nat Methods* **19**, 1622–1633 (2022). <https://doi.org/10.1038/s41592-022-01673-2>]

- *Innovation.* Wellman is the birthplace of many inventions and discoveries now in widespread use. In 2022, royalties generated ~\$24M of total revenue, there were 36 new invention disclosures, 178 new US and international patents were issued, and 19 sponsored research/license agreements initiated engaging ~\$3M of research revenue.
- *World Health.* We pursue collaborative research on problems from every continent with emphasis on child health, malnutrition, infection, environmental change, trauma, and cancer in developing countries.
- *Education.* We offer CME and special courses, a regular seminar and monthly lecture series, 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.
- *Magic.* The “Magic Wand” initiative at MGH, led by Lilit Garibyan, MD, PhD, launched 8 clinician-driven, problem-driven collaborative research projects spanning 4 departments: anesthesia (3), general surgery (2), orthopedic surgery (2), and laryngology (1). Based on a generous donation from Valentin Gapontsev, PhD, a second round of projects are aimed to begin in 2023.



The gold standard for colon cancer diagnosis is colonoscopy and biopsy, skillful procedures that require bowel preparation and sedation of patients. Prof. Gary Tearney (pathology) and colleagues have made a suite of live-microscopy devices for upper and now, lower GI tract imaging. Shown is a mucosal-contact, self-propelled imager that yields complete 3D reconstruction of the entire colon in minutes without the need for bowel prep. The group has also demonstrated image-guided biopsy and cell sampling capabilities. [Otuya DO, Dechene NM, Poshtupaka D, ... Tearney GJ. Passively scanned, single-fiber optical coherence tomography probes for gastrointestinal devices. *Lasers Surg Med.* 2022;54(7):935-44. Epub 20220616. doi: 10.1002/lsm.23576. PubMed PMID: 35708124; PMCID: PMC9541095.]

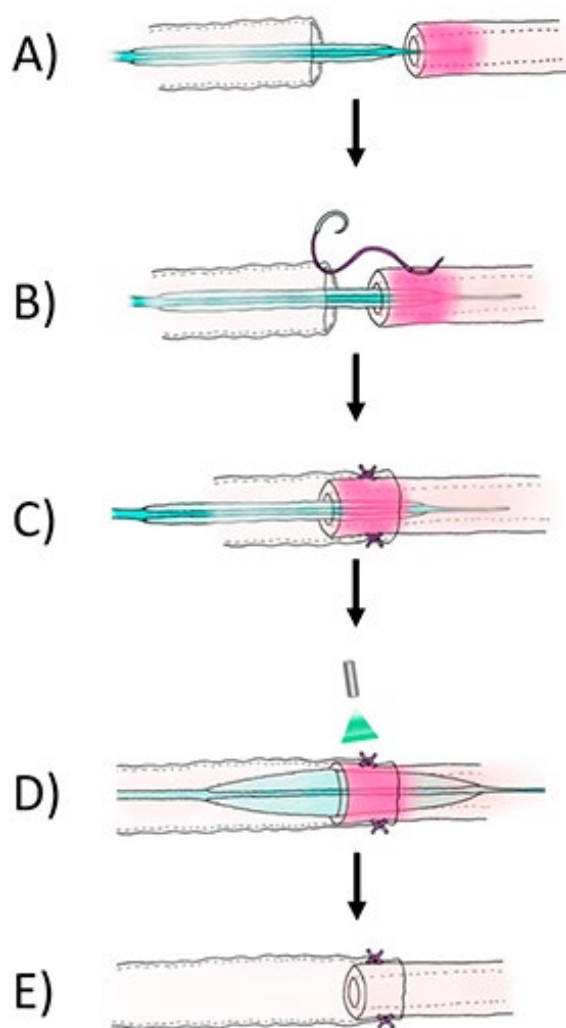
News from the Wellman Center

- Prof. Gary Tearney, MD, PhD opened a new engineering lab at 65 Landsdowne St in Cambridge, capable of design and manufacture of clinical-grade.
- We are starting renovations to Bartlett-4 that includes a new laboratory for Aaron Aguirre, MD, PhD, and an upgraded microbiology lab.
- Prof. Hensin Tsao, MD, PhD became the inaugural Richard Johnson Chair in Dermatology.
- Mei Wu, PhD was promoted to full professor at HMS.
- Prof. Brett Bouma, PhD is honored to join the National Academy of Inventors.
- Prof. Tayyaba Hasan, PhD received a Gold Medal award from the International Photodynamic Association.

Achievements:

2022 Research Highlights

Wellman Center publishes ~3 research papers/week. The highlights are a small sample of our work. In addition to the images and citations below,

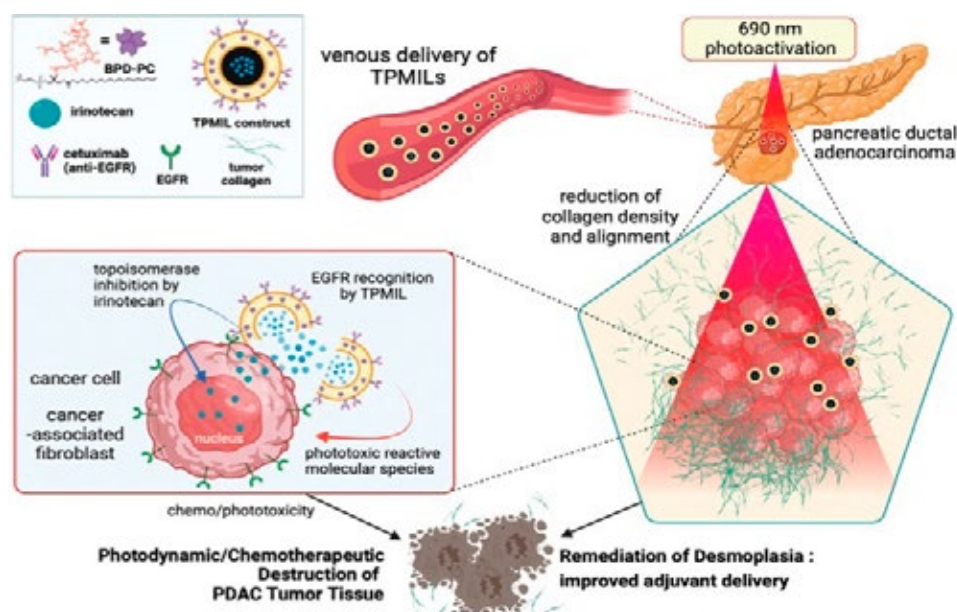


Robert Redmond, PhD and MGH surgery collaborators have developed light-activated tissue bonding via topically-applied rose Bengal photochemistry, for better vascular surgery. In large animals, there is immediate, strong and permanent bonding that remains patent, with minimal restenosis or scarring compared with conventional techniques. A startup company has licensed the technology. [Scott BB, Randolph MA, Guastaldi FPS, Wu RC, Redmond RW. Light-Activated Vascular Anastomosis. *Surg Innov.* 2022 May 21;15533506221104382. doi: 10.1177/15533506221104382. Epub ahead of print. PMID: 35603581.]

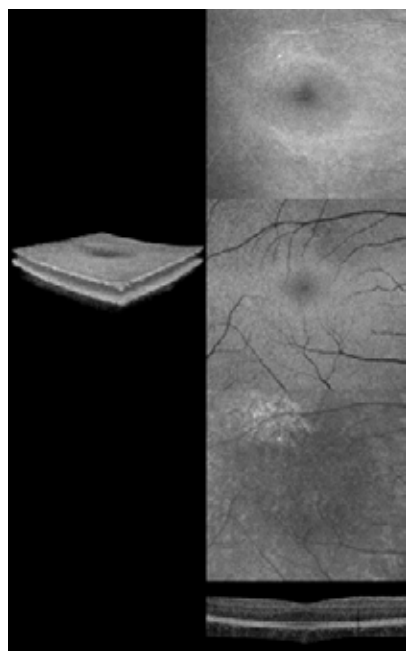
- Mei Wu and colleagues found that gold nanoclusters, which can concentrate in solid tumors and increase electromagnetic field strength through resonance effects, greatly increase efficiency for photodynamic therapy. [Kong YF, ... Wu MX. A NIR-II-emitting gold nanocluster-based drug delivery system for smartphone-triggered photodynamic theranostics with rapid body clearance. *Materials Today.* 2021. Volume 51. 96-107]

Lilit Garibyan and colleagues developed sterile injectable ice slurries that selectively affect lipid-rich cells including adipocytes and myelinated nerves. Excess tongue fat causes a substantial fraction of sleep apnea; scaling up for human studies, injection of ice slurry into swine tongue was found to safely reduce tongue fat [Orestes MI, Tuchayi SM, Wang Y, Farinelli W, Arkun K, Anderson RR, Thomas R, Garibyan L. Safety and feasibility of selective tongue fat reduction with injected ice-slurry. *Laryngoscope Investig Otolaryngol.* 2022 Oct; 7(5):1675-1680. PMID: [36258870](https://pubmed.ncbi.nlm.nih.gov/36258870/); PMCID: [PMC9575057](https://pubmed.ncbi.nlm.nih.gov/PMC9575057/)]

- Tayyaba Hasan and colleagues designed an intra-oral LED source 3D printed delivery device to provide diagnosis and photodynamic therapy for oral cancer in low-resource settings. In India, their clinical trial found 76% complete tumor response over a 5-year follow up period for early oral carcinoma, an endemic disease of the region. [Siddiqui SA, Siddiqui S., Hussain MAB, ... Hasan T. Clinical evaluation of a mobile, low-cost system for fluorescence guided photodynamic therapy of early oral cancer in India. *Photodiagnosis Photodyn Ther.* 2022 Jun;38:102843. doi: 10.1016/j.pdpdt.2022.102843. PMID: 35367616; PMCID: [PMC9177774](https://pubmed.ncbi.nlm.nih.gov/PMC9177774/).]
- Conor Evans and colleagues have synthesized unique optical reporter molecules and incorporated them into devices, that rapidly report and track both pO_2 and pCO_2 of live tissue. There are a host of potential scientific and medical applications. (Cascales, J.P.; Li, X.; Roussakis, E.; Evans, C.L. A Patient-Ready Wearable Transcutaneous CO_2 Sensor. *Biosensors* 2022, 12, 333. <https://doi.org/10.3390/bios12050333>). The same lab developed a hydrophilic (swellable) dressing that handles wound exudates while simultaneously mapping and monitoring wound oxygenation.



Tayyaba Hasan's lab is pursuing an effective treatment for pancreatic cancer, by a strategic combination of light-activated, synergistic mechanisms. EGF-receptor binding was used to target novel multi-functional liposomes, which upon light exposure release an anti-desmoplastic agent, a chemotherapy agent, and a photodynamic therapy agent. In an orthotopic human pancreatic adenocarcinoma model, survival time was increased substantially more than single-agent treatments, with low systemic toxicity. These results pave the pathway to human trials. [Obaid G, Bano S, Thomsen H, ... Hasan T. Remediating Desmoplasia with EGFR-Targeted Photoactivable Multi-Inhibitor Liposomes Doubles Overall Survival in Pancreatic Cancer. *Adv Sci (Weinh)*. 2022 Aug;9(24):e2104594. doi: 10.1002/adv.202104594. Epub 2022 Jun 24. PMID: 35748165; PMCID: PMC9404396.]



Ben Vakoc's laboratory invented two remarkable advances for live optical tomographic imaging. They recently broke the limits for both speed and depth-of-field imaging with optical coherence tomography (OCT). Using a unique optical frequency-comb technology, video-rate OCT of human retina was achieved; a related strategy will allow OCT to provide open and endoscopic surgical field guidance that sees structures beyond the tissue surface, reconstruct the field in 3D, and provide precise distance/size measurements. For quantitative retinal blood flow imaging, a new OCT strategy of detecting dynamic modulation of forward-scattered photons was used. Precise arterial waveforms and flow velocity are measured. These advances are promising for both research and clinical applications. [Nam AS, Braaf B, Vakoc BJ. Using the dynamic forward scattering signal for optical coherence tomography-based blood flow quantification. *Opt Lett*. 2022 Jun 15;47(12):3083-3086.]

Anesthesia, Critical Care and Pain Medicine

Department Report

SEUN JOHNSON-AKEJU, MD, MMSC, CHIEF

Overview:

Research activities at the Department of Anesthesia, Critical Care and Pain Medicine (DACCPM) are an integral aspect of the department's overall mission focusing on patient care, education, research innovation, and community service.

1. DACCPM researchers have national and international reputations and the research activities encompass a broad range of disciplines, focusing on cardiac and pulmonary pathophysiology, molecular and system neuroscience, pharmacology, pain neurobiology, neuroimaging, stem cell research, genetics, comparative outcome research, biomedical engineering, new drug and medical device development, pain medicine, and clinical research.
 - i. DACCPM has over 160 research staff, including MD and/or PhD investigators, post-doctoral fellows, graduate students, administrative and supporting staff, and another 66 research staff with non-employee status.
 - ii. Laboratories and clinical research units are located in the main MGH campus and the MGH-East research facility at the Charlestown Navy Yard.
 - iii. Research activities at DACCPM continue to grow and are currently supported by 117 grants, including 62 NIH grants, and submitted 188 grant applications and reporting as of FY2022. Total grant awards from NIH were increased by over 11% as compared to those of FY2021.
 - iv. In 2022, the DACCPM faculty published 326 journal articles and numerous books/book chapters.

There are three long-term strategic research priorities at DACCPM:

1. Expanding a premier research team: We have been implementing a long-term plan to foster the growth of three tiers of investigators, including i) T32 and K08 trainees, ii) junior and mid-level investigators, and iii) 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 MD and/or PhD investigators, and supplemental salary support for basic science and clinical researchers. During 2022, the department has further enhanced the effort of recruiting future physician-scientists, starting at the annual resident recruitment process with a PRIME track and a director who oversees this effort.
2. Strengthening a research platform that promotes integration between basic science and clinical research: Our research leadership structure consists of a Vice Chair for Research and Innovation and four research directors, under the leadership of the department chief. The research directors are responsible for four strategic focus areas, including Basic Science, Translational

Research and Innovation, Clinical Research, and Research Training and Education. With the advice of our departmental Research Council of 20 elected members (every two years), we have implemented several initiatives to support basic science, translational, clinical and comparative outcome research, including competitive intra-departmental clinical research funding mechanisms that provide financial support for clinical research and an innovative Anesthesia Research Center (ARC), which is an integrative center for clinical and observational studies with a first-tier statistical faculty, project manager, and study coordinators. 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.

3. Using research invention/innovation to advance translational research and support 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.

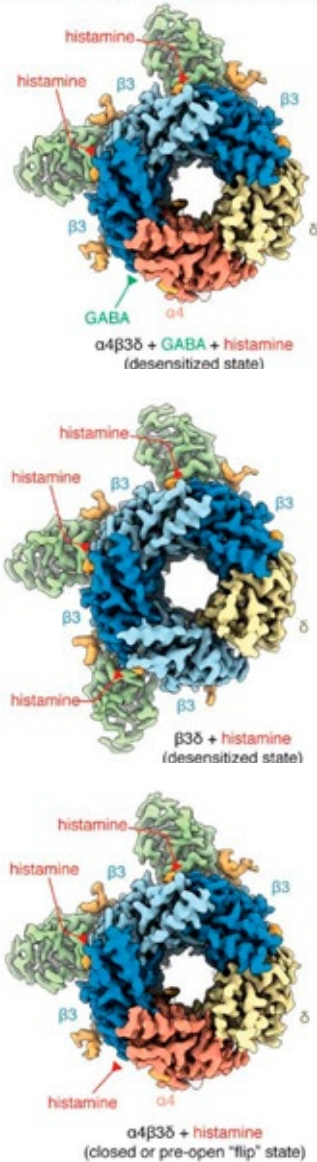
Achievements:

Highlights in Research, Honors, and Awards in 2022:

The excellence of research at the DACCPM is reflected by a combination of basic science, clinical and translational research achievements led by the nation's largest physician-scientist group in the anesthesia field, a large group of top-notch non-clinician PhD investigators, and an engaging clinical staff, fellows, and residents in our department. The following are several representative events and achievements from DACCPM in 2022.

1. DACCPM Next Decade Research Blueprint: During 2022, our departmental Research Council developed a Research Blueprint for the next decade. The goal is to strategize the priorities for research infrastructure, growth of investigators and research staff, development of leading-edge research frontiers, and research invention and innovation. This Blueprint will be implemented during the FY2023 and beyond according to the strategic goals of the department.
2. Highlights of Research Achievements:
 - i. **Differential assembly diversifies GABAA receptor structures and signaling.**
The lab of MGH DACCPM researcher Keith Miller, PhD,

b Dataset 2: + 0.2 mM GABA + 1 mM histamine



Survey of ligands bound in agonist pockets in different datasets.

Figure b shows $\alpha 4 \beta 3 \delta$ and $\beta 3 \delta$ GABAARs solved in the presence of 0.2 mM GABA and 1 mM histamine.

Publication Citation:

Differential assembly diversifies GABAA receptor structures and signalling
Andrija Sente, Rooma Desai, Katerina Naydenova, Tomas Malinauskas, Youssef Jounaidi, Jonas Miehling, Xiaojuan Zhou, Simonas Masiulis, Steven W. Hardwick, Dimitri Y. Chirgadze, Keith W. Miller, A. Radu Aricescu
Nature volume 604, pages190–194 (2022)
PMID: 35355020 PMCID: PMC7612593

published their third *Nature* paper in in as many years. The most recent publication from Dr. Miller's group/collaborators shows that that selected GABAAR arrangements can act as coincidence detectors, simultaneously responding to two neurotransmitters: GABA and histamine. Using assembly simulations and single-cell RNA sequencing data^{8,9}, the group calculated the upper bounds for receptor diversity in recombinant systems and in vivo. They propose that differential assembly is a pervasive mechanism for regulating the physiology and pharmacology of GABAARs.

Publication Citation:

Differential assembly diversifies GABAA receptor structures and signalling
Andrija Sente, Rooma Desai, Katerina Naydenova, Tomas Malinauskas, Youssef Jounaidi, Jonas Miehling, Xiaojuan Zhou, Simonas Masiulis, Steven W. Hardwick, Dimitri Y. Chirgadze, Keith W. Miller, A. Radu Aricescu.
Nature volume 604, pages190–194 (2022)
PMID: 35355020 PMCID: PMC7612593

ii. Post-cardiac Arrest Sedation Promotes Electroencephalographic Slow-wave Activity and Improves Survival in a Mouse Model of Cardiac Arrest.

A study led by investigators in the MGH DACC PM including Drs. Fumito Ichinose, Takamitsu Ikeda, Yusuke Miyazaki, Risako Kato, Eizo Marutani, Ken Solt, and colleagues outside the department was selected as the editor's choice for the December issue of *Anesthesiology*. Researchers investigated the potential benefits of sedation after cardiac arrest. Key takeaways from the study show that administering the sedatives propofol or dexmedetomidine when circulation is restored following cardiac arrest improved survival and brain function in mice. The findings suggest that sedation of patients recovering from cardiac arrest in the intensive care unit may have protective effects on the brain.

Publication Citation:

Post-cardiac Arrest Sedation Promotes Electroencephalographic Slow-wave Activity and Improves Survival in a Mouse Model of Cardiac Arrest.
Takamitsu Ikeda, Edilberto Amorim, Yusuke Miyazaki, Risako Kato, Eizo Marutani, Michael G. Silverman, Rajeev Malhotra, Ken Solt, Fumito Ichinose.
Anesthesiology. 28 Sept. 2022.
PMID: 36170545

iii. Intratumoral injection of schwannoma with attenuated *Salmonella typhimurium* induces antitumor immunity and controls tumor growth.

Neurofibromatosis type 2 (NF2) and schwannomatosis are rare genetic disorders that are associated with the development of non-cancerous tumors that develop throughout the body causing severe pain, major neurologic deficits, and death.

Tumors typically first appear in childhood and can develop throughout life. Surgical resection and radiotherapy are the standards of care for schwannoma but have major limitations. The lack of highly effective and safe treatment options for schwannoma represents a major unmet medical need. The Brenner laboratory in the MGH DACCPM has demonstrated that a direct injection of tumors with a genetically modified and attenuated strain of the bacteria *Salmonella typhimurium* controls schwannoma growth. This strategy represents an immunotherapy that has the potential to target uninjected distal tumors and prevent the development of newly arising tumors.

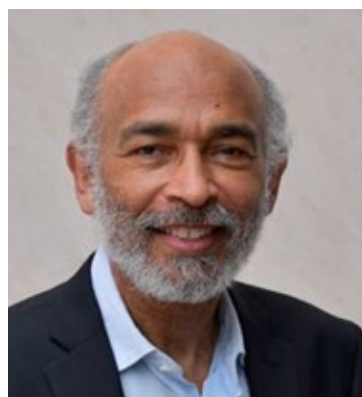
Publication Citation:

Intratumoral injection of schwannoma with attenuated *Salmonella typhimurium* induces antitumor immunity and controls tumor growth

Sherif G. Ahmed, Giulia Oliva, Manlin Shao, Xinhui Wang, John J. Mekalanos, Gary J. Brenner

PNAS June 2022

PMID: 35675425 PMCID: PMC9214496



Emery N. Brown, MD, PhD

Warren M. Zapol Professor of Anesthesia, Harvard Medical School, Massachusetts General Hospital
Edward Hood Taplin Professor of Medical Engineering and of Computational Neuroscience, Massachusetts Institute of Technology

Recipient of the 2022 Pierre M. Galletti Award from the American Institute for Medical and Biological Engineering (AIMBE).

Honors and Awards:

1. Emery Brown, MD, PhD, Mass General anesthesiologist, statistician and director of the Neuroscience Statistic Research Laboratory, received the 2022 Pierre M. Galletti Award from the American Institute for Medical and Biological Engineering (AIMBE)—the highest honor bestowed by the AIMBE! Dr. Brown was chosen for his significant contributions to neuroscience data analysis and for characterizing the neurophysiology of anesthesia-induced unconsciousness.

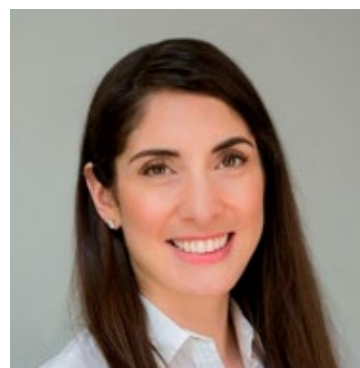
Insert Second Image

2. Karen Nanji, MD, MPH of won first place at The American Society of Anesthesiologists (ASA) annual meeting for her medication safety software. It was selected as the top scientific and educational innovation in recognition of its workflow efficiency and patient safety benefits.

Insert Third Image

3. The Mass General Wellman Center for Photomedicine awarded the following Investigators one-year Magic Wand awards:

- Aranya Bagchi, MBBS, for the project, “Identifying Phytocannabinoids for Treating Pain”
- Hovig Chitilian, MD, for the project, “Universal Linear Ultrasound Transducer Needle Guide”
- Samuel Smith, MD, MPH, for the project, “Monitoring Intraoperative Blood Loss”



Karen C. Nanji, MD, MPH

Physician Investigator
Anesthesia, Critical Care and Pain Medicine,
Massachusetts General Hospital
Assistant Professor of Anesthesia
Harvard Medical School

Awarded first place at the 2022 American Society of Anesthesiologists (ASA) annual meeting for her medication safety software.

JAMES BRINK, MD, CHIEF

Overview:

The Department of Radiology at Massachusetts General Hospital encompasses one of the largest radiology research programs in the world, with 270 research faculty. Research activity in the department is spread across a host of Centers and individual labs dedicated to the development of biomedical imaging technologies and application of those technologies to a broad range of basic science and clinical questions.

Achievements:

Artificial intelligence (AI) continues to redefine the practice of radiology, and Massachusetts General Hospital continues to lead the way in developing and applying AI. In 2022, radiology researchers at the hospital described a host of significant advances. Examples include an AI model that [accurately assesses muscle and fat tissue](#) on routine chest CT¹ and a pre-trained chest radiograph model that [can be easily repurposed for new problems](#) using explainable artificial intelligence (xAI).² Also, during a presentation at the annual meeting of the Radiological Society of North America (RSNA) that was widely covered by CNN and other news outlets, researchers from the [Cardiovascular Imaging Research Center](#) described an AI model that can [predict the 10-year risk of death](#) from a heart attack or stroke using a single chest X-ray.

One of the department's many other strengths in the research realm is its work with neurological disorders and neurodegenerative disease. For instance, in 2022, researchers from the [Gordon Center for Medical Imaging](#) reported an [MRI feature that serves as a marker of disease progression](#) in preclinical autosomal dominant Alzheimer's disease,³ used functional MRI (fMRI) to [show how Parkinson's disease disrupts](#) functional brain network organization,⁴ and tested for the first time in humans a [radiotracer that detects demyelination](#),⁵ a significant contributor to neurological diseases.

Research in the department also encompassed basic science applications in the brain. A team based in the [Athinoula A. Martinos Center for Biomedical Imaging](#), for example, used fast fMRI to [map the specific cascade of neural activity](#) during the transition from sleep to wakefulness,⁶ shedding light on this central but poorly understood aspect of human consciousness. Another Martinos Center group continued its longstanding work exploring the neural correlates of "personal space" and social functioning, reporting their findings from a study of [personal space increases during the COVID-19 pandemic](#).⁷

The past year also saw the introduction of new medical devices. For example, researchers in the [Center for Ultrasound Research & Translation \(CURT\)](#) and colleagues described an [ultrasound-guided handheld robotic device](#) that allows non-specialists—including combat medics in battlefield settings—to access deep arteries and veins for life-saving applications. Another portable device was a [wireless, low-](#)

[cost cerebral oximeter](#) reported by a Martinos Center group.⁸ This device will be especially useful for monitoring older adults, who are generally at risk of a range of brain diseases.

Even beyond the many advances in basic science and translational research as well as in technology development, the Radiology department saw important additions to its infrastructure in 2022—additions both serving and utilizing research in the department. In the Charlestown Navy Yard, the Clinical and Translational Research Unit (CTRU)—a partnership between the Interdisciplinary Brain Center (IBC) and [Institute for Innovation in Imaging \(i3\)](#)—[brings together a multidisciplinary group of experts and a host of advanced technologies](#), including a “virtual reality cave,” to support research into a range of brain diseases and disorders.

Nearby, the new Mass General Brigham Outpatient Imaging Center at Assembly Row in Somerville offers [convenient imaging with cutting-edge techniques](#) developed by Martinos Center researchers. The latter include “fast MRI” techniques that have dramatically reduced the length of MR scans and thus improved both efficiency and patient satisfaction by enabling shorter exam times.

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¹ Bridge CP, Best TD, Wrobel MM, Marquardt JP, Magudia K, Javidan C, Chung JH, Kalpathy-Cramer J, Andriole KP, Fintelmann FJ. A Fully Automated Deep Learning Pipeline for Multi-Vertebral Level Quantification and Characterization of Muscle and Adipose Tissue on Chest CT Scans. *Radiol Artif Intell.* 2022 Jan 5;4(1):e210080. doi: 10.1148/ryai.210080. PMID: 35146434; PMCID: PMC8823460.

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³ Jacobs HIL, Becker JA, Kwong K, Munera D, Ramirez-Gomez L, Engels-Domínguez N, Sanchez JS, Vila-Castelar C, Baena A, Sperling RA, Johnson KA, Lopera F, Quiroz YT. Waning locus coeruleus integrity precedes cortical tau accrual in preclinical autosomal dominant Alzheimer's disease. *Alzheimers Dement.* 2022 Mar 17;10.1002/alz.12656. doi: 10.1002/alz.12656. Epub ahead of print. PMID: 35298083; PMCID: PMC9481982.

⁴ Basaia S, Agosta F, Diez I, Bueichekú E, d'Oleire Uquillas F, Delgado-Alvarado M, Caballero-Gaudes C, Rodríguez-Oroz M, Stojkovic T, Kostic VS, Filippi M, Sepulcre J. Neurogenetic traits outline vulnerability to cortical disruption in Parkinson's disease. *Neuroimage Clin.* 2022;33:102941. doi: 10.1016/j.nicl.2022.102941. Epub 2022 Jan 19. PMID: 35091253; PMCID: PMC8800137.

⁵ Brugarolas P, Wilks MQ, Noel J, Kaiser JA, Vesper DR, Ramos-Torres KM, Guehl NJ, Macdonald-Soccorso MT, Sun Y, Rice PA, Yokell DL, Lim R, Normandin MD, El Fakhri G. Human biodistribution and radiation dosimetry of the demyelination tracer [¹⁸F]3F4AP. *Eur J Nucl Med Mol Imaging.* 2022 Oct 5. doi: 10.1007/s00259-022-05980-w. Epub ahead of print. PMID: 36197499.

⁶Setzer B, Fultz NE, Gomez DEP, Williams SD, Bonmassar G, Polimeni JR, Lewis LD. A temporal sequence of thalamic activity unfolds at transitions in behavioral arousal state. *Nat Commun.* 2022 Sep 16;13(1):5442. doi: 10.1038/s41467-022-33010-8. PMID: 36114170; PMCID: PMC9481532.

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Image Award Finalist
Detail: The world on fire
Giridhar Dasegowda.MBBS
Department of Radiology

Giridhar

DANIEL HABER, MD, PHD, DIRECTOR

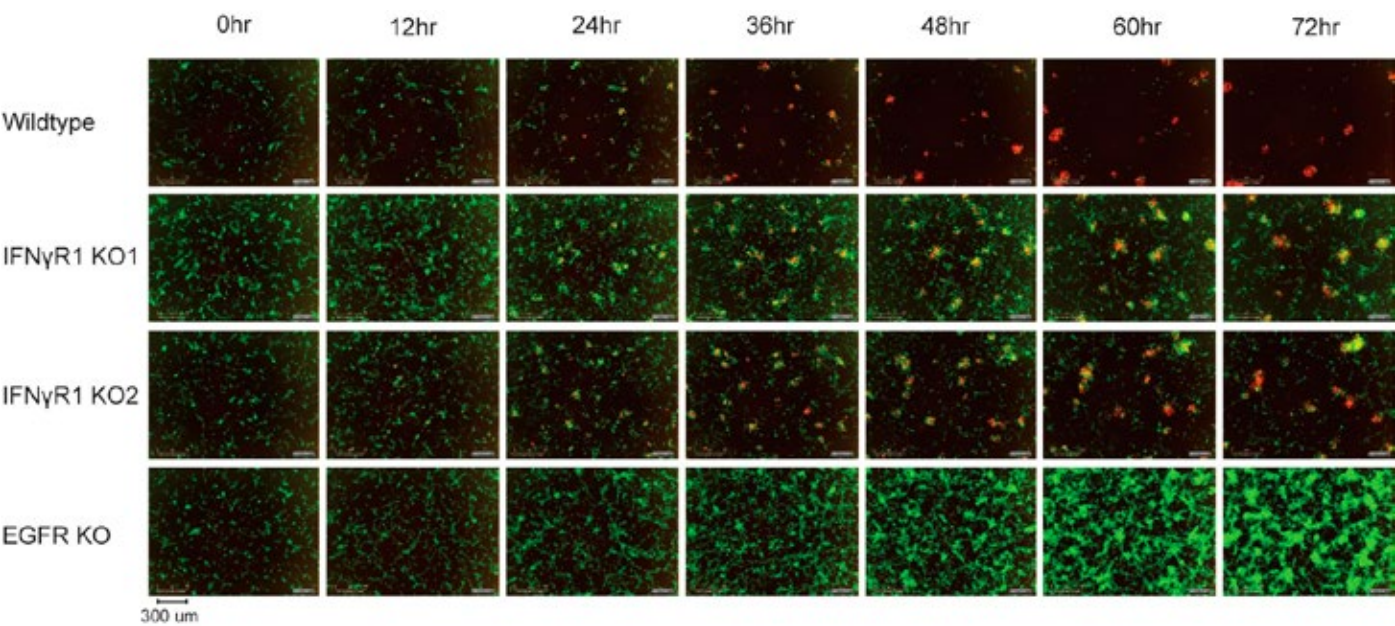
Overview:

MGH Cancer Center

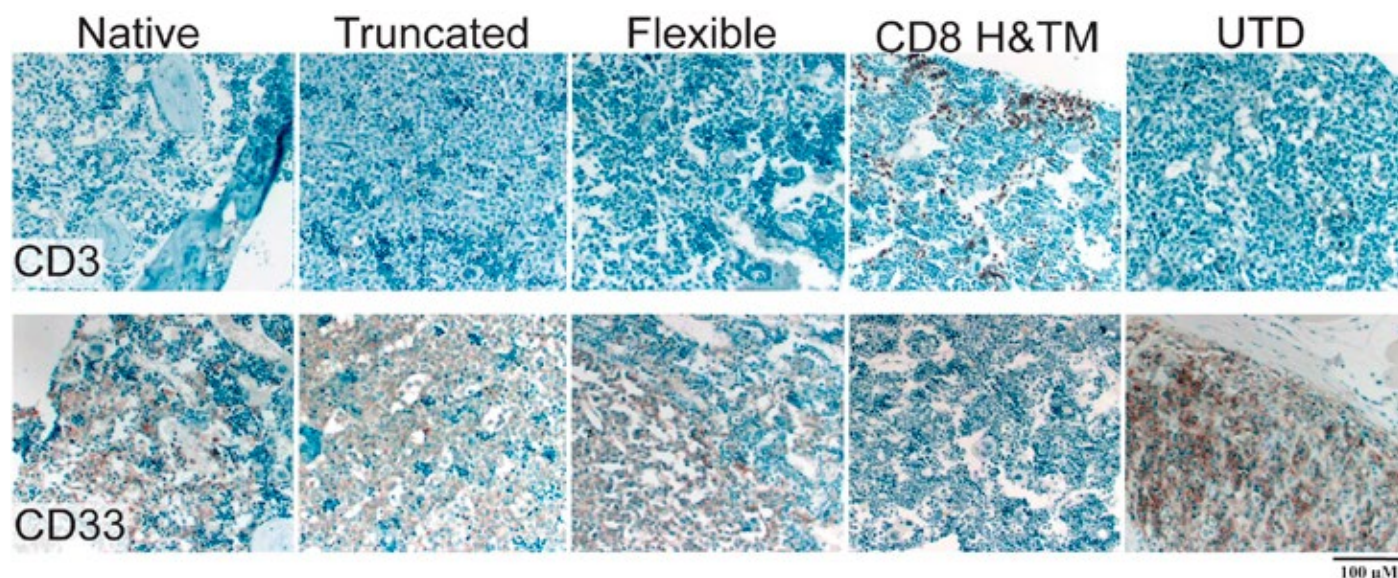
The *mission* of the Massachusetts General Hospital Cancer Center is to deepen our understanding of cancer and to rapidly translate our discoveries into exceptional, personalized care for all patients with cancer. Our researchers conduct fundamental, basic, translational and clinical research within a highly innovative, collaborative and multi-disciplinary environment. We are also committed to teaching and training the next generation of cancer researchers, within a diverse and inclusive research community.

Our *strategic research priorities* include building platforms that enable early 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, engineered T cell therapies and cancer vaccines; and expanding our research on fundamental discoveries on the origin and progression of cancer, which we believe to be the centerpiece of our successful research and translational enterprise.

Our *research highlights* from 2022 include major discoveries and observations from investigators within the multi-departmental Center for Cancer Research (CCR) and the Division of Hematology Oncology



Either wild type, IFN γ R1 knockout (KO), or EGFR (antigen) knockout human glioblastoma U87 cells (green), were incubated at a 1:1 ratio with EGFR CAR T cells (red) and monitored via microscopy for over 72 hours with an IncuCyte. Wildtype tumor cells are killed by EGFR CAR T cells over time, whereas when the target antigen is knocked out (EGFR-KO) the CAR T cells are no longer able to kill. When IFN γ R1 is knocked out, some tumor cells are killed but more survive killing compared to the wildtype condition. (Larson *et al*; CAR T cell killing requires the IFN γ R pathway in solid but not liquid tumours; *Nature* 2022; PMID: 35418687).



(Department of Medicine), both of which are administered through the Cancer Center. Our *highlighted accomplishments* demonstrate our strong culture of collaboration and collegiality, as demonstrated by multiple co-authored manuscripts and cross-laboratory team science.

Achievements:

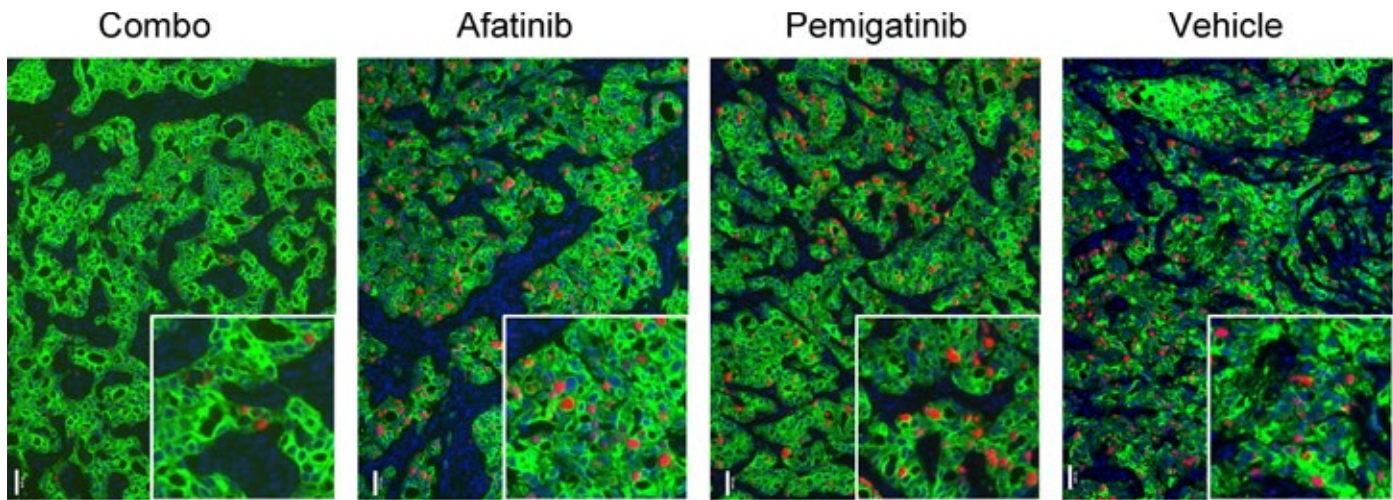
CANCER IMMUNOLOGY AND CAR-T THERAPEUTICS

Chimeric antigen receptor (CAR) therapy: CAR-T cellular immunotherapy has transformed treatments of multiple hematologic malignancies, but its efficacy against solid tumors has been limited. Dr. Marcela Maus and her team demonstrated that liquid and solid tumors differ in their interactions with CAR-T cells. Using genome-wide CRISPR knockout screen in glioblastoma, they found that loss of interferon- γ receptor signaling renders solid tumor cells resistant to killing by CAR-T cells both in vitro and in vivo, an effect that is absent in lymphoma and leukemia cells, distinguishing critical features of CAR-T efficacy. (*Larson et al; CAR T cell killing requires the IFN γ R pathway in solid but not liquid tumours; Nature 2022; PMID: 35418687*).

In a separate publication, Dr. Maus' lab also showed that CAR-T cell therapy in myeloid cancers is enhanced by engineering stabilization of the hinge region of the CD27 construct targeting the leukemic CD70 epitope, thereby providing a novel enhanced CAR-T cell design (*Leick et al, Non-cleavable hinge enhances avidity and expansion of CAR-T cells for acute myeloid leukemia; Cancer Cell 2022; PMID: 35452603*).

In a phase 1/2 clinical trial, led by Drs. Matthew Frigault, Yi-Bin Chen and colleagues demonstrated the high efficacy of the CAR-T product tisagenlecleucel in patients with primary CNS lymphoma, a patient population excluded from previous clinical trials. Complete responses

Immunohistochemistry (IHC) staining in brown of the bone marrow from mice treated with different CD70 targeted CAR-T hinge variants. CD3 staining marks the CAR-T cells (seen in only the CD8H&TM condition) while CD33 identifies residual acute myeloid leukemia which is seen in all the conditions except the CD8H&TM treated group. (*Leick et al, Non-cleavable hinge enhances avidity and expansion of CAR-T cells for acute myeloid leukemia; Cancer Cell 2022; PMID: 35452603*).



Combination treatment with an FGFR inhibitor (pemigatinib) and ERBB inhibitor (Afatinib) is effective in FGFR2+-driven xenograft models of cholangiocarcinoma derived from patients who developed resistance to FGFR inhibitor therapy. The images show staining of the tumors cells (green) for a marker of cellular proliferation (red). The drug combination virtually eliminates tumor cell proliferation whereas the single drugs are ineffective. The boxes in the upper right show higher magnification images. (Wu. et al, *EGFR Inhibition Potentiates FGFR Inhibitor Therapy and Overcomes Resistance in FGFR2 Fusion-Positive Cholangiocarcinoma*, *Cancer Discovery* 2022, PMID: 35420673)

were noted in 50% of patients (*Frigault et al, Safety and efficacy of tisagenlecleucel in primary CNS lymphoma: a phase 1/2 clinical trial. Blood* 2022; PMID 35167655).

Resistance to Immune Checkpoint Inhibitors: Using genetic and pharmacologic tools across multiple experimental model systems, Dr. Russ Jenkins' lab identified a role of the innate immune kinase TANK-binding kinase 1 (TBK1) as a critical immune evasion gene. TBK1 enhances response to PD-1 blockade by lowering the cytotoxicity threshold to effector cytokines, and TBK1 inhibition in combination with PD-1 blockade demonstrates efficacy in patient-derived tumor models. This finding has significant implications for targeting TBK1 as a potentially effective strategy to overcome resistance to cancer immunotherapy (*Sun et al, Targeting TBK1 to overcome resistance to cancer immunotherapy; Nature* 2022 in press).

COVID vaccination in cancer patients: A major challenge of COVID vaccination in patients with cancer has been uncertainty as to whether such patients can mount an effective immune response. Drs. Justin Gainor, John Iafrate and colleagues performed a prospective cohort study of adults with solid-organ or hematologic cancers, finding that neutralizing antibody titers were modestly lower in patients with cancer, regardless of vaccine type. Receipt of chemotherapy in the prior year or current steroids were associated with lower antibody levels, but antibody titers increased in patients who received an additional vaccine dose, suggesting potential benefits of antibody testing in cancer patients and adjustment of vaccination regimens (*Naranbhai.et al, Immunogenicity and Reactogenicity of SARS-CoV-2 Vaccines in Patients With Cancer: The CANVAX Cohort Study, J. Clinical Oncology* 2022; PMID: 34752147).

GENOMICS AND MOLECULAR THERAPEUTICS

Targeted therapies for cholangiocarcinoma: FGFR inhibitors are approved for the treatment of FGFR2-driven cholangiocarcinoma, but the clinical response rate is variable, and drug resistance may emerge rapidly. Dr. Bardeesy and colleagues used genetic screens in patient-derived models of FGFR2 fusion-positive cholangiocarcinoma

to discover that feedback activation of EGFR signaling limits the effectiveness of FGFR inhibitor therapy and drives adaptive resistance mechanisms. Their findings support the potential of combination of FGFR and EGFR inhibitors as an improved treatment option (**Wu. et al, EGFR Inhibition Potentiates FGFR Inhibitor Therapy and Overcomes Resistance in FGFR2 Fusion-Positive Cholangiocarcinoma, Cancer Discovery 2022, PMID: 35420673**).

Molecular dissection of chronic lymphocytic leukemia: Dr. Gaddy Getz and his team integrated genomic, transcriptomic and epigenomic data from over 1,000 patients to build the 'CLL map', identifying 109 new candidate genetic drivers that contribute to this leukemia. This discovery allows subcategorization of CLL into groups with independent clinical outcomes, associated with a combination of genetic, epigenetic and gene expression features (**Knisbacher et al, Molecular map of chronic lymphocytic leukemia and its impact on outcome, Nat Genet 2022; PMID: 35927489**).

Combination therapies in prostate cancer: In an international, randomized, phase 3 trial in patients with hormone-sensitive prostate cancer that is metastatic at presentation, Dr. Mathew Smith and colleagues evaluated the androgen receptor inhibitor darolutamide as compared with placebo, in combination with both androgen-deprivation therapy and docetaxel. They showed that progression-free and overall survival were significantly better in the group treated with all three therapeutic interventions, pointing to a new paradigm for patients with advanced disease at presentation (**Smith M et al, Darolutamide and Survival in Metastatic, Hormone-Sensitive Prostate Cancer, New England Journal Med 2022; PMID: 35179323**).

