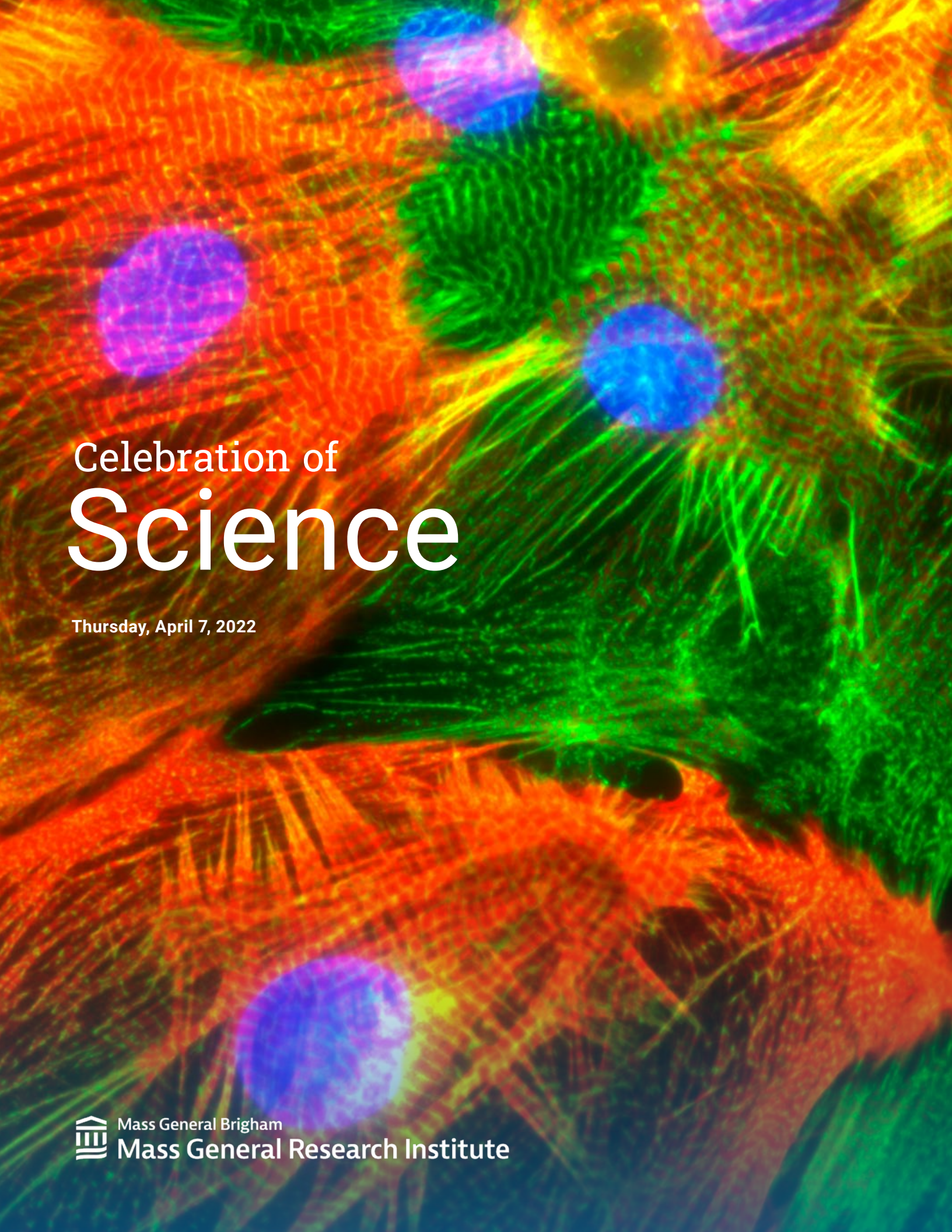

Celebration of Science

Thursday, April 7, 2022

Mass General Brigham
Mass General Research Institute


MASSACHUSETTS GENERAL HOSPITAL
ENTRANCE

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Front cover photo thanks to:
Guoping Li, PhD, Cardiovascular Research Center
"Human Heart Cells from iPSCs"

Martin Research Prizes

2022 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

Nir Hacohen, PhD
Professor, Department of Medicine / Cancer Center

Spatially Organized Multicellular Immune Hubs in Human Colorectal Cancer

Human tumors consist not just of cancer cells, but also immune cells, blood vessels, and other supportive cells. The interactions among these cells determine whether a tumor will shrink or grow, and importantly, whether the neighboring immune cells are able to find and eliminate the tumor. Because of the complexity of the tumor, we developed a more comprehensive approach to discover human colorectal cancers, looking at all the cells and genes present in the tumor and their patterns of interaction. Since human colorectal cancer is one of the most common and deadly forms of cancer, we set out to understand why 95% of colorectal tumors do not respond to modern immunotherapies. We collected tumor samples from 61 patients who generously donated their resected tumors for research, and then measured the expression of all genes in one third of a million cells isolated from these tumors. Our results opened up a new vista on cancers in general, and allowed us to discover that a specific group of cell types show coordinated expression of their genes, implying they communicate with each other. We called these groups of communicating cells ‘hubs” and predicted that they would be located next to each other to allow them to carry out coordinated activities, most importantly, the elimination of cancer cells. Using a leading-edge microscopy method, we visualized the location of these cells, and found that immune cells that recognize and kill tumors form a hub with several other immune cell types and tumor cells, but only in the type of colorectal cancer that is responsive to immunotherapy. These results uncover the basic organization of the anti-tumor immune response in the tumor, provide a way of explaining who responds to immunotherapy, and suggest new strategies for harnessing the immune system to kill cancers.

MARTIN PRIZE FOR CLINICAL RESEARCH

Genevieve Boland, MD, PhD
Associate Professor, Department of Surgery

Evolution of Delayed Resistance to Immunotherapy in a Melanoma Responder

Despite initial responses, most melanoma patients develop resistance to immune checkpoint blockade (ICB). To understand the evolution of resistance, we studied 37 tumor samples over 9 years from a patient with metastatic melanoma with complete clinical response to ICB followed by delayed recurrence and death. Genetic analysis of his tumors revealed co-evolution of seven lineages with multiple convergent, but independent resistance-associated alterations. All recurrent tumors emerged from a genetic tumor lineage characterized by loss of chromosome 15q, with post-treatment tumors acquiring additional genetic events contributing to resistance. Tumor RNA analysis and highly multiplexed imaging of the tumors revealed differences in immune composition among different genetic lineages. Imaging revealed a specific cellular architecture in a subset of tumor cells suggesting they play a role in immune modulation. Tumors acquired at the time of the patient’s death demonstrated distinct tumor patterns depending upon the anatomic location, suggesting tumor cells play different roles in different tumor microenvironments. Broadly, this study establishes a high-resolution map of the evolutionary dynamics of resistance to ICB, characterizes a de-differentiated tumor population in melanoma immunotherapy resistance, and describes site-specific differences in tumor-immune interactions via longitudinal analysis of a patient with melanoma with an unusual clinical course.

MARTIN PRIZE FOR POPULATION HEALTH SCIENCES RESEARCH

Jacqueline Seiglie, MD, MSc
Instructor in Medicine,
Endocrinology Unit
MGH Center for Global Health

Body-mass Index and Diabetes Risk in 57 Low- and Middle-income Countries: A Cross-Sectional Study of Nationally Representative, Individual-level Data in 685 616 Adults

Diabetes is an important global public health problem that is growing most rapidly in low- and middle-income countries (LMICs). Body mass index (BMI) is the most widely used clinical tool to diagnose obesity, a key risk factor for diabetes, but studies that have informed BMI thresholds for diabetes screening have been largely conducted in high-income countries, with relatively few contributions from LMICs. In this study, we characterized the relationship between BMI and diabetes risk across 57 LMICs, totaling >685K participants and spanning 6 world regions. We found substantial variability in the association between BMI and diabetes risk across world regions as well as between women and men. We also found that the risk of diabetes emerged at younger ages and at lower BMI cutoffs in some regions than those currently recommended in global diabetes screening guidelines. Overall, our study highlights geographic variation in the association between BMI and diabetes risk, which can help inform context-specific guidelines to improve diabetes screening in LMICs.

Howard M. Goodman Fellowship

2022 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.

Andrea Edlow, MD, MSc
Assistant Professor of
Obstetrics, Gynecology,
and Reproductive Biology

Cellular Models of Fetal Neurodevelopment in Maternal Immune Activation

Activation of the mother's immune system by chronic conditions such as obesity, and acute conditions such as bacterial or viral infection, has been linked to autism spectrum disorder, attention deficit hyperactivity disorder, anxiety, depression, and cognitive deficits in children, but the underlying mechanisms remain unclear. Microglia, the immune cells of the brain, may play a role, but these cells are not accessible in ongoing human pregnancy and after birth. We breach this gap by examining a population of immune cells in the placenta (Hofbauer cells) that have the same embryonic origin as brain microglia. We will also examine fetal immune cells present in umbilical cord blood. We will evaluate the impact of two maternal exposures, obesity and COVID-19 infection, on activation of these three cell types using both mouse models and human samples. These experiments will permit us to determine whether placental and umbilical cord blood immune cells can provide information about fetal brain immune function. If these more accessible cell types can help identify children at risk for adverse neurodevelopmental outcomes, they can also aid in the development of targeted, personalized interventions to reduce an individual child's risk.

Kamila Naxerova, PhD
Assistant Professor of Radiology,
Center for Systems Biology

Defining the Evolutionary Characteristics of Human Metastasis Across Space and Time

The most pernicious aspect of cancer is that it can sometimes spread to vital organs like the lungs, the liver or the brain. This process is called metastasis and is the cause of death in most cancer patients. Although metastasis plays such a big role in cancer progression, it is surprisingly poorly understood. For example, it is not known whether cancer cells must weather unique challenges when attempting to colonize different organs. We have collected valuable data from colorectal cancer patients that indicate that each organ may present its own "rulebook" to arriving cancer cells and that this rulebook may furthermore change over time, as the disease progresses. Consequently, the genetic composition of metastases in different organs is distinct, with possible implications for how these tumors respond to treatment. In the proposed research, we are planning to investigate the genetic properties of metastases found in different organs and at different progression stages. We hope that our results will eventually lead to better treatments for patients with metastatic cancer.