The Consortia for Improving Medicine with Innovation & Technology

Department Report



Word Cloud RADx Tech Achievements

JOHN A. PARRISH, MD, CEO

Overview

The Consortia for Improving Medicine with Innovation & Technology (CIMIT, <http://cimit.org>) was founded in 1998 by MGH, BWH, MIT, and Draper as a “center without walls” to foster multidisciplinary collaborations that bridge silos of medicine and technology to improve patient care. We have created a successful model for accelerating translational medical research, devices, procedures, and clinical systems by working together with clinicians, scientists, researchers, and engineers to identify gaps, areas of unmet need, and innovative ideas to address those gaps. We then facilitate collaboration across institutions and with companies, foundations, and those investing in new medical technologies to quickly push forward these leading-edge ideas to impact patient care.

In 2022, CIMIT continued to leverage its processes to provide extramural support for The Rapid Acceleration of Diagnostics Tech program (RADx Tech); launch NIH-funded programs in neurotechnology, HIV, maternal health, and MPox; serve as the Coordinating Center for Point-of-Care Technologies Research Networks (POCTRN); hold several Commercialization Readiness Assessment and Accelerator for Solutions in Healthcare (CRAASH) courses; further enhance the Guidance and Impact Tracking System (GAITS) platform, and manage the NIH Blueprint MedTech Pilot program.

Achievements

Rapid Acceleration of Diagnostics Program (RADx Tech)

In 2022, CIMIT continued to support the NIBIB’s RADx Tech program (<https://www.poctrn.org/covid19>) as the Coordinating Center to accelerate the development, validation, and commercialization of innovative point-of-care and home-based tests, as well as improvements to clinical laboratory tests, that can directly detect SARS-CoV-2, the virus that causes COVID-19. Since the launch of RADx Tech on April 29th, 2020, over 100 companies have been supported, 49 EUAs have been granted by FDA, and the COVID-19 testing capacity in the U.S. has been increased by approximately 5 billion diagnostic tests.

Additionally, as part of the RADx Tech Program, CIMIT and MIT collaborated to develop WhenToTest.org (<https://whentotest.org>) and augment its content significantly in 2022. The website started with a mission to provide data-driven recommendations for how organizations, such as schools and businesses, should establish effective and customized testing programs based on their particular risk factors. Building on the success of the organizational platform the website was further developed to include a decision support tool to provide individuals and families with fact-based guidance for when they should be tested for COVID-19.

The Consortia for Improving Medicine with Innovation & Technology

Department Report

Finally, as an extension of the RADx initiative, the NIH launched the Independent Test Assessment Program (ITAP) program in order to accelerate regulatory review and availability of high-quality, accurate, and reliable over-the-counter COVID-19 tests to the public. This program has already contributed to the FDA's rapid EUA authorization of over-the-counter, at-home COVID-19 tests and is now working to develop diagnostic tests for MPox, Multiplex POC tests (including Covid flu with or without RSV) with NIH support.

Point-of-Care Translational Research Network

The Point-of-Care Technologies Research Network (POCTRN), <https://www.poctrn.org> was created by NIH to drive the development of point-of-care diagnostic technologies through collaborative efforts that simultaneously merge scientific and technological capabilities with clinical needs. 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 2022, CIMIT has continued as a Coordinating Center for Year 5 of the 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. In addition to the 5th year cycle, POCTRN has solicited proposals to further advance HIV viral load testing platforms.

Blueprint MedTech Pilot

In June 2021, the Point-of-Care Technology Research Center (POCTRN) at CIMIT, launched a funding opportunity in support of the NIH Blueprint MedTech Pilot program (<https://www.poctrn.org/blueprint-medtech-pilot>). The program's aim is to award collaborative research projects in the early stages of translation that improve the diagnosis and/or treatment of disorders of the nervous system. The program rapidly solicited and reviewed 147 applications with 41 invited to submit a full proposal and 7 projects ultimately receiving Blueprint awards and ongoing support in 2022.

Blueprint MedTech Incubator Hub Program

In 2022, CIMIT received a 5-year award as one of two national Blueprint MedTech Incubator Hubs to develop emerging technologies into commercially viable, clinically focused solutions for disorders of the nervous system. This NIH program, based on CIMIT's work for RADx Tech, is supported by multiple NIH institutes (<https://neuroscienceblueprint.nih.gov/neurotherapeutics/blueprint-medtech/blueprint-medtech-ics-and-contacts>).

CIMIT'S CRAASH Program

In 2022, CIMIT continued to conduct CRAASH programs (<https://www.craash.org>) in support of NIBIB and in support of CIMIT's collaborators in Europe.



When To Test



The Consortia for Improving Medicine with Innovation & Technology

Department Report



CRAASH is a program that facilitates the acceleration of healthcare innovation emerging from academic labs or start-ups into commercialization and clinical practice. It is based on the iCorps program but customized to address the unique challenges in healthcare with industry veterans as faculty. 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 collect evidence to support the assumptions around the entire business (not just the science) through interviews and market testing. Each week teams present and defend findings to a panel of experts, attend lectures, and complete readings. Teams develop a commercialization roadmap based on data from actual customers and other stakeholders. Teams also receive 1:1 mentoring from successful healthcare entrepreneurs and group coaching from commercialization experts and investors.

CIMIT'S GAITS

Based on lessons learned since its first Clinical Impact Study (CIS, <https://www.cimit.org/cis>) in 2010, CIMIT created GAITS in 2017 and further developed its functionality in 2022. GAITS establishes a sequence of 10 healthcare specific milestones that parallel the Department of Defense's well-established Technology Readiness Levels (TRLs). GAITS helps innovators navigate the complex journey of innovation in healthcare and adds significant guidance to teams by defining a 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 to CIMIT's use of GAITS in support of the NIBIB and RADx Tech program with more than 200 Solution Sites. GAITS is now being used by collaborators in the US (MIT and UConn), Europe (EIT Health and Biocat) as well as Australia (MTPConnect). The free version of GAITS (www.gaits.org) has also been well received. In the last calendar year, the usage has been almost 5,000 users in more than 10,000 sessions with about 50% from outside the U.S.

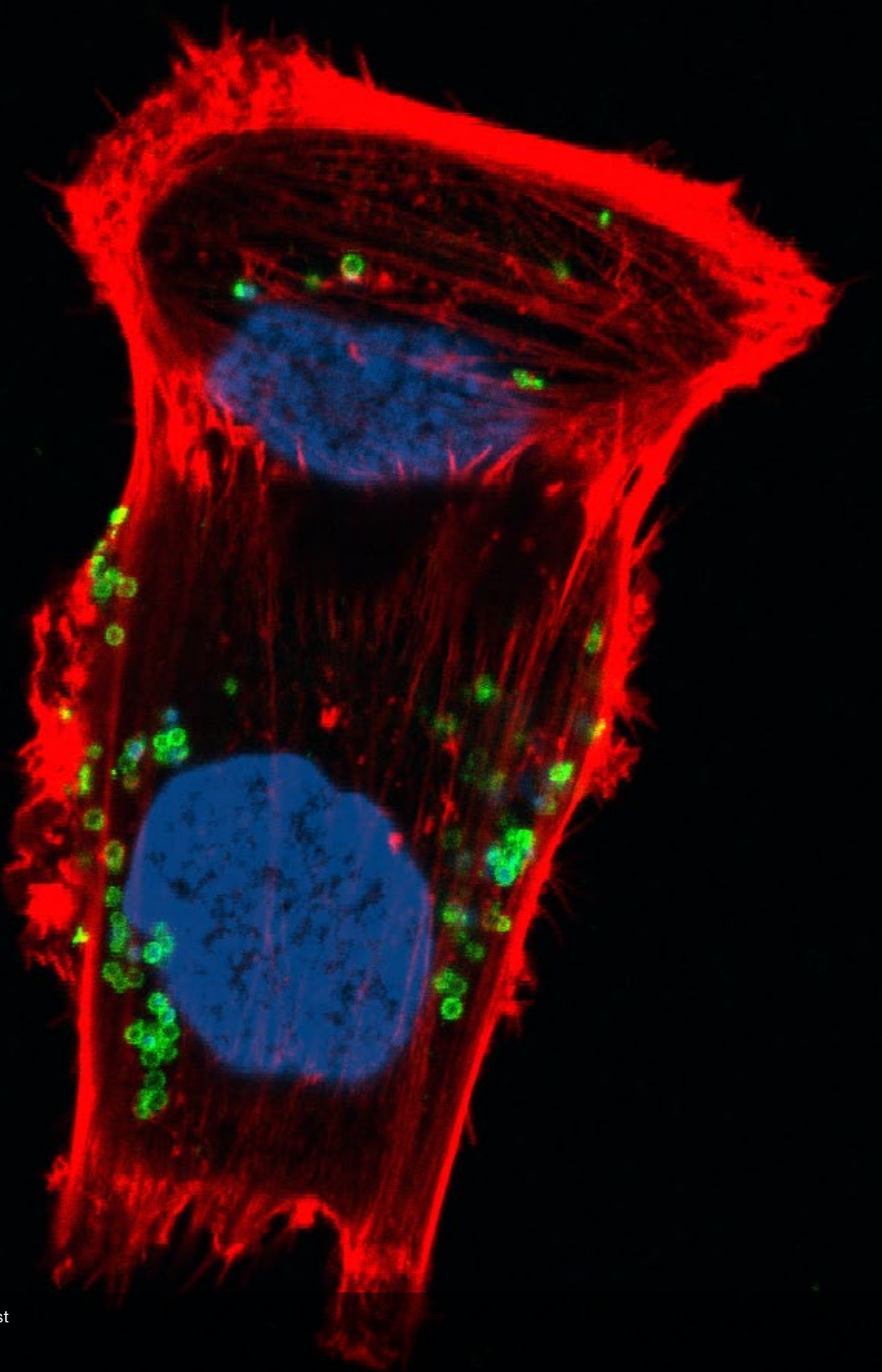


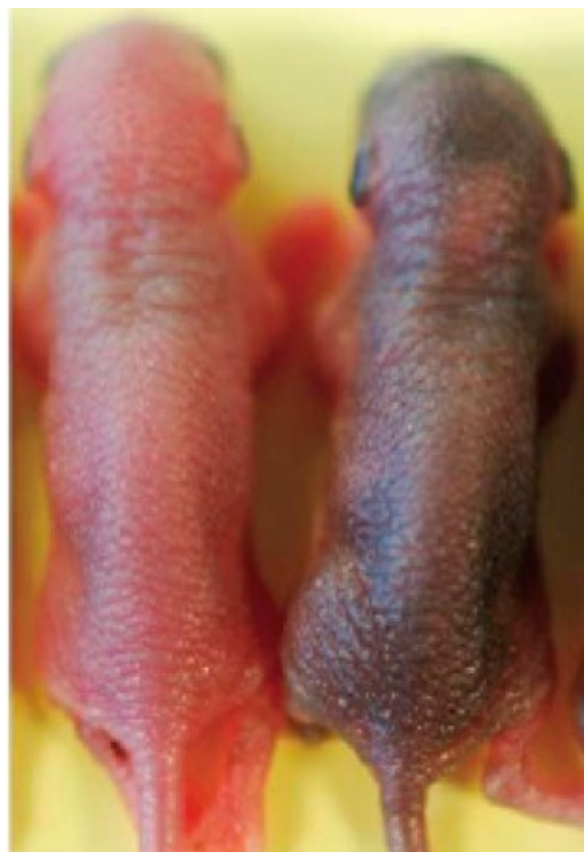
Image Award Finalist
Hocus Coccus
Amita Sekar, PhD
Orthopaedics/Harris Orthopaedics Laboratory

DAVID E. FISHER, MD, PHD, CHIEF

Overview:

MGH Dermatology is home to clinical dermatologic care for a large population of patients while also housing one of the most distinguished historically important contributors to the modern field of skin biology and cutaneous medicine. The department dates back to the 1800's, and housed numerous physician-scientists who introduced breakthroughs in our understanding of many skin conditions and helped establish the modern discipline of dermatology. The first female physician at MGH, Dr. Loretta Cummings, was a Dermatologist in the department in the early 1900s. She bequeathed a portion of her estate to the Dermatology department, the proceeds of which are used to support annual research pertaining to female-related dermatology. During 2022 the ongoing COVID epidemic challenged the four pillars of the department's mission: clinical operations, laboratory research, teaching, and community outreach. Multiple faculty members carried out COVID-related research activities, with Dr. Esther Freeman serving as a national and international leader in cutaneous manifestations of COVID—and director of an international registry of COVID skin manifestations. All department members providing clinical care at MGH Dermatology worked extra hard, providing additional clinic opportunities for patients, in person or virtually, in order to help meet the needs of our patient population.

The department's missions remain focused on delivering outstanding care to patients, carrying out innovative research, educate the next generation of dermatology providers, and providing care to our surrounding community. Care of the homeless population remains a high priority for which the department commits resources in a program spearheaded by Dr. Jennifer Tan and recently attended by Dr. John Trinidad. MGH Dermatology delivers care in approximately 90,000 patient annual visits at the MGH main campus, multiple community care centers and MGH-Northshore in Danvers. Collaborating with the MGH department of Pathology, a community-based Dermatopathology Lab has grown to be one of the busiest across New England. The department provides specialty dermatologic care in Pediatric Dermatology, High-Risk Non-melanoma Skin Cancer, Pigmented Lesions/Melanoma, Dermatologic & Mohs Surgery, Urgent-care, Rheumatologic Dermatology, Laser and Cosmetic Unit, and Inpatient-Consultation Services. The Pigmented Lesions/Melanoma Clinic, the first of its kind in the US, celebrated its 50 year anniversary recently. MGH Dermatology also houses major research programs. These include the Clinical Unit for Research Trials In Skin (CURTIS) and the Cutaneous Biology Research Center (CBRC). CURTIS runs a combination of Industry Sponsored and Investigator Initiated investigations. The CBRC houses 14 Principal Investigators and attracts very substantial federal grant support and diverse Industry funding that includes a longstanding collaboration



with Shiseido Cosmetics in Japan, one of the largest Industry-Academic collaborations in academic history. CBRC research includes 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, and differentiation pathway control. Collaborations exist with MGH Cancer Center and the Broad Institute (where several faculty hold joint appointments) and with numerous departments across MGH and Harvard Medical School. Additional faculty whose academic home is in Dermatology include researchers in the Wellman Center for Photomedicine, an MGH Thematic Center famous for development of numerous devices used in diagnostic or therapeutic aspects of dermatology and other fields.

In 2022 department faculty published 304 scholarly articles and gave 220 speaking engagements. During this period MGH Dermatology held 88 active NIH awards comprising over \$42M. Additional research support included funds from 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 and

Congenital Giant Nevi: human premalignant condition and mouse models

holds the Director position of a newly formed Melanoma Academy for the US department of Defense. The department hosts many visiting trainees including specific initiatives to enhance diversity representation in the field of Dermatology and skin research. Finally, MGH Dermatology particularly prides itself on close interactions and collaborations with most departments across the hospital—in clinical care initiatives, research projects, medical education, and community outreach.

Achievements:

Choi YS, Erlich TH, Von Franque M, Rachmin I, Flesher JL, Schiferle EB, Zhang Y, Pereira da Silva M, Jiang A, Dobry AS, Su M, Germana S, Lacher S, Freund O, Feder E, Cortez JL, Ryu S, Babila Propp T, Samuels YL, Zakka LR, Azin M, Burd CE, Sharpless NE, Liu XS, Meyer C, Austen Jr WG, Bojovic B, Cetrulo Jr CL, Mihm MC, Hoon DS, Demehri S, Hawryluk EB, Fisher DE. Topical therapy for regression and melanoma prevention of congenital giant nevi. *Cell* June 2022;185:1-15.

Genetically engineered mouse models of giant congenital nevi were developed, and exhibited numerous features in common with the human lesions. Novel strategies were tested to achieve regression of the lesions after topical drug administration. One such treatment produced potent regression as well as prevention of melanoma formation.

Bunting MD, Vyas M, Requesens M, Langenbucher A, Schiferle EB, Manguso RT, Lawrence MS, Demehri S*. Extracellular matrix proteins regulate NK cell function in peripheral tissues. *Sci Adv.* 2022 Mar 18;8(11):eabk3327. PMID: 35294229,

This study defines key features of Natural Killer cells, an innate immune population potentially capable of eradicating grafted tissues, virally infected cells, or tumor cells that lack major histocompatibility complex proteins. The investigators demonstrate the importance of extracellular matrix proteins and certain signaling factors that restrict NK cell function within the microenvironment of peripheral tissues of the body.

Wolfson AR, **Freeman EE**, Blumenthal KG. Urticaria 12 Days After COVID-19 mRNA Booster Vaccination. *JAMA.* 2022 May 3;327(17):1702-1703.

Population wide administration of COVID-19 mRNA vaccine emphasizes the importance of novel adverse cutaneous clinical events.

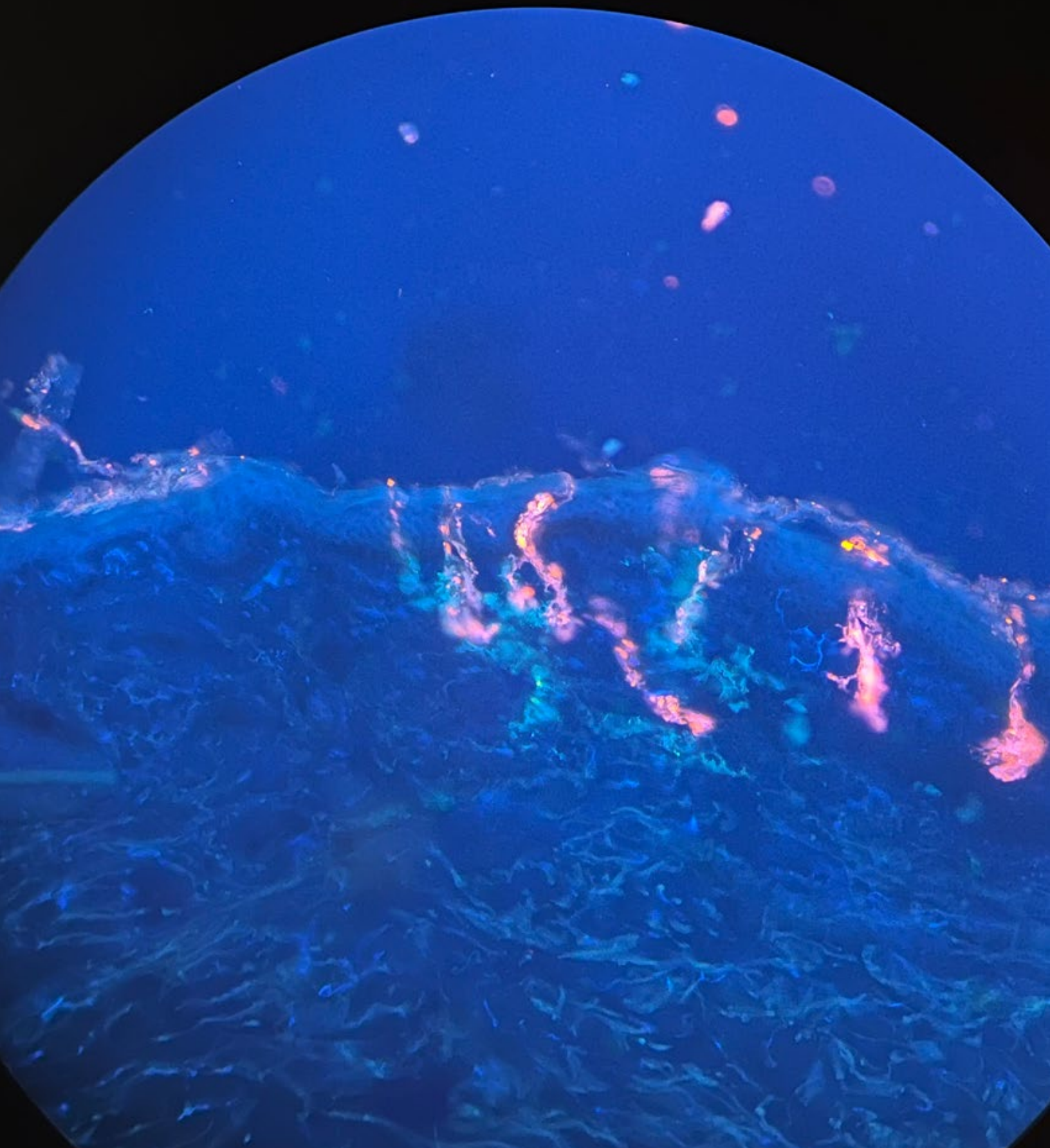


Image Award Finalist
Your Skin is Glowing!
Haley Marks, PhD
Cutaneous Biology Research Center

MICHAEL VANROOYEN, MD, MPH, CHAIR

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, all while providing compassionate and efficient care. Our clinical environment is challenged with ever-increasing patient volume, digital information overload, and in particular the COVID-19 pandemic. These challenges demand timely clinical innovation and adaptation founded in rigorous clinical investigation to inform best practices locally and globally. Our department has met this challenge in 2021.

MGH emergency medicine research has traditionally focused 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 have included: 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, pediatric emergencies, and health services research. Newer areas of investigation included digital health, palliative care, and virtual care.

The department played an integral role in the COVID-19 pandemic of primarily clinical care of acutely-ill COVID-19 patients, but also significantly in research investigation, as was highlighted in our last report. In 2022, we have turned our focus again to non-COVID-19 investigation, using valuable lessons learned from the pandemic. Our contributions include over 300 peer-reviewed publications in 2022 by over 30 contributing faculty. We are proud of our accomplishments and highlight several of these works below.

Goals for 2023:

1. Continue to develop a strong pipeline of relevant clinical investigations to support a robust research infrastructure that drives the departmental research mission.
2. Continue to build and optimize the core research team that includes our senior clinical research program manager and clinical research coordinators.
3. Continue to increase expertise in sample processing and analysis to facilitate expanded investigation in proteomics, metabolomics, genomics, and human microbiome.

4. Continue to work to secure dedicated emergency medicine lab space and capabilities to allow for more sophisticated and robust in-house processing with the goal of further increasing opportunity for NIH- and industry-sponsored funding in these areas.
5. Continue to develop a consistent mechanism for providing electronic clinical data to investigators to carry out health record-based research.
6. Continue to hone departmental resources available to support and optimize our research infrastructure, including grants administration and finance, statistical support, and mentoring young investigators.

Achievements in 2022:

1. Non-anaesthetist-administered ketamine for emergency caesarean section in Kenya: cost-effectiveness analysis. Resch SC, Suarez S, Omotayo MO, Griffin J, Sessler D, **Burke T.** *BMJ Open.* 2022 Oct 5;12(10). PMID: 36198454.

The Global Health Innovations (GHI) Lab directed by Dr. Thomas Burke has for years made significant contributions to emergency care in international underserved regions. One of their many focuses has been delivery of obstetrics and perinatal care with the goal of preventing common complications of childbirth that are easily treated in the US but are often and tragically deadly in some parts of the world. A major issue in underdeveloped countries has been availability of caesarian section surgery, and in large part due to lack of anesthesia capabilities. Institution of Every Second matters for Emergency and Essential Surgery-Ketamine (ESM-Ketamine) in Kenya in 2013 and championed by GHI has had significant impact on perinatal mortality in Kenya. This article summarizes the small cost of this program over a 5-year period that saves 316 maternal and 4736 fetal deaths, an example of the massive effect a simple intervention can have.

2. Analysis of Racial and Ethnic Diversity of Population Served and Imaging Used in US Children's Hospital Emergency Departments. **Samuels-Kalow ME**, De Souza HG, Neuman MI, Alpern E, Marin JR, Hoffmann J, Hall M, Aronson PL, Peltz A, Wells J, Gutman CK, Simon HK, Shanahan K, Goyal MK. *JAMA Netw Open.* 2022 Jun 1;5(6).

Racial, socioeconomic, and gender disparities in medicine have been documented for decades. It is hoped that these disparities do not intrude the realm of the pediatric population. Dr. Maggie Samuels-Kalow has dedicated her research career to studying access to basic emergency care with a focus on lesser represented populations. In this study, Dr. Samuels-Kalow and co-investigators survey over 12 million pediatric emergency department visits and find that non-Hispanic black children receive significantly less emergency imaging than non-Hispanic white children. And this disparity was most pronounced in hospitals that treat a higher

proportion of black children. This unfortunate truth is another important example of healthcare disparity that impacts the most vulnerable subgroup of the population, our children, and is an important finding in developing strategies to mitigate bias.

3. Emergency Medical Service Time Intervals for Patients With Suspected Stroke in the United States. **Cash RE**, Boggs KM, Richards CT, **Camargo CA Jr**, **Zachrisson KS**. *Stroke*. 2022 Mar;53(3).

Emergency medicine research often extends beyond the boundaries of the hospital, and Emergency Medical Services (EMS) constitute an important aspect of emergency care. Dr. Rebecca Cash has devoted much of her research career in studying EMS services and how to best deliver care to acutely-ill patients before they arrive to the hospital. In this study, Dr. Cash teams with Dr. Kori Zachrisson, an emergency stroke expert, to characterize time-to-hospital-transport in acute stroke, a disease where rapid assessment and treatment is critical. There was a wide variation in hospital transport time depending on US region and urban vs rural settings. These findings will provide an important basis for prehospital stroke planning in the future.

4. FcyR-mediated SARS-CoV-2 infection of monocytes activates inflammation. Junqueira C, Crespo Â, Ranjbar S, de Lacerda LB, Lewandrowski M, Ingber J, **Parry B**, Ravid S, Clark S, Schrimpf MR, Ho F, Beakes C, **Margolin J**, Russell N, Kays K, Boucau J, Das Adhikari U, Vora SM, Leger V, Gehrke L, Henderson LA, Janssen E, Kwon D, Sander C, Abraham J, Goldberg MB, Wu H, Mehta G, Bell S, Goldfeld AE, **Filbin MR**, Lieberman J. *Nature*. 2022 Jun;606(7914):576-584.

This publication is a reminder of the impact that emergency medicine research and the enrollment infrastructure in the emergency department played in the COVID-19 pandemic. Our clinical research team was deployed during the pandemic to enroll acutely-ill COVID-19 patients upon arrival to the emergency department. Samples were made available to investigators Harvard-wide, including investigators at Children's Hospital in Boston. It was discovered that COVID-19 virus was directly infecting immune cells and causing massive inflammatory cell death, termed pyroptosis, a root of critical illness and death in COVID-19. This investigation has led to a greater understanding of critical illness in general in COVID-19 and beyond, and has spawned emerging novel therapies.

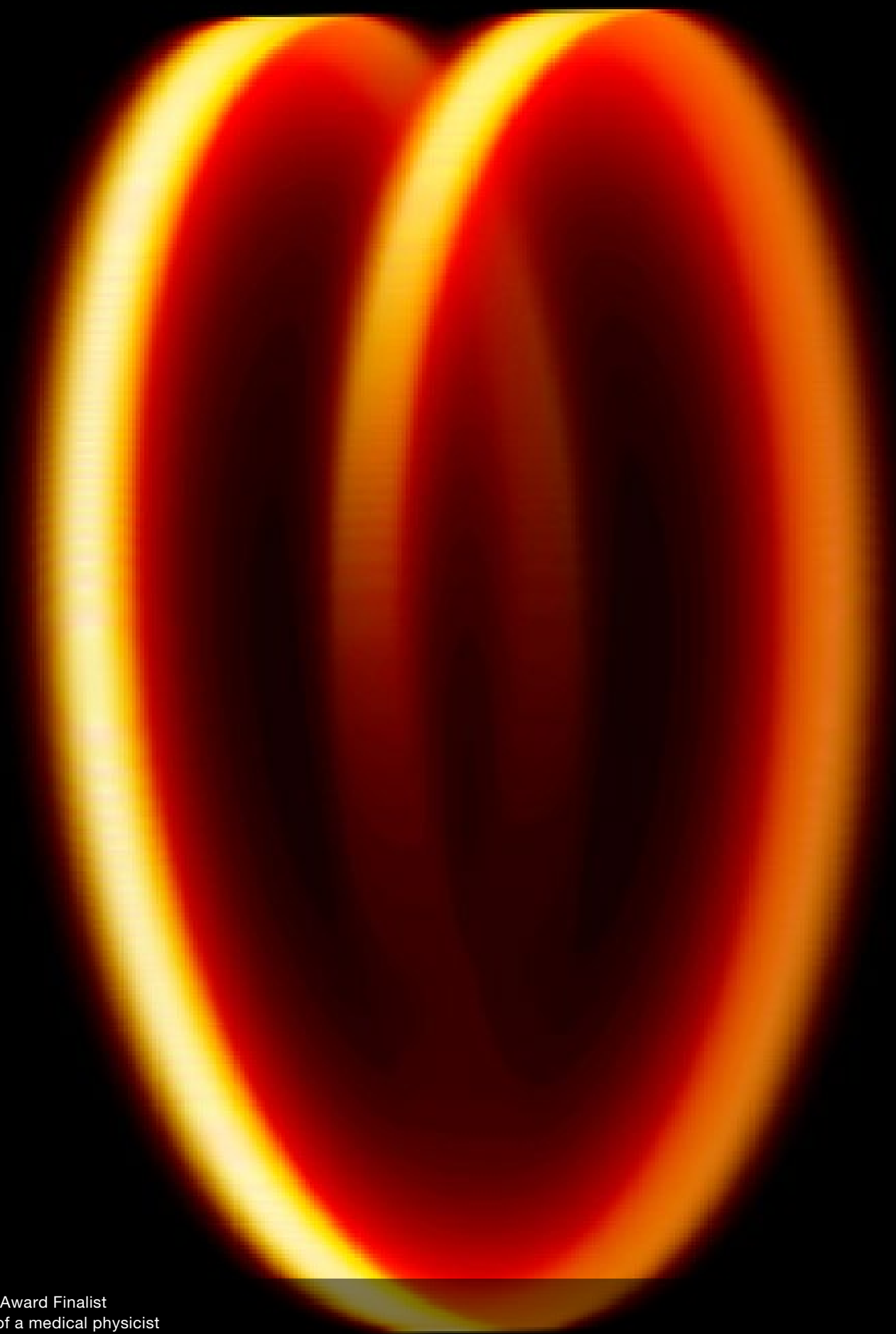


Image Award Finalist
Heart of a medical physicist
Kai Yang, PhD
Radiology/Diagnostic Physics Division

JOSHUA METLAY, MD, CHIEF

Overview:

Driven by its four core pillars of clinical care, education, research, and community health, 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, as well as the MGPO. From high-quality care to diversity and inclusion initiatives to innovative medical discoveries, the Department's faculty and staff hold crucial responsibilities in fulfilling MGH's mission.

The Department cultivates multidisciplinary relationships that will breed success for all four pillars, 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. With research, the Department continues to build a community that incubates innovation that leads to major developments in medicine. The Department boasts internationally known investigators who are dedicated to producing research that advances science and improves care for our patients. Through our multiple, standard-setting research units, centers, and programs, the Department of Medicine has become a leader in medical research.

Achievements:

Division of General Internal Medicine

Research in the **Division of General Internal Medicine** highlights a renewed focus on prevention. As we know, promoting healthy lifestyle is critical to preventing chronic disease and promoting well-being.

Anne Thorndike, MD, MPH and colleagues conducted ChooseWell 365, a trial of hospital employees testing an intervention of behavioral nudges and feedback to promote healthier food choices and prevent weight gain. The overall study demonstrated that the intervention was associated with healthier food choices but did not prevent weight gain. The current study investigated whether the effect of this workplace behavioral intervention differed by employee health literacy and numeracy and found that this intervention increased healthy cafeteria food purchases among individuals of both higher and lower health literacy and numeracy groups. This type of information is critical to equitably deploying health workplace interventions.

Family health history is routinely used to determine whether patients should be screened for heritable conditions; this information is critical for determining personalized recommendations for prevention. A team lead by **Leland Hull, MD, MPH** analyzed survey data from the All of Us Research Program to compare self-reported knowledge of family health history by sociodemographic characteristics. Overall, a minority of All of US participants reported high levels of knowledge about their family health history. Knowledge of family health history was lower among non-white individuals (vs. white individuals), those with a lower household income and those who identify as a gender

or sexual minority (vs. not identify). These findings suggest the need for population level interventions to reach all individuals to promote their understanding of the importance of family health history to personalized prevention.

Endocrine- Diabetes

The MGH Diabetes Center faculty **DM Nathan** (chair), **DJ Wexler** and **ME Larkin** led the planning and ultimately the Executive Committee of the 45-center **Glycemia Reduction Approaches in Diabetes: A Comparative Effectiveness (GRADE)** study, conducted between 2013 and 2021. GRADE was the first to perform a head-to-head comparison of diabetes medications added to metformin and included 5,047 participants (19.8% Black and 18.6% Hispanic) who had diabetes for less than 10 years with a HbA1c of 6.8 to 8.5% at baseline. GRADE compared four common medication classes (sulfonylurea glimepiride, DPP-4 inhibitor sitagliptin, GLP-1 receptor agonist liraglutide, and long-acting insulin glargine) to determine which worked best to achieve and maintain target levels of average blood sugar control (HbA1c) which had been previously shown to reduce long-term complications. Glargine and liraglutide were modestly more effective at maintaining HbA1c target levels than glimepiride or sitagliptin. Liraglutide reduced weight and the occurrence of any cardiovascular disease more than the other three medications but resulted in more gastrointestinal side effects. GRADE has provided, for the first time, a fair head-to-head comparison of medications commonly used to treat T2D in concert with metformin. The results show that maintaining target HbA1c <7% over time is challenging; however, there are differences among medications that can be used by health care providers and patients to select the most appropriate medication to treat T2D. The comparative effectiveness design, long duration and the recruitment of a highly diverse population all made GRADE unique in the annals of diabetes clinical research. The two GRADE companion papers were published in the NEJM in September 2022.

Endocrine- Metabolism Unit

Epidemiologic studies have highlighted both sex-differences in HIV-attributable risks of myocardial infarction (MI) and sex-differences in MI presentations among people with HIV in the U.S. Specifically, the HIV-attributable risk of MI is higher in women than in men, and women with HIV (vs. men with HIV) tend to present more frequently with type 2 myocardial infarction. A team led by **Markella Zanni, MD**, and **Steven Grinspoon, MD**, in the **MGH Metabolism Unit** sought to understand mechanisms underlying sex-differences in HIV-attributable MI risks and sex-differences in MI presentations among people with HIV. They leveraged baseline data from the Randomized Trial to Prevent Vascular Events in HIV (REPRIEVE), an international randomized controlled trial testing whether pitavastatin calcium vs. placebo prevents major adverse cardiovascular events (MACE) among 7,770 antiretroviral therapy (ART)-treated people with HIV, globally. As part of an embedded substudy, a subset of U.S. REPRIEVE participants underwent coronary CT angiography and immune

phenotyping at baseline and two years after randomization. Published in *Clinical Infectious Diseases*, the substudy baseline analysis by Zanni and Grinspoon yielded critical data on sex-differences in subclinical coronary atherosclerotic plaque, immune activation/inflammation, and immune-plaque relationships among US people with HIV. Overall, women with HIV (vs. men with HIV), exhibited a lower prevalence of plaque despite higher levels of inflammation. These findings highlight that among women with HIV, MI risk may be mediated through alternate pathways (e.g. microvascular dysfunction), which are insufficiently characterized by CT-based evaluation of epicardial coronary arteries. Moreover immune-plaque relationships differed by sex for select markers.

Endocrine- Neuroendocrine

States of chronic overnutrition and undernutrition are both associated with impaired bone health and increased fracture risk, but there are no data on bone microarchitecture following short-term controlled nutritional challenges. **Miriam Bredella, MD, MBA, and Karen K. Miller, MD**, and colleagues evaluated the impact of short-term (10 days) of fasting subsequent to 10 days of high-calorie feeding on bone microarchitecture. They hypothesized that fasting would have negative effects on microarchitecture. Contrary to their hypothesis, they found that there was a significant increase in distal tibia total and cortical vBMD, trabecular and cortical parameters as well as strength estimates ($p < 0.05$) during fasting. Moreover, there was an increase in distal radius total and trabecular vBMD ($p < 0.05$). These results suggest that short-term fasting after high-caloric feeding in healthy individuals improves bone health.

Endocrine- Reproductive Endocrine

Despite substantial advances in genomics, the causal genes for several Mendelian disorders remain elusive. The **MGH Reproductive Endocrine Unit** faculty led by **Stephanie Seminara, MD**, undertook a deeper evaluation of next-generation sequencing data from patients with Idiopathic Hypogonadotropic Hypogonadism (IHH), a rare genetic disease that has provided unprecedented insights into the molecular control of human reproduction. The causal basis of IHH in >50% of patients remain unknown. To tackle the missing heritability challenge in IHH, **Meg Lippincott, MD**, led the single nucleotide variant (SNV) analyses in exome sequencing data IHH patients. By targeting genes normally devoid of rare variation in humans, she identified casual mutations in *ARHGAP35*, implicating this Rho-GTPase activating protein as a critical regulator of reproductive competence. Furthermore, this discovery effort, now published in *Genetics in Medicine* journal, also revealed that all IHH patients harboring *ARHGAP35* mutations had co-segregating neurodevelopmental phenotypes, thus unraveling a novel developmental pleiotropy between reproduction and neurodevelopmental disorders.

Rheumatology, Allergy and Immunology

In the **Division of Rheumatology, Allergy, and Immunology** and the **Center for Immunology and Inflammatory Diseases**, **Andrew Luster, MD, PhD**, and **James Moon, PhD**, along with colleagues at BWH and Ragon Institute conducted a longitudinal study of SARS-CoV-2 specific CD4⁺ T cell and antibody responses in patients recovering from COVID with a range of disease severities during the first wave of the pandemic, with the goal of better understanding the role of the T helper-1 (Th1) and T follicular helper (Tfh) cell subsets, which we know are central to long-term immunity against viruses like COVID-19. In a study published in *Science Immunology*, they found that individuals who seroconverted and experienced milder disease were found to have more Th1 and Tfh cells in their blood, and there was an association between circulating Tfh cells and having sustained anti-spike antibodies. This study used novel tetramer reagents developed by the MGH team to specifically detect SARS-CoV-2 specific CD4⁺ T cells and used them to directly analyze CD4⁺ T cell response to infection. Linking the strength of the CD4⁺ T cell response to both improved clinical response and sustained antibody response provide insight into approaches to evaluate future vaccine strategies and prevent COVID-19 infections.

In IgE-mediated food allergies, allergen exposure activates systemic allergic responses. Oral immunotherapy (OIT) is used to treat food allergies through incremental increases in oral allergen exposure. OIT, however, only induces sustained clinical tolerance in a subset of individuals despite increases in circulating allergen-specific IgG in all treated subjects. **Sarita Patil, MD**, and colleagues compared antibodies from subjects with sustained and transient responses. In a study accepted for publication in the *Journal of Clinical Investigation* they demonstrated that specific tolerance-associated conformational epitopes of the immunodominant peanut allergen Ara h 2 were recognized by neutralizing antibodies. These epitopes were only recognized in individualized with sustained tolerance. Antibodies recognizing these tolerance-associated epitopes effectively neutralized the ability of allergen to induce IgE-mediated effector cell activation. This study demonstrates the molecular basis of antibody-mediated protection in IgE-mediated food allergy, defining how these antibodies disrupt IgE-allergen interactions to prevent allergic reactions. Studying the structural and functional basis for neutralizing antibodies demonstrates the clinical relevance of specific antibody clones in antibody-mediated tolerance. Dr. Patil anticipates these findings will form the foundation for treatments of peanut allergy using neutralizing antibodies.

Mongan Institute

Margarita Alegria, PhD, compared the performance of Medicaid managed care (MMC) plans across 19 indicators of access, quality, and outcomes of substance use disorder (SUD) treatment. This cross-sectional study used administrative claims and mandatory assignment to plans of up to 159,016 adult Medicaid recipients residing in 1 of the 5 counties (boroughs) of New York, New York, from January 2009

to December 2017 to identify differences in SUD treatment access, patterns, and outcomes among different types of MMC plans. In patients across all MMC plans, less than 1% with alcohol use disorder engaged in treatment, less than 10% engaged in tobacco treatment, and about 50% engaged in opioid disorder treatment. The results of this cross-sectional study underscore the need for engaging patients in SUD treatment in MMC plans.

Studies show that early, integrated palliative care (PC) improves quality of life and end-of-life (EoL) care for patients with poor-prognosis cancers. However, the optimal strategy for delivering PC for those with advanced cancers who have longer disease trajectories, such as metastatic breast cancer (MBC), remains unknown.

Joseph A Greer, PhD, tested the effect of a PC intervention on the documentation of EoL care discussions, patient-reported outcomes, and hospice utilization in this population. This PC intervention significantly improved rates of discussion and documentation regarding EoL care and delivery of hospice services among patients with MBC, demonstrating that PC can be tailored to address the supportive care needs of patients with longer disease trajectories.

Infectious Diseases

Research in the Division of Infectious Diseases has had a significant impact on understanding the epidemiology, transmission, pathology, treatment, and prevention of COVID-19. Notable papers include **Jake Lemieux's, MD**, Science publication in which he and his team analyzed [6.4 million SARS-CoV-2 genomes](#) to identify mutations associated with fitness and build the algorithms to detect variants of concern early. **Rajesh Gandhi, MD**, and **Erica Shenoy, MD, PhD**, are leaders in leading local and national COVID-19 guidelines. Building on this success, six [Division of Infectious Diseases faculty](#), Ingrid Bassett MD, MPH, Richelle Charles MD, Rajesh Gandhi MD, Howard Heller, Jake Lemieux MD, MPH, and Bruce Walker MD, will be part of the recently funded New England Pathogen Genomic Center of Excellence. The Centers for Disease Control and Prevention awarded \$25 million to the [Massachusetts Department of Public Health](#) who is working with partners across the state including the [Massachusetts Consortium on Pathogen Readiness](#) (MassCPR). The Pathogen Genomic Center of Excellence will play a central role in genomic surveillance and education on emerging and novel pathogens. "The COVID-19 pandemic has exposed critical gaps in our nation's public health readiness to address emerging, rapidly spreading, and evolving infectious diseases," said Jake Lemieux, MD, PhD, co-lead of the MassCPR viral variants working group, an infectious disease specialist at Mass General Hospital, and assistant professor of medicine at HMS. The overarching mission of the effort is to enhance pathogen-sequencing capacity and integrate the resulting genomic data into public health practice throughout New England.

A key focus of clinical trial and analytic work in the Division of Infectious Diseases is discovery and quantitative evidence to support health policy that achieves equity in health outcomes. **Emily Hyle, MD**, was the senior author, along with colleagues, on "[Evaluation of four](#)

[chemotherapy regimens for treatment of advanced AIDS-associated Kaposi sarcoma in Kenya: a cost-effectiveness analysis](#),” published in *Lancet Global Health*. They found that paclitaxel for Kaposi sarcoma, which is infrequently used in Africa, would improve clinical outcomes and be cost-effective at its current price compared with therapies that are most frequently provided in the region, e.g., bleomycin-vincristine. These data have the potential to change practice and save lives. Also evaluating strategies for equity in health outcomes, **Ruanne Barnabas, MD**, together with Kenyan partners, tested the efficacy of single-dose HPV vaccination in the [KENya Single-dose HPV-vaccine Efficacy \(KEN SHE\) Study](#). The results, published in NEJM Evidence, found >97% vaccine efficacy from single-dose bivalent and nonavalent HPV vaccines at 18 months. These results were presented to the UK Joint Committee of Vaccination and Immunization (JCVI) and the World Health Organization (WHO). The JCVI has changed its recommendation to endorse single-dose HPV vaccination ([August 2022](#)) in the UK. In [April 2022](#), the WHO changed their recommendation for either one or two doses of the HPV vaccine for 9-20-year-olds, citing KEN SHE as a pivotal study to support that decision.

Biostatistics Center

The **Biostatistics Unit** is leading the NIH-sponsored Researching COVID to Enhance Recovery (RECOVER) Data Resource Core (DRC). With four-years of support exceeding \$110 million, the RECOVER DRC includes over 70 investigators and staff across MGB, HMS and HSPH. This year we designed and launched three large national cohort studies of long COVID—the Adult, the Pediatric and the Autopsy cohorts—in collaboration with the RECOVER Consortium. In addition to leading the design, our responsibilities include building and maintaining complex data capture systems and storing, managing and analyzing extraordinarily diverse biomedical data on >40,000 SARS-CoV-2 infected and uninfected individuals. Critical scientific questions we aim to address include defining PASC sub-phenotypes, characterizing disease progression and recovery, evaluating risk factors and associated biomarkers, assessing the complex interplay of social determinants of health, understanding underlying mechanisms of disease, differentiating distinctive and related syndromes, and evaluating the impact of repeat infection, vaccination dosing and variants.

Palliative Care and Geriatric Medicine:

Laura Petrillo, MD in the **Division of Palliative Care and Geriatric Medicine** has been working at the intersection of cancer immunotherapy and palliative care and this past year published a study in *Cancer* that captured key palliative care issues for persons living with advanced lung cancer who have targetable mutations. Her paper entitled: “Prognostic communication about lung cancer in the precision oncology era: A multiple-perspective qualitative study” identified a number of themes related to prognostic communication, including how the prospect of targeted therapy led to high and

sometimes unrealistic expectations; the possibility of ever new and potentially beneficial therapies complicates prognostic discussions; and patients' expectations related to their targeted therapy influence their medical decision-making. Learnings from this study call for the development of tailored communication strategies for patients with uncertain trajectories of life-limiting cancer and served as the basis for Dr. Petrillo's Conquer Cancer Foundation and NCI-funded K23 awards.

The National Academy of Medicine and the Agency for Healthcare Research and Quality have both highlighted the need for more dementia palliative care research and the development of a stronger evidence base for dementia palliative care interventions. **Christine Ritchie, MD, MPH**, was the senior member of a team that recently highlighted some of the care gaps (and potential dementia palliative care interventions) in a paper published in the *Journal of Alzheimer's Disease*. The Division is addressing this gap by leading a NIA-funded R25 training grant in the conduct of Dementia Palliative Care Clinical Trials. This year-long training is training investigators from around the country to conduct high quality clinical trials of dementia palliative care interventions.

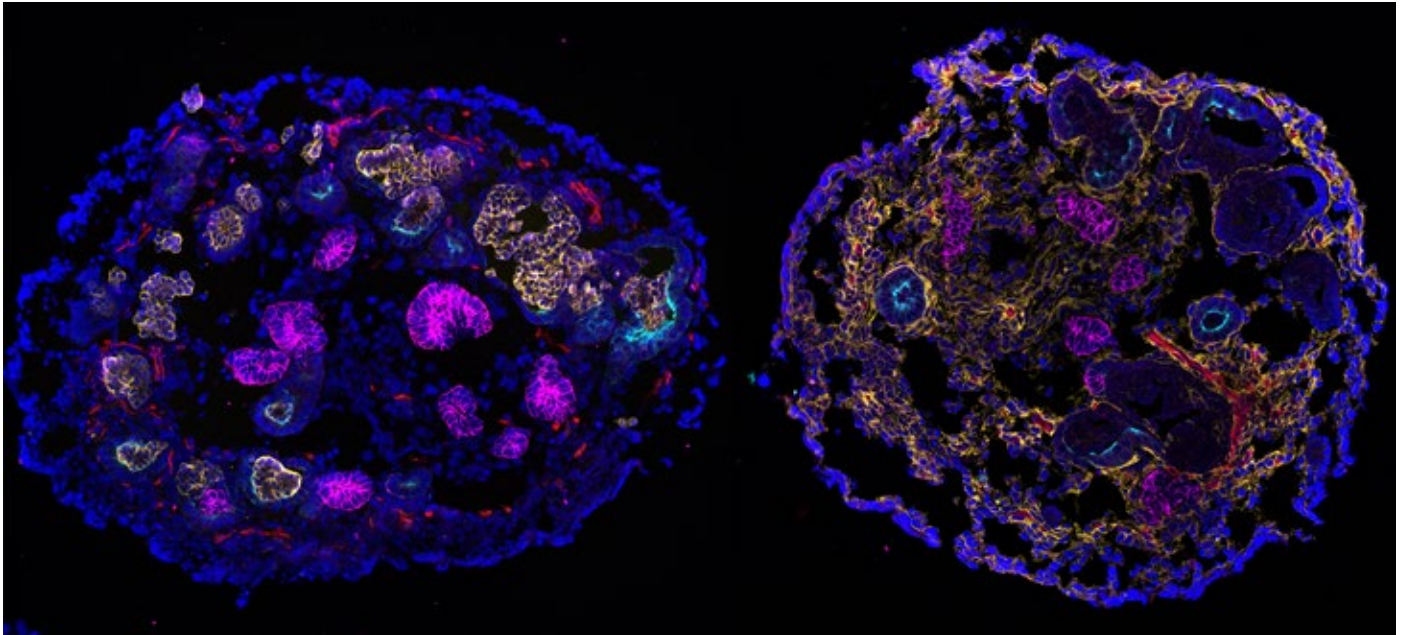
Pulmonary and Critical Care Medicine

Under the leadership of **Lida Hariri, MD, PhD**, a pathologist with joint appointment in Pulmonary and Critical Care Medicine, the division has pioneered the investigation of bronchoscopic optical coherence tomography (OCT) as a noninvasive approach for detecting early lung fibrosis. This has led to several high-impact publications, including a recent publication in the flagship *American Journal of Respiratory and Critical Care Medicine* (PMID 35675552). This technology has substantial additional promise in understanding so-called "long-COVID", leading to a recently awarded Department of Defense (DOD) and Congressionally Directed Medical Research Program (CDMRP)-funded study of COVID-19 survivors with persistent exertional dyspnea (Co-PIs Dr. Ben Medoff and Dr. Hariri).

The second research achievement in pulmonary is ongoing (having been just started in the second half of 2022). With the arrival of a new Chief of Pulmonary and Critical Care Medicine (Dr. Eric Schmidt) in July 2022, the Division has engaged in a review and reorganization of their scientific infrastructure, with attention to improving institutional support for early career investigators as well as encouraging collaborations between established investigators. Under Dr. Schmidt's guidance, the current focus is on the revitalization of clinical research in Pulmonary, as well as the establishment of new clinical biobanks to support translational investigations of the mechanistic heterogeneity of critical illness.

Nephrology

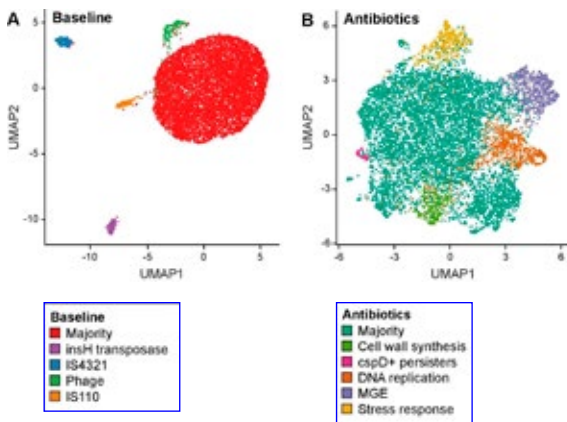
Kidney tubules have the capacity for intrinsic repair, preserving kidney architecture after acute kidney injury (AKI). Yet severe or repetitive tubular injury exceeding this capacity results in failed repair, leading to kidney fibrosis and chronic kidney disease (CKD). Limited treatments



exist for CKD, in part due to our limited knowledge of pathways which promote intrinsic repair. In a recent publication, we resolved the importance of RAD51/FANCD2 in intrinsic repair. These studies began with single-nuclear RNA sequencing of kidney organoids and found that homology-directed repair (HDR) genes including RAD51/FANCD2 were transiently upregulated during intrinsic repair, but down-regulated in incomplete repair. Follow-up studies using mouse and human single cell transcriptomics, and human kidney biopsy samples validated HDR gene up-regulation during tubular repair, and targeted drug screening identified a therapeutic candidate that rescued FANCD2/RAD51 mediated repair to prevent CKD progression in our organoid model. Our hope is that injury models in kidney organoids will facilitate the development of molecular therapies for AKI and CKD.

Chronic kidney diseases and acute kidney injury are mechanistically distinct kidney diseases. While chronic kidney diseases are associated with podocyte injury, acute kidney injury affects renal tubular epithelial cells. Despite these differences, a cardinal feature of both acute and chronic kidney diseases is dysregulated actin cytoskeleton. In prior work, we had shown that pharmacological activation of GTPase dynamin ameliorates podocyte injury in murine models of chronic kidney diseases by promoting actin polymerization. Now in our most recent publication, we establish dynamin's role in modulating stiffness and polarity of renal tubular epithelial cells by crosslinking actin filaments into branched networks. Further, we showed that activation of dynamin's crosslinking capability by a small molecule agonist stabilizes the actomyosin cortex of the apical membrane against injury, which in turn preserves renal function in various murine models of acute kidney injury. Our study provides evidence for the feasibility and highlights the benefits of novel holistic nephron-protective therapies.

Kidney organoids derived from human stem cells contain nephron, stromal, and vascular compartments to model kidney injury and repair.



BacDrop reveals A. Within population heterogeneity driven largely by mobile genetic elements, and B. Heterogeneous responses to antibiotic exposure.

Experimental Medicine Unit:

In a recent study accepted in *Cell*, the Smillie and Hung labs report the development of a new method, BacDrop, that now allows researchers to measure the single-cell transcriptomes across millions of bacterial cells. Single-cell methods in humans have revolutionized our understanding of tissues and disease. However, it has been extremely difficult to extend these methods to bacterial cells due to their relatively small size, chemically diverse cell walls, and lack of polyadenylated messenger RNA. BacDrop solves these long-standing challenges for gram-negative and gram-positive bacteria. The Smillie and Hung labs used BacDrop to study how bacteria respond to antibiotics, using *Klebsiella pneumoniae*, where resistance to last-resort carbapenems is an emerging threat. They discovered rare subpopulations of *K. pneumoniae* that were all but invisible to past work, including cells that express mobile genetic elements that help promote antibiotic resistance, and elusive “persister” cells that are metabolically shielded from multiple forms of antibiotics. The Smillie and Hung labs are next applying BacDrop to study the human gut microbiome, where they hope to reveal hidden bacterial states that are involved in nutrient and drug metabolism, pathogenicity, interactions with the immune system, and infectious and inflammatory diseases.

Interactions between gut and oral cavity microbes with the host are implicated in the pathogenesis of gastrointestinal diseases and chronic inflammation. While prototypical oral bacteria such as *Veillonella* and *Fusobacterium spp* are poor gut colonizers and do not cause disease in healthy individuals, they can be found in the intestinal mucosa in patients with diseases that include inflammatory bowel disease (IBD), colorectal cancer and cystic fibrosis. To understand how they colonize the intestines, Experimental Medicine investigators Eric Brown, Ramnik Xavier, and colleagues studied *Veillonella parvula*, an oral microbe that is significantly increased in abundance in the gut of IBD patients. They found that the bacteria use nitrate, a signature metabolite of inflammation, to switch to anaerobic respiration and turn to organic acids, amino acids, and peptides as carbon sources, fueling its growth. Nitrate respiration, through the *narGHJ* operon, was essential for microbial colonization of the gut in a mouse model of colitis. The team concludes that *V. parvula* takes advantage of the increased free nitrate available in inflammatory conditions to colonize the mammalian gut. An implication of their findings is that reducing inflammation or the abundance of these microbes may interrupt the positive feedback between inflammation and dysbiosis.

Vaccine and Immunotherapy Center:

The Vaccine and Immunotherapy Center’s (VIC) self-assembling vaccine (“SAV”) has taken an important step toward clinical testing under a partnership with the company Voltron Therapeutics (New York, NY). The vaccine, composed of an adjuvanting and carrier protein construct made in advance and used in all SAVs and a variable peptide portion individualized to a specific pathogen, rapidly assembles together in solution into a complete vaccine. The

vaccine is designed to make development more rapid and efficient by maintaining the same design across different vaccines.

In collaboration with Voltron, VIC developed a SAV for cancer caused by human papillomavirus (HPV). Latent HPV infection is implicated in development of cervical cancer and head and neck cancer, resulting in over 37,000 U.S. cases annually. These cancers cannot be treated by the current HPV vaccine. The SAV showed potent immune responses in a mouse model of HPV-induced cancer and resulted in significantly increased survival. Voltron received key guidance from the FDA in 2022 and is preparing to complete development of the vaccine to enable first human studies for treatment of HPV-expressing head and neck cancer.

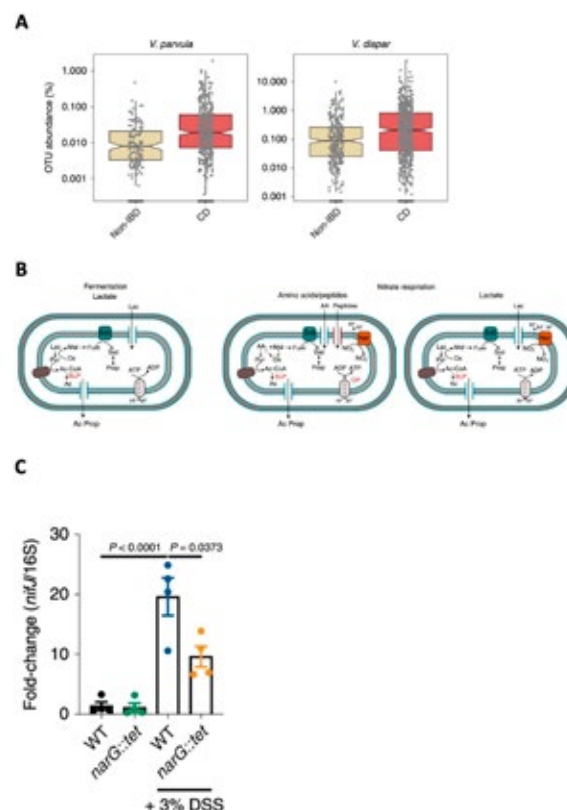
As the COVID-19 pandemic unfolded in the US during the Spring of 2020, the research teams at the Vaccine and Immunotherapy Center (VIC) focused efforts on understanding this new challenge and on developing solutions for the complex suite of disorders associated with this new virus. Among the complications of COVID-19 infection is severe damage to the lining of the lungs, often observed when severely ill patients receive supplemental oxygen or are intubated in intensive care units. This pathology, appropriately named acute respiratory distress syndrome (ARDS) results from the abnormally strong immune system response to the virus and by exposure to high levels of pure oxygen, progressively damaging the fine lining of the lungs. As a severe type of tissue injury caused in part by inflammatory responses, ARDS presented a relevant target for the immunomodulatory B cell therapy being developed in Dr. Ruxandra Sîrbulescu's group at VIC. Dr. Sîrbulescu's team found that purified B cells reduce immune damage and promote recovery in other injuries such as skin wounds and brain trauma. Together with Dr. Mark Poznansky at VIC and Dr. Dusan Hanidziar in the MGH Department of Anesthesia, Dr. Sîrbulescu translated the administration of B cell therapy to a model of aggressive ARDS induced by high oxygen concentrations. Results - in mice thus far - are promising, showing that even a single dose of B cells administered intravenously can significantly reduce multiple inflammatory parameters known to be associated with lung injury in the mouse model and in human patients. Ultimately, the treatment prevented severe tissue damage in the lungs. The team is currently preparing a scientific publication with these initial data and actively exploring the ways this novel therapy has its effect.

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Inflammation-associated nitrate facilitates gut colonization of an oral microbe. A. Increased *Veillonella* in a cohort of 800+ subjects with new-onset Crohn's disease, B. Utilization of nitrate increases metabolic flexibility of *Veillonella*, C. Nitrate reductase activity is required for efficient colonization of *Veillonella* in a mouse model of inflammation.

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Bacterial droplet-based single-cell RNA-seq reveals heterogeneity in bacterial populations and in response to antibiotic perturbation. Peijun Ma, Haley M. Amemiya, Lorrie L. He, Shivam J. Gandhi, Robert Nicol, Roby P. Bhattacharyya, Christopher S. Smillie, Deborah T. Hung. *Cell*. 2022 Dec 22;185(26):4921-4936.e15. doi: 10.1016/j.cell.2022.11.023. PMID: 36563663

Inflammation-associated nitrate facilitates ectopic colonization of oral bacterium *Veillonella parvula* in the intestine. Rojas-Tapias DF, Brown EM, Temple ER, Onyekaba MA, Mohamed AMT, Duncan K, Schirmer M, Walker RL, Mayassi T, Pierce KA, Ávila-Pacheco J, Clish CB, Vlamakis H, Xavier RJ. *Nat Microbiol*. 2022 Oct;7(10):1673-1685. doi: 10.1038/s41564-022-01224-7. Epub 2022 Sep 22. PMID: 36138166



Image Award Finalist
Rainbows in unexpected places
Joshua Spitzberg, PhD, MS
Center for Systems Biology

ROBERT E. KINGSTON, PHD, CHIEF

Overview

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.

Over 200 people, including 15 faculty, 2 junior fellows, approximately 35 staff, and over 150 researchers comprise the Department of Molecular Biology. Our areas of excellence include:

- Chromatin remodeling, long noncoding RNAs, X-chromosome inactivation (Kingston, Lee, Sadreyev), epigenetics, (Hochedlinger, Kingston, Lee, Sadreyev), reprogramming & pluripotency (Hochedlinger).
- Human genetics; mitochondrial metabolism, physiology, and disease (Mootha); and mitochondrial membrane structure and proteins (Mootha, Chao).
- Metabolic and genetic basis of species-specific developmental rates (Díaz Cuadros).
- Plant biology, signaling, and pathogen defense (Sheen). Immune signaling pathways, host-pathogen interaction (Ausubel, Hung, Ruvkun, Sheen, Xavier).
- Cytoskeletal assembly, dynamics, and transport (Subramanian), macromolecular assembly dynamics (Chao).
- Chemical biology (Hung).
- V(D)J recombination (Oettinger), innate and adaptive immunity (Xavier).
- Synapse formation, transmission, and trafficking (Kaplan). Role of neuronal and immune cells in CNS regeneration (Wattus).
- Pathophysiology and somatosensory defects in Autism Spectrum Disorder (Orefice).
- 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).

Achievements

With great excitement, the Department of Molecular Biology recognizes Bob Kingston as he begins his new role as Chief Academic Officer of MGH. Bob joined the department in 1985 and built a world-class research program in chromatin structure, regulation, and epigenetics. In 2005, he succeeded Howard Goodman to become the second Chief of Molecular Biology. As CAO, Bob's responsibilities will encompass the scientific education mission of the hospital, along with the operational mission led by Harry Orf from 2012 until his retirement in 2022. Please join us in extending our gratitude to Harry—himself a former member of the Department of Molecular Biology—and in offering our best wishes to Bob.

We also take this moment to recognize Jeannie Lee and congratulate her as she takes on the role of Interim Chief of Molecular Biology. Jeannie began her career at MGH as Chief Resident of Pathology in 1994. After completing her postdoctoral training in 1997, Jeannie joined the tenure track ranks in the Department of Molecular Biology and HMS Department of Genetics, swiftly rising to become a leader in her field of epigenetic regulation and X-chromosome inactivation. In 2019, Jeannie accepted the role of Vice Chair for Faculty Development in the Department of Molecular Biology. We are grateful to her for her leadership during this period of transition.

The Department of Molecular Biology is excited to welcome a new junior fellow, Sam Wattrus, who joined the Department in January 2023. Sam comes to us having completed his PhD in Leonard Zon's laboratory at the Harvard Stem Cell Institute. For his doctoral studies, Sam uncovered novel interactions between macrophages and nascent blood stem cells that regulate the expansion or elimination of stem cell clones based on cell stress. This was the first report of a quality control mechanism for stem cells *in vivo*. Similar mechanisms are likely induced in high stress environments, such as in stem cell transplant, neoplastic transformation, or tissue regeneration. At MGH, Sam will use the techniques he developed to study the role of neuronal and immune cells in CNS regeneration. The Department of Molecular Biology looks forward to hosting Sam over her first several years as an independent investigator.

We wish to congratulate Margarete Diaz Cuadros, also a junior fellow in our department, who received one of six 2022 International Birnstiel Awards from the Research Institute of Molecular Pathology. This award is presented annually to the top PhD students of molecular life science disciplines. Nominations for the award came from 100 institutions around the world.

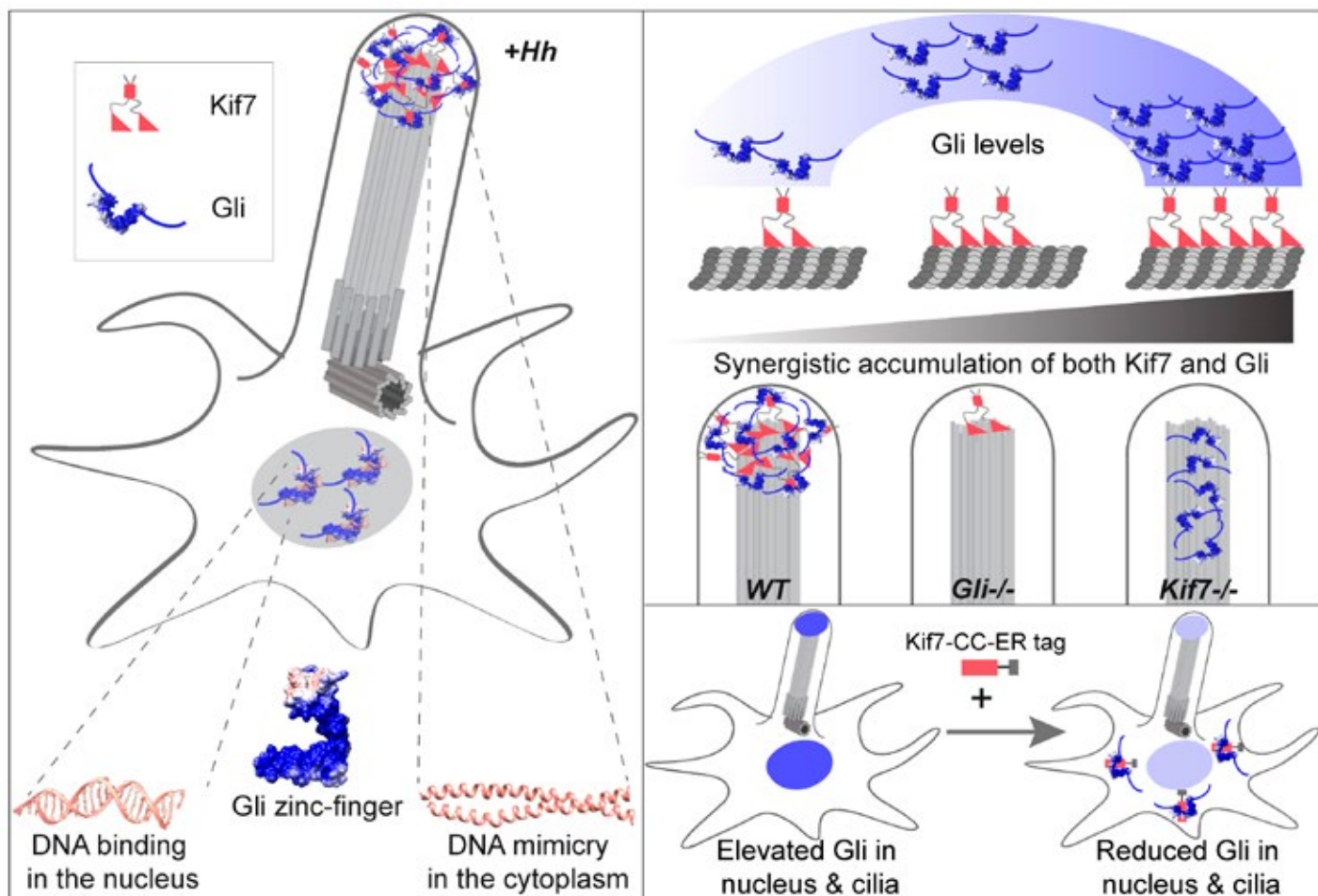


Figure 1. Schematic of the biochemical basis and cellular implications of Kif7-Gli interaction. *Left*: the zinc-finger domain of Gli that binds DNA in the nucleus is co-opted for binding the Kif7-CC out of the nucleus through DNA molecular mimicry. *Top right*: the Kif7-CC acts as a regulatory domain necessary for the graded accumulation of both proteins on microtubules and at the cilium tip in a Gli concentration-dependent manner. *Bottom right*: Kif7-CC peptide can be re-tooled as a reagent for the sequestration of Gli away into the cytoplasm to decrease nuclear and ciliary Gli levels.

Congratulations as well to members of our tenure track faculty: Radhika Subramanian, who was recently promoted to Associate Professor of Genetics, for her Motility & Cytoskeleton Early Career Award from the Biophysical Society (<https://molbio.massgeneral.org/awards/radhika-subramanian-wins-2022-motility-and-cytoskeleton-early-career-award/>); and Lauren Orefice, Assistant Professor of Genetics, for her McKnight Scholar Award (<https://www.mcknight.org/news-ideas/2022-mcknight-scholar-awards/>).

Presented below are two recent research highlights from the department, showcasing our strengths in the fundamental biophysics and biochemistry that give rise to complex biological phenomena and inform potential new therapeutic modalities.

Haque F, Freniere C, Ye Q, Mani N, Wilson-Kubalek EM, Ku PI, Milligan RA, Subramanian R. Cytoskeletal regulation of a transcription factor by DNA mimicry via coiled-coil interactions. *Nat Cell Biol.* 2022 Jul;24(7):1088-1098. doi: 10.1038/s41556-022-00935-7. PMID: 35725768.

Tethering transcription factors outside the nucleus is a well-established mechanism for regulating their activity. This typically involves membrane-bound organelles or the plasma membrane.

In case of an essential animal development pathway, called the Hedgehog signaling, surprisingly it is the microtubule cytoskeleton that is involved in cytoplasmic tethering of the transcription factor Gli (Glioma Associated Oncogene). The final step of Hedgehog signaling involves the entry of Gli into the nucleus where it acts to unleash a cascade of protein production. However, before nuclear entry of Gli it needs to be processed and activated in the cytoplasm and the microtubule based organelle, called the primary cilium. Haque *et al* discovered that a key pathway regulator and ciliary kinesin, Kif7 masquerades as DNA outside the nucleus and limits Gli nuclear entry. We find a unique DNA-mimicry based mechanism by which Gli is tethered to the microtubules at the distal tip of the primary cilia. The coiled-coil dimerization domain of Kif7 mimics the size, shape and surface charge of DNA to interact with the canonical DNA-binding zinc-finger domain of Gli and recruit it to microtubules. The study found that Gli is not a passive cargo, and it increases the kinesin-microtubule affinity, and regulates the recruitment of both Kif7 and Gli at the distal cilia tips upon Hedgehog pathway activation. The Subramanian lab exploited this coiled-coil-based Kif7-Gli interaction to inhibit the nuclear localization of Gli, a strategy that can potentially be used to downregulate erroneously activated Gli and Hedgehog signaling in cancers.

Navarro PP, Vettiger A, Ananda VY, Llopis PM, Allolio C, Bernhardt TG, Chao LH. Cell wall synthesis and remodelling dynamics determine division site architecture and cell shape in *Escherichia coli*. *Nat Microbiol.* 2022 Oct;7(10):1621-1634. doi: 10.1038/s41564-022-01210-z. PMID: 36097171.

Using a combination of fluorescent microscopy and cutting-edge cryo-electron tomography, researchers in the labs of Luke Chao in the MGH Department of Molecular Biology and Tom Bernhardt in the Blavatnik Institute at Harvard Medical School have provided never-before-seen views of double-membraned bacteria as they divide. The work offers new insights into the division process and may aid in the fight against antibiotic resistance, since these drugs typically target bacteria as they divide, when the cell wall and membranes are weakest. Led by postdoctoral research fellows Paula Navarro and Andrea Vettiger, the two groups made the discoveries possible by combining their expertise in bacterial cell division, bacterial genetics, and cutting-edge imaging.



3D surface segmentation rendering of outer-membrane (magenta) and inner-membrane (green) of an *E. coli* division site.



MERIT CUDKOWICZ, MD, MSC, CHIEF

Overview

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 best future neurologists and scientists; 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), which brings together leaders in neurology, psychiatry, and neurosurgery to create essential therapies for patients and allows teams to work collaboratively across specialties to improve patient health to solve brain diseases. More specifically, the Department of Neurology research revenue continues to grow, securing over \$210 million in research funds annually. Our greatest asset in achieving our goals is our talented faculty. Last year we promoted 9 gifted post-doctoral fellows to Instructors and had 19 faculty promotions.

This year we celebrated our 10-year anniversary under Dr. Merit Cudkowicz's leadership. Over the past 10 years the Neurology department has 1) increased the number of our faculty by 50%, 2) published over 10,000 manuscripts in prestigious journals, 3) received \$1.2 billion in research funding and 4) raised \$467 million in philanthropic funds. In addition, under her leadership the department has established 8 cores and centers combined (please see below for details on Department Centers and Cores).

One of our department's greatest 2022 achievements was the FDA approval of two neurological treatments, both efforts were led by our Neurology faculty. 1) Relyvrio, a treatment for amyotrophic lateral sclerosis (ALS); this is the first drug to show benefits of both functional outcomes and survival in patients with ALS. The approval was based on data from the CENTAUR trial, which was designed and coordinated by Drs. Sabrina Paganoni and Merit Cudkowicz from the Healey & AMG Center for ALS at MGH in collaboration with Amylyx Pharmaceuticals. The trial received the 2021 Top 10 Clinical Research Achievement Award from the Clinical Research Forum and the 2021 Martin Prize for Clinical Research at MGH. Dr. Rudolph Tanzi serves as the founding chair of the scientific advisory board of Amylyx and has guided the company since its inception in 2013. 2) Skysona, a gene therapy for the treatment of Cerebral Adrenoleukodystrophy, a rare neurological disease in adolescent boys. Dr. Florian Eichler and team partnered with Boston Children's Hospital and Bluebird Bio on this important treatment option for families. This transformative therapy comes at a time when screening for ALD in newborns is occurring in many states including Massachusetts and provides much needed hope for families and care teams invested in identifying brain disease early, when it is most treatable.

As the pipeline for new potential therapies for neurologic disease is growing there is an unmet demand for clinical trial specialists/experts. Therefore, last year our department created the Associate Chief for Clinical Therapeutic Research and recruited Dr. James Berry for this position. Since joining, Dr. Berry has developed several strategic initiatives to support and connect researchers in the areas of gene and gene-targeted therapies and neuromodulation. To name a few, the Gene Therapy Advisory Council (GTAC) was established as a resource for clinical researchers interested in gene and gene-directed therapies, with a focus on accelerating clinical trials infrastructure. Additionally, the Clinical Trials Operations Committee (CTOC) is tasked with helping resolve unique issues that arise with new research studies and strategizing on developing new policies that will guide researchers with clinical trials operations. Several of our world-renowned faculty members serve on NIH councils, are members of the National Academy, and the National Alzheimer Prevention Act council, and editorial boards of the leading journals in Neuroscience. They lead major disease consortiums (e.g., amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Parkinson's, adrenoleukodystrophy, Stroke and Alzheimer's disease (AD)).

MGH Neurology broadened its efforts to recruit and retain diverse faculty through support and inclusion. The department fostered recruitment by continuing to partner with the MGB Neurology Residency Program, the MGH Center for Diversity and Inclusion, and the HMS Office for Diversity Inclusion and Community Partnership. For the third-year funding from Biogen Foundation facilitated our paid mentored *MGH Youth Neurology Education and Research Program*, focused on research mentorship and career development of Boston area under-represented high school and undergraduate students. To date, the program has engaged 82 students underrepresented in neurology across several MGH Neurology labs (including those of faculty members underrepresented in neurology) under the leadership of Dr. Mejia who was honored last year with the American Neurological Association inaugural Audrey S. Penn Lectureship Award recognizing efforts related to the MGH Youth Neurology Education and Research Program.

Our *MGH Neurology Pathways from Community College (CC) to Neuroscience Career Program* is ongoing. This important initiative is designed to develop meaningful partnerships with the 15 community colleges across Massachusetts to foster the career development of students interested in Neuroscience. Thus far, we have partnered with Bunker Hill Community College and look forward to forging new partnerships with other areas schools once we are able to secure funding for the program.

The Department offers numerous resources to support our research faculty and young investigators including IDC support for foundations and fellowship awards, bridge funding, access to a successfully funded application via our Proposal Library, and a free Biostatistics Consultation Service; providing statistical support to investigators and junior faculty who require help with projects and grant preparation. In an effort to assist early-career investigators bridge the gap between

the clinic and laboratory, the Department also provides mentoring and financial support for early career physician scientists through the Transformative Scholars program. There have been 11 Transformative Scholars to date of which 4 have already attained Career Development Awards. MGH Neurology Grant Reviews Program is ongoing and numerous faculty have benefited from the input of our mentors which has resulted in the submission of successful applications. Lastly, this is the third year for our successful series “**Let’s talk careers in science**” an initiative to introduce alternative career paths to our post-doctoral fellows and junior faculty and to further forge and strengthen our relationship with our industry partners.

Over the years the department of Neurology has established several Centers and cores and their 2022 achievements are highlighted below.

The team at the **Center for Rare Neurological Diseases (CRND)** led by Dr. Florian Eichler is leading the way in precision medicine to treat rare neurological diseases. A focus on gene therapy and other modalities to halt disease progression has led to several advancements to improve the lives of patients. Highlights from the past year include the following:

- Implementation of the first systemic AV gene therapies for Canavan Disease patients, Tay Sachs patients and Sandhoff Disease patients.
- Implementation of the first ASO treatment for Alexander’s Disease.
- Performed clinical trial readiness studies in patients with cystinosis and better-defined disease progression, dysphagia, and myopathy with a goal to further characterize myopathy and potential regenerative treatments (R. Seyedsadjadi).
- Successful development of AV gene therapy for Adrenomyeloneuropathy (AMN) patients that, in partnership with SwanBio Therapeutics, will begin a stage 1 and stage 2 clinical trials with 15 patients in 2023.
- Successful development and feasibility testing of a new high resolution 7T MR imaging outcome in assessment of patients with CMT1A (R. Seyedsadjadi).
- Dr. Patricia Musolino and Dr. Lindsay working in collaboration with Dr. David Chung and Dr. Ben Kleinstiver have received an R01 grant from NINDS to develop Gene Therapy for Smooth Muscle Dysfunction Syndrome, a rare disease caused by a specific genetic mutation in the ACTA2 gene that alters smooth muscle function in the vessels and entire body.
- Dr. Christopher Stephan received a grant to assess potential quantitative measures of disease severity and progression in dystonia and parkinsonism using motion sensors and comparing these measures with proposed biochemical biomarkers.

Sean M. Healey & AMG Center for ALS: The Healey & AMG Center was founded in 2018 to radically accelerate innovations in pursuit of a cure for ALS. Notable highlights and progress in the development of new therapies and new models of care, include:

- Fast-tracking new therapies through the HEALEY ALS Platform Trial. Just 2 years after launch, the team is reviewing results from the first four compounds in the trial and have added a 5th drug with two more joining in early 2023. The platform trial is much faster than a traditional trial, reducing the cost of research by 30% and decreasing the trial time by 50% allowing the team to test several therapies at once.
- The first and only center awarded an NIH grant for an Expanded Access Protocol program, increasing opportunities for individuals with ALS to access experimental compounds and accelerating efforts to build a nationwide network of clinical partners.
- Collaboration with industry partners on two drugs that recently received FDA approval: 1) Amylyx on Amx0035 (RELYVRIO™), which slows the loss of function, 2) Biogen on Tofersen, a gene therapy that helps people with an inherited form of ALS.
- The ALS House Call Program with aims to reduce stress for caretakers of patients affected by ALS, and ALS Parenting at a Critical Time (PACT), supporting the emotional and social needs of both the individual with ALS and their family.
- Bringing together researchers throughout Mass General, Mass General Brigham and globally to advance ALS research; the Center has enabled copious platform trials in Alzheimer's and Parkinson's diseases in addition to developing digital tools that can measure disease progression in several neurodegenerative diseases.

Interdisciplinary Brain Center (IBC): The Interdisciplinary Brain Center (IBC) at MGH is an integrated program supporting the Neurology, Psychiatry, and Radiology departments' research missions in neuroscience. The IBC is the primary stakeholder and manager of the Clinical and Translational Research Unit (CTRU) to serve the clinical research needs of neuroscience investigators across MGB and investigators for the Institute for Innovation in Imaging (i3). The CTRU Core officially opened its doors in Jan 2022, offering clinical research protocol support and the use of state-of-the-art clinical research, phenotyping, and data visualization equipment, along with biofluid biomarker analyses services. Research conducted in the CTRU focuses on complex disorders such as Alzheimer's disease, Parkinson's disease, mood and anxiety disorders, and cancer and cardiovascular disease as related to the brain, among others. In addition, the CTRU is a resource to commercial entities, including pharma, biotech, medical device, and other companies, to facilitate academic-industry partnerships and conduct contractual research. There are currently over 40 MGB faculty utilizing the CTRU Core Facility.

While the individual components of the CTRU are exceptional as standalone entities, its actual value comes from the integration of these specialized resources. The leading-edge facilities are outfitted with advanced digital measurement technologies, data visualization capabilities, virtual reality environments for development and clinical research use; MR-compatible phenotyping equipment (e.g., EEG, other physiological recording technologies) plus a specialized

phenotyping room; multi-channel visual and audio recording with annotation capability; mobile and wearable equipment to continue off-site data acquisition available for sign-out; clinical research staff with expertise and services corresponding to broad and diverse clinical and neuroscience study requirements; and biobanking capabilities and biofluid biomarker analyses services. Co-located 1 floor above the Martinos Center for Biomedical Imaging, uniquely positions the Core to be of maximum benefit to the global neuroscience community.

Outpatient Sleep, Circadian and Activity Rhythms (OSCAR) Core:

The OSCAR Core provides the scientific expertise and technical support to facilitate the rigorous collection, processing, and analysis of outpatient sleep, actigraphy, circadian rhythms, and pupillometry data for human studies. Current Core users include investigators from Neurology, Psychiatry, Dermatology, and Anesthesiology/Genetics; they are using OSCAR Core services to study how sleep (measured using diaries and wrist-worn monitors) is affected in their study populations, how sleep or sleep disorders affects symptoms or outcomes in their study populations, and how pupillometry may be used as a marker of neurologic function.

The **Center for Value-Based Health Care and Sciences:** is an interdisciplinary center focused on developing healthcare systems that promote value through outcomes and effort. This is accomplished by implementing patient-reported outcome measures in learning healthcare systems, investigating the impact of policy decisions, and educating the next generation of providers and researchers on value-based healthcare. In 2022, the Center made major strides toward achieving these objectives through:

1. Value-based Health Care and Sciences Course—This 10-part lecture series continues until January 2023 and hosts internationally recognized value-based sciences and improvement experts. Hundreds of attendees have enrolled from all over the globe.
2. New Collaborations—This year, the Center established quality improvement cycles with clinics and groups within the Neurology department. Currently, new improvement projects are being designed, and the center is open to working with interested MGB teams.
3. The Epilepsy Learning Healthcare System (ELHS) Data Coordinating Center—In addition to collaborations, the Center also leads multi-site learning healthcare systems, ELHS, and PASSION. This Summer, the Center took on the role of ELHS Data Coordinating Center, which led to the growth of our data team.

McCance Center: The McCance Center for Brain Health, launched in 2018, aims to develop, launch, and facilitate the uptake of tools and treatments that prevent dementia, depression, and stroke from ever occurring in the first place. To achieve this, the Center is driving forward basic, translational, clinical, and population-level research, as well as clinical trials to test promising new interventions. This collective body of work leverages big data science and focuses on promoting health equity at each stage—ultimately leading to the

adoption of novel interventions to preserve and promote brain health and prevent brain disease. Some notable highlights in the past year include:

1. **The McCance Clinical Trials Platform.** Effective treatments for neurodegenerative disorders have remained elusive because they are administered too late—when the brain has already deteriorated to the point of dysfunction—and/or they are unsafe in humans. The Center has launched a pipeline for repurposing approved drugs and natural products that are known to be safe and can be used to reduce brain pathology as early as possible, for as long as needed, prior to the onset of symptoms of brain dysfunction. The Center has recruited a leading clinical trialist to catalyze these efforts and has secured philanthropic support to conduct the first such trial.
2. **Brain Care Implementation in Clinical Practice.** When it comes to brain disease, our healthcare system predominantly *reacts*. The Center is bringing together a community of clinicians, researchers, and communicators that are focused on understanding and addressing the barriers—for practitioners, as well as patients and their support systems—to widescale adoption of preventative brain care practices. Recently, the Center has developed a partnership with the Healthy Lifestyle Program at MGH Revere to integrate the McCance Brain Care Score™ (BCS)—a tool designed to motivate patients to manage their modifiable risk factors for brain disease—into their clinical workflow and has launched the Brain Care Virtual Group Visit Series available to all patients with primary care providers at MGH. In addition, the BCS team has engaged nursing and medical resident ambassadors in the Department of Neurology, who are promoting “brain healthy” practices in their patient population. The Center, as part of Mass General’s Outreach Program, also worked with Indian Health Service to bring brain care to the Neurology and Psychiatry units at the Northern Navajo Medical Center (NNMC), and this year, will convene Community Advisory Boards to drive forward informed, equity-focused brain care research initiatives and interventions.
3. **Brain Data Science Platform.** Troves of brain health data exist across institutions but are in silos and offer limited insight into brain health/disease in isolation. The McCance Brain Data Science Platform is a scalable, centralized, collaborative, secure, cloud-based tool that is being made available for brain health researchers everywhere in the world. The platform has already received brain health data from across the U.S. and has launched projects that are applying AI/ML approaches to discover novel indicators of brain health and disease. The Center’s **Human Sleep Project** is the largest of these projects, bringing together ~200,000 polysomnograms in addition to vast amounts of health-related data to discover the sleep-based markers of brain health and disease.
4. **Health Equity in Post-Stroke Outcomes.** Brain health, quality of life, and health risks are impacted by factors that are associated with where people live, work, and learn. The McCance Center has been awarded an 11 million-dollar R01 grant by the NIH for

a nationwide study, called REACH-ICH. The REACH-ICH team—which includes seven academic centers throughout the nation—will measure, for the first time, the facilitators and barriers to engagement in brain care for stroke survivors. Overcoming barriers and leveraging facilitators will enable these vulnerable individuals to improve their brain care and prevent cognitive decline, depression and recurrent stroke. With its focus on communities for whom health inequality is a major concern, REACH-ICH will also generate novel data that can be used to narrow health disparities.

The Center for Neurotechnology and Neurorecovery (CNTR):

The CNTR develops, tests, and deploys novel neurotechnologies to improve the care of people suffering from diseases or injuries of the nervous system. The center's mission includes original research, industry consultation, development of clinical trials, fostering the next generation of researchers in the field and expanding our discussion of the neuroethics surrounding neurotechnologies. The center has been expanding over the last year including moving into new space. Notable highlights in this last year include:

1. Expanded funding in multiple areas. Many of the core faculty of the center have obtained R01 and other NIH and foundation funding. One exceptional example is an award to a team lead by Dr. Eric Rosenthal from the NIH Office of the Director through its new Bridge2AI program to develop a "Patient-Focused Collaborative Hospital Repository Uniting Standards (CHoRUS) for Equitable AI. The grant, totaling ~\$25M over 4 years, focuses on developing a national infrastructure for artificial intelligence (AI) in critical care by: 1) developing the tools and data standards for critical care data science, 2) generating a 100,000-patient, high-resolution, multi-modal, multi-specialty, "AI-Ready" dataset from acute and critical care, 3) establishing ethicolegal and regulatory guidance for AI and machine learning in acute and critical care, and 4) educating a next generation of AI leaders and citizen scientists. The project team includes 21 academic centers as well as FDA, industry, and community partners and is led by Dr. Eric Rosenthal and the CNTR ICU Precision Medicine Program.
2. Fostering early careers of faculty working in neurotechnology and neurorecovery. For example, Dr. David Lin received a 5-year VA Career Development Award entitled "Deconstructing Post-Stroke Hemiparesis for Precision Neurorehabilitation." Other junior faculty in the group have received foundational awards.
3. Promoting discussion of the neuroethics of neurotechnology. Lead by Dr. Michael Young, this component of the center has grown substantially. As an example, Dr. Young co-chaired the International Neuroethics Society conference in Montreal on the theme "*Bringing Neuroethics to Life* Throughout Patient Care, Research, and Policy".
4. Partnering with the United States Special Operations Command (USSOCOM) to study blast-related brain injury in Special Operations Forces. CNTR investigators Dr. Brian Edlow and Dr. Yelena Bodien led the formation of a new partnership between

MGH and USSOCOM, who together launched a comprehensive study to identify the effects of repeated blast exposure on Special Operations Forces Service Members. The study, called ReBlast, is a key component of USSOCOM's initiative to optimize cognitive performance, battle readiness, and career longevity in Special Operations Forces personnel (<https://www.massgeneral.org/neurology/news/2022-04-20-socom-martinos-collaboration>).