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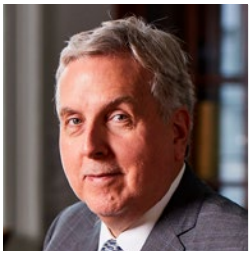

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*Chair Appointment, ‡ Chiefs Council

Massachusetts General Research Institute

Executive Report

THANK YOU, PETER, FOR 18 YEARS OF EXTRAORDINARY LEADERSHIP!

The growth of the MGH research enterprise has continued unabated for more than two decades, growing over 18% this past year alone. And no one deserves more credit for that growth than Dr. Peter Slavin, who stepped down this past year after serving for 18 years as President. During his tenure, the MGH research enterprise experienced remarkable expansion in both size and breadth. Total expenditures increased from $400M in FY03 to over $1B in FY21, with a concurrent increase in principal investigators from 1,100 to over 2,000. The opening of the Simches building, the creation and growth of our five Thematic Centers, the Ragon Institute, the Biobank, the Translational Research Center, and the Mass General Research Institute (MGRI) itself, with a new Scientific Director and Division of Clinical Research, all occurred during Peter's tenure. Their realization is a testament to his leadership, to his understanding that biomedical research drives clinical innovation, and to his unwavering commitment to support that research. This support is perhaps best exemplified by the substantial resources Peter provided to create and sustain three major programs: 1) ECOR's interim support fund (ISF), which has provided over $63M of bridge funding to PI's since its founding in 2006; 2) The philanthropy-driven MGH Research Scholars program, which has provided $500,000 of unrestricted research funding to over 70 'rising star' faculty since its inception in 2011; 3) Research Institute Endowed Chairs, six of which have been established to date to support our most innovative and productive senior faculty.

On behalf of the entire Mass General research community and the Research Institute that will remain a cornerstone of your legacy, thank you, Peter, for all you have done.

A Year of Leadership Transitions

Welcome, David! In September 2021, David Brown, MD, Chair of the Department of Emergency Medicine at MGH and Interim President of Cooley Dickinson Health Care, was named to succeed Peter Slavin as President of MGH. David is a strong supporter of and advocate for the Mass General Research Institute. As Chief of Emergency Medicine, David built his department into a national leader in emergency medicine and disaster planning research. Since becoming President, he has become a student of all things research at MGH and has met with (and is still meeting with) research leaders to get their personal perspectives on the challenges and opportunities facing the research enterprise.

Thank you, Maurizio, and welcome, Judy! In January 2022, Maurizio Fava, MD, stepped down as Director of the MGH Division of Clinical Research (DCR) after becoming Chief of Psychiatry and being named as the new Vice Chair of ECOR. We thank Maurizio for his extraordinary leadership in growing the DCR over the past eight years. Maurizio is succeeded by Judy Hung, MD, Director of the Echocardiography Section within the Division of Cardiology, Director of the Trial Innovation Unit within the DCR, and a Professor of Medicine at Harvard Medical School. Judy's near-term goals are to leverage data and data analytics to better inform and improve support for the clinical research and trial processes.

Thank you, Jerry, and welcome back, Jeanine! This past year, Jerry Rosenbaum, MD, Psychiatrist-in-Chief Emeritus and Director of the Center for Anxiety and Traumatic Stress Disorders and the Center for Neuroscience of Psychedelics, stepped down after two years as Chair of the MGH Awards and Honors Committee. Jerry is succeeded by Jeanine Wiener-Kronish, MD. Dr. Wiener-Kronish is the Henry Isaiah Dorr Distinguished Professor of Research and Teaching in Anesthetics and previously served as Chief of Anesthesia, Critical Care, and Pain Medicine at MGH for many years.

In memoriam, Warren Zapol, MD. In December 2021, MGH lost an extraordinary researcher, leader, colleague, and friend with the passing of Dr. Warren Zapol. Dr. Zapol, our IACUC Chair, dedicated his career to biomedical research and was committed to the ethical use of animals and the protection of animal welfare while pursuing ground-breaking medical advances. He is succeeded as IACUC Chair by James S. Allan, MD, Associate Professor of Surgery and former IACUC Associate Vice-Chair.

MGB Research Transitions. This past year, we also celebrated the service of Mary Mitchell, who retired as the MGB Chief Research Compliance Officer, and Scott Weiss, MD, who stepped down as Director of MGB Personalized Medicine. They are succeeded, respectively, by Heather Cosier, joining MGB from Tufts, and Elizabeth Karlson, MD, from BWH. Welcome, Heather and Beth, and thank you, Mary and Scott, for decades of visionary leadership!

Another COVID Surge...

As I draft this report in early January 2022, the hospital, country, and world continue to battle another COVID surge, this time fueled by the emerging omicron variant. Upwards of 20% of our research and research support staff have been (and are currently being) impacted by either coming down with COVID or being quarantined because of exposure to it. Supply chain production and distribution

issues, coupled with the unavailability of many service and support personnel, have impeded progress of our research programs. Still, our research enterprise grew again to another record with the single largest growth (over 18%) in any single year.

We have been able to successfully sustain our research programs due in large part to the strict adherence to the universal control guidance from Infection Control leadership, as well as the diligent efforts of our 200+ onsite COVID Safety Officers and our building and animal support staff.

As we reflect on another challenging year, let us pause briefly to appreciate all that our research community has accomplished. Thank you for all you have done for the hospital, for keeping each other safe, and for sustaining our extraordinary research enterprise.

...Fails to Curb Record-Breaking Growth

Research revenues for FY21 grew to $1.197B, an $184M (18.1%) increase from FY20. Funding from the National Institutes of Health (NIH) in FY21 grew 9% to over $600M and, notably, funding from industry jumped 35% to $91M, up from $71M in 2020. MGH jumped from the #12 to #8 spot in NIH funding for all institutions and continued its 20+ year run as the #1 ranked independent hospital. The percentage of funding awarded to MGH from the entire NIH extramural budget (our market share) grew to 1.8%, up from 1.6% the previous fiscal year. MGH also accounts for 56% of all research activity across the entire MGB system.

A primary reason for this year's extraordinary growth was the increase in submitted proposals, up 5.5% over last year to 4,971, coupled with a sustained high success rate of 27%, well over the 21% national average. Early indicators for 2022 show continued growth and a strong performance in all funding sectors.

Research Growth Stresses Existing Resources

Space. Last year's 18.1% research program growth has continued to stress our existing research space. While remaining constant at 1.31M NASF (Net Assignable Square Feet), its use density increased 13% this past year. Current outstanding space requests total almost 77,000 NASF (41,375 NASF for wet space and 32,570 NASF for dry space). We anticipate accommodating these requests through a consolidation of dry research space that has accompanied the hybrid and remote work initiatives across the hospital along with conversion of a significant amount of administrative space at MGB headquarters at Assembly Row to dry research. Wet research space needs will need to be accommodated by conversion of existing dry space within wet areas to wet spaces.

Animal Care Program. The 18.1% growth in research in 2021 was accompanied by a concurrent growth in our animal census, stressing our already overcrowded facilities. Adding to this stress, the January 2022 COVID surge has hit our animal care staff especially hard, with over 20% out with COVID or quarantining due to COVID exposure. As of the writing of this report, we have activated our emergency response plan, which calls for a reduction in animal census and request for volunteer animal care workers from our animal research community. To alleviate the stress from growth long term, plans are being developed to move animal breeding and all cage washing operations offsite to a central facility, freeing up much-needed space for onsite animal housing and procedure space.

Recruiting/Retaining Research Support. Our frontline research workers such as lab technicians and clinical study coordinators have always been targets for recruitment by nearby pharma and biotech companies, companies that can afford to offer significantly higher wages than our pay scales. While we have always recruited new graduates aggressively with some success, continued growth in pharma and biotech has made it increasingly difficult for us to find and retain our frontline staff. And the recent rapid growth of our research programs has resulted in even more unfilled job openings. To address this problem, which is being felt across the entire MGB system, HR agreed to raise starting salaries significantly, in some cases as much as 20%, starting January 2022, the time at which this report is being written. We are monitoring our recruiting success rate and are optimistic it will improve.

Highlights of MGRI accomplishments/milestones in 2021

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 2021. These include:

- The committees reviewing interim and internal support provided by ECOR (the Executive Committee On Research) reviewed over 800 applications. They awarded 115 interim support grants, 22 postdoc fellowships, 8 Claflin Distinguished Scholar Awards (that facilitate academic careers of women in science), and 6 Physician and/or Scientist Development Awards (to support the development of research investigators who are considered underrepresented in medicine).

Massachusetts General Research Institute

Executive Report

- The Office of the (MGRI) Scientific Director (OSD), working with Development, added 5 Research Scholars in 2021, bringing total to 70, and is currently preparing to announce the class of 2022, which will bring the Research Scholar total to 75. The OSD and Development also conducted a successful Virtual Lab Day in September 2021. It featured a video virtual tour of scholar research programs and included an informative panel on "Research in the Age of COVID."
- The OSD made significant progress in promoting the MGRI in 2021, with over 300 high-impact papers featured in their Snapshot of Science publication. Their Bench Press blog won three awards from local and national healthcare organizations. Their Social media outlets—Facebook, Twitter, and Instagram—showed continued growth in posts and followers, and they hosted three virtual Science Slams: in February (9 "slammers" and 107 attendees), June (9 "slammers" and 142 attendees) and October (11 "slammers" and 52 attendees). OSD also started a new series in 2021 called QUIIPS ("Quick Interviews with Interesting People"), featuring candid conversations between our researchers. They hosted three QUIPPS events, in March (63 attendees), May (51 attendees) and September (44 attendees).
- The OSD Strategic Alliance group continued its highly successful Bridging Academia and Industry educational program. In 2021, they trained 20 faculty from across 13 departments and thematic research centers, and engaged 42 teaching faculty (22 academia, 20 industry).
- The Division of Clinical Research (DCR) focused much of its developmental efforts in 2021 on its Center for Clinical Research Education (CCRE). A detailed report on CCRE is given below. It includes a dramatic expansion of course offerings and data analytics. These were enabled in July 2021 following conversion from the Learn and Healthstream platforms to the OpenSources platform. CCRE's switch to virtual offerings and a fully remote virtual team due to COVID resulted in dramatic improvements in course quality, quantity, and attendance. As a result, CCRE has become the team of choice to work with on educational offerings for other research-focused groups within MGH and MGB.
- The MGB BioBank continued its steady growth in 2021 with over 130,000 patients now consented and over 56,000 genotyped or sequenced. Over 400 studies and $360M in research activities have been supported to date.
- While the Translational and Clinical Research Centers (TCRC) remained focused in 2021 on continuing COVID-19 related projects that were initiated in 2020, they were delighted to see a significant re-engagement with industry sponsors on a host of non-COVID projects. In 2021, the TCRC initiated 44 new studies (including 12 COVID-related), with 74 total studies ongoing and revenue of $8.4M, substantially higher than previous years.
- Our massive (150,000+ animals) animal care program faced and overcame major challenges in 2021. Critical staffing shortages were addressed by significantly increasing the base wages of our frontline workers, and the emergency response plan was activated to handle the year end COVID surge brought about by the omicron variant. Successful AAALAC and USDA site inspections also occurred in 2021, thanks to extensive preparation and cooperation among, CCM (the Center for Comparative Medicine that manages our 150+ animal care staff), the IACUC (Institutional Animal Care and Use Committee) staff, and our entire animal user community.
- Research Compliance had a busy and productive 2021, with initiatives including: 1) Implementation of a comprehensive Research Compliance Workplan; 2) creation of iLog, a new controlled substance registration and use database; 3) Development of research orientation and lab safety checklists; 4) An improved process for compliant transport of biological specimens.
- The recently renamed CNY Vitalization and Advocacy Committee (originally founded in 2018 as the CNY Quality of Life Committee) successfully petitioned research leadership for financial support to enhance community building. They accomplished this by: 1) Holding Town Hall meetings to allow open discussions and feedback; 2) Holding a monthly Lunch Scientific Seminar Series; 3) Offering Cookies, Coffee and Classical Music events several times throughout the year; 4) Offering Ice Cream Socials in the summer; 5) Working with Research Building Management to bring lunch pop-up shops at CNY; 6) Hosting the Science as Art Event and installing a permanent art exhibit at CNY; 7) Hosting Virtual Trivia nights and, with the MGRI OSD staff, the CNY Science Grand Slam.
- Thanks in large part to the work of our Awards and Honors Committee, over 200 MGH'ers received awards and honors by national and international societies.

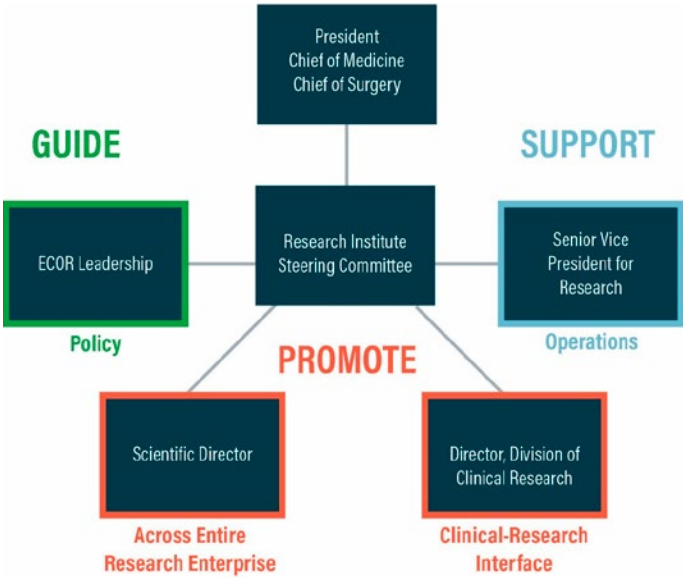
- The MGH Task Force on Equity and Respect in the Research Workforce finalized its recommendations in December and, at the time of writing this report, is putting together a small working group with HR leadership to implement the recommendations.
- Research IS Support team had a busy and very productive 2021. They developed several online modules related to COVID, modules for managing access to research space and for monitoring COVIDPass compliance. They also created a new web-based system to track and monitor intra-hospital shipments of biological samples for research, enhanced the EVALS program for online HR performance evaluations and continued to roll it out across all MGB institutions, deployed the MGH Help and Safety App for mobile phones across the entire MGH community, and established an electronic interface (API) with the new DCR learning management system, OpenCourses.
- The Center for Innovation in Digital Healthcare also had a very productive year. In 2021, it appointed two new faculty (in clinical integration and in outcomes research), secured $8M in new contracted revenue, and completed two clinical trials in the Astra Zeneca research partnership.
- Highlights from MGB Research Support Departments.
  - The MGB Human Research Affairs Office undertook a major reorganization of its IRBs this past year, improving the efficiency of the process and significantly lowering turnaround times of the almost 39,000 protocol reviews it conducts each year.
  - The Clinical Trials Office had a highly productive year in support of MGH investigators and leadership. Overall volume of executed agreements increased significantly from 2083 to 2451. Of this increase, 27% of the volume was driven by COVID-related projects, while the remainder represents growth across numerous therapeutic areas.
  - For the MGB Research Compliance Office, international collaborations and responding to federal concerns about "foreign interference" and research security continued as top priorities for 2021.
  - Research Information Science and Computing (RISC) had a busy 2021. The Research Patient Data Registry (RPDR) was used by almost 1900 scientists obtaining over 5,500 sets of EHR data. RISC built a Big Data Enclave and offered it to researchers thought the Enterprise Data and Digital Healthcare (EDDH) program, enabling secure computation on special data sets from the healthcare system. And the RISC REDCap (Research Electronic Data Capture) program supported over 28,400 research projects in 2021, including 748 COVID projects.
  - In 2021, licensing activity and patent filings and disclosures returned to their FY19 pre-COVID levels, although royalty income fell from $143M to $85M due to a buyout of one of the hospital's orthopedic licenses that took place in 2020. 2021 also saw MGB Innovation engage in several major programs, including raising over $250M for its third investment fund, creating a new Artificial Intelligence and Digital Innovation Fund, and leading the strategy and implementation plan for a system-wide Gene and Cell Therapy Center.
  - MGB Research Management (RM) saw a major increase in NIH compliance requirements in 2021. These new requirements mandate disclosure of all domestic and foreign research activities. RM also implemented new (earlier) internal proposal submission deadlines to ensure there would be sufficient time to properly review applications for compliance with the new federal regulations. The new timelines were well publicized and compliance with them was excellent.

These and other important developments from the past year are reported below, in a sectional format that aligns with the organizational components (Guide, Promote, Support) of the RI governance structure. I conclude the report by "Looking at the Year Ahead", where I discuss the most notable opportunities and challenges facing the research enterprise in 2022.

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.



GUIDE

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

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

Leadership of ECOR

The ECOR Chair is selected from among the Chiefs of MGH Services and Departments. The current Chair is 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 8-9 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 us evaluate our research mission and address challenges we are facing. SAC membership has included Nobel laureates and leaders in science and medicine from academia, industry, and government. Current membership is listed on pages 6 & 7

Warren Triennial Prize and Symposium

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

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 recent 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:
  - 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, and awards approximately 115 internal grants. 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 $53,760. In FY21, 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 FY21, eight women received the Claflin Award.

Abigail Batchelder, PhD, MPH
Assistant Professor
Psychiatry

Esther Rheinbay, PhD
Assistant Professor
MGH Cancer Center

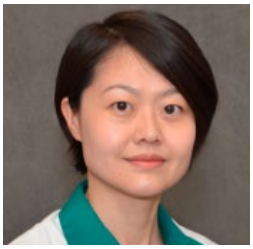
Jamie Jacobs, PhD
Assistant Professor
Psychiatry

Rebecca Sandlin, PhD
Instructor
Surgery

Marcy Kingsbury, PhD
Assistant Professor
Pediatric Service

Melanie Schorr Haines, MD
Assistant Professor
Medicine / Neuroendocrine

Lidia Moura, MD
Assistant Professor
Neurology



Jia Yin, MD, PhD
Assistant Professor
Ophthalmology

Massachusetts General Research Institute

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 (URM), and thereby increase opportunities for URM researchers to advance to senior positions in academic medicine at MGH. To better address the needs of underrepresented faculty at MGH, the CDI and ECOR agreed to fund at least four awards going forward. The total amount of funding per awardee is$180,000 in direct costs. In FY21, six investigators received this award:

Eman Akam, PhD
Instructor
Department of Medicine
Cardiology

Gabriela Hobbs, MD
Assistant Professor
Department of Medicine
Cancer Center

Efren Flores, MD
Assistant Professor
Radiology

Julia Rosenbloom, MD
Assistant Professor
Anesthesia

Yasmin Hernandez-Barco, MD
Instructor
Department of Medicine
Gastroenterology

Karla Ramos-Torres, PhD
Research Fellow
Radiology
Gordon Center for Medical Imaging

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 2021, 70 Scholars have been appointed, each receiving research funding of $100,000 a year for five years.