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 our department, fostering collaboration and innovation
3. Develop a strong pipeline of faculty / develop the next generation of leaders
4. Provide resources to allow all faculty to promote productivity and creativity
5. Expand revenue streams through strategic pursuit of philanthropy and other funding sources
6. Throughout all of these programs, we are making individual efforts to promote diversity, equity and inclusion in the workplace

Achievements

We are proud that:

1. Our department played leading and key roles in the FDA-approval of two neurological treatments in 2022.
2. We secured over \$210M in grant funding
3. We published more than 1503 papers in FY22, with many in high profile journals!

Breakthroughs in Research and Therapeutics

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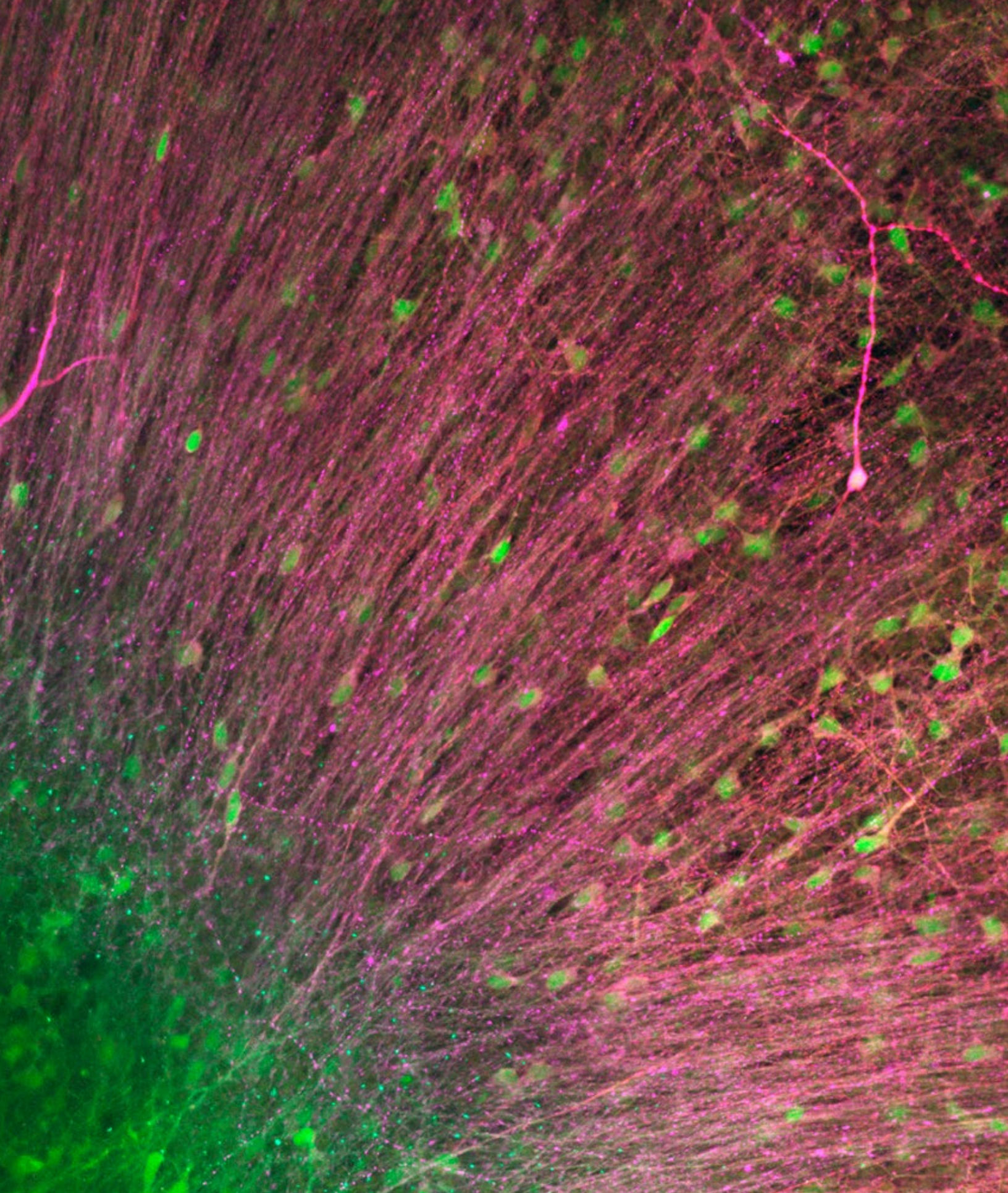


Image Award Finalist
In the Eye of the Storm
Jasmin Richter, MSc
MassGeneral Institute for Neurodegenerative Disease

GAURDIA BANISTER, RN, PHD, CHIEF

Overview

The Yvonne L. Munn Center for Nursing Research continues to advance nursing research dedicated to improving patient and family care outcomes and fostering a work environment that promotes satisfaction, health, and healing for staff, patients, and families. During the past year, nursing research and related scholarship have continued to advance in the Munn Center and the MGH community. Although some research activities were put on hold due to the COVID-19 pandemic, many initiatives have resumed virtually and in person. Dr. Gaurdia Banister, Executive Director of the Institute for Patient Care and Director of the Munn Center, along with nurse scientists Dr. Jenifer Cahill, Dr. Diane Carroll, Dr. Jane Flanagan, Dr. Dorothy Jones, and Dr. Sara Looby, comprise core scientific faculty. They advance inquiry and original research throughout the MGH community by collaborating with other PhD-prepared nurses and nursing staff embedded in the clinical environment. Correspondingly, nurses with a doctorate in practice (DNP) lead, mentor, develop, use and facilitate the translation of evidence into practice.

Strategic Goals 2021-2022

The overall mission of the Munn Center is realized through the implementation of the 2021-2022 strategic goals. They include **Goal 1:** Facilitate MGH nurses' participation in and development of nursing knowledge that aligns with the goals of MGH and Patient Care Services; **Goal 2:** Foster opportunities within the MGH Research Institute to enhance the unique contributions of nursing science; **Goal 3:** Partner with academic and clinical settings and industry to improve the health and well-being of the communities we serve; A) Strengthen ties with academic partners; B. Share nursing research resources across practice settings external to Patient Care Services; **Goal 4:** Expand the impact of nursing science through the development of financial resources that improve patient care delivery and outcomes; **Goal 5:** Strengthen nursing's contributions to patient care outcomes through the use of large data sets.

Achievements

Over the past year, many research highlights deserve recognition. We have focused on four events that showcase the many accomplishments of nurses working to advance research and evidence to generate new knowledge and improve patient care outcomes. This includes 1) Nursing Research Day and Awards, 2) Recognitions, 3) Diversity and Inclusion activities, and 4) Dissemination of information through Publications and International Presentations.

Nursing Research Day and Awards

On May 11, 2022, John Lowe, PhD, RN, FAAN, the Joseph Blades Centennial Memorial Professor at the University of Texas at Austin School of Nursing, served as our Nursing Research Day Speaker. He is a Cherokee Native American tribal member with Creek and Lenape Native American tribal heritage. Dr. Lowe developed the first manualized Talking Circle intervention to reduce substance use and other health risk behaviors among Native American and Indigenous youth in the United States and globally. The National Institutes of Health, Substance Abuse and Mental Health Service Administration, and other organizations and foundations, such as the Rita & Alex Hillman Foundation, have funded his research projects. The Talking Circle intervention has been recognized by the U.S. Department of Justice's Office of Programs as a "Promising Evidence-Based Program" for the well-being of youth, recognized as the first manualized Talking Circle intervention, featured as one of the American Academy of Nursing's "Edge Runners," and most recently featured in the National Academy of Medicine report of The Future of Nursing 2020-2030: Charting a Path to Achieve Health Equity. His presentation was entitled: *Intervention Research to Address the Health Disparity of Substance Use Among Native Youth*.

One award recipient was recognized at this important celebration of Nursing Science.

The Massachusetts General Hospital Nurses' Alumni Association Grant (MGHNAA) - Allie Walpert, MSN, FNP-BC, from the neuroendocrine unit received funding for her study, "A Pilot Study of Research Participant Perspectives on Nurse Management and Communication of Incidental Findings Identified on Research Scans." The MGHNAA grant is supported and named for the Alumni Association of the MGH School of Nursing (1873-1981), whose mission is to support nursing education, professional development, research, community engagement, and record and maintain the history of nursing at Massachusetts General Hospital. The MGHNAA is a 2-year grant that offers a Doctor of Nursing Practice program or an advanced practice nurse graduate of a Master of Science in Nursing program the opportunity to lead a clinically relevant Evidence-Based Practice, Quality Improvement, or Original Research project.

Recognitions

- **The Connell Nursing Research Scholars (CNRS) Program - Debra Manning Lundquist, PhD, RN.** Dr. Lundquist, an early career nurse scientist at the MGH, is seeking to understand the patient experience while part of a cancer clinical trial and working on designing patient-sensitive interventions to improve the experience of clinical trial participants. As (CNRS) scholar, Dr. Lundquist has dedicated her time and resources to disseminating research findings at one regional and three national conferences and submitting manuscripts for publication. She was recently awarded a grant from the *Oncology Nursing Foundation* to conduct a pilot study focusing on a nurse-led, quality-of-life intervention with early-phase



Nursing Research Quarterly Grand Rounds, Connell Research Scholar Celebration

Jennifer Cahill PhD, RN, Nurse Scientist, Yvonne L. Munn Center for Nursing Research; Debra Manning Lundquist PhD, RN, Clinical Research Nurse and Oncology Nurse Scientist from the Termeer Cancer Center; Betty Ferrell, Ph.D., M.S.N., R.N., CHPN, FAAN, FPCN, Director of Nursing Research & Education and a Professor at City of Hope in Duarte, California



A. Clifford Barger Mentoring Award Ceremony

George Q. Daley, MD, PhD, Dean of the Faculty of Medicine, Harvard Medical School; Sara Looby, PhD, ANP-BC, FAAN, Nurse Researcher, Yvonne L. Munn Center for Nursing Research and Assistant Professor of Medicine, Harvard Medical School; Markella Zanni, MD, Associate Professor of Medicine, Harvard Medical School, Metabolism Unit, MGH

clinical trial participants. Additionally, Dr. Lundquist was selected to participate in the *American Society of Clinical Oncology (ASCO) Integration of Palliative Care Guidelines Expert Panel*.

During her CNRS experience, Dr. Lundquist received mentoring from external nurse scientist, Betty Ferrell, PhD, RN, MA, CHPN, FAAN, FPCN, the Nursing Research & Education Director, and a Professor at the City of Hope Medical Center in Duarte, CA. Dr. Ferrell was recently named a Living Legend in the American Academy of Nursing and has received the Oncology Nursing Society Lifetime Achievement Award. Her research has focused on pain management, quality of life, palliative care, and end-of-life care with patients experiencing cancer. Dr. Ferrell was at MGH for two days presenting Nursing Research Grand Rounds and talking with nurses, clinicians in palliative care, and leadership across the MGH community about her research and scholarship.

- **Jane Flanagan, PhD, RN, AHN-BC, ANP-BC, FAAN** - In 2022, Dr. Jane Flanagan, a nurse scientist in the Munn Center for Nursing Research and Associate Professor and the Department Chairperson at the Connell School of Nursing, officially began her tenure as President of the Eastern Nursing Research Society (ENRS). Established in 1988, ENRS is one of four regional groups across the United States committed to creating nurse researchers and scholars committed to advancing nursing science nationally. An annual Research Conference offers students and scholars an opportunity to share their research and network with researchers from around the region and beyond.

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- **Sara Looby, PhD, ANP-BC, FAAN** - Dr. Sara Looby, a nurse researcher at the Munn Center for Nursing Research and Assistant Professor of Medicine at Harvard Medical School, was the recipient of the A. Clifford Barger Mentoring Award from the Harvard Medical School Office for Diversity Inclusion and Community Partnership. This prestigious Award was developed to honor the memory of Dr. A. Clifford Barger, who devoted his career to bringing out the best in those who studied, trained, and worked at Harvard Medical School. The Excellence in Mentoring Awards were established to recognize the value of quality mentoring relationships and their impact on professional development and career advancement in basic/clinical medicine, research, teaching, and administration. Dr. Looby is the first nurse to receive this distinguished honor.
- **Diane Carroll, PhD, RN, FAAN, FAHA, FESC** Dr. Diane Carroll, nurse researcher in the Munn Center for Nursing Research, was recently recognized by the American Academy of Nursing for her program, [Fall Tailoring Interventions for Patient Safety \(TIPS\)](#), which was named an Academy Edge Runner. *Edge Runners* are evidence-based, nurse-designed, innovative models of care or interventions with significant, demonstrated outcomes to improve health, impact cost, and influence policy.

Diversity and Inclusion Activities

Research efforts continue to facilitate the development of research investigations by participating on MGH committees, engaging in interdisciplinary research, promoting grant development, and supporting research development that addresses diversity, equity, and inclusion related to nurses and underserved, diverse populations. The projects to follow highlight research related to this area of inquiry:

- Health Research Services Administration Research and Funding (HRSA)** - The Massachusetts League of Community Health Centers have partnered on an HRSA-funded (HRSA-22+110 # U3MHP45385) grant project entitled *"Promoting Resilience and mental Health Among Health Professional Workforce"*. Dr. Gaurdia Banister (Project PI), and Dr. Dorothy Jones from the Munn Center for Nursing Research, along with co-investigators Dr. Elyse Parks and Dr. *Louisa Sylvia* from the Mongan Institute and Project Manager Meghan Feldpausch are participating in this project that will support staff providing care to meet the needs of patients in medically underserved communities and establish evidenced based protocols to promote resilience, mental health, and wellness among these care providers. Assessment data from surveys and listening sessions at selected community centers have been collected to date. They are now being analyzed to facilitate protocols and resources to foster the project goals.
- Munn Team-Lead Diversity Research Project** -The Munn Team-Lead Diversity Research Project team completed a research study entitled *"Nurse Sensitive Clinical Indicators of patients during the first surge of Covid 19"*. The Connell-Jones Endowed Chair for Nursing and Patient Care Research funded this study during the pandemic. The project has been disseminated in the literature and presented at the Council on the Advancement of Nursing Science (CANS) national research conference in Washington, DC. Study findings support using a nurse-guided assessment framework to address patient responses to immediate health problems and guide health promotion, healthcare equity, and inclusion within underserved patient communities.

Connell Jones Diversity Research Scholars (DRS) -The second annual Diversity Research Institute was held during the summer of 2022 to nine diverse staff nurses seeking to learn more about the role of nursing research in addressing health inequities in nursing. The goals of the Connell Jones Diversity Research Scholars Program are to create opportunities for:

- A:** Exposure to successful racially diverse researchers and scholars at MGH and external academic sites who will provide guidance with elucidating career paths in research;
- B:** Mentoring in the scholar's area of interest, including guidance towards establishing a research question; this includes collaboration on a mentored research project with racially diverse nurse researchers;



Connell-Jones Endowed Chair for Nursing and Patient Care Research Diversity Research Scholars

Standing: Sarbesh Chalise, MSN, CNP Neurology, Moriah McCloskey, BSN, RN, Ellison 11, Cardiac, Miriam Khan, BSN, RN, Bigelow 7, Medicine, Ana Medina, BSN, RN, Ellison 12, Medicine, Tricia Gordon, MSN, CNP, Orthopedics, Alexis Seggalye, BSN, RN, White 11, Medicine, Karphly Vilus, BSN, RN, White 7, Surgical

Kneeling: Roberta Nunez, BSN, RN, Blake 12 Intensive Care, Renee Monfiston, BSN, RN, Phillips 22, GYN/Surgical



Jane Flanagan, PhD, RN, AHN-BC, ANP-BC, FAAN, Nurse Scientist, Yvonne L. Munn Center for Nursing Research, President, Eastern Nursing Research Society

C: Participation in regular meetings with racially diverse researchers and scientists and the program director;

D: Participation in didactic sessions through the MGH Center for Diversity and Inclusion and affiliated institutions designed to enhance and facilitate learning about the research process.

The program, under the leadership of Dr. Gaurdia Banister and facilitated by a diverse cohort of nationally recognized nurse scholars, is designed to deliver an innovative curriculum and explores diversity, equity, and inclusion within the framework of nursing research. Outcomes from the last two Institutes include four scholars that have matriculated into doctoral programs in nursing research.

Dissemination of information through Publications and International Presentations

Many research and evidence-driven papers were disseminated in high-impact, peer-reviewed international nursing and other related journals. Scholarly inquiry and data-driven presentations were delivered by nurses at conferences and international forums, globally. Examples of this work are included below:

Publications

Allen, D.H., Arthur, E.K., Blazey, M., Brassill, K., **Cahill, J.E.**, Cooley, M.E., Fadol, A.P., Hammer, M.J., Hartrafnt, S., Murphy, B., Nolan, T., Sun, V., Whisenant, M., Yoder, L. A Scoping Review on the Nurse Scientist Role within Health Care Systems. *Worldviews on Evidence-Based Nursing*. 2022 Dec 14. Online ahead of print.

Banister G, Carroll DL, Dickins K, Flanagan J, Jones D, Looby SE, Cahill JE. Nurse-sensitive indicators during COVID-19. *International Journal of Nursing Knowledge*. 2022 May 17.

Blanchard HT, **Carroll DL**, Astin F. Patient experience of informed consent for diagnostic coronary angiogram and follow-on treatments. *British Journal of Cardiac Nursing*. 2022 Jun 1:1-9.

Callans K, **Carroll DL**, McDonough A. Parental experience of hypoglossal nerve stimulator implantation in adolescents with Down Syndrome and obstructive sleep apnea. *Journal of Pediatric Nursing*. 2022 Oct 31.

Flanagan J, Post K, Hill R, DiPalazzo J. Feasibility of a Nurse Coached Walking Intervention for Informal Dementia Caregivers. *Western Journal of Nursing Research*. 2022 May;44(5):466-76.

Jones, D. , Antonelli, M. *Margaret Newman*. In M.R. Alligood (Ed.), *Nursing theories, theorists and their work*, 10th Edition (pp. p 354-369). St. Louis, MO., Elsevier, 2022.

Jones, D., Herdman, T. H., de Cassia Gengo e Silva Butcher, R. (2021). Clinical reasoning: From assessment to diagnosis. In H. Herdman, S. Kamitsuru, C. Takao Lopez, *Nursing diagnosis: Definitions and classifications, 12th Edition*. (pp.109-125).N.Y., N.Y., Thieme, 2022.

Looby SE, Kantor, A, Burdo, TH, Currier, JS, Fichtenbaum, CJ, Overton, ET, Aberg, JA, Malvestutto, CD, Bloomfield, GS, Erlandson, ET, Cespedes, M, Kallas, EG, Masia, M, Thorton, AC, Smith, MD, Flynn, JM, Kileel, EK, Fulda, E, Fitch, KV, Lu, MT, Douglas, PA, Grinspoon, SK, Ribaud, HJ, Zanni, MV. Factors associated with systemic immune activation indices in a global primary cardiovascular disease prevention cohort of people with HIV on antiretroviral therapy. *Clinical Infectious Diseases*. 2022 Mar 2. Online ahead of print.

Naranbhai V, Garcia-Beltran WF, Chang CC, Mairena CB, Thierauf JC, Kirkpatrick G, Onozato ML, Cheng J, St Denis KJ, Lam EC, Kaseke C, Tano-Menka R, Yang D, Pavlovic M, Yang W, Kui A, Miller TE, Astudillo MG, **Cahill JE**, Dighe AS, Gregory DJ, Poznansky MC, Gaiha GD, Balazs AB, and Iafrate AJ. Comparative Immunogenicity and Effectiveness of mRNA-1273, BNT162b2, and Ad26. COV2. S COVID-19 Vaccines. *The Journal of infectious diseases*. 2022 Apr 1;225(7):1141-50.

Stanton, AM, Goodman, GR, Robbins, GK, **Looby, SE**, Williams, M, Psaros, C, Raggio, G. Preventing cardiovascular disease in midlife women with HIV: An examination of facilitators and barriers to heart health behaviors. *Journal of Women and Aging*. 2022 Feb;1-20.

Presentations

- **Cahill, J.** Nurse Sensitive Indicators During COVID-19 / Platform (selected abstract)
Council for the Advancement of Nursing Science, State of the Science Congress on Nursing Research Washington, DC.
- **Banister, G.** Racism in Healthcare. Addressing Cancer Care, Equity & Systemic Racism in HealthCare, Dana Farber Cancer Institute. Online Conference, Boston, MA.
- Bertocchi, L.; Andreti, S.; Emedio, S.; **Jones, D.** Translation and Validation of the Functional Health Pattern Assessment Screening Tool (FHOAST) for Improving Patient Outcomes in Practice. Selected by the Scientific Committee for oral presentation at the Live Streaming Virtual ACENDIO Conference Online.
- **Cahill, J.** Exploring the Role of the Nurse Scientist in the Clinical Oncology Setting / Platform (selected abstract). Council for the Advancement of Nursing Science, State of the Science Congress on Nursing Research Washington, DC.
- **Jones, D.,** Ditomassi, M., Duffy, M. Evaluating the psychometric properties of power as influencing change (PIPPC) scale evaluation. Eastern Nursing Research Society, Providence, RI.



The American Academy of Nursing Edge Runner Award Ceremony

Diane Carroll, PhD, RN, FAAN, FAHA, FESC, Nurse Researcher, Yvonne L. Munn Center for Nursing Research; Patricia C. Dykes PhD, MA, RN, FAAN, FACMI, Associate Professor of Medicine, Brigham and Women's Hospital; Ann Ann Hurley, DNSc FAAN, FGSA (not pictured), Senior Nurse Scientist at Brigham and Women's Hospital

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)** and the **Deborah Kelly Center for Clinical Research** are our Department's arenas for connecting and supporting basic and clinical scientists whose primary research emphasis includes infertility, maternal-fetal interaction, aging, and gynecologic cancers. The centers provide 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. Together their overall research mission is to overcome through basic, translational, and clinical research.

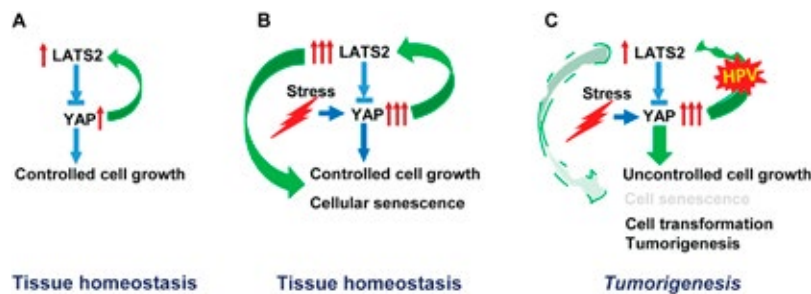
Mass General Global OB/GYN integrates three core missions to address the unmet promise of reproductive health care for all women throughout the world by providing care, bolstering education and training, and conducting innovative research. We strive to ensure that our efforts are guided by the locally relevant needs of our partners and the women they serve. Within the research arena, Global OB/GYN at Mass General carries out its mission by focusing on implementation and operational research guided by innovation and local partners to both widen the evidence base for the care of women in resource-poor settings and directly impact service delivery both domestically and abroad. Along 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:

1. Human papillomavirus targets the YAP1-LATS2 feedback loop to drive cervical cancer development.

Human papillomavirus (HPV) infection is very common in sexually active women, but cervical cancer only develops in a small fraction of HPV-infected women, suggesting that unknown intrinsic factors associated with the unique genetic/genomic background of the high-risk population play a critical role in cervical carcinogenesis. Although our previous studies have identified the hyperactivated *YAP1* oncogene as a critical contributor to cervical cancer, the molecular mechanism by which YAP1 drives cervical cancer is unknown. In the present study, we found that although

the hyperactivated YAP1 caused a malignant transformation of immortalized cervical epithelial cells, it induced cellular senescence in cultures of primary human cervical epithelial cells (HCvECs). However, the hyperactivated YAP1 induced malignant transformation of HCvECs in the presence of high-risk HPV E6/E7 proteins, suggesting that the hyperactivated YAP1 synergizes with HPV to initiate cervical cancer development. Our mechanistic studies demonstrate that YAP1, via up-regulating LATS2, formed a YAP1-LATS2 negative feedback loop in cervical epithelial cells to maintain homeostasis of cervical tissue. Intriguingly, we found that high-risk HPV targets LATS2 to disrupt the feedback loop leading to the malignant transformation of cervical epithelial cells. Finally, we report that mitomycin C, an FDA-approved drug that could upregulate LATS2 and drive cellular senescence in vitro and in vivo, induced a regression of cervical cancer in a pre-clinical animal model. Thus, high-risk HPV targeting the YAP1-LATS2 feedback loop represents a new mechanism of cervical cancer development. **PMID: 35761037**



Schematic illustrations showing the proposed mechanism by which HPV interacts with YAP1 oncogene to induce cervical carcinogenesis.

Our research results demonstrate that YAP and LATS2, the upstream suppressor of YAP, form a YAP-LATS2 negative feedback loop to maintain the homeostasis of cervical epithelium. Under physiological conditions, the feedback loop is functional, and activation of YAP in cervical epithelial cells leads to increased expression of LATS2, which can inactivate YAP via phosphorylating YAP and retain YAP in the cytoplasm, leading to the blockage of cell proliferation and tissue homeostasis (A). Under certain circumstances, YAP protein may be over-activated by intrinsic and extrinsic stresses (e.g., YAP1 gene amplification). If the YAP-LATS2 negative feedback loop still functions in these cells, hyperactivated YAP could induce cellular senescence via high expression of LATS2, resulting in controlled cell growth and tissue homeostasis (B). Infection of high-risk HPV results in the expression of E6 and E7 oncoproteins in cervical epithelial cells. These oncoproteins can disrupt the YAP-LATS2 feedback loop, leading to uncontrolled cell proliferation, transformation, and cervical carcinogenesis (C).

2. US Incidence of Late-Preterm Steroid Use and Associated Neonatal Respiratory Morbidity After Publication of the Antenatal Late Preterm Steroids Trial, 2015-2017

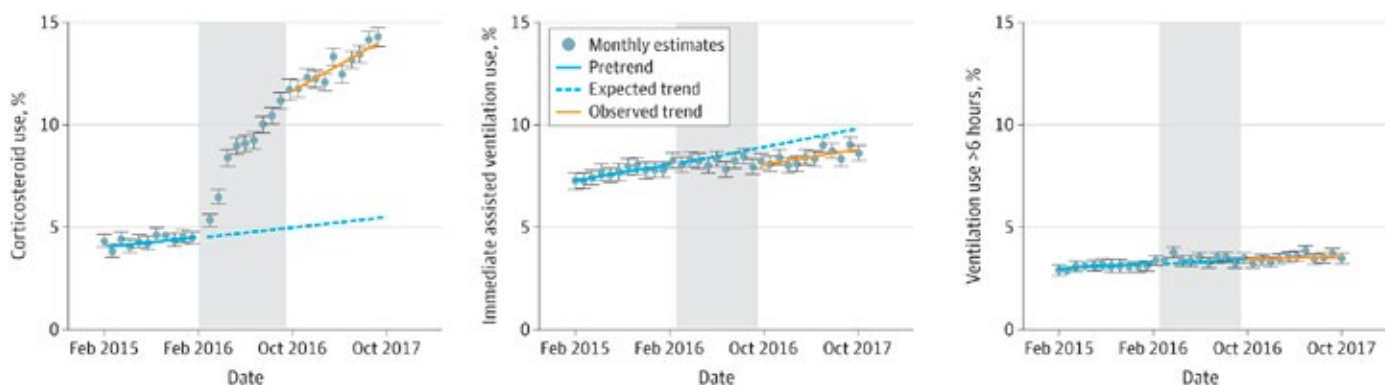
IMPORTANCE: The Antenatal Late Preterm Steroids (ALPS) trial demonstrated a 20% reduction in the risk of respiratory complications in neonates at risk for a late-preterm birth who were exposed to antenatal corticosteroids compared with those who were not.

OBJECTIVE To assess whether new evidence of steroid administration for neonatal respiratory benefit in the late-preterm period is associated with changes in obstetric practice and the use of assisted ventilation for the neonate after delivery.

DESIGN, SETTING, AND PARTICIPANTS: This cross-sectional study of US births from February 1, 2015, to October 31, 2017, as ascertained from US natality data, included live-born, singleton neonates born between 34 and 36 completed weeks of gestation to people without pregestational diabetes. An interrupted time series analysis using Poisson regression models was conducted. Data were analyzed from July 11, 2022, to November 9, 2022.

EXPOSURES: Public dissemination of the ALPS trial results, which occurred during a 9-month period from February 1, 2016 (first published online), to October 31, 2016 (time of the last major professional society's guideline update in the months after the trial's publication).

MAIN OUTCOMES AND MEASURES: Steroid use, any assisted ventilation use, and assisted ventilation use for more than 6 hours immediately after the dissemination period. **RESULTS** A total of 707 862 births were included, divided among the 12-month predissemination period (n = 250 643), dissemination period (n = 195 736), and 12-month postdissemination period (n = 261 493). Most births were at 36 weeks of gestation (53.9% in the predissemination and postdissemination period; P = .10). Small but significant differences were found between the predissemination and postdissemination period cohorts: there were more individuals 35 years or older (19.5% vs 17.9%), fewer White individuals (67.8% vs 69.8%), and more publicly insured individuals (50.5% vs 50.1%) in



The adjusted models included the following covariates: completed weeks of gestation, maternal age, maternal race, maternal ethnicity, primary payer for birth encounter, and delivering practitioners. The gray shaded area represents the dissemination period (February to October 2016).

the postdissemination period compared with the predissemination period, respectively ($P < .001$ for all). Compared with what rates were expected based on the predissemination trends, the adjusted rate of steroid use increased from 5.0% to 11.7% (adjusted incidence rate ratio [IRR], 2.34; 95%CI, 2.13-2.57), and assisted ventilation use decreased from 8.9% to 8.2% (adjusted IRR, 0.91; 95%CI, 0.85-0.98) after the dissemination period. No change was observed in assisted ventilation use for more than 6 hours (adjusted IRR, 0.98; 95%CI, 0.87-1.10).

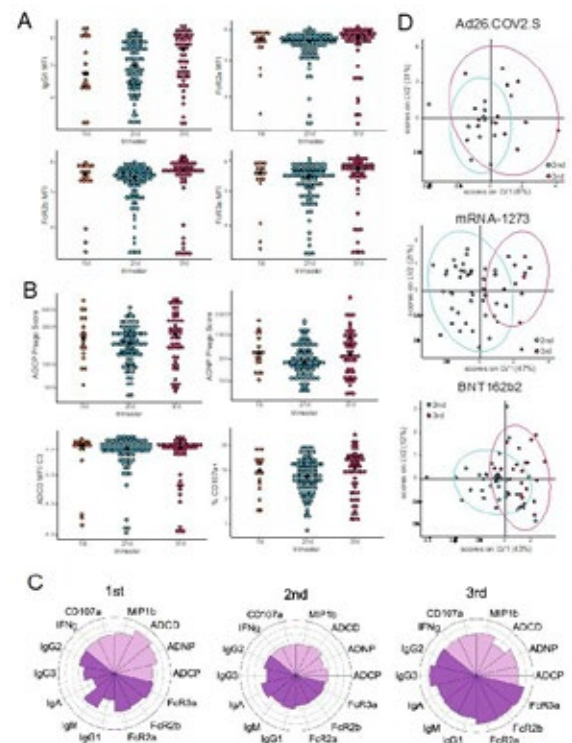
CONCLUSIONS AND RELEVANCE: These findings suggest that there was an immediate change in practice of administering antenatal steroids and a reduction in neonatal morbidity among latepreterm births associated with the dissemination of the ALPS trial, suggesting that this evidence may be translating into a reduction in immediate respiratory morbidity outside the context of a clinical trial.

3. Maternal immune response and placental antibody transfer after COVID-19 vaccination across trimester and platforms.

The availability of three COVID-19 vaccines in the United States provides an unprecedented opportunity to examine how vaccine platforms and timing of vaccination in pregnancy impact maternal and neonatal immunity. Here, we characterize the antibody profile after Ad26.COV2.S, mRNA-1273 or BNT162b2 vaccination in 158 pregnant individuals, and evaluate transplacental antibody transfer by profiling maternal and umbilical cord blood in 175 maternal-neonatal dyads. These analyses reveal lower vaccine-induced functions and Fc-receptor binding after Ad26.COV2.S compared to mRNA vaccination, and subtle advantages in titer and function with mRNA-1273 versus BNT162b2. mRNA vaccinees have higher titers and functions against SARS-CoV-2 variants of concern. First and third trimester vaccination results in enhanced maternal antibody-dependent NK-cell activation, cellular and neutrophil phagocytosis, and complement deposition, relative to second trimester. Higher transplacental transfer ratios following first and second trimester vaccination may reflect placental compensation for waning maternal titers. These results provide novel insight into the impact of platform and trimester of vaccination on maternal humoral immune response and transplacental antibody transfer.

4. Impact of Topical Interventions on the Vaginal Microbiota and Metabolome in Postmenopausal Women: A Secondary Analysis of a Randomized Clinical Trial. JAMA Netw Open. 2022 Mar 1;5(3):e225032

BACKGROUND: Close to half of women have vulvovaginal discomfort after menopause, which can significantly impact quality of life. **Methods:** This is a secondary analysis of a subset of samples from a randomized clinical trial of vaginal estradiol tablet + placebo gel, vaginal moisturizer + placebo tablet or dual placebo for treatment of moderate-severe vulvovaginal discomfort in postmenopausal women. In the primary trial analysis, there were no significant differences in reduction of vaginal symptoms among women using the estradiol



Trimester of vaccination affects vaccine-induced antibody titer in maternal samples

(A) The dot plots show the Spike-directed IgG1 and FcR-binding in maternal samples by trimester of vaccination. Significance was determined by Kruskal-Wallis test. No significant differences were found. The black diamond represents the group median.

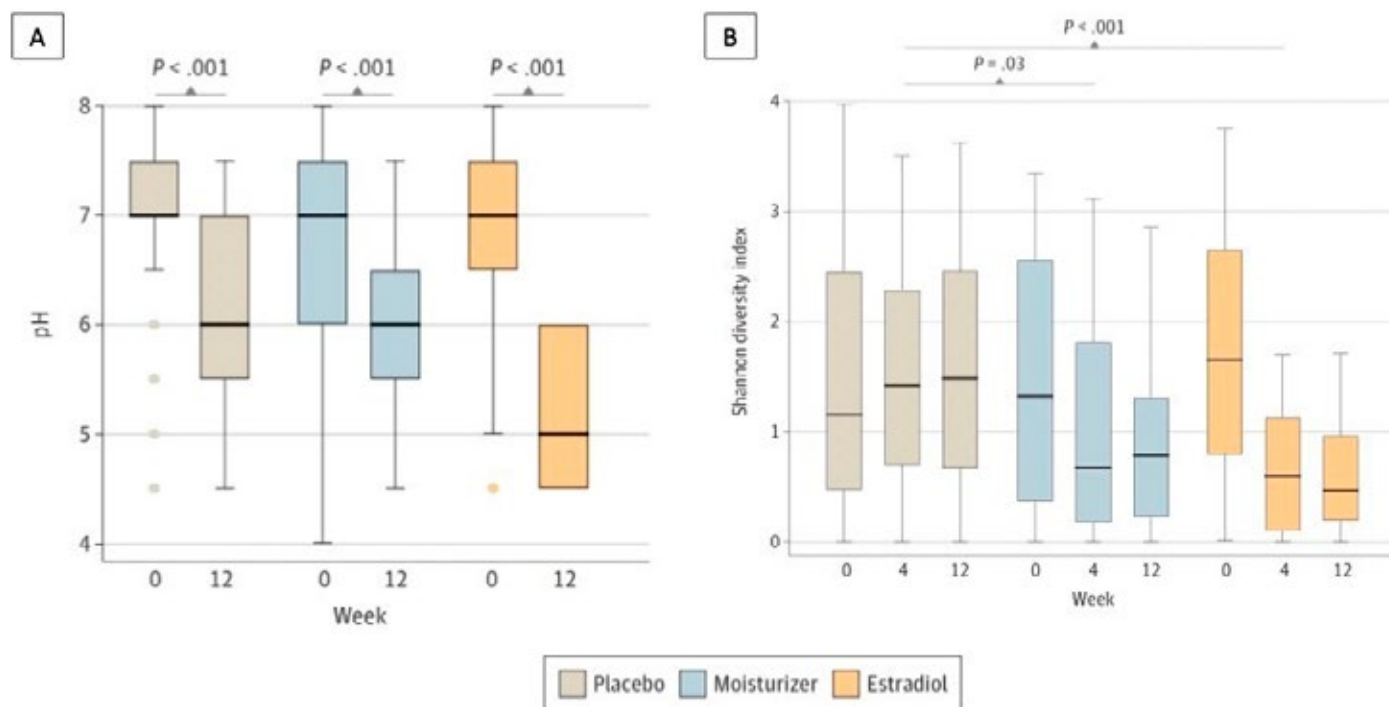
(B) The dot plots show the Spike-directed antibody-dependent cellular phagocytosis (ADCP), antibody-dependent neutrophil phagocytosis (ADNP), antibody-dependent complement deposition (ADCD) and antibody-dependent NK cell degradation, as measured by % CD107a + NK cells, in maternal samples by trimester of vaccination. Significance was determined by Kruskal-Wallis test. No significant differences were found. The black diamond represents the group median.

(C) The polar plots show the mean percentile rank for Spike-specific features in first, second, and third trimester of vaccination.

(D) A PLSDA was built using LASSO-selected antibody features in maternal plasma for mothers who received Ad26.COV2.S, mRNA-1273, or BNT162b2 using trimester of vaccination as the outcome variable. Each dot represents a sample, with the color representing the trimester. The ellipses represent the 95% confidence interval for the trimester.

Obstetrics and Gynecology

Department Report



Change in pH (A) and microbial diversity (B) over 12 weeks of treatment with vaginal estradiol tablet + placebo gel, vaginal moisturizer + placebo tablet, or dual placebo. Although each arm had a significant decrease in pH, only the estradiol arm has a significant reduction in microbial community diversity, which is accompanied by an increase in *Lactobacillus* or *Bifidobacteria*.

vaginal tablet or vaginal moisturizer compared to women using the placebo regimen. We performed 16S rRNA sequencing of vaginal swabs, as well as metabolomic analysis.

RESULTS: We compared pre- and post-treatment samples from the estradiol tablet ($n = 48$), vaginal moisturizer ($n = 45$) or dual placebo ($n = 51$) arms. We found that women using the vaginal estradiol tablet had substantial changes in their vaginal microbiota and metabolome compared to the placebo group. There were increases in the abundance of lactobacilli and bifidobacteria, along with increases in metabolites that contribute to low pH such as lactate among the estradiol users compared to the placebo group. Such changes were not observed among women using vaginal moisturizer despite both groups showing reductions in vaginal pH.

CONCLUSION: This study demonstrated that a decrease in vaginal pH alone was insufficient to change the vaginal microbiota. While the changes with estrogen were somewhat expected, the observation that low-pH vaginal products don't change the vaginal microbiota is contrary to some expectations, and suggests that "low pH" products may not be as helpful as their marketing claims.



Image Award Finalist
Janitor: Avengers of Mass General Hospital
Venkatesh Pooladanda, MS, PhD
Obstetrics and Gynecology, Vincent Center for Reproductive Biology

JOAN W. MILLER, MD, FARVO, CHAIR

Overview:

The research mission of the Mass Eye and Ear/Mass General Hospital 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 for ocular melanoma, photodynamic therapy for macular degeneration, anti-VEGF therapies for various neovascular eye diseases, and the Boston Keratoprosthesis, which together have saved sight or improved vision for millions of people worldwide.

Today, scientific collaboration and information—leveraged from modern genetics/genomics and big data—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 important foci.

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-in-human, CRISPR-based gene editing clinical trial for any disease, developed for the treatment of retinal degeneration associated with Leber congenital amaurosis (LCA). A pioneer in big data research, the department's Clinical Data Science Institute continues to leverage big data to build stronger health profiles and predictive models that will ultimately improve the diagnosis and treatment of eye diseases. As we continue to pursue these promising research areas, we are confident that treatment breakthroughs and cures are imminent for many blinding diseases.

The department is also dedicated to fostering an inclusive, diverse, and equitable community—across our department, institutions, and even more broadly at a national level. Building a diverse department strengthens our ability to provide world-class care to our patients, while also bolstering our education and research efforts. Inclusion, diversity, and equity (IDE) are core values, central to our mission and culture. We are proud to have a faculty made up of over 50% women, with many serving in leadership roles, and we recognize the need to continue to diversify our department by taking steps to include all demographics underrepresented in medicine and science.

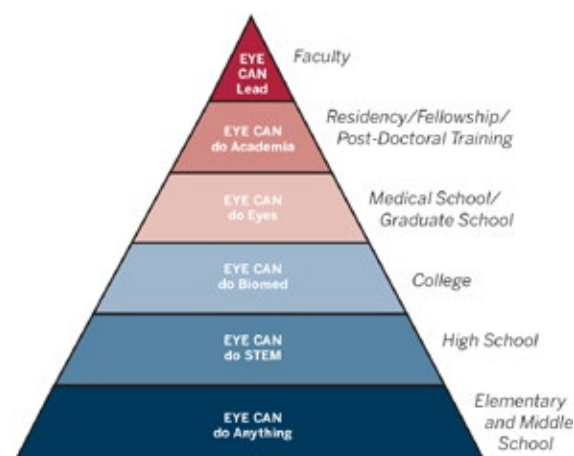
Highlighted accomplishments for the Department of Ophthalmology in 2022 are grouped thematically below:

Achievements:

Inclusion, Diversity, and Equity (IDE)

Over the past several years, the Department of Ophthalmology has launched a number of new programs with the goal of supporting and providing more opportunities to those underrepresented in medicine and science. Our IDE leaders, **Joan W. Miller, MD, James Chodosh, MD, MPH, Alice Lorch, MD, MPH, Joseph Arboleda-Velasquez, MD, PhD, and Ankoor Shah, MD, PhD**, are driving several of our initiatives to increase diversity department-wide.

- The **EYE CAN Program**, envisioned by **Drs. Shah, Lorch, and Miller**, incorporates initiatives to diversify the pipeline of individuals interested in ophthalmology at every level of the professional development cycle—from school-aged children to faculty leaders—creating a feeling of inclusion and encouraging each individual to believe “EYE CAN.”
 - The **Harvard Retinal Imaging Laboratory Undergraduate Minority Mentorship Program**, launched in 2021 and led by **John B. Miller, MD**, provides a semester-long mentoring program offering premedical students at Harvard College who identify as underrepresented in medicine and science the opportunity to gain early exposure to ophthalmology. **Edward Lu, MD**, a PGY1 resident, and **Augustine Bannerman**, a Retinal Imaging Laboratory research associate, developed a didactic and experiential program that pairs each student with a mentor and gives students an opportunity to contribute to a research project, participate in laboratory meetings, critically analyze data, and write scientifically. In 2022, this program was expanded to include undergraduate students from Massachusetts Institute of Technology.
 - Launched in 2021, the **Harvard Ophthalmology Research Scholars Program** provides rising second-year medical students from underrepresented and disadvantaged groups an immersive, eight-week experience in ophthalmology and vision research at Mass Eye and Ear. Developed by **Drs. Arboleda-Velasquez and Chodosh** and now overseen by **Drs. Arboleda-Velasquez and Silas Wang**, the program pairs students with a vision scientist to develop research skills and a physician in ophthalmology to gain clinical experience. Scholars are provided an opportunity to publish their work at the end of the program and continue to receive support and guidance as they prepare their applications for ophthalmology residency programs. For an additional opportunity to network and gain inspiration from alumni and faculty presentations, the Scholars from the previous year are invited back to attend the Harvard Ophthalmology Annual Meeting and Alumni Reunion.
 - **Dr. Alice Lorch** is leading a pilot program, funded in part by an MGH United Against Racism grant, that provides comprehensive ophthalmology care and disease screening to underserved communities in the Boston area. Screenings are held in Revere



The EYE CAN Pyramid. The EYE CAN Program is a multi-tiered approach to improve diversity in our faculty ranks by starting with school-aged children and encouraging them to believe “EYE CAN do anything.”



Claes Dohlman, MD, PhD, 2022 Champalimaud Laureate. Dr. Dohlman (seated) is pictured with family members following presentation of the 2022 António Champalimaud Vision Award in Lisbon, Portugal.

at the Mass General Revere Health Center and in Jamaica Plain at the Brookside Community Health Center. More than 20% of patients screened have findings of diabetic retinopathy or other eye pathology that requires follow up and potential treatment.