The 2021 Class of Mass General Research Scholars:

Robert Anthony, PhD
Frisbie Family MGH Research Scholar 2021-2026
Associate Professor
Department of Medicine,
Center for Immunology and Inflammatory Diseases

Travis Baggett, MD, MPH
MGH Research Scholar 2021-2026
Associate Professor
Department of Medicine

Priscilla Brastianos, MD
Terry and Jean de Gunzburg MGH Research Scholar 2021-2026
Associate Professor
Department of Medicine
Cancer Center

Olivia Okereke, MD, MS
Terry and Jean de Gunzburg MGH Research Scholar 2021-2026
Associate Professor
Psychiatry

Tim Padera, PhD
Rullo Family MGH Research Scholar 2021-2026
Associate Professor
Radiation Oncology

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 4 for more information on the 2022 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. While we have always offered prizes in Fundamental research and Clinical research, we added a third category in Population Health Sciences this year Please see pages 2–3 for more information on the three 2022 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 2006-2021 are still working within the institution. Since the program's inception in 2006, ECOR has awarded over $62.7M of interim support funding. Our investigators have gone on to leverage these funds ten-fold, bringing in $657M 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 $7.4M to date.

Awards and Honors Committee

The summer of 2014 saw the creation of the MGH Committee on Awards and Honors. After serving for five years as chair Samuel Their, MD, president of MGH from 1994-1997, stepped down and passed the baton to Jerry Rosenbaum, MD, 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.

The MGH Committee on Awards and Honors is now chaired by Jeanine Wiener-Kronish, MD. Dr. Wiener-Kronish is the Henry Isaiah Dorr Distinguished Professor of Research and Teaching in Anaesthetics and previously 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 now focuses on a limited number of distinguished honorific societies, awards and ensuring equity in its nominations.

Some of the major awards and prizes received by MGH investigators in 2021 include the following:

National Academy of Medicine
Vamsi Mootha, MD (Molecular Biology)
Renee Salas, MD, MPH (Emergency Medicine)
Reisa Sperling, MD (MGH/BWH Neurology)

National Academy of Inventors
Xandra Breakefield, PhD (Neurology)
Patricia Donahoe, MD (Surgery, Pediatric Surgery)

American Association for the Advancement of Science (AAAS) Fellow
Lee Zou, PhD (Cancer Center)

American Academy of Child and Adolescent Psychiatry (AACAP) Pilot Research Award for Attention Disorders
Robyn Thom, MD (Psychiatry)

American Academy of Dermatology Gold Medal Award
R. Rox Anderson, MD (Dermatology, Wellman Center)

American Academy of Nursing Fellow
Virginia Capasso, PhD, CNP, CNS, CWS, FACCWS (Munn Center for Nursing Research)

American Association for the Study of Liver Diseases, President
Raymond Chung, MD (Medicine, Gastrointestinal Division)

American Association of Obstetricians and Gynecologists Foundation Pilot Innovation Award
Adeline A. Boatin, MD, MPH (Obstetrics and Gynecology)

American Association of Physicists in Medicine (AAPM) John S. Laughlin Young Scientist Award
Clemens Grassberger, PhD (Radiation Oncology)

American Association of Physicists in Medicine (AAPM) Science Council Associate Mentorship Program Fellow
Arthur Lalonde, PhD (Radiation Oncology)

American Association for the Study of Liver Disease (AASLD) Fellows
Uzma Shah, MD, MBBS (Pediatrics)

American Association of Physicists in Medicine Fellow
Gregory Sharp, PhD (Radiation Oncology)

American Cancer Society Postdoctoral Fellowship Award
Meng-Ju Wu, PhD (Cancer Center)

American College of Cardiology (ACC) Chief Innovation Officer
Ami Bhatt, MD (Medicine, Cardiology)

American College of Surgeons Jacobson Innovation Award
Patricia Donahoe, MD (Surgery, Pediatric Surgery)

American Medical Association Dr. Edmond and Rima Cabbabe Dedication to the Profession Award
Fatima Cody Stanford, MD, MPH, MPA, MBA (Medicine-Gastroenterology, Pediatrics-Endocrinology, Weight Center)

American Neurological Association Audrey S. Penn Lectureship Award
Nicte Mejia, MD, MPH (Neurology)

American Physical Society Fellow
Matt Rosen, PhD (Martinos Center)

American Physical Society Topic Group on Medical Physics Vice Chair
Jennifer Pursley, PhD (Radiation Oncology)

American Psychiatric Association (APA) 2021 Bruno Lima Award in Disaster Psychiatry
Giuseppe Raviola, MD, MPH (Psychiatry)

American Society for Clinical Investigation
Eugene Rhee, MD (Medicine, Nephrology)
Alexander Tsai, MD, PhD (Psychiatry)
Xu Yu, MD (Ragon Institute)

American Society for Metabolic and Bariatric Surgery Integrated Health Circle of Excellence Award
Stephanie Sogg, PhD (Weight Center, Medicine, Psychiatry)

American Society for Radiation Oncology (ASTOR) Leadership Pipeline Program
Rachel Jimenez, MD (Radiation Oncology)
Sophia Kamran, MD (Radiation Oncology)

American Society of Gene and Cell Therapy (ASGCT) 2021 Outstanding New Investigator Award
Benjamin Kleinstiver, PhD (Pathology)

American Society of Transplantation 2021 Innovation Award
Jay Fishman, MD (Medicine, Infectious Disease,)

ASGCT Outstanding New Investigator Award
Marcela Maus, MD, PhD (Cancer Center)

Association for the Advancement of Medical Instrumentation (AAMI) 2021 Technical Committee Award
Julian Goldman, MD (Anesthesia)
AAMI COVID-19 Response Team

Autism Speaks Pilot Grant
Karen Chenausky, PhD, CCC-SLP (Institute of Health Professions)

Bill and Melinda Gates Foundation Grand Challenge Award
MGH Reproductive Endocrine Unit

Boston University's Center for Antiracist Research Affiliate Faculty
Tiffany Hogan, PhD, CCC-SLP (Institute of Health Professions)

BRAIN Investigator & 2021 Research Grant Awardee
Alessio Fasano, MD (Pediatrics)

Brain Tumour Charity Future Leaders Fellowship
Tyler Miller, MD, PhD (Pathology)

Brigham Health Stepping Strong Center Innovator Awards
Justin Brown, MD (Neurosurgery)
Jenna Galloway, PhD (Center for Regenerative Medicine)
Cornelia Griggs, MD (Surgery, Pediatric Surgery)
Peter Masiakos, MD (Surgery, Pediatric Surgery)

Canada Gairdner International Award
Joel Habener, MD (Molecular Endocrinology, Medicine)

Cancer Research Institute (CRI) Merck Fellow
Nilesh Talele, MSc, PhD (Radiation Oncology)

Cell Mentor's list of 1,000 Inspiring Black Scientists in America
David Alagpulinsa, PhD (Medicine, Infectious Disease)
Emery Brown, MD, PhD (Anesthesia, Critical Care and Pain Medicine)
Sherri-Ann Burnett-Bowie, MD, MPH (Medicine)
Jonathan Jackson, PhD (Neurology)
Victoria Parker, PhD (Radiology)
Camille Powe, MD (OBYN, Medicine, Diabetes)

Chan Zuckerberg Initiative Grant
Gordon Harris, PhD (Radiology)

Clarivate Analytics' Highly Cited Researchers List
To view all 55 MGH researchers that made the list, please visit: https://recognition.webofscience.com/awards/highly-cited/2021/

Clinical Research Forum 2021 Top Ten Clinical Research Achievement Award
Sabrina Paganoni, MD, PhD (Physical Medicine and Rehabilitation)

College of American Pathologists (CAP) Board of Governors 2021 Pathologist of the Year Award
W. Stephen Black-Schaffer, MD (Pathology)

Connell-Jones Endowed Nursing Chair for Nursing and Patient Care Research-Diversity Research Scholars (DRS)
Luis Brigida, RN (Cancer Center)
Rosebud Mayanja-Sserebe, RN (OBGYN)
Emma Chong, RN (Medicine, Cardiology)
Claudia Guillen, CNP (Medicine, Chelsea HealthCare Center)
Joanna Karanja, RN (Neurology)
Ashley Kariuki, RN (Surgery)
Jhoana Yactayo, RN (Medicine)
Rute Teixeira, CNP (Pediatric Urology)

Damon Runyon Physician-Scientist Training Award
Albert Kim, MD (Cancer Center)

Department of Defense Reconstructive Transplant Research Program (RTRP) Investigator-Initiated Research Award
Leonardo Riella, MD, PhD, FASN, FAST (Medicine, Nephrology)

DF/HCC CURE Mentor Appreciation Award
Leo Cheng, PhD (Pathology, Radiology)

Doris Duke Charitable Foundation Clinical Scientist Development Award
Diane Chan, MD, PhD (Neurology)

European Society for Photobiology (ESP) Award for Excellence in Photobiological Research Medal
Tayyaba Hasan, PhD (Wellman Center)

German National Academy of Sciences
Thomas Bortfeld, PhD (Radiation Oncology)

Global Blood Therapeutics Access to Excellent Care for Sickle Cell Patients (ACCEL) Grant
MGH Center for Sickle Cell Disease

Grass Foundation American Neurological Association Award in Neuroscience
Alberto Serrano-Pozo, MD, PhD (Neurology)

Harvard Medical School 2021 Excellence in Mentoring Awards: A. Clifford Barger Excellence in Mentoring Award
Lorenzo Berra, MD (Anesthesia)
Douglas M. Dahl, MD (Urology, Urologic Oncology)
Jason Efstathiou, MD, PhD (Radiation Oncology)

Harvard Medical School 2021 Excellence in Mentoring Awards: William Silen Lifetime Achievement Award
Daniel Rosenthal, MD (Radiology)
Elizabeth Van Cott, MD (Pathology)