- **Silas Wang, MD**, has been participating in the MGH Rural Medicine Program. This program, in partnership with the Rosebud Sioux Tribe in South Dakota and the Indian Health Service, provides medical and ophthalmologic care to the Rosebud Indian Reservation, a chronically underserved community. As part of this program, Dr. Wang travels to Rosebud, South Dakota twice a year to provide care.

Pioneering Cornea Research Recognized by Champalimaud Foundation

Internationally recognized as the founder of modern corneal science, **Claes Dohlman, MD, PhD**, was presented with the 2022 António Champalimaud Vision Award for his immense contributions to vision research that have forever changed the way conditions of the cornea are understood and treated. Over the course of his seven-decade career at Schepens Eye Research Institute of Mass Eye and Ear and the Mass Eye and Ear/Mass General Hospital Department of Ophthalmology, Dr. Dohlman spearheaded investigations of corneal physiology that have laid the groundwork for clinical practice in dry eye disease, corneal burns, wound healing, corneal transplantation, and keratoprosthesis. As a result, his work has helped improve the vision and lives of millions of people around the world. Dr. Dohlman received the award, considered the “Nobel Prize of Vision” along with Gerrit R. J. Melles, MD, PhD, founder of the Netherlands Institute for Innovative Ocular Surgery (NIIOS) and the Melles Cornea Clinic in Rotterdam.

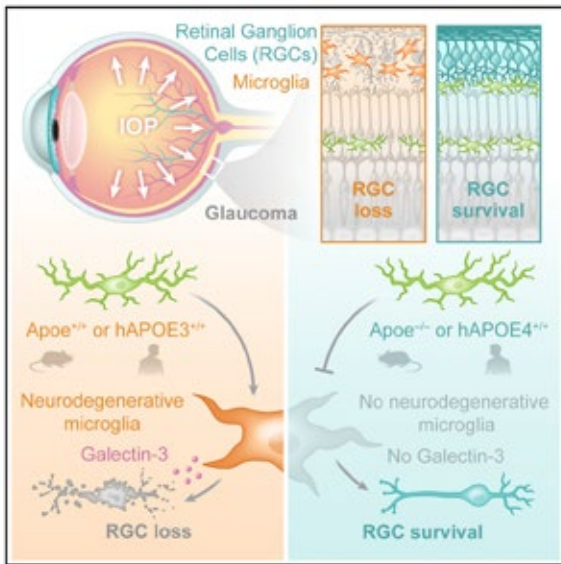
This is the second time Harvard Ophthalmology and Mass Eye and Ear researchers have received this prestigious honor—we are the only ophthalmology department to win the award twice and boast the most Champalimaud Laureates to date. In 2014, six Harvard Ophthalmology researchers won the António Champalimaud Vision Award for their contributions to identify vascular endothelial growth factor (VEGF) as the major driver for angiogenesis in the eye, which underlies the pathology of many blinding retinal disorders, leading to the development of novel anti-VEGF treatments.

Big Data and Clinical Data Science

In 2020, the Department established the Clinical Data Science Institute with the goal of building more robust health profiles and predictive models to ultimately improve diagnosis and treatment of eye diseases. Led by co-directors **Lucia Sobrin, MD, MPH**, and **Tobias Elze, PhD**, the Clinical Data Science Institute utilizes multiple registries and databases to answer questions about ophthalmic diseases, both common and rare. One of these databases—the Intelligent Research in Sight (IRIS®) Registry—was established by the American Academy of Ophthalmology in 2013 and is the nation’s first electronic health record-based comprehensive eye disease and

condition registry. Researchers can use these data to accelerate clinical innovation and enhance clinical knowledge. Combining data from both private optometry and ophthalmology practices and academic medical centers, the IRIS® Registry currently holds de-identified information for over 80 million unique patients and over two billion unique diagnoses. Mass Eye and Ear is one of the four academic groups selected nationwide and awarded unique access to the IRIS® Registry. Led by co-principal investigators **Drs. Joan W. Miller** and **Alice C. Lorch**, researchers and clinician scientists in the department have published over 10 manuscripts since 2020 using this database.

- A research team led by **Nazlee Zebardast, MD, MSc**, investigated the effectiveness of trabeculectomy and glaucoma drainage device (GDD) surgery performed with concurrent cataract surgery (phacoemulsification). Results from this study demonstrated that although reoperation rates were relatively low for all procedures, surgeries performed with phacoemulsification were associated with lower reoperation rates (Ciociola et al., *Ophthalmology Glaucoma*, 2022 Jul 14: S2589-4196(22)00115-6). While stand-alone procedures resulted in greater reduction of intraocular pressure compared to combined procedures, visual acuity was improved in procedures combined with cataract surgery. These findings suggest that combining glaucoma and cataract procedures is a reasonable treatment option for patients with coexistent glaucoma and cataract disease.
- **Jia Yin, MD, PhD, MPH**, and colleagues described the characteristics of neurotrophic keratopathy (NK) in the US. NK is a rare, degenerative corneal disease associated with decreased or absent corneal sensation in which patients can experience breakdown of the corneal epithelium, impaired healing, sterile corneal ulceration, melting, and perforation. Since NK is classified as an orphan disease with little epidemiological data, the IRIS database provided an opportunity to investigate clinical data from a large number of patients. Based on the IRIS Registry data, the prevalence of NK is 21.34 cases per 100,000 patients, and is most commonly associated with herpetic keratitis and diabetes (Bian et al., *Ophthalmology*, 2022 129:1255-1262). Additional analyses found several demographic characteristics, history of diabetes, corneal transplantation, and herpetic keratitis related to significantly worse VA at initial NK diagnosis.
- **Nazlee Zebardast, MD, MSc**, led a study examining patterns of standard glaucoma surgery (trabeculectomy or glaucoma drainage devices, GDDs) versus novel glaucoma surgical techniques (minimally invasive glaucoma surgery, MIGS) in the US. The results of this study indicated that glaucoma type may influence the choice of glaucoma procedures and the decision to perform concurrent, as well as sequential, surgical procedures (Yang et al., *Ophthalmic Epidemiology*, 2022 29:4, 443-451). Given that the long-term safety and efficacy of MIGS is poorly understood, and that the use of MIGS



Apolipoprotein E4 (APOE4) impairs the response of neurodegenerative retinal microglia and prevents neuronal loss in glaucoma. APOE-Galectin-3 signaling regulates cytotoxic neurodegenerative retinal microglia in glaucoma and the *APOE4* allele attenuates microglial neurodegenerative phenotype and protects neurons in glaucoma.

Reprinted from *Immunity* 55, Margeta et al., Apolipoprotein E4 impairs the response of neurodegenerative retinal microglia and prevents neuron loss in glaucoma, 1-18, 2022, with permission from Elsevier.

procedures has been substantially increasing in recent years, this study highlights the need for further research to compare the safety and effectiveness of MIGS procedures versus standard glaucoma interventions for various types of glaucoma.

APOE Gene in Glaucoma Protection

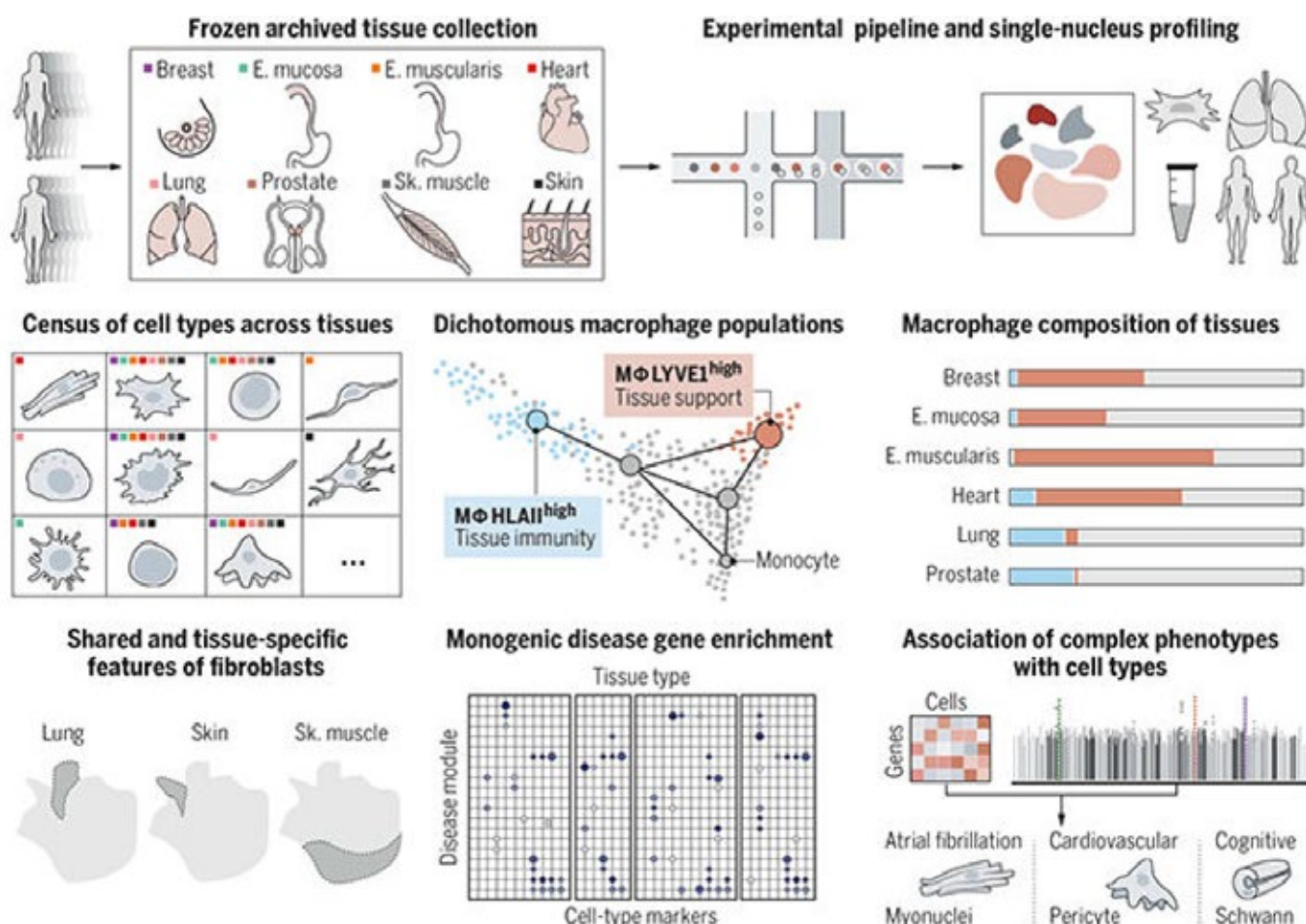
While glaucoma is a leading cause of blindness, little is known about the underlying mechanisms that lead to the loss of retinal ganglion cells that results in vision loss. There are currently no treatments to directly promote survival of retinal ganglion cells. A team of scientists at Mass Eye and Ear and Brigham and Women's Hospital led by **Milica Margeta, MD, PhD**, demonstrated that the *APOE4* gene variant—known to increase the risk for Alzheimer's but decrease risk of glaucoma in humans—functions by blocking a disease cascade that leads to the destruction of retinal ganglion cells in glaucoma (Margeta et al., *Immunity* 2022 55:1-18). Additionally, using mouse models, they showed that retinal ganglion cell death can be prevented by inhibiting galectin-3, a carbohydrate binding protein, which is regulated by *APOE*. These results emphasize the critical role of *APOE* in glaucoma and suggest that galectin-3 inhibitors hold promise as a treatment for glaucoma.

Novel Cell Atlas for Multiple Human Tissues Reveals Discoveries Underlying Complex Diseases

A collaborative team of scientists from the Broad Institute of Massachusetts Institute of Technology and Harvard have developed a first-of-its-kind cross-tissue cell atlas, and in collaboration with a research team at Mass Eye and Ear led by **Ayellet V. Segre, PhD**, have uncovered new clues for specific cell types and genes involved in complex diseases. While genetic studies of common human diseases have linked many genetic variants to disease risk, understanding the role of the implicated genes and cell types through which the genes affect disease is challenging. Complex diseases are often caused by dysfunction of more than one cell type or tissue. Thus, profiling the cell types and genes that are active in each cell type across multiple tissues or organs is necessary. Previous research has primarily focused on single-cell atlases derived from one particular healthy or diseased tissue. In this study, the research team described, for the first time, a novel cross-tissue cell atlas derived from an analysis of nuclei from 25 frozen samples from eight tissue types (Eraslan et al., *Science* 2022 376(6594):eable4290). The findings from this study should increase understanding of the cellular and genetic underpinnings of complex disease, including heart disease and cancers.

Telemedicine in Ophthalmology

Ophthalmic telemedicine provides the opportunity to increase patient access to care, improve efficiency of clinical screening, and decrease healthcare costs by allowing physicians to remotely evaluate patients. This, in turn, should allow ophthalmologists to spend more in-person time with patients requiring advanced management, procedures, or



Cross-tissue snRNA-seq atlas in eight frozen, archived adult human tissues. Tissue sites and experimental pipeline (top row). The resulting atlas enables a cross-tissue census of tissue-specific and shared cell types (middle left). Differentiation trajectories and compositional analysis of dichotomous macrophage populations improve our understanding of tissue residency (middle center and right). Analyses of fibroblasts across tissues reveals tissue-specific and shared fibroblast features and their functional interpretation (bottom left). Robust and scalable computational methods enable comprehensive associations of monogenic and complex disease to tissue-specific and shared cell populations (bottom center and right). E. mucosa, esophagus mucosa; E. muscularis, esophagus muscularis; Sk. muscle, skeletal muscle.

From: Eraslan et al., Single-nucleus cross-tissue molecular reference maps toward understanding disease gene function. *Science*.2022 376(6594):eable4290. Reprinted with permission from AAAS.

surgery. The use of telemedicine in ophthalmology has grown in recent years, and with the COVID pandemic, innovation within ophthalmic telemedicine rapidly advanced to allow ophthalmologists to provide ongoing care to their patients across a variety of ocular disorders.

- Developments in telemedicine hold significant promise for the provision of care to patients with age-related macular degeneration (AMD) who may have limited health care access. This was especially true during the COVID pandemic, where in-person evaluation of patients at risk of vision loss was not always safe or feasible. A review by **John B. Miller, MD**, and **Grayson W. Armstrong, MD**,

MPH, discussed current telemedicine applications for the care of patients with AMD and potential future use cases (Armstrong and Miller, *J Clin Med* 2022 11:835). To date, telemedical care of patients with AMD has been explored through in-person imaging of patients with remote evaluation by a retina specialist, remote consultation of retinal specialists by general ophthalmologists, and through home-based remote patient monitoring of patients with high-risk AMD. Each model of care has shown promise in detecting exudative AMD in at-risk populations and ensuring patient access to subspecialists.

- While a useful tool, telemedicine has been shown to have reduced uptake among historically marginalized populations within multiple medical specialties, particularly during the COVID pandemic. A retrospective study led by **Grayson W. Armstrong, MD, MPH**, evaluated disparities in the delivery of ophthalmic telemedicine at Mass Eye and Ear during the COVID pandemic and identified several factors that predicted reduced acceptance of telemedical care, including increased age, a primary language other than English, Black race, educational level of high school or less, and male sex (Aziz et al., *JAMA Ophthalmol* 2021 139(11):1174-1182). Additionally, the researchers identified features that were prognostic of utilizing a telephone virtual visit rather than a video-based visit—increased age, having a disability, being retired, being unemployed, and educational level of high school or less. These results indicate that implementation of telemedicine may inadvertently increase health disparities for historically marginalized populations and underscore the importance of focusing on identifying equitable ways to deliver virtual healthcare. Furthermore, outreach to vulnerable populations is important to encourage continued care, especially for patients with diseases such as diabetic retinopathy and glaucoma that are more prevalent in historically marginalized populations, and which require continued management.

Alpha-Melanocyte-Stimulating Hormone Is Critical to Corneal Graft Survival

Corneal endothelial cells, critical for maintaining corneal transparency, are gradually lost with aging and in certain conditions. In particular, corneal transplantation leads to an increased rate of endothelial cell loss resulting in tissue edema, opacity, and ultimately, graft failure. Previous studies have shown that α -melanocyte-stimulating hormone (α -MSH), a neuropeptide found in normal aqueous humor and that is in direct contact with corneal endothelial cells, regulates both innate and adaptive immune responses. A research team, led by **Reza Dana, MD, MSc, MPH, Ula V. Jurkunas, MD, and Jia Yin, MD, PhD, MPH**, have used a mouse model of corneal transplantation to show that α -MSH, acting through the melanocortin receptor 1 (MC1R), has a direct cytoprotective effect on the survival of corneal endothelial cells after transplant. Loss of α -MSH/MC1R signaling led to 100% graft swelling and failure, even in syngeneic transplantation (Marzidovšek et al., *Am J Pathol* 2022 192(2):270-280). The results from this study lay the

groundwork for new approaches to preventing corneal endothelial cell loss during tissue storage and after transplantation.

Systematic Review: Multi-decade Antibiotic Resistance of Ocular Bacteria in the US

Since 2009, the Antibiotic Resistance Monitoring in Ocular microorganisms (ARMOR) surveillance study has been assessing antibiotic resistance in vitro for bacterial isolates sourced from ocular infections in the US. In this analysis, **Paulo Bispo, PhD**, and colleagues have compared antibiotic susceptibility for common ocular bacterial pathogens from 32 published US studies spanning multiple decades against rates from the first 10 years of data from the ongoing nationwide ARMOR study. Data from local and regional US datasets were generally consistent with that from the national ARMOR surveillance study, and across all studies there was a high in vitro resistance to fluoroquinolones, macrolides, and methicillin/oxacillin among staphylococci, and multidrug resistance was prevalent among methicillin-resistant staphylococci (Bispo, et al., *Ophthalmol Ther* 2022 11:503-520). These findings validate the use of ARMOR data when choosing empiric therapy if local antibiotic susceptibility data are unavailable.

Ophthalmology Innovation

The Mass Eye and Ear/Mass General Hospital Department of Ophthalmology continues to be a nidus for translational innovations. While this year's global financial state has created a general slowdown in Industry Research and Development, several programs have led to the licensing of technology and startups—all dedicated to improving the lives of our patients.

- **Akouos** was founded in 2017 using technology from **Luk Vandenberghe, PhD**, of Mass Eye and Ear to develop gene therapies to treat hearing loss. Akouos was granted Orphan Drug designation by the European Union in August 2021 for their gene therapy to treat otoferlin gene-mediated hearing loss. In October 2022, it was announced that Eli Lilly and Company would acquire Akouos for an expected aggregate value of \$610 million.
- The Mass Eye and Ear/Mass General Hospital Department of Ophthalmology was issued approximately **33 patents** during calendar year 2022.
- In 2022, multiple tech transfer options and licensing agreements were executed with companies, including: CureVac AG; Aerie Pharmaceuticals, Inc.; Novartis Pharma AG; Kera Therapeutics, Inc.; and Ciendias Bio, Inc.

Otolaryngology, Head and Neck Surgery

Department Report

MARK VARVARES, MD, FACS, CHIEF

Overview:

The Department of Otolaryngology–Head and Neck Surgery at Massachusetts Eye and Ear/ Massachusetts General Hospital is home to one of the largest groups of researchers and collaborators devoted to developing cutting-edge treatments for disorders of the ear, nose, throat, head, neck and brain. The department’s strategic goal is to leverage its culture of close collaborations among clinical practitioners and basic scientists to advance how these disorders are understood, and to translate that understanding into the development of new treatments.

Using a broad portfolio of approaches to investigate diseases, the department continues to be a global leader of research in this area. In 2022, investigators from the department have continued to make advancements in machine learning diagnostics, uncover new biomarkers for head and neck cancer and demonstrate the safety and efficacy of hypoglossal nerve stimulation for children with Down syndrome. Together, they’re laying the groundwork for the future standard of ear, nose and throat care.

Achievements:

Select 2022 Research Highlights:

Artificial intelligence model outperforms clinicians in diagnosing pediatric ear infections

The vast majority of children in the United States have had at least one ear infection before the age of three. When left untreated, these infections can lead to numerous complications, including hearing loss and developmental delays. Conversely, over-treatment from a misdiagnosis can lead to antibiotic resistance and render medications ineffective against future infections. To ensure the best outcomes for children, clinicians must diagnose ear infections as accurately and early as possible. However, the conventional diagnostic accuracy of ear infections in children from a physical exam is routinely below 70 percent. A team of researchers led by **Matthew G. Crowson, MD**, has developed an artificial intelligence model shown to be significantly more accurate than clinicians at diagnosing pediatric ear infections in the first head-to-head evaluation of its kind. In a study published in *Otolaryngology–Head and Neck Surgery*, the model, called OtoDX, was more than 95 percent accurate in diagnosing an ear infection in a set of 22 test images compared to 65 percent accuracy among a group of clinicians—consisting of ENTs, pediatricians and primary care doctors—who reviewed the same images. **Michael S. Cohen, MD**, and **Christopher J. Hartnick, MD, MS**, were also listed as authors on the study.

Crowson MG, Bates DW, Suresh K, Cohen MS, Hartnick CJ. “Human vs Machine” Validation of a Deep Learning Algorithm for Pediatric Middle Ear Infection Diagnosis. *Otolaryngology–Head and Neck Surgery*. 2022. Doi: 10.1177/01945998221119156

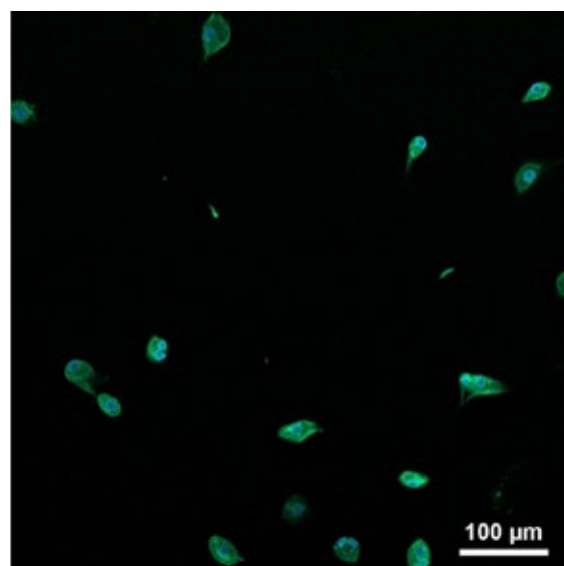
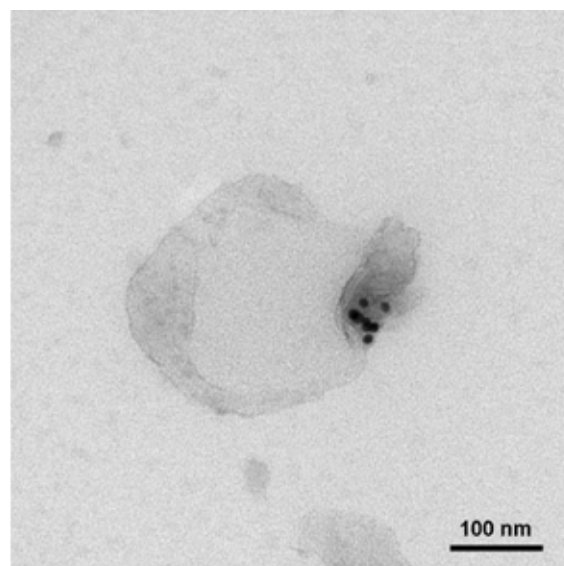
Biological explanation uncovered for why upper respiratory infections are more common in colder temperatures

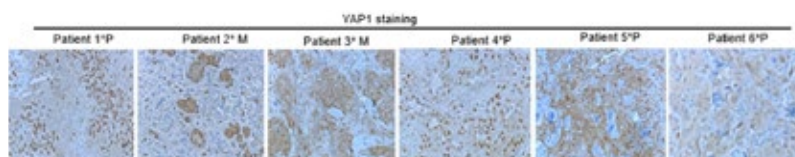
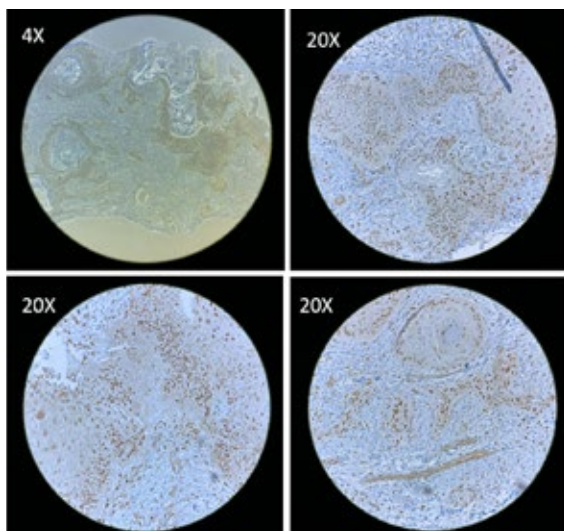
The nose is one of the first points of contact between the outside and inside of the body, making it a natural line of defense against pathogens. While prior Mass Eye and Ear research has shown how tiny extracellular vesicles (EVs) are released inside the nose to fight off bacteria, little is known about how the nose protects against viruses, which are often the cause of some of the most common upper respiratory infections. In a recent study published in *The Journal of Allergy and Clinical Immunology*, **Benjamin S. Bleier, MD, FACS; Di Huang, PhD**; and a team of researchers from Northeastern University would not only confirm a similar EV response against viruses entering the nose, but would also offer the first biological mechanism for why viruses like the common cold, flu and COVID-19 are more likely to spike in colder seasons. Over the course of the study, healthy volunteers were taken from a room temperature environment and exposed to 4.4° C (~40° F) temperatures for 15 minutes, during which time the temperature inside the nose was found to have fallen about 5° C (~9°F). The researchers applied the reduction in temperature to collected nasal tissue samples and observed a blunted immune response. The quantity of EVs secreted by the nasal cells decreased by nearly 42 percent and the antiviral proteins in the EVs were also impaired, which led to a doubling of viral concentration within the cells.

Huang D, Taha MS, Nocera AL, Workman AD, Amiji MA, Bleier BS. Cold exposure impairs extracellular vesicle swarm-mediated nasal antiviral immunity. The Journal of Allergy and Clinical Immunology. 2022; December. Doi: 10.1016/j.jaci.2022.09.037

Biomarker discovered for utilization of epigenetic inhibitors in a majority of head and neck cancers

In the past decade, the expression of specific genes—or epigenetic regulation—has emerged as a viable pathway for the development of head and neck cancer therapeutics. One signaling pathway in particular, the Hippo-YAP pathway, has garnered significant attention in recent years. The pathway is responsible for homeostasis and organ development, and alterations to the expression of several genes in the pathway are linked to approximately 50 percent of all head and neck cancers worldwide. In a study published in *Cell Reports*, **Srinivas Vinod Saladi, PhD**, and a team of researchers uncovered a biomarker that, if identified early enough, could help treat a majority of head and neck cancers using specific epigenetic inhibitors. Upon analyzing the Cancer Gene Atlas and assessing drug sensitivity in specific cancers, Dr. Saladi and his colleagues discovered that cells with mutations in a gene called *FAT1* on the Hippo pathway failed to block a cooperative mechanism between proteins YAP1 and BRD4, which resulted in out-of-control cell growth and a subsequent cancer progression. Dr. Saladi suggests that, by identifying patients with a *FAT1* mutation, researchers could test how small molecules might disrupt this cooperative YAP1-BRD4 mechanism, thereby preventing head and neck cancer cell growth at a microscopic level.





N Chen, G Golczer, S Ghose, et al. "YAP1 Maintains Active Chromatin State in Head and Neck Squamous Cell Carcinomas That Promotes Tumorigenesis Through Cooperation With BRD4." *Cell Reports*. 2022; Vol 39 (11). Doi: 10.1016/j.celrep.2022.110970

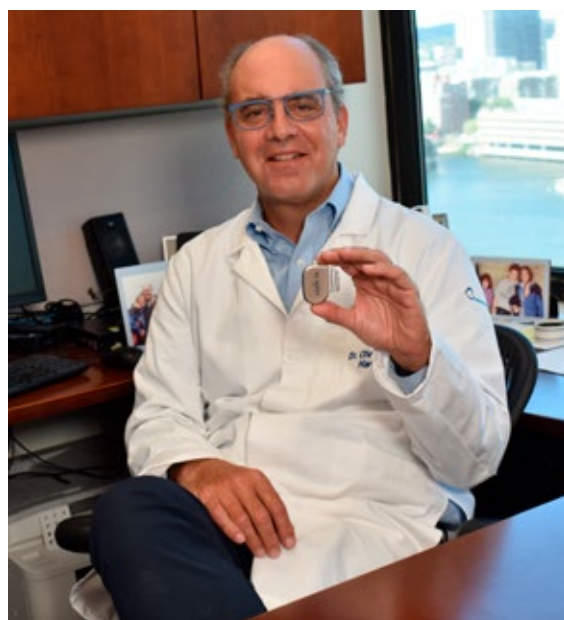
Hypoglossal nerve stimulation proven safe and effective for children with Down syndrome who also experience obstructive sleep apnea

For any child, obstructive sleep apnea can result in daytime sleepiness, behavioral issues and learning challenges. The condition is particularly prevalent in children with Down syndrome. In fact, about 80 percent of children with Down syndrome have obstructive sleep apnea, compared to 5 percent of the general pediatric population. Several anatomic and physiologic features characteristic of children with Down syndrome can render primary treatments, such as adenoidectomies and tonsillectomies, ineffective and continuous positive airway pressure machines intolerable. For the first time ever, a multicenter clinical trial led by **Christopher Hartnick, MD, MS**, and **Brian Skotko, MD, MPP**, has established the efficacy and safety of using a hypoglossal nerve stimulator device to treat obstructive sleep apnea in children with Down syndrome. In a study published in *JAMA Otolaryngology—Head and Neck Surgery*, the device was shown to dramatically reduce sleep apnea events and improve the quality of life for adolescents with Down syndrome. Feedback from families of children enrolled in the study also suggested that the device might also help improve neurocognition.

Yu PK, Stenerson M, Ishman SL, et al. *Evaluation of Upper Airway Stimulation for Adolescents With Down Syndrome and Obstructive Sleep Apnea*. *JAMA Otolaryngology—Head and Neck Surgery*. 2022; 148(6): 522-528. Doi: 10.1001/jamaoto.2022.0455

New artificial intelligence tool developed to predict efficacy of botulinum toxin injections for patients with dystonia

Dystonia is a chronic movement disorder that causes abnormal postures and repetitive movements from involuntary muscle contractions. Dystonic symptoms are often painful and negatively impact an individual's quality of life. Botulinum toxin injections are a standard treatment to temporarily manage dystonic symptoms, yet a significant cohort of these patients receive no benefit from these injections. There are no objective biomarkers of treatment response to determine who might benefit from injections, which limits the proper utilization of botulinum toxin for dystonia treatment. In a study published in *Annals of Neurology*, a team of researchers led by **Kristina Simonyan, MD, PhD, Dr Med**, has developed a novel deep learning platform that can help determine which patients with dystonia



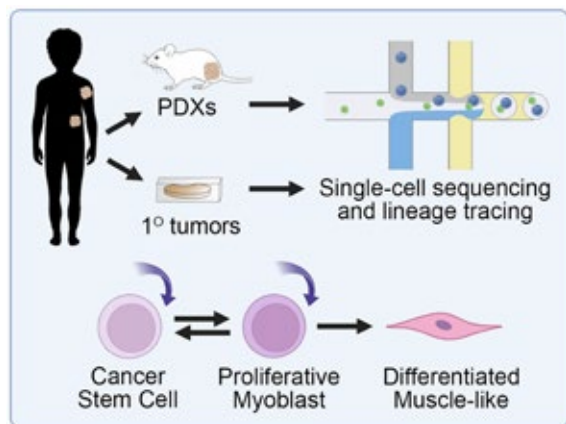
would benefit from botulinum toxin injections. According to the study, the platform, referred to as DystoniaBoTXNet, used a 3D convolutional neural network and raw structural brain MRIs to discover the neural biomarker of botulinum toxin efficacy in 284 patients with four different types of dystonia. The platform achieves an overall accuracy of 96.3 percent in predicting treatment efficacy in 19.2 seconds per case.

Yao D, O'Flynn LC, Simonyan K. Novel Neural Network Biomarker of Botulinum Toxin Efficacy in Isolated Dystonia. Annals of Neurology. 2022, November. Doi: 10.1002/ana.26558

Predicting auditory nerve loss using a word recognition test

Hearing is not just about volume. While hearing aids can be effective in bringing back sound volume, most hearing aid patients report great difficulties with speech intelligibility. The discovery of a new type of inner-ear damage at Mass Eye and Ear in 2009 helped make sense of this phenomenon. Referred to as cochlear synaptopathy, or hidden hearing loss, the nerve damage affects how clearly sounds are heard. Identifying how much hidden hearing loss exists in a living human could one day help clinicians determine who is a candidate for regenerative therapies. However, the only method to date for quantifying the amount of nerve damage is through harvesting the temporal bones of cadavers. After examining data from nearly 96,000 ears examined at Mass Eye and Ear in one of the largest retrospective studies of its kind, a team of researchers led by **Stéphane F. Maison, PhD, CCC-A**, developed a word-score model that can help estimate the amount of hidden hearing loss, or cochlear nerve damage, in humans. Published in *Scientific Reports*, findings made by the researchers suggest the model could lead to better evaluations of cochlear nerve damage in patients and the associated speech-intelligibility deficits that come with neural loss.

Grant KJ, Parthasarathy A, Vasilkov V, et al. Predicting Neural Deficits in Sensorineural Hearing Loss From Word Recognition Scores. Scientific Reports. 2022; 12, 8929. Doi: 10.1038/s41598-022-13023-5



Single cell sequencing and lineage tracing of human rhabdomyosarcomas identified stem cell hierarchies and developmental origins of human muscle cancers that were shared in human development. Patient-derived xenografted (PDX) rhabdomyosarcoma muscle cancers. Wei et al., *Nature Cancer* 2022.

DAVID N. LOUIS, MD, CHIEF

Overview:

Pathology plays a critical and substantial role in academic medicine as a natural connection between the diagnosis of human disease and experimental biomedical investigation. Major advances in molecular pathology and pathology informatics continue to accelerate the pace of diagnostic and translational research. In turn, the rapidity and frequency of interactions between clinical and scientific areas makes this an exciting time in the field of pathology. Laboratory-based scientific research is a major component of MGH Pathology and is complemented by productive clinical research activities. As a result, MGH Pathology provides an exciting stage for basic and translational research.

MGH Pathology Research has grown considerably over the past two decades, building an exceptional and well-funded group of basic science and translational investigators. Over the past several years, we have leveraged our world-class expertise in genome editing and clinical genome sequencing to expand our understanding of the functional significance of DNA sequence variants; used animal modeling and patient tissue analysis to progress new therapies into clinical trials; innovated computational and bioinformatic analyses to better refine the underlying mechanisms of human disease and cancer; and fostered new collaborations and interactions throughout the MGH. We believe that these efforts will help to ensure that MGH Pathology faculty remain at the forefront of their fields, enabling us to continue advancing our understanding and diagnosis of human diseases.

Achievements

Single-cell analysis and functional characterization uncover the stem cell hierarchies and developmental origins of rhabdomyosarcoma. Wei Y, Qin Q, Yan C, Hayes MN, Garcia SP, Xi H, Do D, Jin AH, Eng TC, McCarthy KM, Adhikari A, Onozato ML, Spentzos D, Neilsen GP, Iafrate AJ, Wexler LH, Pyle AD, Suvà ML, Dela Cruz F, Pinello L, Langenau DM. *Nature Cancer*. 2022;3(8):961-975.

Rhabdomyosarcoma (RMS) is a common pediatric cancer of muscle. RMS is prone to relapse, which is driven by a small fraction of tumor cells. Here, Langenau, Pinello, and colleagues identified a wide diversity of functional cell states in RMS and identified a novel cancer stem cell that expresses epithelial-to-mesenchymal markers and shares similarity to a bipotent, muscle mesenchyme progenitor that can make both muscle and osteogenic cells. These cancer stem cells are therapy-resistant and drive tumor growth after stress. They also discovered that fusion-positive RMS express a highly specific gene program found in muscle cells transiting from embryonic to fetal development at 7-7.75 weeks of age, suggesting an early transformation event in the genesis of this aggressive disease subtype. This work illustrates that stemness hierarchies are shared in human muscle development and rhabdomyosarcoma.

Polarization-Sensitive Endobronchial Optical Coherence Tomography for Microscopic Imaging of Fibrosis in Interstitial Lung Disease. Nandy S, Berigei SR, Keyes CM, Muniappan A, Auchincloss HG, Lanuti M, Roop BW, Shih AR, Colby TV, Medoff BD, Suter MJ, Villiger M, Hariri LP. *Am J Respir Crit Care Med*. 2022;206(7):905-910.

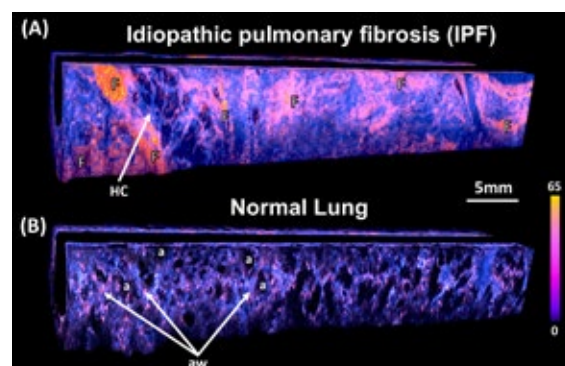
Fibrotic interstitial lung diseases (fILD), including idiopathic pulmonary fibrosis (IPF), are characterized by excessive collagen deposition with fibrotic remodeling. Microscopic diagnosis and assessment of fibrosis distribution, quality (destructive versus non-destructive fibrosis), and progression over time remains challenging. High-resolution computed tomography (HRCT) has limited resolution and cannot detect early microscopic changes. Surgical lung biopsies (SLB) have increased morbidity/mortality risks. By contrast, polarization-sensitive endobronchial optical coherence tomography (PS-EB-OCT) is a low-risk, bronchoscope-compatible, volumetric, microscopic imaging modality that detects endogenous birefringence from collagen in fibrosis. Here, Nandy et al. assessed the diagnostic accuracy of PS-EB-OCT for fILD diagnosis compared to SLB in fifteen subjects (8 IPF and 7 non-IPF ILDs). This work demonstrated that PS-EB-OCT has 100% accuracy for diagnosis of microscopic fILD. Quantitative birefringence measurements differentiated destructive fibrosis, non-destructive fibrosis, and normal parenchyma. This has major clinical potential for early diagnostic, prognostic, and therapeutic monitoring purposes in fILD.

Human acute inflammatory recovery is defined by co-regulatory dynamics of white blood cell and platelet populations. Foy BH, Sundt TM, Carlson JCT, Aguirre AD, Higgins JM. *Nature Communications* 2022;13(1):4705.

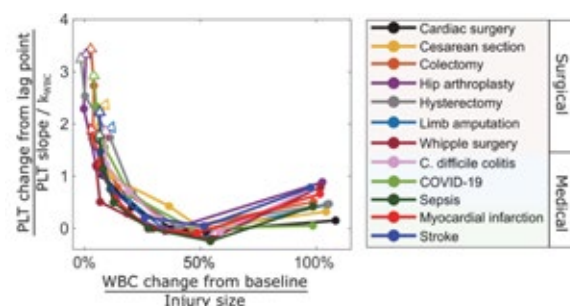
Elevation of white blood cell count (WBC) and altered levels of other acute phase reactants are cardinal signs of inflammation, but the dynamics of these changes and their resolution are not well established. Our study identified universal features of the inflammatory responses of patients who successfully recovered after acute illnesses or surgery such as COVID-19, heart attack, sepsis, or trauma. These features include precise paths that white blood cell and platelet counts follow as they return to normal. This work also provides a generic approach for identifying high-risk patients: 32x relative risk of adverse outcomes for cardiac surgery patients, 9x relative risk of death for COVID-19, 9x relative risk of death from sepsis, and 5x relative risk of death for myocardial infarction.

Next-generation ALK inhibitors are highly active in ALK-positive large B-cell lymphoma. Soumerai JD, Rosenthal A, Harkins S, Duffy J, Mecca C, Wang Y, Grewal RK, El-Jawahri AR, Liu H, Menard C, Dogan A, Yang L, Rimsza LM, Bantilan K, Martin H, Lei M, Mohr S, Kurilovich A, Kudryashova O, Postovalova E, Nardi V, Abramson JS, Chiarle R, Zelenetz AD, Louissaint A. *Blood*. 2022;140(16):1822-1826.

Anaplastic lymphoma kinase (ALK)-positive large B-cell lymphoma (ALK-LBCL) is a rare lymphoma with plasmablastic morphology and driven by oncogenic ALK fusions. Patients with ALK-LBCL typically relapse on standard chemotherapy and have dismal outcomes.

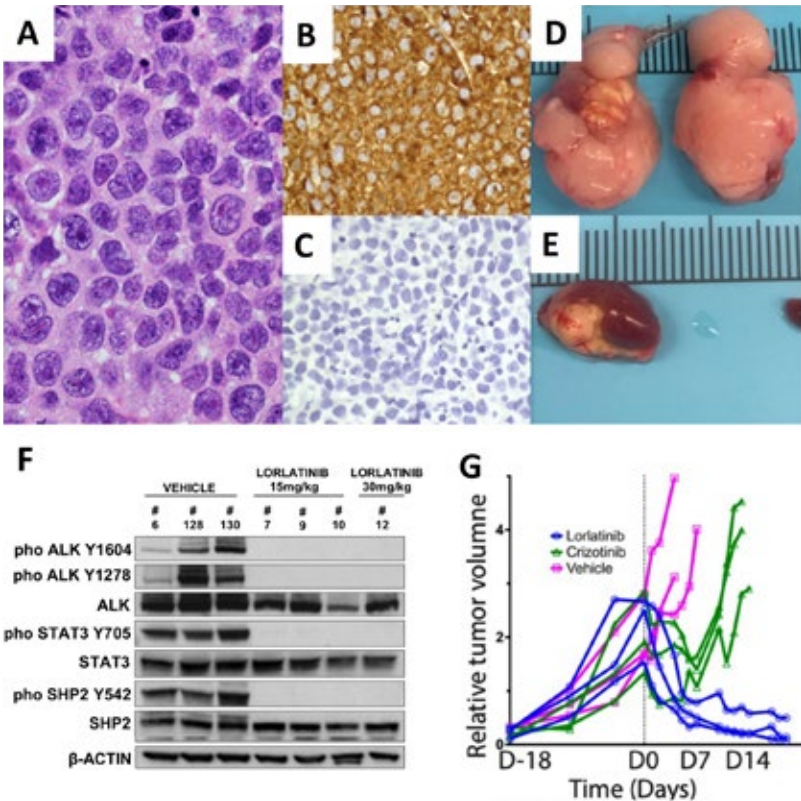


PS-EB-OCT visualizes fibrosis distribution and quantitatively distinguishes fibrosis type in interstitial lung disease (ILD). Volumetric in vivo PS-EB-OCT birefringence images from (A) IPF, showing spatially-heterogeneous, dense destructive, highly-birefringent fibrosis (F) with subpleural predominance and embedded honeycombing (HC). (B) Normal lung parenchyma appears as evenly-spaced, round alveoli (a) and lattice-like alveolar walls with low-birefringence (aw). Birefringence colormap (right of panel B) in degrees per 100µm: blue (no birefringence (0 degrees per 100µm)) to orange (high birefringence (65 degrees per 100µm)). Nandy et al., *Am J Respir Crit Care Med*. 2022.



Patients who recover well from common major diseases follow a newly-discovered universal recovery trajectory that is defined by exponential decay of white blood cell (WBC) count and delayed linear growth of platelet (PLT) count. This recovery trajectory can be personalized for each patient to enable optimal management of diseases that involve acute inflammatory responses. Foy et al., *Nature Communications* 2022.

Treatment with ALK inhibitor (ALKi) crizotinib has only been associated with limited responses. Here, Soumerai et al. succeeded in creating the first patient-derived xenograft (PDX) models of ALK-LBCL, harboring the same oncogenic molecular alterations characterizing the patient lymphoma. Treatment with next-generation ALK inhibitors lorlatinib and alectinib resulted in significant tumor reduction when compared with vehicle-treated mice. The authors then translated these encouraging results in the clinic by treating four ALK-LBCL patients with alectinib, resulting in complete remission in 3 of 4 patients, including 2 patients who remain in remission 14 and 28 months following stem cell transplantation. This work illustrates how PDX models can be used to test novel therapeutic strategies for rare diseases and translate their use into clinical practice.



Lorlatinib ALK inhibitor induced rapid tumor regressions in ALK-positive large B-cell lymphoma patient derived xenografts (PDXs). A-C) Generation of ALK-positive large B-cell lymphoma PDXs. Morphology of ALK-LBCL (A), showing strong ALK1 expression (B) and negativity for CD20 (C). D-E) Lorlatinib shows activity in ALK-positive large B-cell lymphoma PDXs. PDX tumors treated with vehicle (D) or Lorlatinib after 4 days of treatment. F) Lorlatinib induced a complete block of ALK phosphorylation, in turn disrupting activation of downstream signaling pathways, including abrogation of STAT3 and SHP2 phosphorylation. G) Lorlatinib induced rapid tumor regression and crizotinib induced only transient tumor regression followed within 7 days. Soumerai et al., *Blood* 2022.

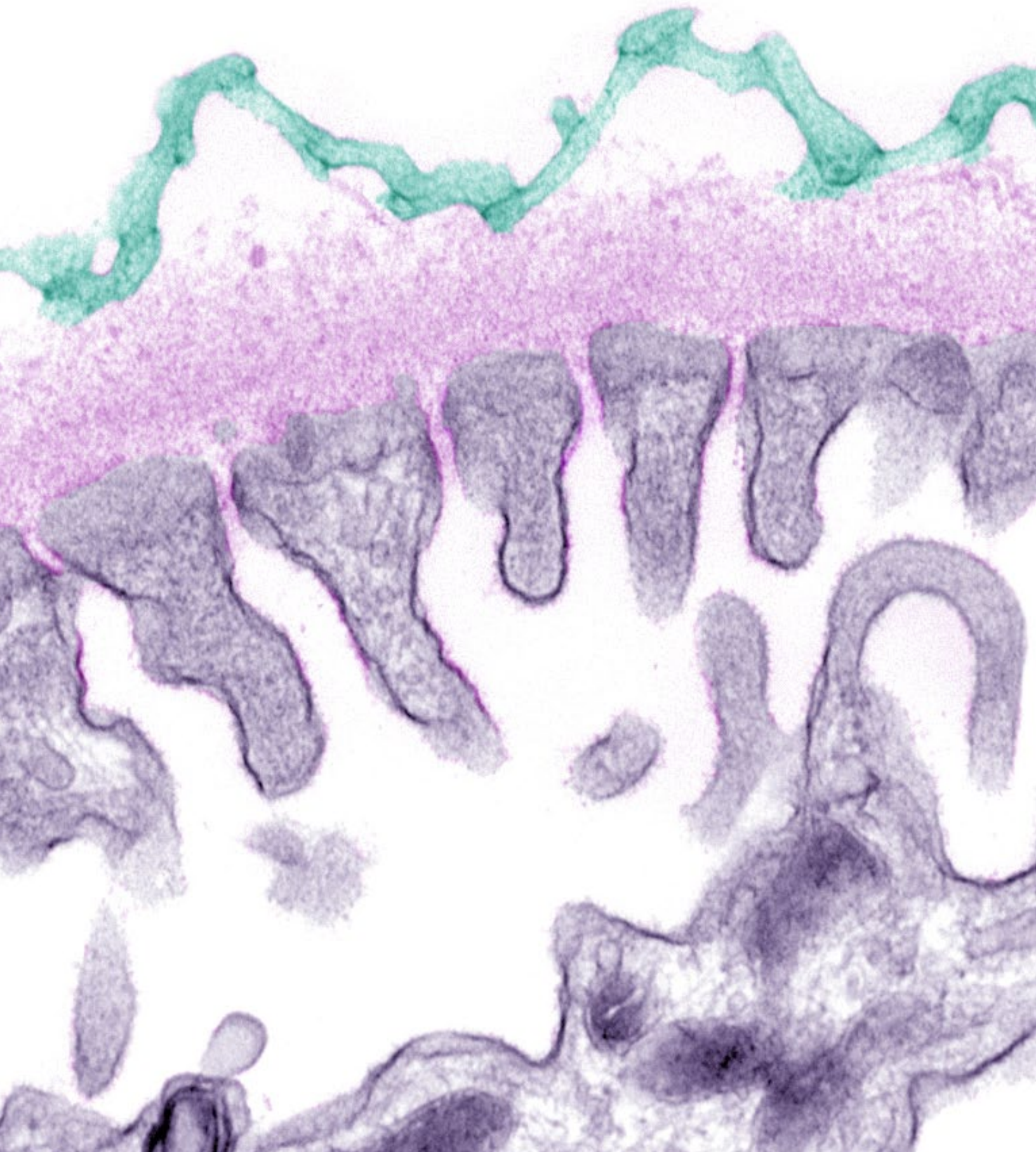


Image Award Finalist
Ultrafiltration 1
Maxwell Roth, MD
Pathology

RONALD E. KLEINMAN, MD, CHIEF

Overview:

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, social and environmental events beginning during gestation and continuing into childhood can strongly influence disease onset during childhood and beyond, we are expanding 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 infancy and 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. Furthermore, since the beginning of the COVID-19 pandemic we have supported the MGH effort to develop diagnostic and therapeutic tools to face this unprecedented scientific and clinical challenge. To support this effort, we have established a Pediatric Biobank that has collected biospecimens from more than 2100 children exposed or affected by SARS-CoV2 infection, including 50 children with Multiorgan Inflammatory Syndrome (MIS-C). We are currently focused on the following specific research missions:

Adolescent Medicine

The overall mission of the division of Adolescent Medicine is to elevate the health and well-being of adolescents and young adults throughout Boston, New England, and the US through cutting-edge clinical care, research, medical education, and advocacy. The focus of the division. The division provides primary and subspecialty care for adolescents and young adults across a range of conditions, including eating disorders, menstrual disorder, contraceptive counseling, sexually transmitted infections, pelvic pain, weight management, mental health, and substance use. Historically a division focused on clinical care, in 2022, the Division of Adolescent and Young Adult Medicine took its first steps to establishing itself as a leading national research group.

Under the leadership of its Chief, Scott Hadland, MD, MPH, MS, the Division secured its first R01 from the National Institute on Drug Abuse, as well as several other grants from the National Institutes of Health, Centers for Disease Control and Prevention, Patient-Centered Outcomes Research Institute, and American Heart Association. Funding will be used to lead analyses of national Medicaid data to identify gaps in addiction treatment for US youth, and to lead on-site universal, primary care-based screening and intervention for youth who use substances.

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 affected 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 Wayne Shreffler, MD, PhD, 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). The first major paper from this cohort has just been accepted to JACI In Practice (Impact Factor >7).

To complement the discovery efforts, Michael Pistiner, MD, MMSc, 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 Michael Pistiner, MD, MMSc, 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. Michael Pistiner, MD, MMSc, has brought in >300K of new funding for this program.

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. In 2019 we were awarded additional funding (UM2) for this project. 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 (for example, Marfan syndrome and Loeys Dietz syndrome). We are also involved in health services research specifically in the area of patient safety and quality as it pertains to pediatric cardiology. We have ongoing investigations evaluating diagnostic accuracy of cardiac imaging, investigations evaluating of parental health literacy among congenital heart disease families, and studies of resource use among patients undergoing congenital heart surgery. Our preventative cardiology service has collaborated with the Harvard T.H. Chan School of Public Health on projects to examine outpatient and wireless means to track physical activity and caloric intake. This year we published on means to distinguish MISC from other inflammatory disorders in children.

Critical Care Medicine

A major research 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, ingestions, 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. Lastly, in the midst of the SARS CoV-2 pandemic, our division dedicated itself to understanding life-threatening complications of SARS CoV-2 infection in children and to identifying the most effective therapies for the novel Multisystem Inflammatory Syndrome in Children due to SARS CoV-2 infection.

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 and bone imaging techniques coupled with investigations of circulating hormones important in appetite regulation, and carbohydrate, fat and bone metabolism. Current areas of ongoing investigation include an assessment of homeostatic and hedonic food motivation pathways in the brain in relation to appetite regulating hormones and trajectories of eating disorders in females 10-22 years old, an evaluation of estrogen as a neuromodulatory factor for cognitive flexibility and reward responsiveness in adolescents and adults with restrictive eating patterns, an assessment of metabolic and bone outcomes following weight loss surgery in youth 14-25 years old, and evaluation of the impact of oxytocin on weight and metabolic outcomes in children and adolescents with obesity. Other areas of interest include investigations of bone metabolism in youth with type 1 diabetes, novel technologies related to diabetes care including cystic fibrosis related diabetes, the impact of administration of the growth hormone releasing hormone analog, tesamorelin, on carbohydrate and fat metabolism, and studies that engage both mothers and fathers in obesity prevention within the first 1000 days of life. 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. Currently the Pediatric Endocrine faculty include

three researchers with R01 funding and one with K23 funding (another is pending receipt of the K23 NOA).

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 in regard to the interaction of small intestinal and blood brain barriers in the context 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 (MIBRC).

The MIBRC also took the lead of repurposing the research of many of its members to work on COVID-19-related research, mainly focusing on the effort of establishing a large pediatric biobank at Mass General for Children (MGC). Samples (including nasal swabs, saliva, urine and stool) from more than 2,100 children, including over 50 children affected by Multisystem Inflammatory Syndrome in Children (MIS-C), have been collected to date, creating one of the largest pediatric COVID-19 biobanks in the nation. 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. As part of this work, we address key pediatric health issues such as obesity, autism, smoking, addiction, and stress. 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:

- Providing comprehensive, high-quality care to children with special health care needs, including autism spectrum disorder through collaborations such as the Autism Care Network, and international network of 20 autism specialty clinics.
- 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.
- Childhood obesity prevention and treatment, including understanding the role physical activity, diet, access to health food, 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.
- Work on engaging fathers and resiliency interventions for fathers of children with special health care needs.
- Health outcomes of HIV-infected adolescents and adolescents at risk for HIV infection.
- Understanding the drivers of mental illness and mental wellbeing across the lifespan
- Testing the impact of resiliency interventions for parents of children with special health care needs.
- Understanding how substance use in pregnant and parenting women impacts the health of children and families.

Genetics and Metabolism

The Division of Medical Genetics and Metabolism at MGHfC provides diagnostic analyses and cares for individuals with developmental, congenital and metabolic 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, mitochondrial diseases as well as in Down syndrome. 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 disorders. In collaboration with our pediatric colleagues, we have multi-disciplinary programs and clinics for children with brain tumors, sarcomas, 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. One of these studies evaluated the use of PET-MRI in staging children with solid tumors. We are hoping to be able to continue to utilize PET-MRI rather than PET-CT to minimize radiation exposure to children. An ongoing study involves serial peripheral blood assays to identify and quantitate cell free DNA and exosomes from children with medulloblastoma and

Ewing's sarcoma to track tumor response and progression. . Our brain team has been examining the long-term outcomes of Proton Beam RT for children with medulloblastoma and participating in innovative Phase 1 clinical trials. Our long-term survivor clinic is a vital component of our program for tracking late effects of therapy and connecting patients with appropriate caregivers. We are active members and co-investigators in an international clinical research group known as the Children's Oncology Group, co-investigators of a Hodgkin lymphoma consortium led by St. Jude Children's Research Hospital, and members of a Pacific Neuro-oncology consortium (PNOC). Verena Göbel, MD, 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. David Sweetser's, MD, PhD, lab is focusing on the interaction of the bone marrow microenvironment and leukemic stem cells. The tumor microenvironment is a growing area of investigation in cancer pathogenesis. We have long standing research projects with our colleagues in pathology who are studying the molecular pathogenesis of medulloblastoma and Ewing's sarcoma. Examples of these collaborations include Miguel Rivera's, MD, research using epigenome editing tools to examine the genetic drivers in Ewing sarcoma and medulloblastoma. In the area of Hematology, we have had significant growth in our pediatric stroke and Hemophilia programs. Eric Grabowski, MD, ScD leads these initiatives, and his lab has made an important discovery for the treatment of Enterohemorrhagic Hemolytic Uremic syndrome.

Infectious Disease

The Pediatric Infectious Disease Unit has been active in both basic science and in translational/clinical research. Jason Harris's, MD, 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*. He has also initiated a series of studies relating to the serologic response to SARS-CoV 2 infection. In addition, Jason Harris's, MD, has turned to the problem of antibiotic resistance in pediatric infections and has published a provocative report demonstrating the surprisingly high rate of gram negative bacteremia due to multiply resistant isolates among children hospitalized with pneumonia. H Warren's, MD, pivotal discovery over the past several years of the differential genomic responses between humans and mice to sepsis and inflammation and led to the establishment of a large multicenter project to investigate mechanisms responsible for species-specific sensitivity to inflammation. The consortium has completed its investigations and is preparing publication of its findings. Chadi El Saleeby, MD, has been developing refined vancomycin dosing algorithms for hospitalized children. Mark Pasternack, MD, 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).

Lurie Center for Autism

At the Lurie Center for Autism our primary focus is to improve the lives of individuals and families affected by autism spectrum disorder (ASD) and other neurodevelopmental conditions through exceptional clinical care and multi-faceted research. Importantly, these activities go hand and hand. The clinical observations and insights arising from interactions with patients guide our evolving research priorities, and in turn, new research discoveries are incorporated into clinical practice. Our goal is to achieve integration of these activities in near real time.

The Lurie Center has a strong commitment to lifelong care. Over 40% of the patients seen at the Lurie Center are adults, which is an unusually high percentage for a center focused on neurodevelopmental conditions. Research targeting the clinical concerns of adults with ASD and related conditions, like Williams syndrome and Down syndrome, has been largely overlooked and is extremely important as patients' needs and health concerns change with age. Notably, many of the over 20 clinical trials currently ongoing at the Lurie Center enroll adults. For example, Chris Keary, MD, a psychiatrist at the Center, is launching a phase 2 trial for adults with ASD to examine the potential efficacy of a new therapeutic for irritability and social communication deficits. In parallel, psychiatrist Robyn Thom, MD, is leading two trials that include adults to assess the effectiveness of a pharmacological intervention and a cognitive-behavioral intervention, respectively, for anxiety in people with Williams syndrome. Finally, depression, like many psychiatric comorbidities, is underrecognized, undertreated, and understudied in adults with Down syndrome. Michelle Palumbo, MD, and Robyn Thom, MD, recently conducted a retrospective chart review of adults with Down syndrome which showed that SSRIs were generally well tolerated and effective, although with some side effects. This report is among the first to investigate SSRI use in this population and highlights the need for further research in this area, including a prospective, randomized trial to inform treatment decisions in adults with Down syndrome.

Beyond therapeutic trials, the Lurie Center is engaged in several studies that use brain imaging technologies to better characterize neurodevelopmental conditions. Robyn Thom, MD, is partnering with Nicole Zurcher, PhD, (of the Martinos Center) to study the cerebral vasculature in adults with Williams syndrome. People with Williams syndrome are at increased risk for cardiac problems, but it is not known if they are also at increased risk for cerebral vasculature pathology as they age. In addition, Dr. Zurcher, along with Jacob Hooker, PhD, (Scientific Director of the Lurie Center), are developing neuroimaging methods to characterize what may be an "inflammatory subtype" of autism. To do this, the researchers first had to develop new protocols that would enable participants to feel comfortable in the scanner through gradual familiarity with the equipment and scanning environment. The researchers, in collaboration with Michael Levy, MD, MPH, (Neuroimmunology & Neuroinfectious Disease) and Chris McDougle, MD (Lurie Center Director), are additionally investigating blood-borne markers of neuroinflammation in people with ASD. A

better understanding of the role of immune molecules and signaling pathways in ASD may have significant implications for treatment.

Other studies at the Lurie Center are developing technology-based strategies to enhance behavioral and cognitive therapies and to help determine mechanisms underlying sleep disturbances and sensory sensitivities in individuals with ASD. For example, along with researchers at the Lincoln and Media Labs of MIT, Lisa Nowinski, PhD, (Director of Non-physician Services) and Chris McDougale, MD, are conducting a study of vocal, facial, and movement biomarkers of ASD that will ultimately help to improve communication and language development for patients who are minimally verbal. Additionally, Ann Neumeyer, MD (Lurie Center Medical Director) has teamed up with Dara Manoach, PhD and Dimitrios Mylonas, PhD (both of the Martinos Center) to assess the impact of melatonin on sleep spindles in children with ASD. Sleep spindles, measured by electroencephalography (EEG), result from brief oscillations originating in the thalamus that can be detected in the cortex. The team will determine if fewer spindles correlate with sleep disruption, impaired sensory gating, and more severe sensory sensitivities in children with ASD and whether melatonin increases spindles.

Importantly, clinical and translational research at the Lurie Center is coupled to preclinical research such that clinical observations and insights can be explored mechanistically in preclinical studies. For example, Evan Bordt, PhD, has developed a mouse model that points to early life inflammation altering mitochondrial function in adulthood. The preclinical program is growing with the recruitment of two new research faculty (Drs. Angelica Torres-Berrío and Sudhir Thakurela) to further investigate the epigenetic underpinnings of ASD and the transcriptional network that drives changes to brain circuitry during early brain development.

As the research program grows over the next few years, we aim to maintain a strong focus on expanding our collaborative network across MGB and in the wider bio and tech communities to address questions about the biological underpinnings of ASD and related disorders, methods to assess changes in symptom severity with treatment, and approaches that improve patient care.

Neonatology and Newborn Medicine

The research effort in the Division of Newborn Medicine is multifaceted and ranges from developmental lung biology to quality improvement to psychology. All research projects share a common mission: to advance scientific knowledge aimed at improving the care and treatment of our very vulnerable patients and their families. Our research portfolio is reflective of the broad clinical spectrum of issues in our patient population—from extremely low gestational age neonates and the myriad medical issues they face, to full-term infants with various congenital anomalies and those born with physiologic dependence to opioids due to in-utero exposure. Our basic research focuses on the identification of molecular pathways that link prematurity, genetic factors, and in-utero and early life

exposure to the health of our patients in infancy and beyond. We have built patient-specific stem cell and animal models of early childhood diseases to identify these molecular pathways as therapeutic targets. Our translational research focuses, in large part, on neuroprotection strategies, including an examination of those factors that affect neurodevelopmental outcomes following perinatal neurological insults and in-utero substance exposure. More recently we have complimented this work with studies on the healthy inequities and the psychologic resilience (and vulnerability) of our patients and their caregivers.

Nephrology

Research activity in pediatric nephrology is focused on defining genetic defects leading to kidney disease, with or without changes in mineral ion homeostasis, and to thereby gain basic insights into biology. These efforts will improve diagnosis, management, and clinical outcome. Our group thus continues to contribute to the molecular definition of monogenic forms of nephrotic and nephritic renal diseases, and other inherited disorders involving the kidney, including the identification of LRP2 variants contributing to glomerular loss of early progressive kidney disease and the role of coenzyme Q10 in steroid-resistant nephrotic syndrome. We furthermore helped assessing kidney function in patients with spinal muscular atrophy and sickle cell disease, and in collaboration with colleagues at the NIH, our group contributed to the evaluation of mineral ion and bone abnormalities in patients with nephropathic cystinosis.

Besides these efforts, we have a major focus on the discovery of molecular defects that cause rare genetic disorders affecting the regulation of mineral ion homeostasis. Of particular interest is the identification of genetic mutations leading to different forms of pseudohypoparathyroidism (PHP) and hypoparathyroidism (HP). In addition to our previous contributions, we recently identified a novel deletion within the GNAS locus without leading to loss-of-methylation at one of the differentially methylated regions within GNAS. We furthermore showed that patients with PHP1B due to a STX16 deletion do not develop PTH-resistance before the age of two years. Thus, screening children of affected and unaffected female carriers of STX16 deletion, need to be followed through laboratory testing thus allowing early treatment, if indicated, and consequently avoiding potentially severe sequelae from hypocalcemia and/or hyperphosphatemia, including basal ganglia calcifications. Most recently, a novel retrotransposon insertion leading to autosomal dominant PHP1B was discovered through long-read DNA sequencing, which had escaped detection through conventional whole genome sequencing. This 2.8-kb insertion contains a polyadenylation signal, which could imply that an mRNA involved in establishing methylation at exon A/B undergoes polyadenylation prematurely, which can now be explored further once cell lines from an affected patient from this family are available. We also developed a “humanized” mouse in which the endogenous PTH/PTHrP receptor (PTHr1) is replaced with the cDNA encoding the human PTHR1. This engineered mouse has no obvious phenotype

thus allowing, through iGONAD, the introduction of mutations that are responsible for Jansen's disease. "Humanized" mice with the H223R mutation show major growth plate abnormalities and some laboratory abnormalities typically observed in the human disease, but most of these animals die by two months of age. In contrast, mice with the T410R mutation are viable and allowed the generation of F1 and F2 generations, and also show profound growth plate abnormalities. These mice can now be used to explore the efficacy of PTH inverse agonists (PTH-IA) in an attempt rescue their skeletal defects and their abnormalities in regulating mineral ion homeostasis. These studies will provide pre-clinical data for the development, through the NIH-TRND program, of PTH-IA for the treatment of patients affected by Jansen's disease. GMP-grade PTH-IA is currently being tested through the NIH in toxicology studies and if no obvious side effects are observed in long-term studies in rats, the first clinical trials in adult patients affected by Jansen's disease will be started towards the middle of 2023. We are furthermore involved in the search for novel factors involved in the regulation the production of FGF23, a major phosphate-regulating hormone and we have identified the mechanism through which a novel PTH mutation leads to the secretion of a biologically inactive proPTH, rather the mature PTH(1-84).

Pediatric Palliative Care

The research mission of the MGHfC Pediatric Palliative Care Service is dedicated to enhancing quality of life and ease physical, spiritual, and emotional suffering for patients with serious or life limiting illnesses and their families. With our interdisciplinary approach we support and advocate for informed decision making through exploration of a patient and families' wishes and goals. We collaborate with a child's primary and specialist teams to tailor communication and foster understanding of medical information that patients and caregivers receive. We apply evidenced based strategies in the relief of pain and other symptoms. Our team prioritizes a holistic and compassionate approach to honoring a child's personhood as they navigate their illness within the context of their family, culture, and community.

Pulmonary

The research focus of the Pulmonary Division has remained broad and continues to have a significant COVID-19 focus. The first area of research, led by Lael Yonker, MD is the immunological basis of MIS-C and COVID inflammation. Lael Yonker, MD also continues to work on airway inflammation in cystic fibrosis (CF) airway. Other areas of COVID research are the mechanisms of spread and long haul COVID, led by Peter Moschovis, MD, MPH, and Bernard Kinane, MD. The third area lead Thomas Kinane, MD, and Florian Eichler, MD, focuses on gene therapy in Canavan's disease. They are using AAV to deliver ASPA gene to affected neurons. The fourth area of research, led by Bernard Kinane, MD, Christopher Hartnick, MD, and Kevin Gipson, MD, MS, is using artificial intelligence to read polysomnograms. Finally, in the area of education research, Ben Nelson, MD, established a CPC type program that publishes in cases in Pediatric Pulmonology.

Rheumatology

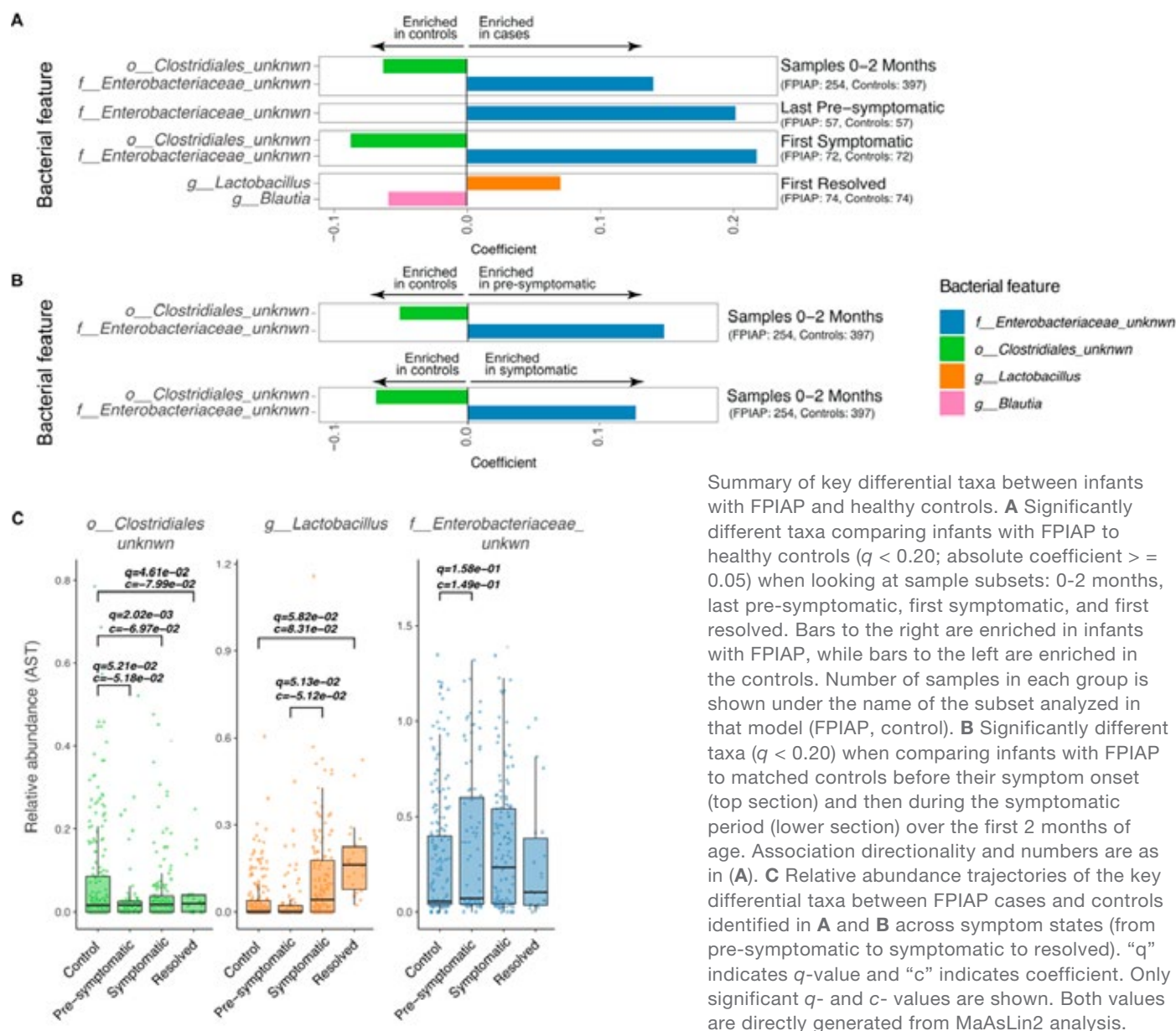
Investigators in the Pediatric Rheumatology Program lead and participate in clinical research that include observational research studies, as well as investigator-initiated outcomes and adverse event studies, across a wide range of childhood-onset rheumatic diseases. As part of such research efforts, our faculty members are continuing 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.

Other research in our program has focused 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 (Dr. Rothman and Dr. Natter), short- and long-term outcomes from the PCORI-funded CARRA Registry STOP-JIA clinical trial (the largest pragmatic treatment trial of patients with polyarticular JIA to date) (Dr. Natter), expert reviews article regarding usage of the EHR for enhancing care in pediatric rheumatology (Dr. Natter), and ongoing research collaborations with colleagues in Oral Maxillofacial Surgery at MGH and elsewhere regarding evidence-based, multidisciplinary assessment and treatment of JIA-associated temporo-mandibular joint arthritis that have resulted in multiple peer-reviewed publications (Dr. Rothermel and Dr. Natter).

Achievements:

Allergy & Immunology

This study is the first to identify differences in the infant gut microbiome, in some cases prior to the development of symptoms, in children who develop Food Protein-Induced Allergic Proctocolitis (FPIAP), a common manifestation of food allergy that presents in the first months of life and that is a risk factor for subsequent allergic disease, including IgE-mediated food allergies. In this work, we analyzed 954 longitudinal samples from 160 infants in a nested case-control study (81 FPIAP and 79 matched controls) from 1 week to 1 year of age by 16S rRNA ribosomal gene sequencing as part of the Gastrointestinal Microbiome and Allergic Proctocolitis (GMAP) study. We found key differences in the microbiome of infants with FPIAP, most strongly a higher abundance of a genus of Enterobacteriaceae and a lower abundance of a family of Clostridiales during the symptomatic period. We saw some of these significant taxonomic differences even prior to symptom onset (see last pre-symptomatic, panel A). There were no consistent longitudinal differences in richness or stability diversity metrics between infants with FPIAP and healthy controls (not shown). Complex interactions between the gut microbiome and immune cells in infancy are thought to be part of the pathogenesis for the marked rise in pediatric allergic diseases,

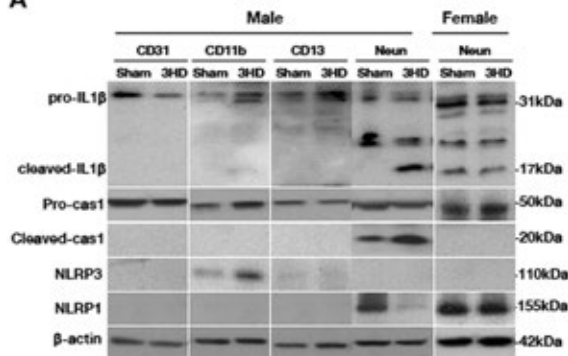


particularly food allergies. As FPIAP is the earliest recognized food allergy in infancy and is associated with atopic dermatitis and subsequent IgE-mediated food allergy later in childhood, this study provides a foundation for more mechanistic investigation into the pathogenesis of FPIAP and subsequent food allergic diseases in childhood.

Featured paper: Martin VM, Virkud YV, Dahan E, Seay HL, Itzkovits D, Vlamakis H, Xavier R, Shreffler WG, Yuan Q, Yassour M. **Longitudinal disease-associated gut microbiome differences in infants with food protein-induced allergic proctocolitis.** Microbiome. 2022 Sep 23;10(1):154. doi: 10.1186/s40168-022-01322-y. PMID: 36138438 Free PMC article.

Summary of key differential taxa between infants with FPIAP and healthy controls. **A** Significantly different taxa comparing infants with FPIAP to healthy controls ($q < 0.20$; absolute coefficient > 0.05) when looking at sample subsets: 0–2 months, last pre-symptomatic, first symptomatic, and first resolved. Bars to the right are enriched in infants with FPIAP, while bars to the left are enriched in the controls. Number of samples in each group is shown under the name of the subset analyzed in that model (FPIAP, control). **B** Significantly different taxa ($q < 0.20$) when comparing infants with FPIAP to matched controls before their symptom onset (top section) and then during the symptomatic period (lower section) over the first 2 months of age. Association directionality and numbers are as in (A). **C** Relative abundance trajectories of the key differential taxa between FPIAP cases and controls identified in A and B across symptom states (from pre-symptomatic to symptomatic to resolved). “ q ” indicates q -value and “ c ” indicates coefficient. Only significant q - and c - values are shown. Both values are directly generated from MaAsLin2 analysis. All models in this panel take into account all five variables: (a) case/control or symptoms, (b) mode of delivery, (c) age at visit, (d) diet, and (e) probiotics use in the first year of life

A



Evidence for cell-specific activation of inflammasome proteins after three repetitive closed head injuries in adolescent mice. A, Representative Western blot for IL-1b, caspase-1, NLRP1, and NLRP3 in immunopanned CD311 endothelial cells, CD11b1 myeloid cells, CD131 pericytes, and negatively selected neurons in sham versus 3HD mice brain at 14 months after injury. The blot shows activation of the NLRP1 inflammasome in neurons at 14 months after injuries.

Critical Care Medicine

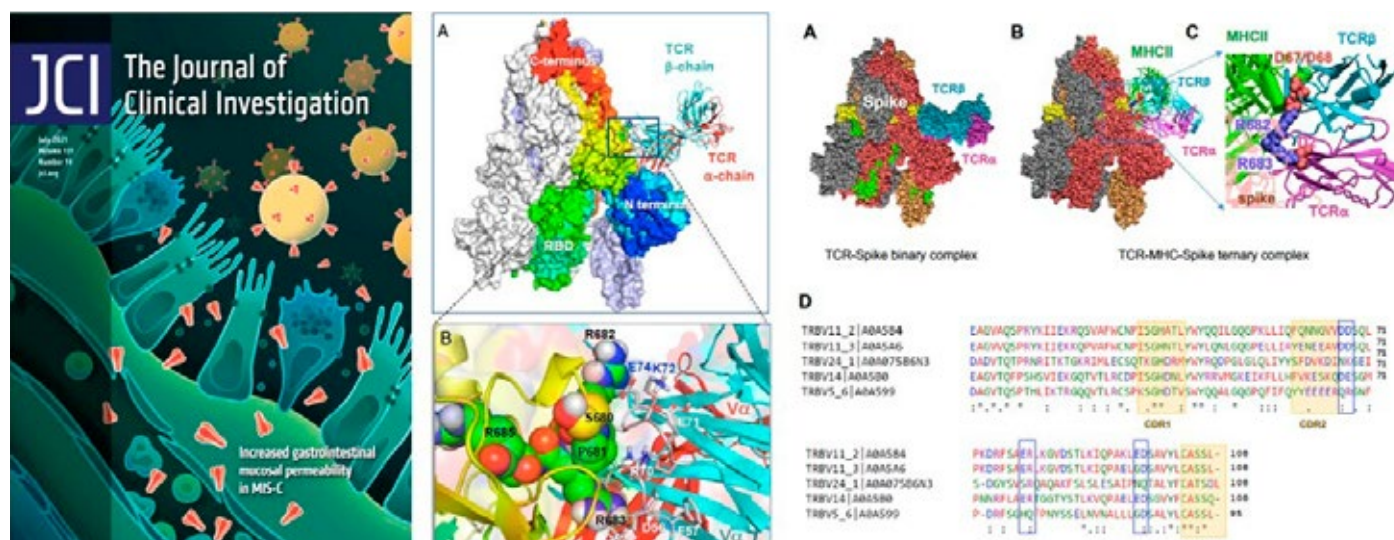
M. Whalen - Repetitive mild traumatic brain injury (mTBI) in children and adolescents leads to acute and chronic neurologic sequelae and is linked to later life neurodegenerative disease in epidemiological studies. However, the biological mechanisms connecting early life mTBI to neurodegeneration remain unknown. Using an adolescent mouse repetitive closed head injury model that induces progressive cognitive impairment in males and anxiety in females in the absence of overt histopathology, we examined transcriptional and translational changes in neurons isolated from sham and injured brain in the chronic phase after injury. At 14 months, single-nuclei RNA sequencing of cortical brain tissue identified disruption of genes associated with neuronal proteostasis and evidence for disrupted ligand-receptor signaling networks in injured mice. Western blot analysis of isolated neurons confirmed altered proteostasis, including inflammasome activation, accumulation of misfolded, hyperphosphorylated tau, and altered expression of proteins suggestive of impaired translation. Strikingly, these changes were observed in male but not female mice. Mice genetically deficient in interleukin-1 signaling were protected from postinjury cognitive deficits, inflammasome activation, and accumulation of misfolded tau in cortex and cerebellum. Together, our findings provide evidence for neuronal inflammasome activation and impaired proteostasis as key mechanisms linking repetitive mTBI in adolescence to later life neurologic dysfunction and neurodegeneration, and suggest pharmacological targets to interrupt the biochemistry of neurodegeneration in adolescents with repetitive mTBI. the data were published this year in the Journal of Neuroscience¹.

Featured paper: Wu L, Kalish BT, Finander B, Cao T, Jin G, Yahya T, Levy ES, Kukreja B, LaRovere ES, Chung JY, Lo EH, Brown-Whalen A, El Khoury J, Kaplan DL, Whalen MJ. **Repetitive Mild Closed Head Injury in Adolescent Mice Is Associated with Impaired Proteostasis, Neuroinflammation, and Tauopathy.** J Neurosci. 2022 Mar 23;42(12):2418-2432. doi: 10.1523/JNEUROSCI.0682-21.2021. Epub 2022 Feb 1. PMID: 35105673; PMCID: PMC8944232.

Gastroenterology, Hepatology & Nutrition

Mucosal Immunology and Biology Research Center

Lael Yonker, MD, established and leads the MGH Pediatric COVID-19 Biorepository, collecting biospecimens from over 2,100 children with COVID-19 or MIS-C, newborns born to mothers with COVID-19 or mRNA vaccination, children receiving the COVID-19 vaccine, children with long COVID, and pediatric controls. Together with other MIBRC investigators, including Drs. Evan Bordt and Alessio Fasano, Dr. Yonker established productive collaborations with researchers within Harvard institutions and across the world to investigate the impact of COVID-19 on children. Her most impactful findings were that 1) children are capable of carrying high levels of infectious virus despite minimal symptoms 2) MIS-C is caused by SARS-CoV-2 antigenemia originating from a viral nidus within the GI tract, with viral antigens leaking across a zonulin-mediated permeable mucosal barrier,



and 3) through in-depth functional humoral immune profiling, she showed that children mount safe and effective responses to mRNA vaccination.

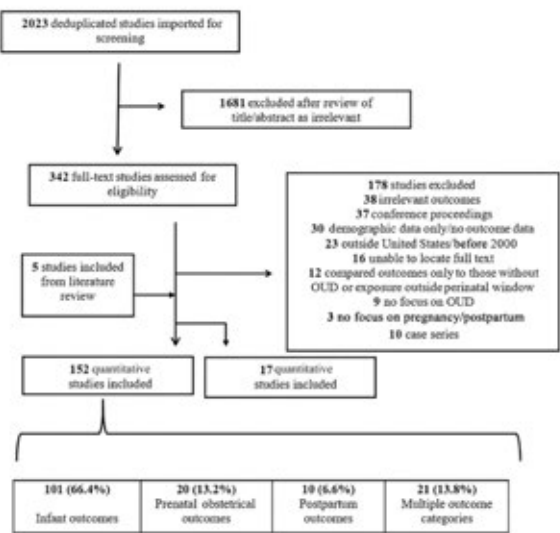
She has also shown that treatment of MIS-C with larazotide acetate, a zonulin antagonist, appears to be an effective treatment for MIS-C. She has established a multi-center clinical trial to assess the safety and efficacy of larazotide in the treatment of MIS-C in a Phase 2 clinical trial. Since the outset of the COVID-19 pandemic, she has published 32 manuscripts in high impact journals including *Cell*, *Nature Medicine*, *Journal of Clinical Investigation*, and *Journal of Pediatrics*, with several additional manuscripts in preparation or under review. Her research has gained much media attention, and has been highlighted in *TIME*, *The Atlantic*, *People* magazine, and many other high-profile news outlets. In summary, Dr. Yonker has made significant contributions to our understanding of how children are impacted by and contribute to the COVID-19 pandemic.

Featured paper: Yonker LM, Swank Z, Gilboa T, Senussi Y, Kenyon V, Papadakis L, Boribong BP, Carroll RW, Walt DR, Fasano A.

[Zonulin Antagonist, Larazotide \(AT1001\), As an Adjuvant Treatment for Multisystem Inflammatory Syndrome in Children: A Case Series.](#) Crit Care Explor. 2022;10(2):e0641.

Neonatology and Newborn Medicine

Racial/ethnic inequities are well documented in both maternal-infant health and substance use disorder treatment outcomes. To systematically review research on maternal-infant dyads affected by opioid use disorder (OUD) to evaluate for racial/ethnic disparities in health utilization or outcomes and critically assess the reporting and inclusion of race/ethnicity data. Of 2023 articles reviewed, 152 quantitative and 17 qualitative studies were included. Among quantitative studies, 66% examined infant outcomes ($n = 101$). Three articles explicitly focused on evaluating racial/ethnic differences among dyads. Among quantitative studies, 112 mentioned race/



Preferred Reporting Items for Systematic Reviews and Meta-Analyses review schematic: maternal-infant outcomes classification.

ethnicity, 63 performed analyses assessing for differences between exposure groups, 27 identified racial/ethnic differences, 22 adjusted outcomes for race/ethnicity in multivariable analyses, and 11 presented adjusted models stratified by race/ethnicity. None of the qualitative studies addressed the role that race, ethnicity, or racism may have had on the presented themes. Few studies were designed to evaluate racial/ethnic inequities among maternal-infant dyads affected by OUD. Data on race/ethnicity have been poorly reported in this literature. To achieve health equity across perinatal OUD, researchers should prioritize the inclusion of marginalized groups to better address the role that structural racism plays.

Featured paper: Schiff DM, Work EC, Foley B, Applewhite R, Diop H, Goullaud L, Gupta M, Hoepfner BB, Peacock-Chambers E, Vilsaint CL, Bernstein JA, Bryant AS. **Perinatal Opioid Use Disorder Research, Race, and Racism: A Scoping Review.** *Pediatrics.* 2022 Mar 1;149(3):e2021052368. doi: 10.1542/peds.2021-052368. PMID: 35156121; PMCID: PMC9044279.



Image Award Finalist
The Science Tooth Fairy
Alison Hoffnagle, MA
Center for Genomic Medicine

MAURIZIO FAVA, MD, CHIEF

Overview:

Psychiatric disorders are the leading cause of disability worldwide. As has been noted by many, these disorders have increased because of the global COVID pandemic, creating another public health crisis: a “pandemic within the pandemic”. The MGH Department of Psychiatry is dedicated to alleviating the suffering and burden of mental illness through its four-fold mission of clinical care, training and education, community service, and research.

Clinical Care: The Department of Psychiatry provides care for our patients and their families across the full spectrum of psychiatric, psychological and substance use disorders, both for adults and children/adolescents. The department’s more than 700 psychiatrists, psychologists, nurse practitioners, and social workers serve as clinicians, researchers, supervisors and/or teachers, and include some of the field’s most accomplished specialists. For its exceptional patient care, the MGH Department of Psychiatry has been rated the #1 department of psychiatry in 20 of the past 28 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*.

Professional Education: Each year, we train over 150 adult and child/adolescent psychiatry residents, psychology interns, and clinical post-doctoral fellows (both psychiatrists and psychologists) to be leaders in their areas of specialization. Further, over 40 postdoctoral fellows train with us across neuroscience, research psychology, and other fields.

In addition, our educational efforts reach tens of thousands of health professionals through our Division of Public and Professional Education’s Psychiatry Academy and its dozens of webinars, live conferences and more. The Psychiatry Academy also offers Mass General Visiting, the goal of which is to reduce the risks and disparities associated with physician shortages in health care systems across the country. Through Mass General Visiting, 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: The Department of Psychiatry partners with local organizations through its Division of Public and Community Psychiatry 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. Since 2013, we have been engaged in a hospital-wide Substance Use Disorders (SUDS) initiative, which includes 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.

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, conducting important clinical and translational investigations. 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 FY23, the department projects that our faculty will receive close to \$100 million in research funding, continuing its record of successful funding despite a challenging environment. Further, our researchers published over 1660 original articles in 2022, including several in top journals.

Special Note on COVID-19—As all hospital clinical departments have been, the Department of Psychiatry was/continues to be significantly affected by the COVID-19 global pandemic. We have the advantage of being able to conduct most of our outpatient visits through telehealth and were able to quickly pivot quite seamlessly to that platform, soon seeing over 95% of our patient visits virtually. On the inpatient psychiatry, consultation psychiatry, and emergency psychiatry services, on-site care is required, but our dedicated attending faculty and trainees rose to the occasion and adapted to new workflows and physical modifications to see patients safely.

Key Recruitments

- **Matthew Sacchet, MD**—is an assistant professor at Harvard Medical School and the director of the Meditation Research Program at Massachusetts General Hospital. Dr. Sacchet and his team advance the science meditation in both clinical and non-clinical contexts. Since 2012, Dr. Sacchet has authored over 80 publications and his research has been presented over 125 times and cited over 4000 times. Dr. Sacchet has been awarded funding from the National Institute of Mental Health (NIMH), National Science Foundation (NSF), Dimension Giving Fund, National Center for Advancing Translational Sciences (NCATS), Ad Astra Chandaria Foundation, Phyllis & Jerome Lyle Rappaport Foundation, Brain & Behavior Research Foundation (BBRF), BIAL Foundation, Gatto Foundation, and The Ride for Mental Health. His research has received coverage by major media outlets including CBS, NBC, NPR, TIME, and The Wall Street Journal, and in 2017 Forbes Magazine named him as one of its “30 Under 30”.
- **Taylor Burke, PhD**—is an assistant professor of psychology in the Department of Psychiatry at Harvard Medical School and a licensed clinical psychologist. She is the director of Pediatric Computational Health in the Center for Precision Psychiatry and associate director of suicide research in the Division of Child and Adolescent Psychiatry at Massachusetts General Hospital. The

primary aim of Dr. Burke's research is to advance the prediction and prevention of self-injurious thoughts and behaviors (SITBs) among youth and young adults. Dr. Burke uses novel methodologies and computational approaches to improve the identification of individuals at risk to better intervene and prevent SITBs and has published over 70 peer-reviewed articles and book chapters in this area. She also has obtained grant funding totaling approximately \$2.0 M. Dr. Burke holds a five-year NIMH career development award that focuses on using passive mobile sensing, adolescent sleep, and physical activity assessment, and advanced computational approaches to idiographic modeling to develop proximal risk models for increases in suicidal ideation. She also has other ongoing research supported by the American Foundation for Suicide Prevention and the NIMH.