Harvard Medical School 2021 Excellence in Mentoring Awards: Young Mentor Award
Fatima Cody Stanford, MD, MPH, MPA, MBA (Medicine-Gastroenterology, Pediatrics-Endocrinology, Weight Center)
Benjamin P. Kleinstiver, PhD (Pathology)

Harvard Medical School (HMS) Shirley Driscoll Dean's Leadership Award for the Enhancement of Women's Careers
Miriam Bredella, MD (Radiology)

Human Organ, Physiology, and Engineering (HOPE) Program Grant
Ryuji Morizane, MD, PhD (Medicine, Nephrology)
Leonardo Riella, MD, PhD, FASN, FAST (Medicine, Nephrology)

Infectious Diseases Society of America, HIV Medicine Association, Board of Trustees, Chair
Rajesh T. Gandhi, MD (Medicine, Infectious Disease)

International OCD Foundation Michael Jenike Young Investigator Award
Sarah O'Dor, PhD (Pediatrics)

International Society of Neuropathology President
David N. Louis, MD (Pathology)

International Society of Porphyrins and Phthalocyanines Thomas Dougherty Award for Excellence in Photodynamic Therapy
Tayyaba Hasan, PhD (Wellman Center)

International Society of Psychiatric Genetics President
Jordan Smoller, MD, ScD, Center for Genomic Medicine, Psychiatry)

Lasker Foundation Essay Contest
Trisha Pasricha, MD (Medicine, Gastroenterology)

Lundbeck Foundation 2021 Brain Prize
Michael Moskowitz, MD (Radiology, Neurology)

Lymphoma Research Foundation Lymphoma Scientific Mentoring Program Award
P. Connor Johnson, MD (Cancer Center, Hematology Oncology)

Massachusetts Medical Society 2021 Henry Ingersoll Bowditch Award for Excellence in Public Health
Paul Biddinger, MD (Emergency Medicine)

Medal of the World Federation of ADHD (Attention Deficit Hyperactivity Disorder)
Joseph Biederman, MD (Psychiatry)

Muscular Dystrophy Association Development Grant
Xin Jiang, PhD (Neurology)

National Academy of Medicine (NAM) Scholars in Diagnostic Excellence Program
Efren Flores, MD (Radiology)

National Black Nurses Association (NBNA) Lifetime Achievement Award
Gaurdia E. Banister, RN, PhD, NEA-BC, FAAN (Munn Center for Nursing Research)

National Institute on Aging Paul B. Beeson K76 Emerging Leaders in Aging Research Career Development Award
Felipe Jain, MD (Psychiatry)

National Institute of Allergy and Infectious Diseases (NIAID) MERIT R37 Award
Edward Ryan, MD (Medicine, Infectious Disease)

National Institute on Disability Independent Living and Rehabilitation Research Switzer Fellowship
Ariel Schwartz, PhD (Institute of Health Professions)

National Latino Behavioral Health Association Lifetime Achievement Award for Latino Behavioral Health Research
Margarita Alegria, PhD (Medicine, Mongan Institute, Psychiatry)

New England Society Silver Lamplighter Award for Healthcare Communications (NESHCo)
Mass General Research Institute Bench Press

NIH Director's Early Independence Award
Hong Hsi Lee, MD, PhD (Martinos Center)

NIH Director's Transformative Research Award
Seok-Hyun Andy Yun, PhD (Wellman Center)

Nutrition Obesity Research Center (NORCH) Pilot and Feasibility Awards
Chika Anekwe, MD, MPH (Medicine, Weight Center)
Armen Yerevanian, MD (Medicine, Endocrinology)

Nutrition Obesity Research Center (NORCH) Mentoring for Diversity and Inclusion Award
Fatima Cody Stanford, MD, MPH, MPA, MBA (Medicine-Gastroenterology, Pediatrics-Endocrinology, Weight Center)

Orthopaedic Research Society William H. Harris Award
Alireza Borjali, PhD (Orthopaedics)

Patient Centered Outcomes Research Institute (PCORI) Awards
Jennifer Temel, MD (Cancer Center)
Areej El-Jawahri, MD (Cancer Center, Hematology Oncology)
MGH Cancer Outcomes Research and Education Program (CORE)
Division of Palliative Care
Louisa Sylvia, PhD (Psychiatry)

Pew Latin American Fellow in the Biomedical Sciences
Carlos Rivera Álvarez, PhD (Molecular Biology)

Prostate Cancer Foundation (PCF) Young Investigator Awards
Shervin Tabrizi, MD (Radiation Oncology)
Sophia Kamran, MD (Radiation Oncology)
Keyan Salari, MD, PhD (Cancer Center)

Radiation Oncology Institute (ROI) Biomarkers for Radiation Oncology Research Award
David Miyamoto, MD, PhD (Radiation Oncology)

Radiation Research Society Vice President-Elect
Jan Schuemann, PhD (Radiation Oncology)

Rapid Acceleration of Diagnostics in Underserved Populations (RADx-UP) Coordination and Data Collection Center (CDCC) Community Collaboration Pilot Grant
The Kraft Center for Community Health COVID Response Team
Priya Gupta, MD, MPH (Charlestown Health Care Center, Medicine)

Rollins School of Public Health Alumni Association Distinguished Achievement Award
Fatima Cody Stanford, MD, MPH, MPA, MBA (Medicine-Gastroenterology, Pediatrics-Endocrinology, Weight Center)

Simons Foundation Autism Research Initiative (SFARI)
Andrea Edlow, MD (OBGYN)

Society for Medical Decision Making (SMDM) John M. Eisenberg Award
Daniel Singer, MD (Medicine, Internal Medicine)

U.S. Department of State Fulbright Global Scholar Award
Brett Nelson, MD, MPH, DTM&H (Pediatrics)

Uniformed Services University (USU) Women's History Month
Christina Faherty, PhD (Pediatrics)

Williams Syndrome Association Early Investigator Award
Robyn Thom, MD (Psychiatry)

Women of Color Magazine's 2021 Excellence in STEM Education STEM Achievement Award
Eleonor Pusey-Reid, DNP (Institute of Health Professions)

Women in Ophthalmology (WIO) Scientific Contribution Award
Janey Wiggs, MD, PhD (Ophthalmology, MEEI, MGH)

PROMOTE

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

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

- 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 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
Internal communications: We continue to create and distribute our newsletter communications to help promote the remarkable work of our research community. Our most popular, Snapshot of Science, is a monthly newsletter sent to nearly 10,000 people that includes a listing of publications from high impact scientific and medical journals in which Mass General researchers are lead authors with accompanying lay summaries. In 2021, we featured over 300 high-impact papers in the Snapshot of Science. The goal of this newsletter is to promote awareness of new Mass General research studies within our community, help the Research Institute establish relationships with individual researchers, and encourage researchers to think critically about translating their science for a broad audience. We

use the format of this newsletter to help us think about communicating to the external community, especially through social media. Additionally, we continued publishing monthly issues of our From the Lab Bench email newsletter, which typically features two or three articles about research at the hospital as well as news and updates from the Office of the Scientific Director.

The Research Institute Blog: Our blog, Bench Press, is in its fourth 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 blog won three awards from local and national healthcare organizations in 2021:

1. Owen J McNamara Excellence in Writing Award, “What Makes This Coronavirus So Unique? A Look at the Virology of SARS-CoV-2”, NESHCo Lamplighter Awards
2. Silver, Single Item & Series Division: Blog/Vlog, NESHCo Lamplighter Awards
3. Gold, Excellence in Writing-Blog, “What Makes This Coronavirus So Unique? A Look at the Virology of SARS-CoV-2”, NESHCo Lamplighter Awards

Social Media: In 2021, we posted 60 research stories on Facebook (through 12/22/2021) and reached 247K people. We currently have over 6,300 followers. The MGRI Twitter account has over 7,750 followers and is used primarily as a tool to engage and support the scientific community at Mass General and beyond. In 2021, we posted approximately 950 tweets (the vast majority of which were highlights of studies in high impact journals) and gained almost 2,050 followers. Our MGRI Instagram account has 1.2K followers. Posts on the MGRI Instagram page reached 109,211 people in 2021.

Communicating Science: The Research Institute has launched a series of initiatives designed to help our scientists better communicate the importance of their research to the general public. During the COVID-19 pandemic it has not been possible to host these activities in person, but we have successfully pivoted to holding virtual events. We were able to host three virtual Science Slams: in February (9 “slammers” and 107 attendees), June (9 “slammers” and 142 attendees) and October (11 “slammers” and 52 attendees). We also started a new series called QUIIPS (“Quick Interviews with Interesting People”) featuring candid conversations between our researchers. We hosted three QUIPPS events, in March (63 attendees), May (51 attendees) and September (44 attendees).

In tandem with those self-produced events, we also invited three expert consultants in science communication to work with the research community over the course of 2021. SpeechSkills, a nationally recognized leader in training professionals to hone their virtual presentations, held three separate workshops in March, April and June for the Anne Klibanski Scholars. In March at Research Council, coach Melissa Marshall led a virtual training session called "Talk Nerdy to Me: Dynamic Virtual Delivery" with 108 attendees. In June, the Alan Alda Center for Communicating Science's Creating Connections program held a two-hour live, online workshop for Mass General researchers designed to help scientists and researchers learn to engage and inspire diverse audiences through effective communication, with 48 people in attendance.

We are planning more virtual events for the new year, with the hopes that we may also be able to return to in-person events as well.

Internship Program: We also continued our communications internship program, which is designed to give aspiring science writers from local colleges an opportunity to write stories and social media posts about Mass General research. We hosted 2 interns in 2021.

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, 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 2021, we bestowed five new MGH Research Scholar awards, bringing the total number of MGH Research Scholar $500,000/five-year awards granted over the past 10 years to 70. 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. Since 2015, we have also established six 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—including Drs. Slaugenhaupt, Orf, Cudkowicz, Fava, Kingston and others—partnered with our Development Office colleagues to host numerous virtual meetings and events with donors and prospects throughout 2021, including the popular Mass General Research Institute LAB DAY on September 22. LAB DAY 2021 was held virtually and featured pre-filmed laboratory tours by two MGH Research Scholars combined with live talks and questions. The event also included a panel on "Research in the Age of COVID," featuring four MGH Research Scholars, moderated by a donor from our external volunteer Mass General Research Institute Advisory Council, which was very well received.

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

In 2015, we developed and launched the Strategic Alliances initiative with the objective of helping our investigators establish productive collaborations with industry (pharma, medical device, biotech) and venture communities at all stages of their work, from fundamental research 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 key leaders in industry and ventures, we have been able to push many of our programs forward in 2021.

The initiative is built on 3 pillars: Challenge-Driven Programs, Training and Education, and Research Community Building.

Challenge-Driven Programs: Our challenge-driven programs come from research "themes" collected from departments and centers across Mass General. In total, we have built eight SA programs around Epigenetics, Cancer Immunotherapy, Neuroinflammation in Neurodegeneration, the Microbiome, Cardiometabolics, Rare Diseases, Antimicrobial Resistance, and Sleep that bring together 228 investigators from 21 departments and centers across the institution. In total, we have organized 64 industry-focused sessions during which our investigators presented these programs to selected industry executives. Our goal is to continue to build collaborations between Mass General investigators and our industry partners that improves 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 academia and industry working together, 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 2021, we trained 20 faculty from across 13 departments and thematic research centers, and engaged 42 teaching faculty (22 academia, 20 industry). 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, and research support groups across MGH and MGB.

The research portfolio provides a common understanding of the science at Mass General, serving as a comprehensive foundation for promoting our research enterprise. In 2021 we worked with 25 investigators across 9 departments and centers to advance their projects across many fields of medicine (including radiation, neurology, dermatology) and involving many biological mechanisms (including immune tolerance, metabolism, sleep spindles), modalities (including sialylation, immunotherapy, stem cells), and technology (proton therapy, advanced imaging, high-throughput screening).

We continue to host the Portfolio Café series. At these sessions, investigators are invited to introduce the most important question their lab is working to solve to representatives from MGH Development Office, MGRI Office of the Scientific Director, and MGB Innovation. This introduction helps investigators advance their research programs by forming new and diverse connections with internal teams involved in building partnerships with donors, industry, and ventures. This year we hosted 4 sessions

featuring presentations from 8 investigators across 5 departments and centers.

We continue to help investigators to engage in several MGB Innovation programs such as the Innovation Discovery Grants, Innovation Fellows, Boston Scientific Corps Translation In-Kind, NIBR Global Scholars, Pfizer CTI, and Sanofi iAwards; we worked with 4 investigators to prepare their applications.

We continue to promote the Strategic Alliances 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 5 invited talks describing the Strategic Alliances Initiative in 2021.

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

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

Founded in 1996, the Division of Clinical Research (DCR) of the Mass General Research Institute, formerly known as the MGH Clinical Research Program (CRP), is now entering its 26th year.

Since its inception, the DCR has had a simple and constant mission: to increase the quality, quantity, and efficiency of translating basic science advances into improved care for our patients. Last year, DCR faculty had provided over 470 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, QI, Innovation), as well as the Harvard Catalyst.

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

DCR Centers

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

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

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

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

Community Access, Recruitment, and Engagement (CARE) Research Center, Jonathan Jackson, PhD
The CARE Research Center uses a community-led, collaborative model of partnership and engagement to conduct groundbreaking research on poor accrual

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

Pediatric Translational Research Center (PTRC), Alessio Fasano, MD

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

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

DCR Units

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Center for Clinical Research Education, Karen K. Miller, MD & Andrew Nierenberg, MD

About the Center for Clinical Research Education (CCRE)
The CCRE is a production team capable of creating technology to support curriculum development and delivery, using online, remote, and hybrid learning models. The CCRE is a virtual event management team which produces educationally focused virtual events such as Clinical Research Day, Special Lectures, and MGH Research Council meetings.

Our switch to virtual offerings and a fully remote virtual team only started in 2020. We have turned this response to the COVID-19 pandemic into our competitive advantage. With a fully remote team focusing on virtual offerings, we can spend less time on in person logistics and more time on the quality of our offerings. With the virtual tools available to us, we were able to increase efficiently and effectively the quantity of courses and instances we offered to our audience in 2021 compared to 2017-2020. In short, our courses have improved in quality, quantity, and attendance since we have switched to a virtual team. We have become the team of choice to work with on educational offerings for other research focused groups within MGH and MGB.

History
The Center for Clinical Research Education (CCRE) has a history of supporting the Division of Clinical Research and the MGH clinical research community through hosting education events and developing and maintaining a robust curriculum of clinical research education.

Figure 1. A brief history of the CCRE

1996	The Clinical Research Program (CRP) was established to support clinical research at Mass General Hospital. The CRP included an Education Unit charged with training the Mass General research community with clinical research best practices.
2003	Education unit hosted the first ever Clinical Research Day to highlight excellent clinical research being done across Mass General Hospital.
2010	Expanded educational offerings to include on demand courses in addition to live courses.
2015	CRP was renamed the Division of Clinical Research (DCR) under the newly established Mass General Research Institute (MGRI).
2016	Education Unit was renamed the Center for Clinical Research Education (CCRE).
2017	Hired an Instructional Designer to develop interactive on demand trainings.
2018	Started tracking consultation services using an in-house web-based consultation portal.
Mar 2020	Because of COVID-19 Pandemic, transitioned all DCR's educational offerings to virtual formats.
Oct 2020	Hosted the first Virtual Clinical Research Day using an in-house web-based virtual event portal.
Jul 2021	Introduced a new Learning Management System (LMS), OpenCourses.

Mission
The mission of the CCRE is to 1) Provide engaging educational experiences to researchers and staff to support the advancement of clinical research; and 2) Support the educational goals of the DCR, MGB oversight entities, and the research community through developing models, methods, programs, and tools for educational and virtual event management.

Vision
The vision of the CCRE is to 1) Be a national leader in educational programming for clinical research; and 2) Be a leader within the MGB system in educational programming.

Values
- **Learner focus.** We prioritize ensuring the learner retains and remembers what they need to know. We aim to engage our learners and present content that is valuable, useful, and interesting to the widest audience possible.

- **Diversity, equity, and inclusion.** We strive to reach the widest audience with accessible offerings on flexible platforms and with diverse representation in our content and our SMEs. We strive to normalize equity in our offerings.
- **Collaboration and Transparency.** We work towards creating a collaborative and transparent working environment with our SMEs and learners. We prefer open-source technologies to deliver our educational offerings.
- **Innovation and Agility.** We prioritize innovation and agility, accomplish goals and complete projects in a timely fashion, and pivot quickly in response to the changing needs of our audience and stakeholders.

Goals

The goals of the CCRE are 1) Improve clinical research outcomes at MGH through comprehensive and engaging clinical research curriculum for investigators and staff. Through improved clinical research outcomes, we will positively impact patient care; 2) Facilitate peer networks of investigators and research staff to support learning and knowledge transfer within these communities; and 3) Develop and share best practices for educational programming, virtual events, and curriculum management in Research.

Services and Resources

A brief description of our services and resources follows. Our accomplishments in 2021 for each of these services are discussed in more detail in section 3.

- **OpenCourses**. Our one stop shop learning management system.
- **Clinical Research Curriculum**. Our comprehensive and engaging clinical research education for investigators and study staff.
- **DCR Abstract Submission Application**. Our internally developed application for managing abstract submission, peer review, award selection, and virtual poster session events.
- **DCR Course Development Model**. Our method of assisting leaders and subject matter experts in developing engaging Live and On Demand courses.
- **Clinical Research Day**. An annual celebration of clinical and translational investigators at MGH and their accomplishments. It serves as an opportunity for sharing ideas among researchers and leaders that may contribute to strategic thinking and future planning.
- **DCR Consultations**. DCR faculty provide a variety of one-on-one consultations and project support services to assist investigators with their research. Consultation requests are managed through an internally developed website to track requests, consultation activities, and support.

CCRE Accomplishments in 2020-2021

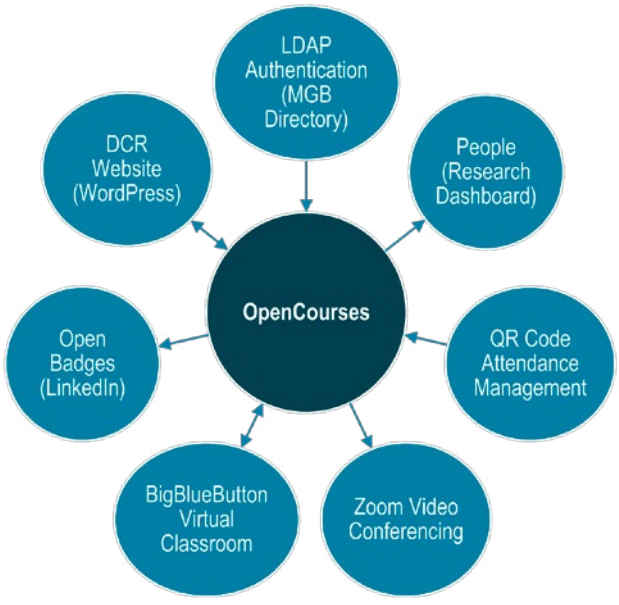
OpenCourses

The CCRE implemented a brand-new learning management system (LMS) to host all courses both live and on-demand. The LMS was built using the open-source software Moodle with customizations for our needs, and we branded it OpenCourses. For an overview of the features of OpenCourses, please visit: https://indd.adobe.com/view/026a7cef-ad44-4fbe-bcd5-958017d3108b/ . OpenCourses went live in July 2021. OpenCourses allows us to host on-demand courses, course registrations, and course materials and content for learners to access directly. This greatly reduces the need to communicate individually with learners about the location of course materials and recordings. It allows us to create hybrid courses that leverage previously recorded or produced content with minimal effort and increased benefit to learners.