Initiation of Two Important Departmental New Centers

- **The Center for Racial Equity and Justice** grew out of a task force on anti-racism that Maurizio Fava, MD, Chair of the Department of Psychiatry, established in 2020 amid growing societal awareness about the pervasive and destructive effects of racism. Moreover, we were increasingly cognizant of the mental health impacts of racism and the importance of addressing this issue in psychiatry. We asked the questions: What are the mental health impacts of racism? As a community of professionals in mental health, how do we address these impacts and better promote racial equity moving forward? The task force identified the need for a new Center dedicated to these efforts. The goal of the MGH Psychiatry Center for Racial Equity and Justice is to establish an anti-racist culture in the department, support diversity, equity, and inclusion (DEI) and put forward racial equity and justice solutions relevant to psychiatry.
- **The Center for Digital Mental Health** is a hub for digital health innovation, and the sharing of ideas and resources, within the Massachusetts General Hospital Department of Psychiatry. Directed by Dr. Sabine Wilhelm, the Center began as a think tank in 2019 and has grown to over 95 members who are energized by the joint goal of applying technology to address mental health needs. Specifically, members share a vision that technology-based solutions are critical for addressing the severe imbalance between the demand for mental health care and the scarcity of existing resources.

Achievements

Gilman JM et al, 2022 Effect of Medical Marijuana Card Ownership on Pain, Insomnia, and Affective Disorder Symptoms in Adults: A Randomized Clinical Trial.

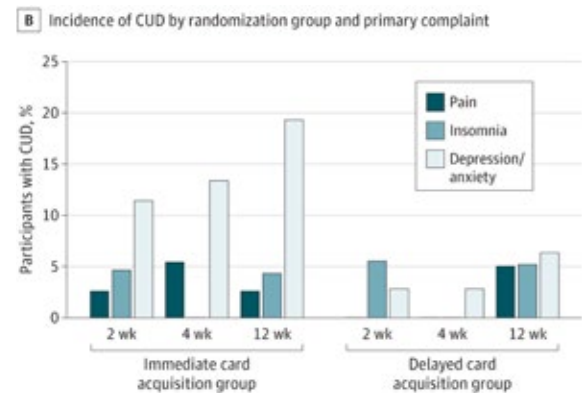
Cannabis is increasingly used for common medical problems such as pain, insomnia, anxiety, and depression, though we have minimal knowledge of the benefits or risks of cannabis product use for these problems. Risk of developing cannabis use disorder among different populations who may choose to use cannabis for medical problems are not known. Prior to this study, there had been no randomized

clinical trials of dispensary-purchased, patient-determined doses of cannabis via the system in place for physician recommendation and cannabis product regulation and distribution of cannabis that used in 38 US states and much of the world. This randomized controlled trial tested the degree to which participants who received medical cannabis cards (MMC), compared to those assigned to a 12-week waitlist control condition (WLC), experienced improved pain, sleep, depression, or anxiety and adverse outcomes such as new-onset symptoms of cannabis use disorder (CUD) or cognitive impairment. In this sample, obtaining a MMC was associated with improved self-reported sleep quality, no significant improvement in pain, anxiety, or depression, and increased risk for developing CUD, particularly in those seeking cannabis to relieve anxiety or depression. Results of this study underscore the critical importance of developing a sufficient evidence base to allow assessment of benefits and risks of all therapeutics and strongly support well powered studies of longer duration and similar design to better estimate the risks of developing cannabis use disorder among those using dispensary cannabis for medical purposes.

Gilman JM, Schuster RM, Potter KW, Schmitt W, Wheeler G, Pachas GN, Hickey S, Cooke ME, Dechert A, Plummer R, Tervo-Clemmens B, Schoenfeld DA, Evins AE. Effect of Medical Marijuana Card Ownership on Pain, Insomnia, and Affective Disorder Symptoms in Adults: A Randomized Clinical Trial. *JAMA Netw Open*. 2022 Mar 1;5(3):e222106. PMID: 35302633, PMCID: PMC8933735

Lee YH et al, Association of Everyday Discrimination With Depressive Symptoms and Suicidal Ideation During the COVID-19 Pandemic in the All of Us Research Program.

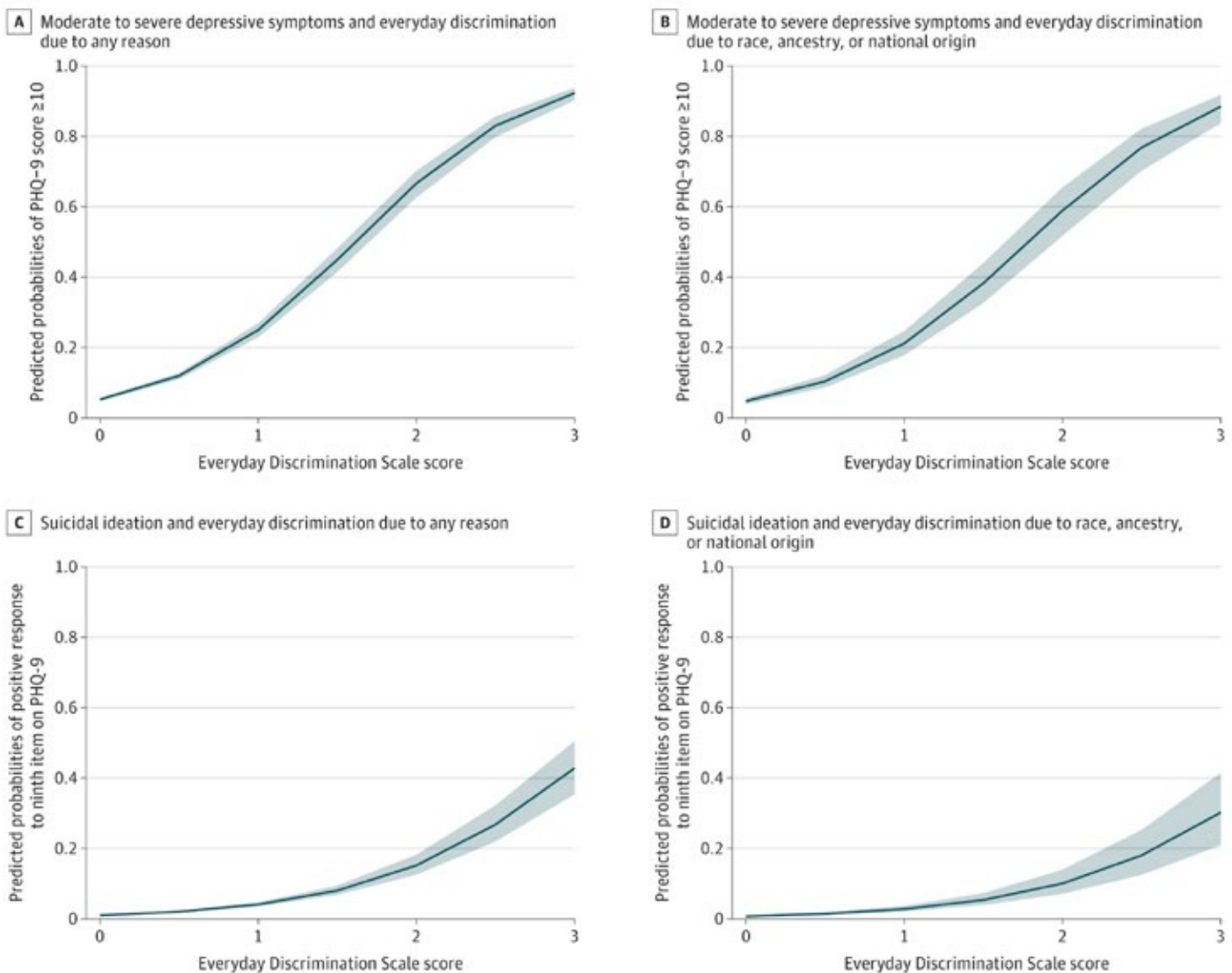
The COVID-19 pandemic has coincided with an increase in depressive symptoms as well as a growing awareness of health inequities and structural racism in the United States. Leveraging the unique scale and diversity of the NIH *All of Us* Research Program, a longitudinal cohort study recruiting 1 million or more participants reflecting the broad diversity of the United States, our team examined the impact of everyday discrimination on moderate to severe depression and suicide ideation during the early phase of the COVID-19 pandemic. Participants completed the monthly COVID-19 Participant Experience (COPE) survey, a brief online survey administered to determine how the pandemic has affected people over time, including questions on COVID-19 symptoms, physical and mental health, social distancing, economic effects, and coping strategies. The Everyday Discrimination Scale was used to measure discrimination events during the last month (e.g., being treated with less courtesy or respect, being considered dishonest or threatening). Depressive symptoms and suicidal ideation were measured using the 9-item Patient Health Questionnaire (PHQ-9), with a score of 10 or greater indicating moderate to severe depressive symptoms. Using repeated assessments of 62,651 participants from May to July 2020, we fitted mixed-effects models and applied inverse probability weights to account for non-random probabilities of completing the voluntary survey. Remarkably, the study demonstrated that



Frequency of Cannabis Use and Incidence of Cannabis Use Disorder (CUD) Diagnoses in Immediate vs Delayed Card Acquisition
B, Cannabis use disorder was defined as 2 or more CUD symptoms on an 11-point scale. The odds of developing CUD were 2.9-fold higher in the immediate card acquisition group vs the delayed card acquisition group (adjusted odds ratio, 2.88; 95% CI, 1.17-7.07; $P = .02$).

everyday discrimination was associated with significantly increased odds of depression and suicidal ideation, and the strength of this relationship depended on the main reason for everyday discrimination, survey timing, self-reported race, and pre-pandemic mood disorder diagnosis. On average, individuals experiencing discrimination more than once a week were more than 17.7 (95% CI: 13.5-23.2) times as likely to report moderate to severe depressive symptoms and were nearly 10.8 (95% CI: 7.8-14.8) times as likely to report suicidal ideation. Moreover, the association with depressive symptoms was

Figure1. Predicted Probabilities of Moderate to Severe Depressive Symptoms and Suicidal Ideation According to Level of Everyday Discrimination



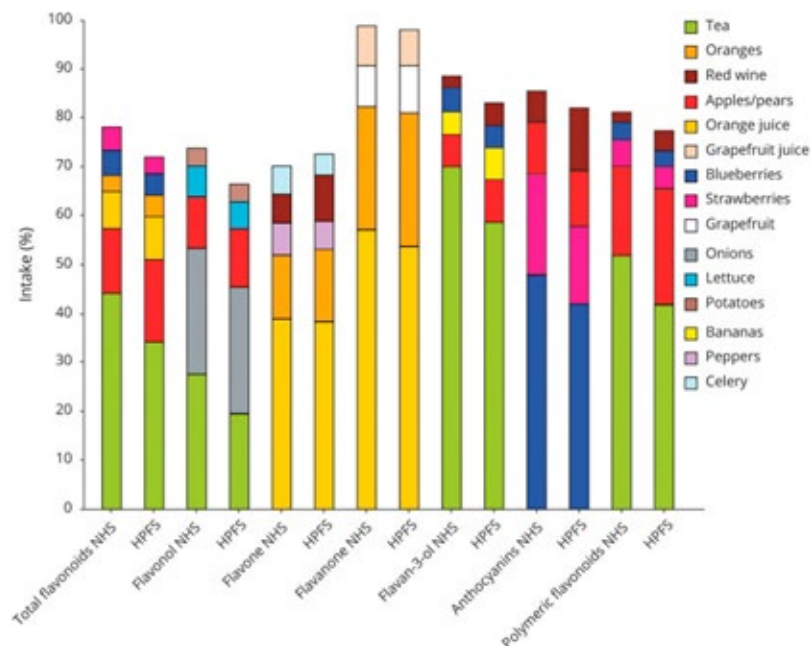
Scores for the 9-item Patient Health Questionnaire (PHQ-9) that were greater than or equal to 10 were classified as moderate to severe depressive symptoms. Any positive response to the ninth item of the PHQ-9, which evaluates thoughts of death or self-injury within the last 2 weeks, was considered a positive indicator for suicidal ideation.

greater when the main reason for discrimination was race, ancestry, or national origins among Hispanic or Latino and non-Hispanic Asian participants. Lastly, at high levels of everyday discrimination, the likelihood of depression was similar among those with or without a pre-pandemic mood disorder diagnosis. To our knowledge, this work is the largest and most diverse study examining the complex and dynamic relationship between discrimination and adverse mental health outcomes during the COVID-19 pandemic.

Lee YH, Liu Z, Fatori D, Bauermeister JR, Luh RA, Clark CR, Bauermeister S, Brunoni AR, Smoller JW. Association of Everyday Discrimination With Depressive Symptoms and Suicidal Ideation During the COVID-19 Pandemic in the All of Us Research Program. *JAMA Psychiatry*. 2022 Sep 1;79(9):898-906. doi: 10.1001/jamapsychiatry.2022.1973. PMID: 35895053; PMCID: PMC9330278.

Yeh T-S et al, Long-term Dietary Flavonoid Intake and Subjective Cognitive Decline in US Men and Women.

In a recent paper published in the journal *Neurology*, Dr. Deborah Blacker and colleagues at the Harvard T.H. Chan School of Public Health showed that dietary flavonoids, a group of compounds found in many fruits and vegetables, were associated with reduced risk of Subjective Cognitive Decline (SCD), which can sometimes represent the first symptoms of a dementia like Alzheimer's disease. The study was conducted in two large groups of health professionals in the United States (49,493 female nurses and 27,842 men in a variety of health professions) followed for several decades. The carefully



Major Food Sources of Flavonoids By Subclass^a

^aAverage for 1984 to 2006 in the Nurses' Health Study (NHS) and 1986 to 2002 in the Health Professionals Follow-Up Study (HPFS).

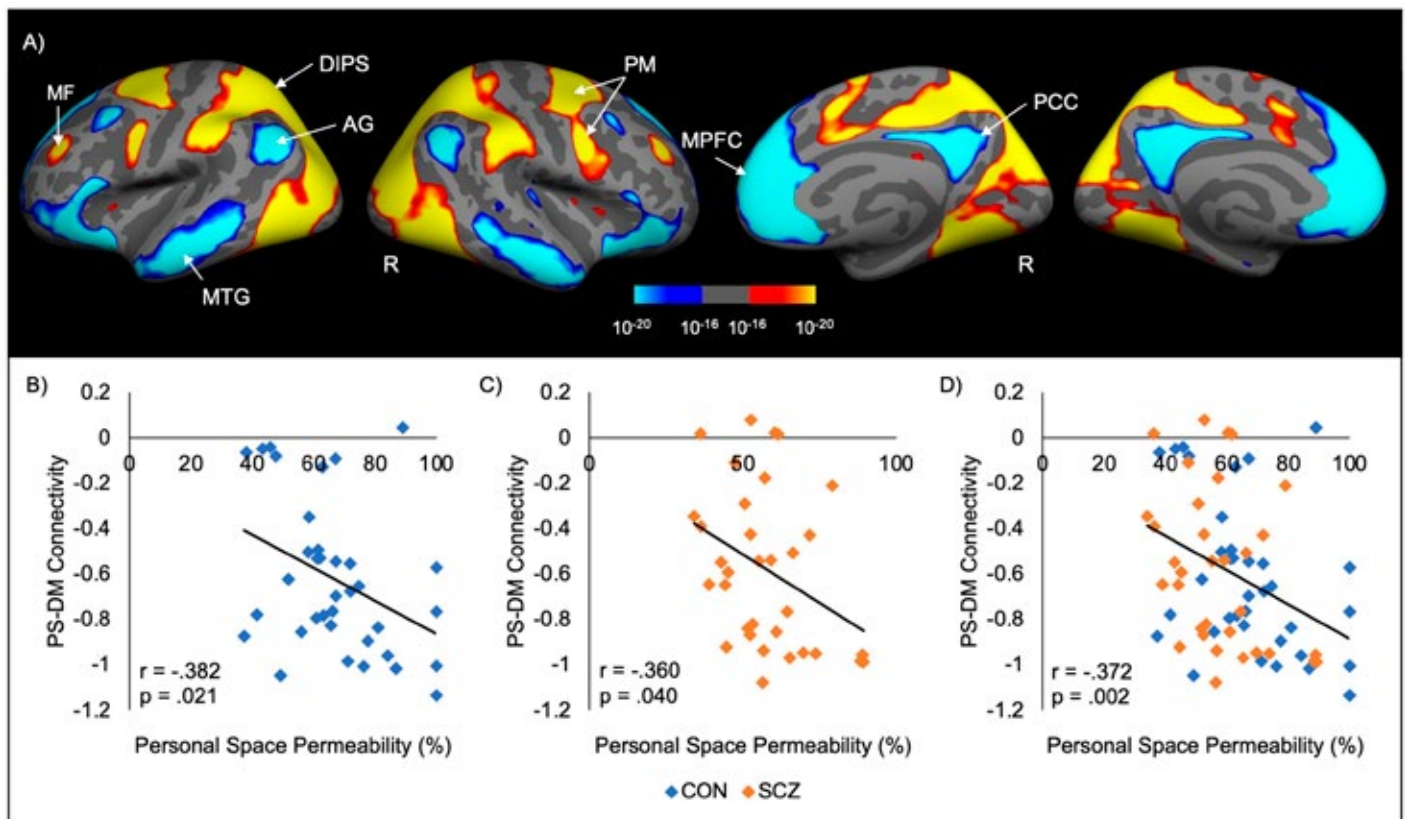
conducted analyses found that the highest quintile of flavonoid intake (based on the average over 5-7 Food Frequency Questionnaires at 2-4 year intervals) had about a 20% lower odds of SCD as the lowest quintile, with greater reductions for some specific flavonoid subtypes or individual flavonoid-rich foods. Many flavonoid-rich (e.g., strawberries, oranges, grapefruits, citrus juices, apples/pears, celery, peppers, and bananas) were significantly associated with lower odds of SCD. These findings stress the potential importance of “eating the rainbow” for cognitive health in late life (as illustrated in Figure 2, where the colors of the bars indicate the intake of specific subtypes of flavonoids in individual foods), and overall underscore the need to ensure access to fruits and vegetables for everyone.

Yeh T-S, Yuan C, Ascherio A, Rosner BA, Willett WC, Blacker D. Long-term Dietary Flavonoid Intake and Subjective Cognitive Decline in US Men and Women. *Neurology*. 2021;97(10):e1041-e56. doi: 10.1212/wnl.00000000000012454.

Zapetis SL, et al, Neural correlates of variation in personal space and social functioning in schizophrenia and healthy individuals.

Impaired social functioning is one of the most disabling aspects of having a serious mental illness like schizophrenia, and yet there are no medicines or therapies available to treat these impairments. Also, we do not have quantitative tools for measuring social functioning that can be used by clinicians to monitor this symptom. To address these gaps in knowledge and clinical care, Dr. Daphne Holt and her team have been studying quantifiable aspects of social behavior and the function of brain circuits involved in generating those behaviors. One social behavior they have studied is the regulation of interpersonal distance or “personal space”, which is the comfortable distance people automatically maintain from others. This work has shown that reliably measurable features of personal space, such as its size and the permeability (or rigidity) of its boundaries, are closely related to aspects of day-to-day social functioning. Personal space characteristics are also linked to the responses and connectivity of a brain network involved in attending to the space near the body initially identified in primates. Intriguingly, many of the brain-behavior relationships involving personal space and its neural correlates are observed in both people with schizophrenia and in healthy people without schizophrenia, suggesting that measurements of personal space-related behaviors could serve as general markers of social functioning that reflect the integrity of the responsible neural system across and within different populations.

Zapetis SL, Nasirivanaki Z, Luther L, Holt DJ. Neural correlates of variation in personal space and social functioning in schizophrenia and healthy individuals. *Schizophr Bull*. 2022 Jun 5. PMID: 35661903, <https://doi.org/sbac052>



The strength of the functional connectivity of a network of brain regions involved in regulating personal space (PS) with the default mode (DM) network is significantly correlated with levels of a marker of social functioning, personal space permeability (the flexibility of the boundary of personal space). This correlation was found in a group of people with schizophrenia ($n=33$) and in a group of healthy control subjects ($n=36$). Maps of the connectivity of the dorsal intraparietal sulcus (DIPS) region in panel A show the main nodes of the PS and DM networks (the PS network includes the DIPS, premotor area (PM) and middle frontal gyrus (MF); the DM network includes the medial prefrontal cortex (MPFC), angular gyrus (AG), middle temporal gyrus (MTG), and posterior cingulate cortex (PCC)). Scatter plots illustrate the significant correlations between PS-DM connectivity and personal space permeability in the healthy (B), schizophrenia (C) and combined (D) samples.

In the DIPS connectivity maps of panel A, warm colors indicate areas with a positive correlation with the DIPS seed region, while cool colors indicate areas with a negative correlation with the DIPS seed region. R, right hemisphere; CON, healthy control subjects; SCZ, schizophrenia subjects.

ANTHONY ZIETMAN, MD, CHIEF

Overview:

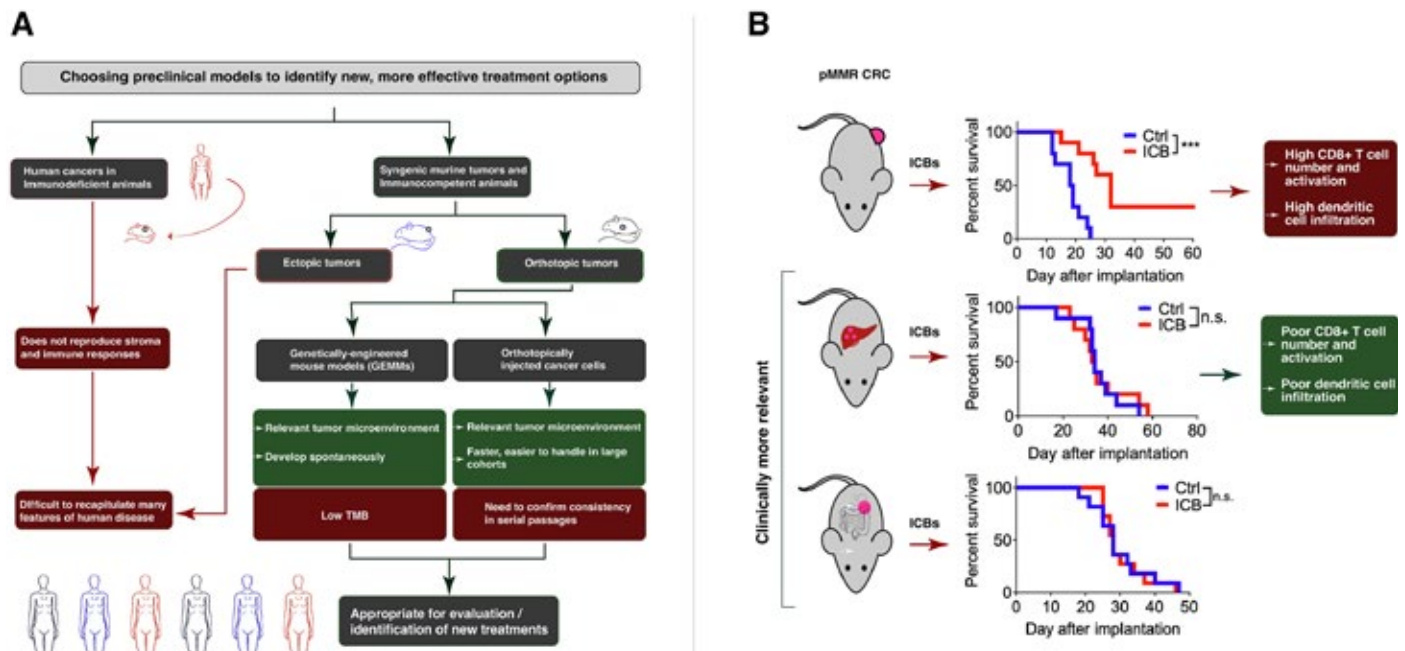
The Mass General Department of Radiation Oncology had approximately **\$21.8M** TOTAL in research expenditures in Fiscal Year 2022. Nearly **45%** of this research funding originated from federal support. The department continues to have an impressive record as a highly collaborative research team, reflected in the rich publication record of our faculty with over **274** publications in 2022. Additionally, in 2022, the Department of Radiation Oncology maintained **42** active clinical trials, and **244** clinical trial accruals.

The main areas of research in the department of radiation oncology are clinical, translational, physics and biology. The primary focus of the clinical research program is a robust radiation oncology clinical trials program, which is embedded in the Cancer Center Protocol Office (CCPO) but functions as its own “disease site”. Additionally, there are numerous clinical registries and databases, including a pediatric cancer registry and proton registry. Closely linked to the clinical research program is translational research program. This program, supported by a biomarker research group, is evaluating radiation response in clinically annotated specimens using techniques such as whole exome sequencing, bulk and single cell RNAseq, spatial transcriptomics, ctDNA, and circulating cytokines. The translational program provides links to the physics and biology programs as well. The physics program performs active investigation in bio-mathematical modeling, outcome modeling, Monte Carlo simulations, and optimization of intensity-modulated photon and proton therapy. The biology program encompasses an active radiation biology program, led by Dr. Henning Willers, a tumor microenvironment program led by Dr. Rakesh Jain (Edwin Steele lab), and cancer biology investigators as well. This breadth of research often intersects in large scale projects, including a Program Project Grant (P01) in proton therapy which integrates clinical data, biological investigations and physics investigations, linked by a translational infrastructure. It is anticipated that MGH will continue to lead the field of radiation oncology as a greater focus is placed on precision medicine as it pertains to radiotherapy.

Department General Achievements:

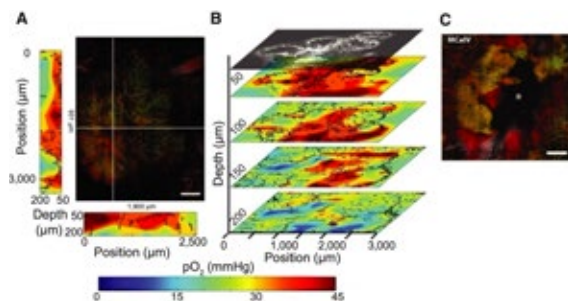
The inaugural Mass General Brigham Collaborative Radiation Oncology Research Retreat took place on Thursday, September 30, 2022. This hybrid retreat was well-attended, with 100 people attending in person and 50 people joining via Zoom. **Hosted jointly by the chiefs of BWH Radiation Oncology and MGH Radiation Oncology**, the retreat celebrated the research accomplishments of our departments while exploring areas of possible collaboration. In his opening remarks, MGH Radiation Oncology **Interim Chief Anthony Zietman, MD**, quoted the UK political slogan “Better Together” to reflect his hope for the BWH and MGH Radiation Oncology departments, a theme echoed by **BWH Rad Onc Chief**

Daphne Haas-Kogan, MD. In the session on “Healthcare Disparities & Equity,” **Sophia Kamran, MD** noted frankly that earlier efforts to increase UIM (Underrepresented in Medicine) populations in the field of Radiation Oncology did not meet targets, and improvements in this area are crucial, since the “the end goal of patient innovation is affected.” The bulk of the research retreat was devoted to showcasing research highlights and future opportunities for collaboration. Sessions on Artificial Intelligence/Big Data, Liquid Biopsies, Advanced Technologies, Harvard Radiation Oncology Program Presentations, Tales from the Bench and Radiation Immuno-Oncology, and a Panel Discussion on Clinical Trials, featured talks by both MGH and BWH



The local tumor microenvironment matters (from Ho et al. Cancer Cell 2022).

Preclinical studies of cancer immunology and immunotherapy should include orthotopic tumor models where tumors develop/grow in their native tumor microenvironment (TME). Patient-derived xenografts (PDX) are widely used in preclinical studies where the tissue or cells from a patient's tumor are implanted into an immunodeficient or humanized mouse. However, these models lack many components of human stroma and a fully functional immune system; thus, may not recapitulate many features of human TME. In addition to being expensive, these models may not be clinically relevant when used for testing TME-targeted agents. Similarly, subcutaneous murine tumor models, although grown in mice with intact immune system, and widely used due to convenience and lower costs, may not recapitulate the native TME and yield results that are not clinically relevant. By contrast, orthotopic tumors arising in genetically engineered mouse models (GEMMs) or implanted in the correct organ location have a native TME and the mice have an intact immune system. Each of these orthotopic models has advantages and disadvantages. For example, the former arise spontaneously and reproduce carcinogenesis while the latter grow more predictably and are easier to handle in large cohorts for drug testing. However, GEMMs have a lower tumor mutational burden than their human counterparts, while the cancer cell lines used for implantation may drift over serial passaging. Thus, it remains critical to validate any preclinical results using patient data to ensure the clinical relevance of the model to human disease. Appropriate animal models may not necessarily predict clinical success, but they are more likely to provide relevant information to guide clinical development and reduce the number of clinical failures and their associated financial and human costs. B. Ho et al. (2021) showed that when mismatch repair-proficient colorectal cancer (pMMR CRC) cells were grown in the flank as subcutaneous tumors, they responded to immune-checkpoint blockers (ICBs), unlike in CRC patients. By contrast, when the same pMMR CRC cells were grown in their natural microenvironment such as in the colonic wall as primary colon tumors, or in the liver as colon cancer liver metastasis, they did not respond to ICBs, which better recapitulated clinical observations. (Reproduced from Ho et al. 2021)



Simultaneous angiography and oxygen tension measurements reveal an abnormal function of tumor vessels and the dependence of oxygen tension on the distance to the nearest vessel (from Martin, Lanning et al. Clin Can Res 2022).

The large panel shows a maximum intensity depth projection of MCalV tumor angiography with an oxygen tension heat map to the left and bottom of the angiography image. The depths of the heat maps go from 50 mm to 200 mm and are taken from the planes noted by the white lines in the angiography image. In the angiography, color denotes depth (from deep to shallow: green, red, white). The color scale of the oxygen heat maps is shown in the bottom panel (blue indicates 0 mmHg oxygen tension, whereas red indicates 45 mmHg). Black outlines on the oxygen heat maps indicate the morphometry of the tumor vessels. Scale bar, 500 mm in all panels. B, Oxygen tension maps from 50 mm, 100 mm, 150 mm, and 200 mm deep within the tumor are shown in A. The angiographic depth slice at 50 mm is shown above the 50 mm deep oxygen heat map for comparison. Black lines on the oxygen heat maps indicate the morphometry of the tumor vessels. C, Angiography of an MCalV tumor. Asterisk (*) indicates an area lacking perfused vessels. Color denotes depth (from deep to shallow: green, red, white).

researchers. Attendees noted the overlapping interests of BWH and MGH researchers and the benefit to collaborating more closely.

Finally, during the concluding Reflections and New Directions session of the retreat, **Dr. Zietman** and **Dr. Haas-Kogan** announced a new grant mechanism, the **Accelerator Awards**, to be awarded for joint collaborations between MGH and BWH researchers. There will be 2 awards of \$30,000 direct costs per award, for a one-year project period (April 2023 through March 2024). As this award is intended to foster research collaborations across the institutions, one PI each from BWH and MGH is required for each application.

Theodore Hong, MD was appointed the first Vice-Chair for Scientific and Research Affairs for the Department of Radiation Oncology. Dr. Hong is a committed clinical and translational trialist, he leads our P01 grant, and has held an impressive portfolio of important roles within the Cancer Center and the MGPO.

Clinical Research and Radiation Biology Research Achievements:

The founding chair of our department and a pioneer of radiation therapy, **Herman D. Suit, MD, DPhil**, sadly passed away at the age of 93 in California in July 2022. An obituary describing Dr. Suit's legacy was written by **Anthony Zietman, MD**, and published in The Cancer Letter. During his extraordinary career, Dr. Suit authored more than 400 peer-reviewed articles, served as president of the American Society of Radiation Oncology (ASTRO) and the Radiation Research Society, and was named the Andres Soriano Professor of Radiation Oncology at HMS. He has received countless awards including the National Association for Proton Therapy's Lifetime Achievement Award and was inducted into the Giants of Cancer Care Program.

Rachel Jimenez, MD, and **Sophia Kamran, MD**, have been selected to participate in the ASTRO Leadership Pipeline Program (formerly known as the Pipeline Protégé Program). This program is a career development program aimed at increasing diversity among ASTRO leadership, which supports ASTRO's core value of diversity and inclusion.

Shervin Tabrizi, MD, is awarded with the Young Investigator Award from Prostate Cancer Foundation (PCF). PCF Young Investigator Awards are intended to identify a cohort of future research leaders who will keep the field of prostate cancer research vibrant with new ideas, and offer career and project support for early career physicians and scientists who are committed to advancing the prostate cancer field.

William Hwang, MD, PhD, has been named, the American Association for Cancer Research (AACR) 2022 NextGen Star. Dr. Hwang presented his research, "Multicellular spatial community featuring a novel neuronal-like malignant phenotype is enriched in pancreatic cancer after neoadjuvant chemotherapy and radiotherapy" at the AACR Annual Meeting in April 2022.

William Hwang, MD, PhD, is also a recipient of the Neuroendocrine Tumor Research Foundation Pilot Project Award! This award is given to investigators with the skills and knowledge to study neuroendocrine cancers in altering ways.

Sophia Kamran, MD, received a Young Investigator Award from the Prostate Cancer Foundation for her project titled, “Dissecting Tumor-Immune Dynamics and Radiotherapy Response in Oligometastatic Prostate Cancer.”

Sophia Kamran, MD, newly named inaugural Director of Diversity, Equity, and Inclusion in the Department of Radiation Oncology published a first-author research article titled “Intersectional Analysis of U.S. Medical Faculty Diversity over Four Decades” in the *New England Journal of Medicine*. This work was featured in a segment on NPR’s Morning Edition as well.

With a grant from the 1440 Foundation (Canopy Cancer Collective), **Theodore Hong, MD, Lorraine Drapek, NP, Jessica Meurer, NP, and Allison Bannon, CCRP**, have collaborated with top institutions across the country to create consistent top-level care for pancreatic patients who come through the cancer center. The purpose of this grant is to provide the support and resources needed to deliver superior outcomes for pancreatic patients and caregivers, while ensuring that all members of the care team are working at the top of their license.

Jay Loeffler, MD, former Chief of MGH Radiation Oncology, has been recognized with the National Association for Proton Therapy’s 2022 Lifetime Achievement Award.

Integrating breast reconstruction and post-mastectomy radiotherapy is challenging, but there is now a machine learning nomogram that can estimate complication risk. Physicians can use this online tool to help select the optimum surgical or radiation approach for their patients.

In a recent study, led by **George Naoum, MD, MMSCI**, (former Mass General Research Fellow currently at Northwestern Memorial Hospital) and **Alphonse Taghian, MD, PhD**, over 35 different data points for more than 1,600 patients were analyzed to build a machine-learning nomogram. The research article was published in *Plastic and Reconstructive Surgery*, the leading journal in plastic surgery, and was selected for several podcasts and journal clubs featured online by the journal.

Rachel Jimenez, MD, received the 2022 Claflin Distinguished Scholar Awards from the MGH Executive Committee on Research and the 2022 Advanced Clinical Research Awards (ACRA) for Diversity and Inclusion in Breast Cancer from Conquer Cancer.

Shannon MacDonald, MD, and research fellow, **Myrsini Ioakeim Ioannidou, MD**, received a grant from the Adenoid Cystic Carcinoma Research Foundation (ACCRF) to build the first MGH ACC Clinical Database in RedCap, including data on natural history of the disease, treatment characteristics, tumor control outcomes and late sequelae for all ACC cases.

A new clinical guideline from ASTRO provides recommendations on the use of radiation therapy to treat patients with isocitrate dehydrogenase (IDH)-mutant grade 2 and grade 3 diffuse glioma. Listen to the Podcast on the guideline, featuring **Helen Shih, MD**.

Shannon MacDonald, MD, and Julia Berv, PA's, perspective piece “Losing Contact — Covid-19, Telemedicine, and the Patient–Provider Relationship” that was recently published in the New England Journal of Medicine.

Jen Powers, NP received a nomination for the national APP of the Year Award. Jen was nominated for her extraordinary care of MGH patients.

Carina Shiau, a Clinical Research Coordinator working with Dr. Hwang, was selected as a winner of the Mass General Celebration of Science 2022 Poster of Distinction Award.

Myrsini Ioakeim Ioannidou, MD has been selected to serve as the new ARO Diversity, Equity, and Inclusion editor.

New Grants:

National Institutes of Health has awarded **David Miyamoto MD, PhD** a R01 award from 9/1/2022 to 8/31/2026. “Blood-based monitoring of bladder-sparing trimodality therapy for muscle-invasive bladder cancer.” 1R01CA259007-01A1

William Hwang, MD, PhD was awarded a NIH-National Institutes of Health award, 1K08CA270417-01 for “Elucidating cancer-intrinsic mechanisms of perineural invasion in pancreatic cancer” from 7/1/2022 to 6/30/2027.

Conquer Cancer Foundation of the American Society of Clinical Oncology has given grants to **Rachel Jimenez, MD** for “A randomized clinical trial to study the impact of emerging radiation techniques on cardiac injury in the treatment of women with breast Cancer” from 7/1/2022 to 6/30/2025.

Rachel Jimenez, MD has received the MGH ECOR - Claflin Distinguished Scholar Award for “Accelerated Proton Therapy for Breast Cancer and Impact on Cardiac Function” during 7/1/2022 and 6/30/2024.

Burroughs Wellcome Fund gave **William Hwang, MD, PhD** the Career Awards for Medical Scientists from 9/1/2022 to 8/31/2027.

Henning Willers, MD, received a lung cancer concept grant from the Department of Defense to identify ways to carbonize proton beam therapy, 1/1-12/31/2022, W81XWH2210024.

Henning Willers, MD, was named Co-Leader of the Developmental Research Program of the newly funded Dana-Farber/Harvard Cancer Center Specialized Program of Research Excellence (SPORE) in Lung Cancer (PD Sequist, Barbie) 8/1/2022 – 7/31/2027.

Physics Achievements:

On the evening of Thursday, October 13, the Physics Division gathered for its annual retreat for the first time since 2019. The purpose of this event was to not only showcase our staff's work but to relax and unwind together, something we have not done in years. The event opened with kind words from **Thomas Bortfeld, PhD**, **Tiffany Zewe, MBA**, and **Anthony Zietman, MD**. This discussion was then followed up with a Physics update from David Gierga, PhD, and Dosimetry updates from **Brian Napolitano, CMD**. The event took place in the library of the Hampshire House set up to allow guests to mingle and view the various exhibits displayed while enjoying food and drink. There was a total of ten presentations each with a different topic. Toward the end of the evening **Susu Yan, PhD**, and **Maryam Moteabbed, PhD**, presented award winners for best exhibits. In first place was **Ali Ajdari, PhD**, who presented a poster about "Mid-treatment prediction of radiotherapy-induced cardiac toxicity in NSCLC patients". In second place came **Peter Jermain** who presented a poster on "Treating CNS patients with a gantry-less horizontal proton beamline: A robust optimized treatment planning study". In third place was **Nick Depauw, PhD**, who presented a poster on "LET weighted dose reoptimization for pediatric ependymoma proton therapy."

Drs. Grassberger, Paganetti, Pursley, Xing, Shin, Hammi, Lucas McCullum (CRC), and the other authors of "HEDOS—a computational tool to assess radiation dose to circulating blood cells during external beam radiotherapy based on whole-body blood flow simulations" has been awarded the Roberts' Prize for Best Paper in Physics in Medicine and Biology.

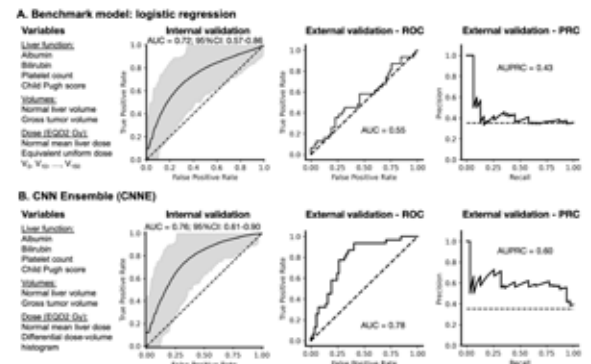
Dr. Ibrahim Chamseddine was recognized with the 2021 Prince Alwaleed bin Talal Research Fellowship, which was awarded in 2022, for his project "Artificial Intelligence-Enabled Treatment Personalization in Radiotherapy."

Thomas Bortfeld, PhD, will become the Andres Soriano Endowed Chair at Harvard Medical School. With this endowed chair Harvard is recognizing not only his extraordinary contributions to radiation physics, but those of the incredible physics research team that he has assembled and nurtured in our department.

Harald Paganetti, PhD, was honored with The Particle Therapy Co-Operative Group (PTCOG), Robert R. Wilson Award for Significant Contributions to the field of Particle Therapy. This distinguished award, named after the first scientist to propose particle therapy for the treatment of cancer, is presented to an individual active in the field recognizing their cumulative achievements in particle therapy.

Thomas Bortfeld, PhD became an honorary member of European Society for Radiotherapy and Oncology (ESTRO).

In order to study neutron energy distribution, the group of physics students from Suffolk University Neutron Research Project needed a neutron source. This was made possible through a collaboration with Mass General Radiation Oncology. In the early stages of the



Internal and external validation convolutional neural network model developed for predicting liver toxicity after proton and photon therapies. The model is evaluated using the receiver operating characteristic and the precision-recall curves, and is benchmarked with logistic regression.



Pancreatic cancer spatial transcriptomics:

The lethality and treatment-refractory nature of pancreatic cancer are largely mediated by collaborative interactions between cancer cells and other cell types in the tumor microenvironment, including cancer-associated fibroblasts and immune cells. By constructing a high-resolution molecular landscape of the multicellular subtypes and spatial communities that compose pancreatic cancer and the dynamic remodeling associated with cytotoxic selection pressure, additional therapeutic vulnerabilities are identified to augment precision oncology efforts in pancreatic cancer.

project, the students worked under the guidance of **David Gierga, PhD** to measure neutron energy distributions for one of the Varian TrueBeam™ linear accelerators. Subsequently, the group transitioned to performing their experiments using an AmBe source in the Francis H. Burr Proton Center. This work would not have been possible without the guidance and dedication provided by **Joe McCormack**, who is one of the engineers in the proton center. The group published their findings in the Journal of Undergraduate Reports in Physics. They also presented a virtual poster during the annual meeting of the American Physical Society (APS).

Physics residents **Rachael Hachadorian, PhD**, and **Casey Lee, PhD**, both received SCAMP Fellowships from the American Association of Physicists (AAPM).

Physics resident, **Stephanie Bennett, PhD**, won the AAPM Annual Jack Fowler Young Investigator Award.

Resident physics residency graduate, **Davide Brivio, PhD**, received the AAPM Research Seed Grant.

For the second summer in a row, MGH Physics Division offered a Diversity Summer Fellowship in which undergraduate students from backgrounds typically underrepresented in physics are introduced to medical physics. This year, **Alejandro Bertolet, PhD**, mentored **Marcus (MJ) Lindsey**, a rising senior at Claremont McKenna College in California.

This year **David (Bo) McClatchy, PhD**, volunteered to mentor a Summer Undergraduate Fellow through the American Association of Physicists in Medicine (AAPM) Summer Undergraduate Fellowship Program. The fellow was **Eric Hornfeck**, a Physics major and rising senior at the University of South Florida, who previously worked in the US Air Force.

The Department of Medical Physics at the University of Wisconsin-Madison initiated a special small-scale meeting this August that aims to empower early-career investigators in Medical Physics. The meeting was named the Emerging Leaders of Academic Medical Physics (ELAMP) Symposium. Sixteen early-career investigators were selected to join this meeting based on their recent research in Medical Physics and future vision of the field. The emerging leaders from MGH were early-career researchers from the Department of Radiation Oncology: **Dr. David Bo McClatchy, Dr. Lena Nenoff, and Dr. Ibrahim Chamseddine**.