System Integrations

OpenCourses has user authentication through MGB Active Directory and sends course completion data to People. The figure below describes the full systems integrations available for OpenCourses.

Figure 2. Learning Systems Environment



As shown in figure 2, OpenCourses works with a suite of technology enhanced tools to:

1. **LDAP Authentication (MGB Active Directory):** Enable seamless authentication to the site. A synchronization task runs at every log-in to ensure all user information such as username, email, institution, department, is up to date.
2. **People (Research Dashboard):** Report course completion data on the People application.
3. **QR Code Attendance Management:** Manage attendance in live classes using QR codes to mark learner attendance.
4. **Zoom Video Conferencing:** Allow easy access to Zoom meeting rooms for conferencing and online learning.
5. **BigBlueButton Virtual Classroom:** Improve the online learning experience with virtual classrooms.
6. **Open Badges (LinkedIn):** Collect awarded course certificates and share to LinkedIn.
7. **DCR Website (WordPress):** Browse and register for courses on the DCR website. The CCRE is currently working on this integration.

Constructivist Learning Model

Oftentimes, adult learners face many challenges in acquiring new skills and knowledge in the workplace. Adult learners are met with heavy workloads and a demanding workforce that prevents them from reaching their full potential. Additionally, learning is different for everyone. Not everybody receives, processes, or retains information the same way, so it is important to cater to different learning styles. In particular, the CCRE considers the perspective of constructivism as it relates to knowledge, adult learning, motivation, and implications for teaching. Constructivism explains learning as a process of constructing meaning; it is the how's of learning and thinking (Merriam et al., 2007). There are two (2) major strands of the constructivist perspective: (1) Cognitive constructivism, and (2) social constructivism (Kanselaar, 2002). Cognitive Constructivism considers the importance of understanding individual learning needs or how one constructs knowledge (assimilation and accommodation), and social constructivism considers the importance of social interactions (knowledge community) in one's thinking process. Both of these strands of constructivism provide a complimentary basis for providing a learning environment that is best suited for adult learners.

The learning environment of OpenCourses is guided by this constructivist perspective. For adult learners, learning is self-directed; adult learners take initiative to formulate and pursue learning goals of their own accord. Within a constructivist framework, technology is a means to expand cognition and cater to different learning needs. Technology, in other words, serves as a tool for adult learners to self-direct their learning. OpenCourses offers many technological tools to cater to various learning needs, abilities, and styles of adult learners, thus information can be delivered in a highly targeted and effective way:

- **Informative Tools:** Allow repositories of digital knowledge in various formats.
- **Communicative Tools:** Enable communication between the instructor(s) and the learner(s).
- **Constructive Tools:** Help learners construct knowledge.
- **Co-constructive Tools:** Help learners construct knowledge in a collaborative way.
- **Situating Tools:** Situate learners in learning environments where they may experience the work context, such as simulations, role-play etc.).

With these constructivist tools, OpenCourses promotes learners' critical thinking and creativity by linking learning to practice, reflection, case study, and exploration. OpenCourses' tools and activities (e.g., forums, assignments, quizzes, polls, SCORM, etc.) can be used to guide the learning process in a collaborative and interactive manner. Oftentimes, much of online learning presents static information, with little opportunity to practice. With OpenCourses, the CCRE aims to create a more transformational learning experience for adult learners.

Course Metrics

As we utilized 3 different platforms over the course of 2021, our course metrics are reported for January–June for courses hosted with Learn and Healthstream, and then separately for July–December for courses hosted with OpenCourses.

Table 1. Course Metrics for January–June 2021

CCRE Jan-Jun 2021 Summary	Live (Learn)		On Demand (Healthstream)	
	Unique	Total	Unique	Total
Courses	63	92	25	25
Learners Enrolled	*N/A	*N/A	*N/A	5071
Learners who Completed	2301	3575	*N/A	*N/A

*N/A - data not available

Table 2. Course Metrics for July–December 2021

CCRE Jan-Jun 2021 Summary	Live		On Demand		Grand Totals	
	Unique	Total	Unique	Total	Unique	Total
Courses	58	161	26	26	84	187
Learners Enrolled	2400	6537	883	1434	2714	7971
Learners who Completed	1711	3643	431	747	1877	4390

*Data reported here are through 12/15/2021.

Figure 3. Courses July-December 2021

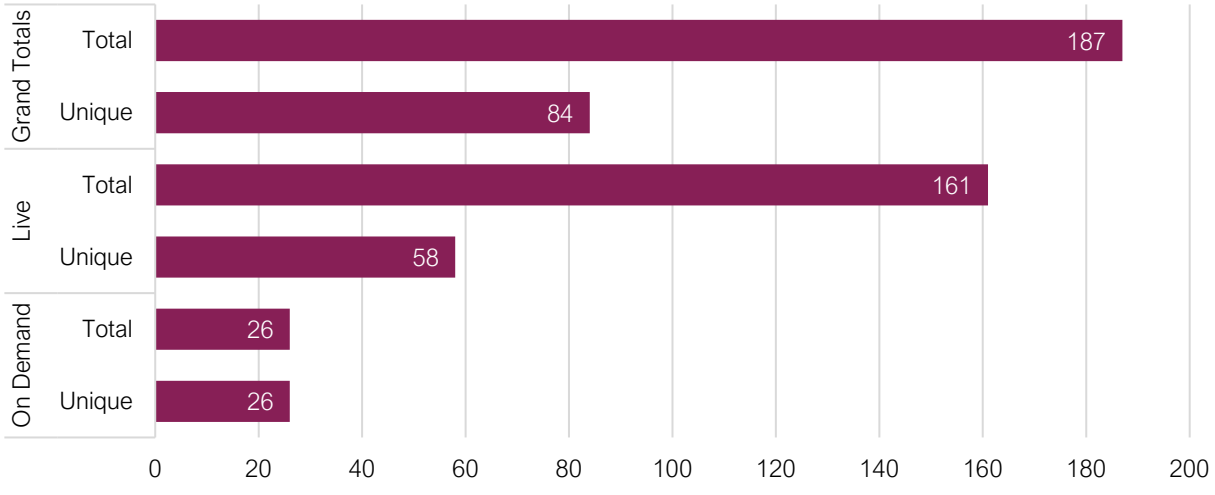
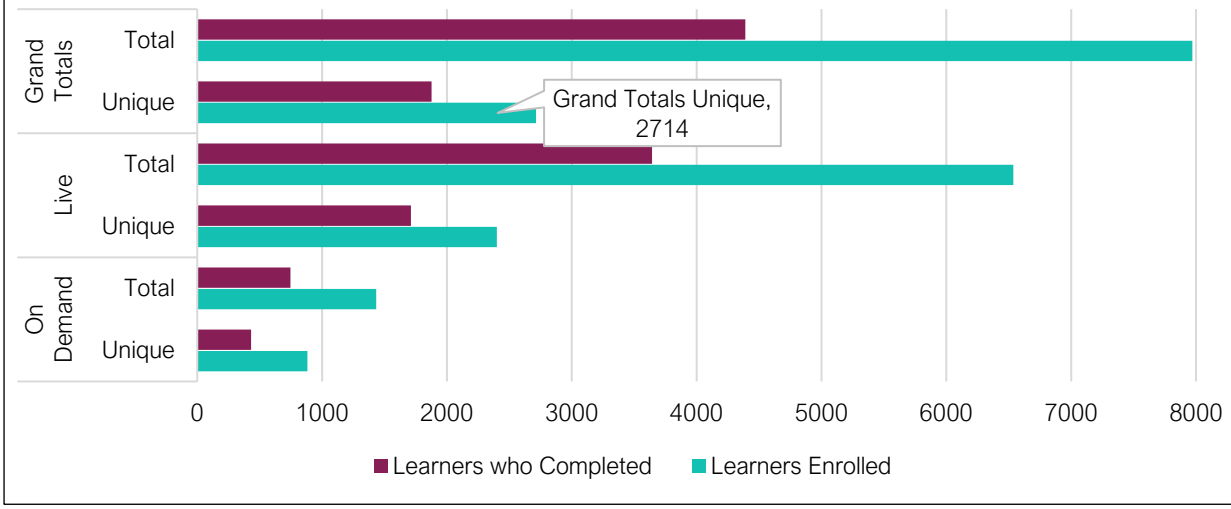


Figure 4. Learner Enrollments and Completions July-December 2021



As shown in Table 2, Figure 3, and Figure 4, OpenCourses analytics allow us to collect more detailed information on our courses and learners. In the six months OpenCourses has been live, we have offered 58 unique live courses, 26 on demand courses, and a total of 187 courses. We had just under 8000 enrollments in just a 6-month period, representing 2700 unique learners as well as 1800 active learners, i.e., those who completed at least one course.

Figure 5 compares courses and learner interest from 2017-2021. We can see that over these five years, the trends for both number of courses as well as number of interested learners increase every year. For total courses, while the general trend is increasing, it is interesting to note that from 2019 to 2020 the number of live courses offered decreased by almost half (see call out boxes in figure 5), which can be explained by the COVID-19 pandemic and immediate and unanticipated switch to virtual; however, the number of total learners who attended live courses in that same time span increased by more than 10%. For total learner interest, the numbers reported here under-represent learner interest as they do not include learners who enrolled in live course but did not attend. Despite this caveat, we do see a general trend of increased learner interest year over year. However, there is a slight decrease in interest in our on demand courses in 2021 compared to 2020 (see grey squares in figure 5), but we attribute this to our reduced advertising for on demand course in 2021. We anticipate improving this metric in 2022 when we implement our updated advertising strategy. In summary, while we see temporary changes in total courses and learner interest in the past 5 years, both metrics show growth overall and highlight the CCRE's competitive advantage.