Alejandro Bertolet, PhD, was awarded the 2022 Jack Fowler Award by the Radiation Research Society recognizes an outstanding junior investigator/faculty for exceptional work in radiation oncology, medical physics, and/or radiobiology.

Fernando Hueso González, PhD, received the 2022 Bruce Hasegawa Young Investigator Medical Imaging Science Award. This award is given annually to a young individual in recognition of significant and innovative technical contributions to the field of medical imaging science.

Jessica Fagerstrom, PhD, MEd, DABR, has been selected as the first winner of The Karen Doppke Award for Women in Medical Physics.

Susu Yan, PhD, has received the Mass General Center for Faculty Development's Anne Klibanski Visiting Scholars Award.

New Grants:

Thomas Bortfeld, PhD, received a new grant from the **NIH/NCI (R01 CA266803-01A1)** "An Ionizing Radiation Acoustics Imaging (iRAI) Approach for guided Flash Radiotherapy" from Sep 20, 2022 to Aug 31, 2027.

Thomas Bortfeld, PhD, received a new grant from the **NIH/NCI (R01CA266275)** "Automated interactive definition of the clinical target volume in radiation oncology" from Jan 6, 2022 to Dec 31, 2026.

Jan Schuemann, PhD, received a new grant from the **NIH/NCI (R01CA266419-01A1)** "Using experimentally-guided multi-scale modeling to determining the mechanism of FLASH tissue sparing" from 9/5/2022 to 7/31/2027.

Alejandro Bertolet Reina, PhD, received a new grant from the **NIH/NCI (K99 CA267560)** "Radiation dosimetry for a-particle radiopharmaceutical therapy and application to pediatric neuroblastoma" from 12/10/2021 to 11/30/2026.

Tumor Biology (Edwin Steele Laboratories Achievements):

Rakesh K. Jain, PhD, and **Dai Fukumura, MD, PhD** were named Highly Cited Researchers, for the 9th and 4th time in a row, respectively. This designation by Clarivate™ identifies the world's most influential researchers (those who have been most frequently cited by their peers over the last decade).

Rakesh K. Jain, PhD, has ranked #57 in United States and #92 in the world on the Research.com's 2022 Ranking of the Best Scientists in the World. Dr. Jain was also recognized with the 2022 Best Scientist Award. [<https://research.com/scientists-rankings/medicine/us>]

Rakesh K. Jain, PhD, received the 2022 Szent-Györgyi Prize for Progress in Cancer Research from The National Foundation for Cancer Research (NFCR). https://youtu.be/Y9nTa9uF_oM

A team of researchers led by **Rakesh K. Jain, PhD**, developed a new microscopy method to image oxygen levels within cells and tissues in relation to blood vessels. They found that both an antiangiogenic agent and an angiotensin-receptor blocker (losartan) improve oxygenation in mouse tumor models, but to varying degrees depending on tumor type and dosage. Their findings also suggest that combining the two therapies is likely to achieve the best results. This article published in *Clinical Cancer Research* was included in the Mass General's May 2022 press release.

A phase I clinical trial led by researchers at Atrium Health Levine Children's Hospital and Rakesh K. Jain PhD, Dan G. Duda, DMD, PhD, and David Ebb, MD of MGH showed promising results for a

new blocking antibody therapy blocking PIGF. This trial was based on a 2013 Cell paper by Rakesh K. Jain, PhD and colleagues that demonstrated that blocking the PIGF/NRP1 pathway in medulloblastoma models caused tumor regression, decreased spread to the spinal cord, and prolonged survival. The trial results published in *Clinical Cancer Research* were included in the Mass General's July 2022 press release.

A team of researchers from Mass General, including **Dan G. Duda, DMD, PhD**, and Brigham and Women's Hospital has reprogrammed the tumor microenvironment of liver cancer by using mRNA nanoparticles. This article was included in the Mass General's Feb 2022 press release.

Timothy P. Padera, PhD, Chaired the Gordon Research Conference on "Lymphatic Vessels as Multifaceted Regulators of Health and Disease", in Lucca, Italy between October 30 - November 4, 2022.

Pinji Lei, PhD, a postdoctoral Research Fellow in the E.L. Steele Laboratories, won the **2022 Science Slam** at the **MGH Postdoc Retreat** for his presentation "Single cell analysis of breast cancer lymph node metastasis reveals cancer cell plasticity and MHC class II-mediated immune regulation".

Katarina Ruscic, MD, PhD, a postdoctoral Research Fellow in the E.L. Steele Laboratories and Director of Anesthesia for Plastic, Reconstructive and Breast Oncology Surgery at Massachusetts General Hospital, received a 2022 International Anesthesia Research Society (IARS) Mentored Research Award titled "The Effects of Anesthetics on Lymphatic Vessel Contractility".

Lutz Menzel, PhD, a postdoctoral Research Fellow in the E.L. Steele Laboratories, received a postdoctoral fellowship from the German Research Fund (DFG).

Ashwin Kumar, a graduate student working in the Steele Labs, who has been named a winner of the Celebration of Science 2022 Poster of Distinction Award for his poster "Addition of Losartan to FOLFIRINOX and Chemoradiation Downregulates Pro-Invasion and Immunosuppression-Associated Genes in Locally-Advanced Pancreatic Cancer."

New Grants:

Rakesh K. Jain, PhD, received the NIH/NCI grant R01CA269672 (2022–2027) for the project titled "Reprogramming the tumor microenvironment to improve immunotherapy of glioblastoma" The goal of this R01 is to improve the outcome of α PD1 in GBM by co-targeting WNT signaling.

Rakesh K. Jain, PhD, received a grant from the Niles Albert Research Foundation (2022–2023) entitled "Improving immunotherapy of glioblastoma using losartan: Bench-to-bedside". The major goal of this grant is to identify biomarkers for response and mechanisms of action for combined losartan and immunotherapy to improve treatment of glioblastoma patients.

Dan G. Duda, DMD, PhD, received funding from the Andrew L. Warshaw, M.D., Institute for Pancreatic Cancer Research for their project titled, “Establishing the Role of MET as a Predictive Biomarker and Target for Sensitization to FOLFIRINOX in Early Pancreatic Ductal Adenocarcinoma.” This project is a collaboration with **Theodore S. Hong, MD**.

Timothy P. Padera, PhD received an NIH Exploratory Research Grant (R21AG072205) from that National Institute on Aging titled “Reversing aging-induced lymphatic dysfunction to improve immune function”.

Lei Xu, MD, PhD, received funding from NIH/NINDS R01 grant (2022-2027) for the project titled, “Co-Targeting IL-6 and EGFR signaling for the treatment of schwannomatosis and

associated pain”. The goal of the project is to test novel therapeutic strategies to control schwannomatosis tumor growth and pain.

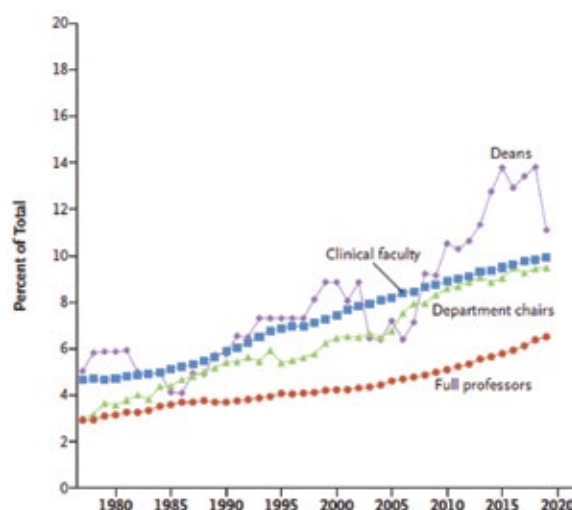
Lei Xu, MD, PhD, received funding from the American Cancer Society (2022-2024) for the project titled, “Reprogramming the tumor microenvironment to enhance immunotherapy”. The major goal of this grant is to investigate the effect of modulating the tumor microenvironment on enhancing treatment efficacy in ovarian cancer models.

Lei Xu, MD, PhD, received funding from Children’s Tumor Foundation (2022-2024) for the project titled, “Profile losartan-induced changes in the tumor microenvironment and inflammation in NF2 VS patient samples”. The goal of this project is to examine changes induced by losartan treatment in patients.

Lei Xu, MD, PhD, received funding from the Department of Defense (2022-2026) for the project titled, “Screening trial for pain relief in Schwannomatosis (STARFISH)”. The major goal of this grant is to study the analgesic effect of erenumab-aooe, an FDA-approved CGRP receptor inhibitor, in SWN patients with moderate-to-severe pain.

NEW FELLOWSHIPS:

Meghan O’Melia, PhD, a postdoctoral Research Fellow in the E.L. Steele Laboratories, received a National Institutes of Health NRSA Postdoctoral Fellowship (F32CA275298) from the National Cancer Institute titled “Enhanced antigen-lymphocyte interactions to improve immune checkpoint blockade in breast cancer”.



Longitudinal Trends of URM Clinical Faculty, Full Professor, Department Chairs, and Medical School Deans. The distribution of underrepresented in medicine (URM) clinical faculty, full professors, department chairs and medical school deans is shown as a percentage of the total in each group for the period from 1977 through 2019. According to the Association of American Medical Colleges definition, URM status refers to person identifying as Black, Hispanic, non-Hispanic Native Hawaiian or other Pacific Islander, or non- Hispanic American Indian or Alaska Native. Owing to low representation, the y axis extends to 20%.

Ragon Institute of MGH, MIT & Harvard

Department Report

BRUCE WALKER, MD, DIRECTOR

FACUNDO BATISTA, PHD, ASSOCIATE DIRECTOR

Overview

The mission of the Ragon Institute, established in 2009, is to harness the immune system to prevent and cure human disease. Our strategy is to combine cross-disciplinary research and flexible funding to allow the full power of scientific knowledge to be applied in achieving immunologic solutions to global medical problems. Our initial goal of making an effective global HIV vaccine is still underway, despite a recent failure to protect in a Phase 3 trial in Africa. We have also used the same platform to generate an effective COVID vaccine in collaboration with Johnson and Johnson. At the same time, we have expanded to address other diseases of global importance, including tuberculosis, influenza, Zika, malaria, autoimmunity, and cancer. With rapid progress on our new building in Kendall Square (completion in Q1 of 2024) and the establishment of an endowment, we are well positioned to make accelerated progress toward our goals.

Achievements

1. Toward an HIV Cure

Untreated HIV infection is typically associated with progressive disease development of AIDS, but in studies that began 30 years ago we identified persons who are able to control HIV spontaneously, without the need for antiviral therapy. Importantly, we have been able to link this to HIV genetics (Pereyra et al., *Science* 2010), CD8 T cell targeting of highly mutationally constrained sequences in HIV (Gaiha et al., *Science* 2019) and selective removal of integrated proviruses from genic regions of the chromosome (Jiang *Nature* 2021). Dr. Xu Yu at the Ragon Institute has now identified a second person in whom HIV cure appears to have been achieved by their own immune response (Turk et al., *Ann. Intern. Med.* 2022). Moreover, Dr. Yu and Dr. Mathias Lichterfeld at the Ragon Institute have determined that long-term antiviral therapy leads to progressive loss of intact



Artist's rendition of the new Ragon Institute building at 600 Main Street, Cambridge, planned to open in 2024.

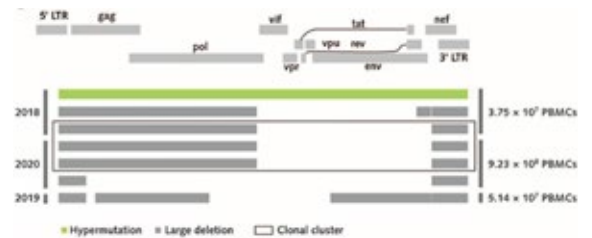
proviruses that are integrated in genic regions, which are those that are able to reinstate productive infection (*Nat. Med.* in press). They have also for the first time been able to identify the phenotype of cells that harbor replication competent proviruses (*Nature* in press), paving the way for new approaches to selectively eliminate these cells as a path to HIV cure.

2. A mechanistic understanding of booster vaccines

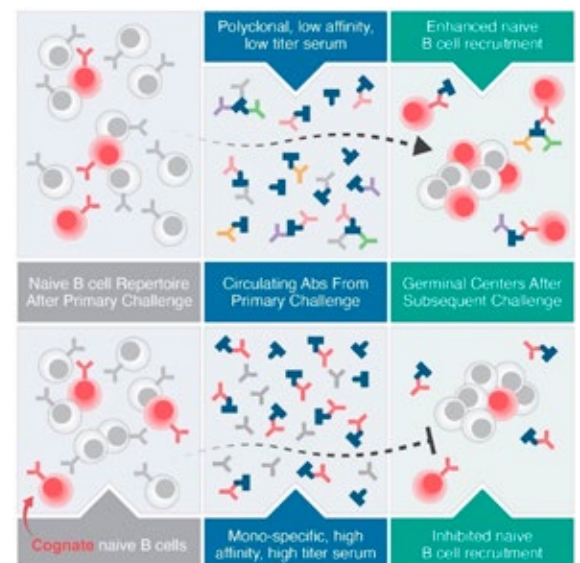
The COVID pandemic has revealed the need to boost durable, high level antibody responses, but little has been known about what leads to these responses. Ideally, secondary exposure to a pathogen either by infection or vaccination elicits a boost in immune responses by recruiting antigen-specific B cells to germinal centers (GCs), but the mechanisms governing the recruitment to GCs on secondary challenges remain unclear. In a recent paper published in *Immunity*, Dr. Facundo Batista's lab used preclinical SARS-CoV and HIV mouse models to demonstrate that the antibodies elicited during primary humoral responses shape the naive B cell recruitment to GCs during secondary exposures (Tas et al., *Immunity*, 2022). The antibodies from primary responses could either enhance or, conversely, restrict the GC participation of naive B cells: broad-binding, low-affinity, and low-titer antibodies enhanced recruitment, whereas, by contrast, the high titers of high-affinity, mono-epitope-specific antibodies attenuated cognate naive B cell recruitment. Thus, the directionality and intensity of that effect was determined by antibody concentration, affinity, and epitope specificity. Circulating antibodies can, therefore, be important determinants of antigen immunogenicity. Future vaccines may need to overcome-or could, alternatively, leverage-the effects of circulating primary antibodies on subsequent naive B cell recruitment.

3. Establishment of a clinical trials site in South Africa for bench to bedside research

In 2012 the Ragon Institute, together with collaborators at the University of KwaZulu-Natal in South Africa, established the FRESH (Females Rising through Education, Support and Health) Program in Umlazi, South Africa, a program that is a combined pathway out of poverty, HIV prevention and female empowerment initiative coupled with basic science research on HIV transmission (Dong *Sci. Trans. Med.* 2019). Nearly 85% of the more than 2000 women to have graduated from the nine-month curriculum have been placed in jobs, internships, school or have started their own businesses, while at the same time key insights related to the earliest events in hyperacute infection have been defined (Ndhlovu *Immunity* 2015; Ndhlovu et al., *Sci. Trans. Med.* 2019; Kazer et al., *Nat. Med.* 2021). This site, established at a shopping mall to prevent issues related to stigma, has now been outfitted as a clinical trials site, complete with pharmacy. Two trials are underway, one is an attempt at HIV cure through administration of broadly neutralizing antibodies and a TLR agonist in persons treated with antiretroviral therapy prior to peak viremia in hyperacute infection (see #1 above), which builds on our finding that immediate treatment of hyperacute infection leads to



Virologic characteristics of the Esperanza patient identified by Dr. Xu Yu and colleagues. Depicted are the results of sequencing of approximately one billion cells, showing no intact integrated HIV proviruses. LTR = long terminal repeat; PBMC = peripheral blood mononuclear cell.



The Batista Lab used preclinical SARS-CoV and HIV mouse models to demonstrate that the antibodies elicited during primary humoral responses shape the naive B cell recruitment to GCs during secondary exposures.



The image on the left shows the first participant in the HIV cure trial getting ready to take a TLR agonist. The image on the right is of the first participant in the vaginal microbiome modulation trial. Both photos were taken at the FRESH study site in Umlazi, South Africa.



Structure-guided design to engineer an influenza immunogen enriched for a conserved viral site (left) by the Schmidt Lab (right).

enhanced T cell immune responses (Ndhlovu et al., *Sci. Trans. Med.* 2019), rendering this cohort ideal for cure studies. The second is a trial involving modulating the vaginal microbiome from proinflammatory flora to *Lactobacillus crispatus*, which is considered the dominant “normal” vaginal flora and is associated with decreased risk of HIV transmission (Anahtar et al., *Immunity* 2016; Grosman et al., *Immunity* 2017). Other studies (Bloom et al., *Nat. Microbio.* 2022) are defining specific inhibitors of bacteria involved in development of bacterial vaginosis and HIV transmission risk that pave the way for additional interventional studies.

4. Toward a universal influenza vaccine

The Ragon Institute began with the goal of making an effective HIV vaccine and has expanded to include a focus on multiple other pathogens. Work on HIV, albeit not yet resulting in success, has provided a platform to make a Zika vaccine and a COVID vaccine, the latter now being used globally. At the same time Ragon faculty are working on other pathogens of global importance including TB, Ebola, malaria, influenza, as well as autoimmunity and cancer immunology. In the past year the Schmidt Lab at the Ragon Institute has made important progress toward the design of a universal influenza vaccine immunogen to overcome mutational escape from neutralizing antibodies. Antibodies targeting conserved, mutationally constrained epitopes are often broadly protective but remain minor components of the repertoire. In a paper published in *Cell Reports* (Caradonna et al., 2022), Dr. Aaron Schmidt and colleagues have used insights derived from their structural studies to develop an epitope-enriched immunogen presenting a higher copy number of the influenza hemagglutinin (HA) receptor-binding site (RBS) epitope relative to other B cell epitopes. Immunization in a partially humanized murine model imprinted with an H1 influenza shows H1-specific serum and >99% H1-specific B cells being RBS-directed. Single B cell analyses show a genetically restricted response that structural analysis defines as RBS-directed antibodies engaging the RBS with germline-encoded contacts. These data show how epitope enrichment expands B cell responses toward conserved epitopes and advances immunogen design approaches for next-generation viral vaccines that are currently being pursued at the Ragon Institute.



Image Award Finalist
Detail: The world on fire
Giridhar Dasegowda.MBBS
Department of Radiology

Giridhar

KEITH D. LILLEMOR, MD, CHIEF

Overview

Mission

The mission of the Department of Surgery is to advance patient care through clinical excellence, research and training the next generation of academic surgeons. Our department has one of the most broad and robust surgical research programs in the world. We foster basic, translational, and health services research activities in the full range of surgical subspecialties with a goal of advancing knowledge and improving patient care. To accomplish this mission, our investigators engage in multiple scientific disciplines to solve everyday challenges in clinical surgery. We serve a diverse group of patients, and our research enterprise is similarly diverse, being distributed among multiple Centers and clinical Divisions within the Department of Surgery and across disciplines throughout Mass General. We believe that progress is made at the interface of disciplines and that we thrive on working with colleagues outside of surgery to solve problems we treat in the operating room.

Focus and Strategic Priorities

In her new role as Vice Chair of Research for the MGH Department of Surgery (DOS), **Genevieve M. Boland, MD, PhD**, is creating a robust research infrastructure to support the academic mission of members of the DOS including trainees, clinical faculty, and non-clinical faculty. In addition, her goals are to create protections and opportunities for research trainees in non-clinical tracks and expand opportunities for exposure to academic surgery in students underrepresented in medicine (URIM). The goal is to create a diverse, vibrant, interactive, and innovative academic program to support the academic development of the entire surgical community (trainees, junior faculty, senior faculty, and leadership). Updates include a framework across the department with streamlined and accessible resources, creation of opportunities for community building and engagement, and enhancements to encourage collaboration both within the department of surgery and with affiliated institutions, network partners, and national programs. Ultimately, our goals are aligned with MGB priorities to support cutting-edge research, train the next generation of surgeons and scientists, and increase end-user satisfaction and success with academic productivity while improving equity and transparency

Achievements

You have neuronal stem cells in your subcutaneous fat

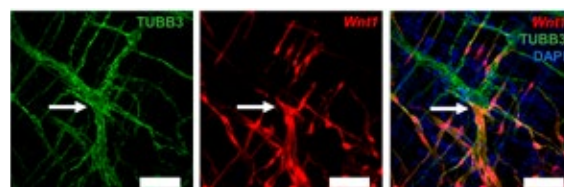
The concept that cells from fat tissue can be isolated and induced to acquire the traits of neurons and glia has been known for 20 years, but the identity of this neurogenic stem cell population has remained elusive. Diseases affecting the nervous system are notoriously difficult to treat, necessitating the development of new therapies for this urgent unmet clinical need. Neural stem cell (NSC) regenerative

therapy is a promising approach to alleviating diseases of the nervous system by replacing damaged neurons or by producing neurotrophic factors that protect them or stimulate their repair. This approach requires an autologous source of NSC. The accessibility and ease of isolation make subcutaneous fat tissue a favorable candidate over other potential NSC sources. This has led to numerous preclinical studies and clinical trials utilizing fat-derived stem cells for diseases of the peripheral and central nervous system. Thus far, clinical success has been mixed, largely due to a lack of biological understanding of the therapeutically active cell population within the assortment of fat-derived cells that are administered.

Results from a study by **Rhian Stavelly, PhD**, a junior investigator in the Pediatric Surgery Research Labs and in the laboratory of **Allan Goldstein, MD**, identified a specific stem cell population in the fat that possesses the ability to differentiate efficiently into neurons and glia, offering great therapeutic potential. This population was observed to be derived from Schwann cells that reside along nerve fibers that innervate and travel through the fat. Utilizing this biological insight, the authors developed methods to enrich and purify this neurogenic stem cell population, which they call subcutaneous adipose tissue-derived neural stem cells (SAT-NSCs), from both mouse and human adipose. The therapeutic potential of SAT-NSCs was examined in preclinical models of neurointestinal diseases, including gastroparesis and Hirschsprung disease. SAT-NSCs integrated in the gastrointestinal tract in mice, migrated, differentiated into neurons and glial cells, and restored neuromuscular function in these mouse models. The successful isolation, expansion, purification, and transplantation of mouse and human SAT-NSCs represents a major advancement in the field of regenerative medicine.

Objective, Point of Care Coagulation Testing to Guide Thromboprophylaxis Post Revascularization

Peripheral artery disease (PAD), caused by atherosclerotic chronic arterial occlusion of lower extremities, is endemic in elderly populations. PAD prevalence increases with age and often requires extremity artery bypass or endovascular stenting to increase limb blood perfusion. Thrombosis of these bypass grafts or stents that results in reduced blood flow to lower extremities is the leading cause of amputation in elderly patients. The incidence of early graft/stent thrombosis after extremity revascularization is 17%, and up to 50% of elderly patients (≥ 60 years) die within 1 year of amputation. Therefore, accurate identification of elderly patients who are at high risk of graft/stent thrombosis is critical to inform targeted thromboprophylaxis interventions that can prevent graft/stent loss and subsequent amputation, but currently no such strategy exists. Ascertaining the longitudinal, varied impact of each thrombotic risk factor on a coagulation profile is currently not feasible because there are a myriad of extrinsic/intrinsic factors that interact to impact coagulation variably in individual elderly patients. Furthermore, hypercoagulability in elderly patients can be transient. The current strategy to prevent thrombosis in elderly patients relies on a standard “one size fits all” antiplatelet/



Representative images of the integration between subcutaneous adipose tissue-derived neural stem cells (SAT-NSCs), expressing Wnt1-tdTomato, and the endogenous enteric ganglia (arrows), expressing beta-Tubulin (TUBB3), after transplantation to the colon. Scale bars, 50 μ m.

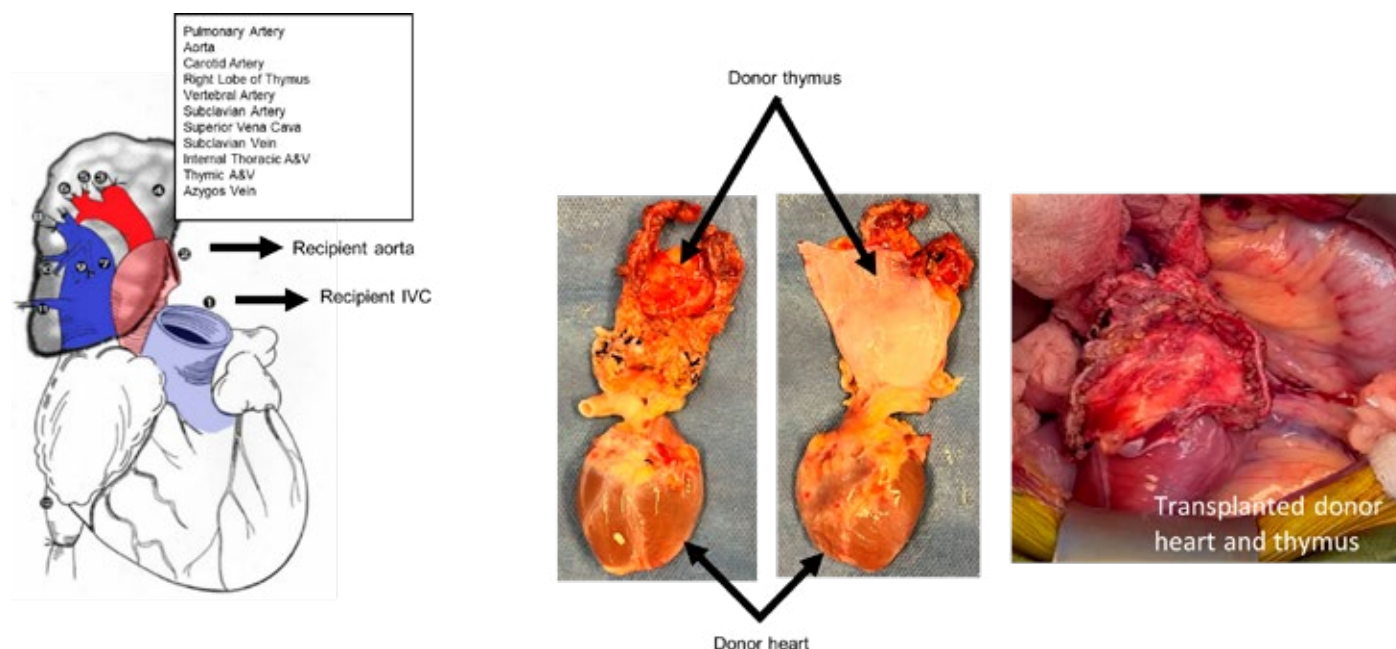
anticoagulation approach, which is inappropriate and dangerous given the dual high risks of life-threatening thrombotic and hemorrhagic complications with under- or over-treatment.

Building on previous coagulation assay data, **Anahita Dua, MD**, and collaborators have developed an objective, precise algorithm that accounts for all the factors impacting an individual patients coagulation profile at a given timepoint which can be used to 1) predict which patients are at risk of thrombosis and 2) mitigate that thrombotic risk by dosing antiplatelet/anticoagulation medication to identified platelet inhibition cut-points thereby keeping the patient in a “coagulation sweet spot.” Data from their prospective study of 144 patients showed that the novel strategy of combining longitudinal point-of-care coagulation assays, whole blood thromboelastography (TEG) and platelet mapping (PM), identified individualized mechanisms of hypercoagulability prior to a thrombotic event, providing ample opportunity for targeted intervention with antiplatelet medication. They identified that in patients with PAD, maintaining a 30.2% platelet inhibition cut-point decreased the risk of graft/stent thrombosis by 50% in the 6 months post revascularization procedure. For every 1% increase in platelet inhibition there was a 5% decrease in the hazard of experiencing a thrombotic event. They built upon this research by publishing further data characterizing the clinical and Platelet Mapping profiles of female and male patients undergoing lower extremity revascularization as it is known that women have higher amputation rates than men even with lower co-morbidities. In their study, Dua and colleagues documented that Platelet reactivity was higher across clinical phases and antiplatelet regimens for females compared to males indicated that increased rate of graft thrombosis and subsequent amputation in females may be mitigated by increasing antiplatelet medication dosages. Dua and team also published data in the Journal of Vascular Surgery detailing the significant variability in the response to both mono- and dual antiplatelet therapy in PAD patients undergoing lower extremity revascularization once again supporting the notion that an objective, point of care test which can confirm platelet inhibition is adequately achieved may be the answer to the current imprecise antiplatelet/anticoagulation administration post revascularization. Finally, using the point of care coagulation testing, this team was also the first to provide a quantitative link between prothrombotic viscoelastic coagulation profiles with the development of infection/dehiscence in PAD patients. Cut-points of > 33.2 mm MA, > 46.6% platelet aggregation, or < 55.8% platelet inhibition were associated with infection which could be predicted 19 days prior to clinically detection providing time for the physician to potentially intervene and prevent clinical sequelae. To further this research, the team was recently awarded an National Institute of Health (NIH) R21 exploratory grant to further develop the predictive model and form the basis of an ultimate randomized control trial.

Achieving Heart Allograft Tolerance via *en bloc* Heart and Thymus Cotransplantation in Nonhuman Primates

A fundamental and enduring challenge in human organ transplantation is preventing the recipient's immune system from rejecting the donor organ. In order to preserve function of the transplanted organ, these patients require lifelong immunosuppression. While this protects their transplant, it simultaneously increases their risk of infection and cancer, in addition to other chronic medical issues. Eliminating the need for chronic immunosuppression would dramatically benefit patient and allograft survival. Several groups in the Center for Transplantation Sciences are working towards this goal. By combining donor bone marrow transplantation with solid organ transplantation, **Joren Madsen, MD, DPhil**, and his colleagues in the Center for Transplantation sciences have induced long term tolerance of cardiac allografts in nonhuman primates (NHPs), with complete withdrawal of immunosuppression. However, the development of heart allograft tolerance was dependent on cotransplantation of a kidney from the same donor. Interestingly, some organs are prone to achieving tolerance (livers and kidneys), while others are not (heart and lungs). Preliminary work by Dr. Madsen's lab has found that this difference could be related to the development and expansion (or lack thereof) of regulatory T cells, which protect the organ from the deleterious effects of the recipient immune system.

Because cotransplantation of a kidney together with every heart is untenable in humans (due to shortages in organ availability), another approach is needed to translate this into a clinically relevant protocol. To this end, Dr. Madsen's lab has started investigating *en bloc* heart and thymus cotransplantation in NHPs as an alternative to heart

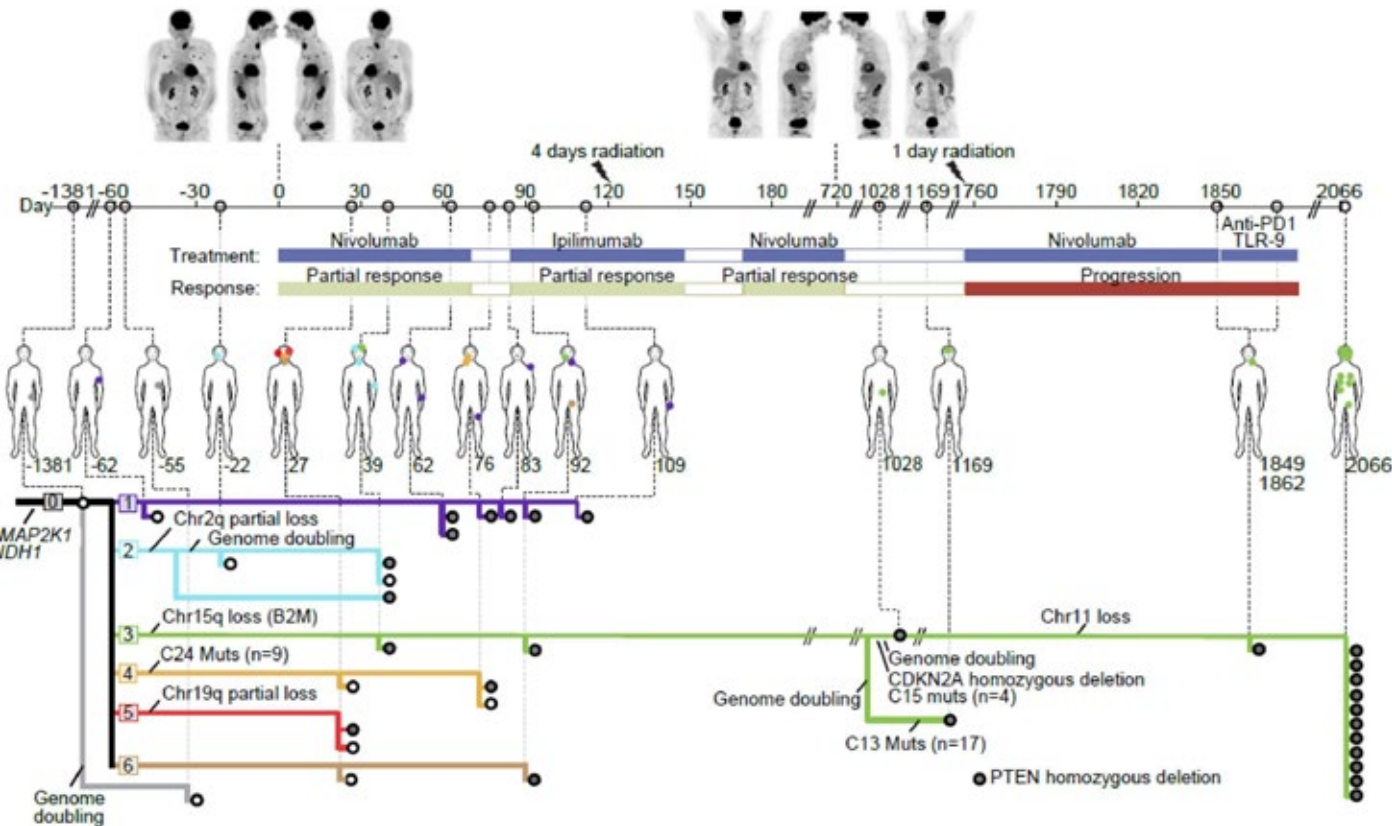


Heterotopic heart *en bloc* thymus transplantation technique.

and kidney cotransplantation to achieve durable tolerance. In this model, the thymus is harvested together with the heart, preserving its blood supply, and transplanted into the recipient as a composite graft (Figure 1). The thymus was chosen as a substitute for the kidney because it contains the largest amount of regulatory T cells in the body and has the ability to eliminate deleterious T cells that might attack donor cells while simultaneously promoting the development of regulatory T cells specific to donor antigens. A similar protocol of cotransplanted vascularized thymus has been successfully implemented in swine. This new experiment in NHPs represents the next step towards developing a protocol for clinical application in humans.

How does cancer evade the body and lead to treatment resistance?

Despite immense progress in harnessing the patient’s own immune system to fight cancer, there remains a lack of insight into mechanisms of resistance that emerge over time. By examining the genomic, transcriptomic, and proteomic changes occurring within one individual patient over the course of 9 years, **Genevieve Boland, MD, PhD**, and her team described tumor evolution and immune editing that occurred within a patient with metastatic melanoma treated with



Integrated clinical course and phylogenetic characterization of longitudinal tumor biopsies.

immunotherapy who initially responded to therapy, but eventually succumbed of their disease.

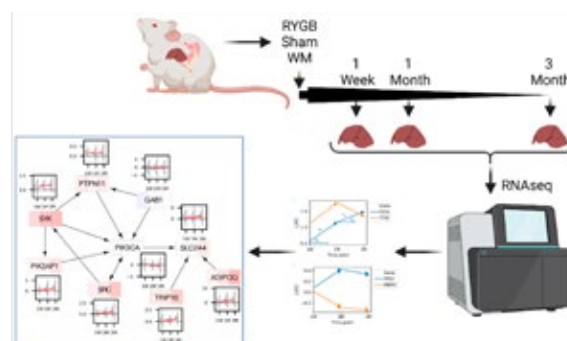
The study builds off work done in collaboration with **Dr. Boland and David Fisher, MD, PhD**, Chair of Dermatology, examining melanocyte lineage-specific immune recognition which identified a less differentiated tumor program (similar to neural crest cells) as a potential contributor to immunotherapy resistance. Current work is ongoing to determine how certain tumor subpopulations modulate the tumor microenvironment to create a more immunosuppressive milieu, thereby allowing therapy resistance and disease progression.

Learning from bariatric surgery to develop novel therapies for metabolic syndrome

The discovery of novel druggable targets for metabolic diseases, such as type 2 diabetes, obesity, and non-alcoholic fatty liver disease (NAFLD), has recently been fueled by the application of multi-omics technology to elucidate metabolic and signaling mechanisms of disease progression and amelioration. Roux-en-Y Gastric Bypass (RYGB) surgery, along with sleeve gastrectomy, is a potent and long-term treatment available for obesity, and lead to significant improvement in a large number of obesity-associated sequelae, including complete resolution of NAFLD. Therefore, understanding the molecular mechanisms through which RYGB rewires liver function may lead to the identification of novel therapeutic targets for metabolic syndrome driven indications.

Time-series omics data are particularly useful for studying the dynamic behavior of biological systems and provide novel insight into disease progression and amelioration at the molecular level. However, conventional omics analysis workflows often fall short for these data because they implicitly rely on pair-wise statistical comparisons either between two experimental conditions at a single time-point, or between two time-points under one experimental condition, neither of which effectively capture the underlying molecular mechanisms that span multiple timescales. To address this, **Nima Saeidi, PhD**, and his team recently developed a novel graph network-based analysis workflow designed to identify modules enriched with biomolecules that share common dynamic profiles, where the network is constructed from all known biological interactions available through the KEGG resource (<https://pubmed.ncbi.nlm.nih.gov/35448506/>).

They further applied this methodology to time-series RNAseq transcriptomics data collected on rodent liver samples following RYGB to elucidate the molecular pathways involved in the improvement of as NAFLD. The team demonstrate that this approach leads to the discovery of less intuitive network modules that may have been overlooked with conventional PEA techniques, providing a framework for identifying novel drug targets for NAFLD and other metabolic syndrome co-morbidities.



Schematic Representation of the Approach for Developing a Computational Biology Platform to Analyze Dynamic Omics Data

MICHAEL L. BLUTE, SR., MD, CHIEF

Overview

The research program in the Department of Urology at the MGH involves a wide breadth of funded and unfunded endeavors investigating a range of topics across the field of Urology. Our faculty are involved in basic, translational and clinical research activities with grants from federal funding sources, foundations and industry partners. Our collaborative relationships with our colleagues in Pathology, Radiology, Medical Oncology and Radiation Oncology help to facilitate our team approach to urologic research. We also maximize our collaborative research efforts with our colleagues across the greater Boston academic community, including investigators across the Harvard institutions and MIT. Our residents and Urologic Oncology fellows are actively involved in our research endeavors with dedicated research time during their training.

Current Research Activity and Infrastructure

The department is committed to advancing urologic research through impactful clinical and translational research in urologic oncology, nephrolithiasis, pediatric urology and benign urologic disease. The department supports research efforts that focus on health sciences and patient outcomes, advances in surgical technique and translational research.

Our active dedicated research laboratories include the Urologic Clinical Outcomes and Translational Research Laboratory, under the direction of Adam Feldman, MD, MPH, the Urology-Pathology Research Laboratory, directed by Chin-Lee Wu, MD, PhD, and the Urologic Oncology Translational research lab under the direction of Keyan Salari, MD, PhD. In addition to active clinical databases in urologic cancers, nephrolithiasis and benign prostatic disease, we have developed biospecimen banks, including a genitourinary tumor bank and a urine specimen bank in prostate and bladder cancers. Tissue, blood and urine biospecimen banks in renal cell carcinoma are also available via our collaboration with our colleagues in medical oncology. We actively collaborate as funded co-investigators with our clinical and research colleagues at MGH and DFHCC, including David Miyamoto, MD, PhD of Radiation Oncology at MGH, Leo Cheng, PhD in the AA Martinos Center for Biomedical Imaging and Eli Van Allen, MD, PhD of Medical Oncology at DFHCC.

Achievements

Notable Research Awards:

Dr. Keyan Salari continues his work as the recipient of the American Urological Association Research Scholar Award as well as the Prostate Cancer Foundation Young Investigator Award, both for his translational research efforts investigating the Role of Homologous Recombination Deficiency and Immune Response in Early-Stage Prostate Cancer. These are both mentored career development

awards, under the mentorship of Dr. Adam Feldman here at MGH and Dr. Eli Van Allen at DFHCC.

Urologic oncology fellow, Dr. Affan Zafar obtained a mentored research award from the Mass General Brigham Office of Graduate Medical Education (GME) Center of Expertise (COE) in Healthcare Quality and Patient Safety to investigate quality measures in patients undergoing cystoscopic resection of bladder tumors. This research is under the mentorship of Dr. Adam Feldman.

Publications in 2022

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Early experience with UGN-101 for the treatment of upper tract urothelial cancer - A multicenter evaluation of practice patterns and outcomes.

Woldu SL, Labbate C, Murray KS, Rose K, Sexton W, Tachibana I, Kaimakliotis H, Jacob J, Dickstein R, Linehan J, Nieder A, Bjurlin MA, Humphreys M, Ghodoussipour S, Quek ML, O'Donnell M, Eisner BH, Feldman AS, Matin SF, Lotan Y.

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PMID: 36424224

Progress and Promise of Biomarker Discovery and Development in Urologic Disease.

Feldman AS.

Urol Clin North Am. 2023 Feb;50(1)

PMID: 36424088

Designing a quality assurance process for quality control of nuclear magnetic resonance metabolomics studies of human blood.

Muti IH, Gonzalez Sanchez-Dahl M, Zhong AB, Weng J, Füzesi MV, Kivisäkk P, Hyman BT, Arnold SE, Feldman AS, Mercaldo ND, Cheng LL.

NMR Biomed. 2022 Nov 4:e4868.

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Detection of clinically significant prostate cancer by transperineal multiparametric magnetic resonance imaging-ultrasound fusion targeted prostate biopsy in smaller prostates.

Dahl DM, Kim MM, Wu S, Lin SX, Crotty RK, Cornejo KM, Harisinghani MG, Feldman AS, Wu CL.

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PMID: 36008257

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Steiner A, Schmidt SA, Fellmann CS, Nowak J, Wu CL, Feldman AS, Beer M, Cheng LL.

Cancers (Basel). 2022 Apr 26;14(9):2162.

PMID: 35565290

Active surveillance for intermediate-risk prostate cancer.

Nayan M, Carvalho FLF, Feldman AS.

World J Urol. 2022 Jan;40(1):79-86. Epub 2022 Jan 19.

PMID: 35044491

Integrative clinical and molecular characterization of translocation renal cell carcinoma.

Bakouny Z, Sadagopan A, Ravi P, Metaferia NY, Li J, AbuHammad S, Tang S, Denize T, Garner ER, Gao X, Braun DA, Hirsch L, Steinharter JA, Bouchard G, Walton E, West D, Labaki C, Dudani S, Gan CL, Sethunath V, Carvalho FLF, Imamovic A, Ricker C, Vokes NI, Nyman J, Berchuck JE, Park J, Hirsch MS, Haq R, Mary Lee GS, McGregor BA, Chang SL, Feldman AS, Wu CJ, McDermott DF, Heng DY, Signoretti S, Van Allen EM, Choueiri TK, Viswanathan SR.

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Combination MRI-targeted and systematic prostate biopsy may overestimate gleason grade on final surgical pathology and impact risk stratification.

Yu A, Yamany T, Mojtahed A, Hanna N, Nicaise E, Harisinghani M, Wu CL, Dahl DM, Wszolek M, Blute ML, Feldman AS.

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PMID: 34544650

A machine learning approach to predict progression on active surveillance for prostate cancer.

Nayan M, Salari K, Bozzo A, Ganglberger W, Lu G, Carvalho F, Gusev A, Schneider A, Westover BM, Feldman AS.

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urolonc.2021.08.007. Epub 2021 Aug 29.

PMID: 34465541

Transperineal multiparametric magnetic resonance imaging-ultrasound fusion-targeted prostate biopsy combined with standard template improves perineural invasion detection.

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PMID: 34461132

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PMID: 33642229

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PMID: 36180422

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Prostate. 2022 Apr;82(5):584-597.

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Tokuyama N, Saito A, Muraoka R, Matsubara S, Hashimoto T, Satake N, Matsubayashi J, Nagao T, Mirza AH, Graf HP, Cosatto E, Wu CL, Kuroda M, Ohno Y.

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PMID: 34716417

Benign Urologic Disease

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Image Award Finalist
an abstract depiction of the lab space i spent the summer in
Aarushi Gandhi
Student Center for Genomic Medicine