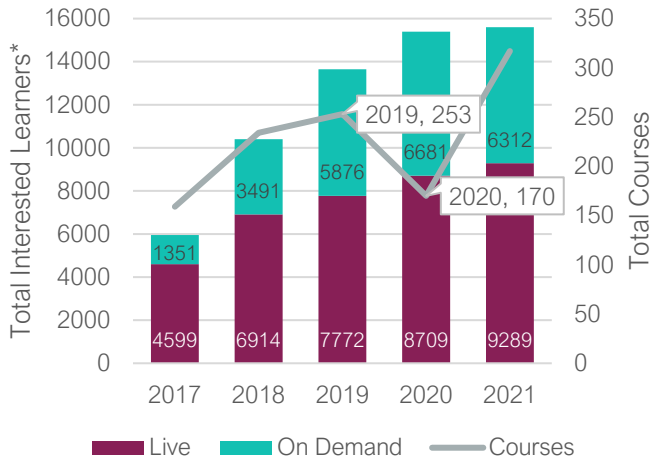
A summary of highlights from a selection of our most popular courses is included here.

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 yearly 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. Learners in this course are highly motivated and engaged in the content, and 2021 was no different. This course was well suited for implementation using our new LMS OpenCourses.

As you can see in table 3, interest in the course was much higher, the cohort size was 30% larger, and the engaged learners, i.e., those who attended more than half the sessions, almost doubled. This speaks to the more convenient nature of the virtual live classroom environment for our adult learners.

Figure 5. Live and On Demand Courses and Learner Interest Over Time



* Total Interested Learners is the sum of learners who attended live courses plus learners who enrolled in on demand courses.

Table 3. Comparison of DCCT Metrics 2020 and 2021

DCCT Metrics	2020 (Learn)	2021 (OpenCourses)
Enrolled	48	116
Application Approved	42	58
Attended 8+/15 Sessions	20	38

During this course, we collected feedback from both the course directors and the learners on the course content and the use of our learning technologies. The course directors, Greg Robbins and George Papakostas, gave positive feedback about the ease of use of OpenCourses. In particular, they believe that OpenCourses has made managing DCCT easier, improved the process of administering assignments and course materials, reviewing applications, and providing feedback to leaners. Feedback from the course directors included comments such as, "Single location for everything, better for student feedback!"; or "[What I liked most about OpenCourses is] Having everything at one spot."

As shown in figure 6, the impact of OpenCourses on DCCT has been overall very positive for its learners. To highlight a few, 70% of learners strongly agree and 30% of learners agree that the organization of the course in OpenCourses helped them understand underlying concepts more clearly. In addition, 45% of learners strongly agree and 30%

Figure 6. Design and Conduct of Clinical Trials Learner Feedback for 2021

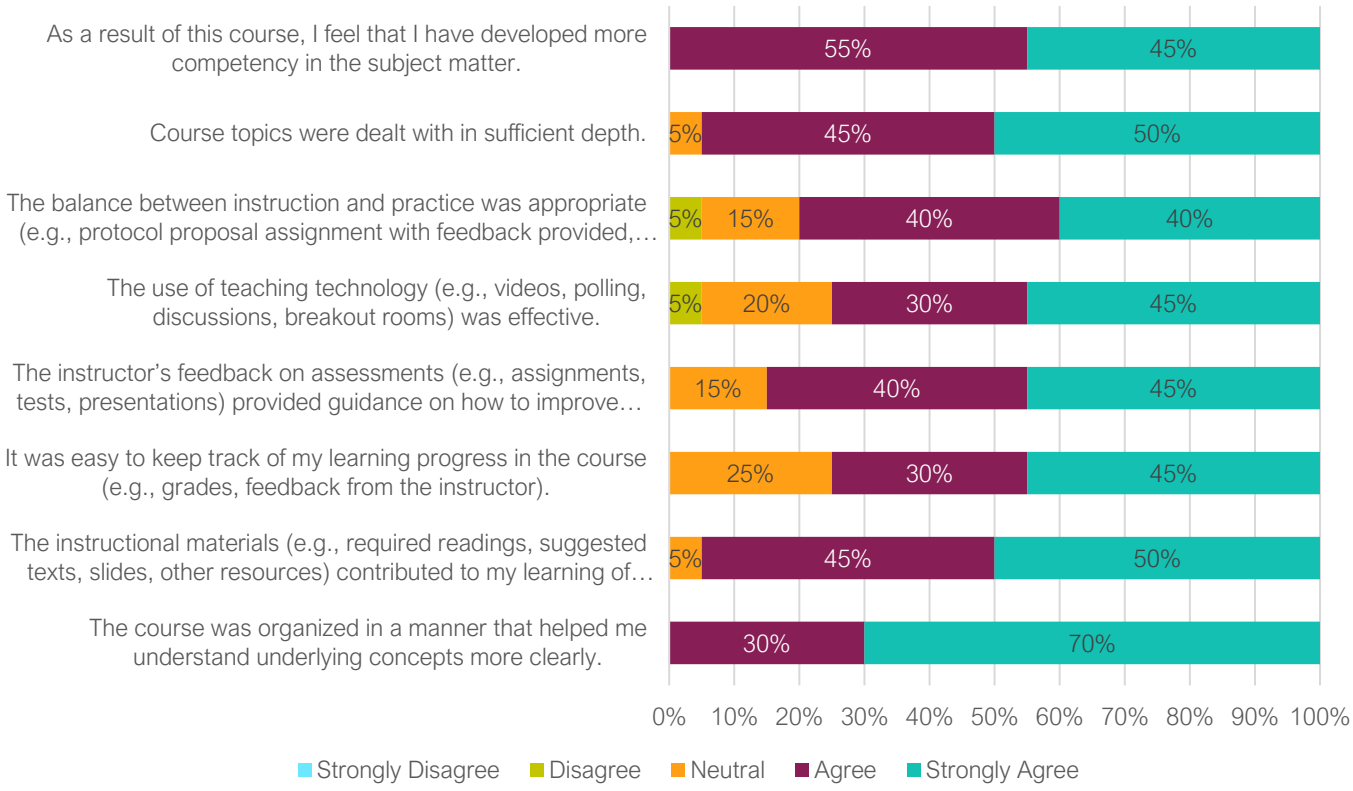


Table 4. Mid- and Post-Course Survey Questions and Examples

Question	Examples
Overall, what do you like most about OpenCourses?	This is my first course using this platform. I've found it easy to use and intuitive. Availability of PowerPoint slides on the course site. Easier interface compared to Harvard Catalyst, or Healthstream. Great selection of courses. Easy to navigate. Accessible layout for notes, excellent topics in clinical trials.
Overall, what are your thoughts on the delivery of this course through OpenCourses?	Very organized. Incredible virtual course. Great platform. Excellent.

Note: Examples include responses from two (2) surveys that were administered mid-course and post-course.

of learners agree that it was easy to keep track of their learning progress in OpenCourses. In terms of developing competency, 45% of learners strongly agree and 55% of learners agree that this course helped them develop more competency in the subject matter.

As shown in figure 6 and table 4, we got excellent feedback and reviews regarding learners' experience with using OpenCourses for this course. Overall, OpenCourses serves to be an excellent platform to facilitate the learning experience for participants in DCCT.

Good Clinical Practice in Research at an Academic Research Institute

Good Clinical Practice in Research at an Academic Research Institute (GCP) is another very popular course. It focuses on conducting compliant clinical research according to international standards and is designed for both investigators and research study staff. Developed in collaboration with MGB Human Research Affairs, this is a 4-5 session course that is offered semi-annually and culminates in learners completing a post-test to assess their knowledge. This course is more efficiently managed using our new LMS OpenCourses. In the spring section of this course, offered prior to OpenCourses Go Live, all 4 team members were required to manage attendance, session recording, manually communicating with learners, individually sharing recordings with learners, and manually tracking attendance/recording receipt as well as post-test completion and grading. The fall section of the course was managed by one team member with attendance collection, recording sharing and view tracking, learner evaluation collection, and post-test completion tracking and grading all happening automatically in OpenCourses. We also collect more evaluation data with OpenCourses, and this is likely because it lives on the same webpage as the course materials that learners are already visiting and reviewing.

As shown in table 5, there is a drastic increase in learner interest comparing Spring 2020 to prior sections. This is due to our switch to virtual. The more recent sections have similar metrics for attendance and post-test completion when comparing Fall 2020 and the 2021 sections to the 2019 sections. While currently the most recent section seems low, these data are not yet final as the Fall 2021 section of the course does not close until January 2022. These data suggest that this continues to be a valuable course to our learners, and we are still reaching our audience with online formats compared to in person ones.

As shown in figure 7, our learners have positive experiences with the GCP course in OpenCourses. All respondents agree or strongly agree that navigation of the course page is intuitive; and 77% strongly agree and 15% agree that the ability to access and download course materials is convenient and supports their learning.

As shown in figure 7 and table 6, we got excellent feedback and reviews regarding learners' experience with using OpenCourses for this course. Overall, OpenCourses serves to be an excellent platform to facilitate the learning experience for participants in GCP.

Conquering the K

Conquering the K is another popular and impactful multi-session course. This course aims to guide learners in successfully drafting career development grants, also know as K grants. It includes didactic information as well as small group workshops on learner drafts of grant sections. It was originally envisioned in two tracks: one for clinical investigators and one for fundamental researchers. In 2020, the two tracks were both offered in February, prior to the switch to all virtual. In 2021, the two tracks were combined into one course offered virtually in February, and then developed into a hybrid course which went live in September.

As you can see in table 7, there was a marked increase in enrollment between 2020 and 2021. We attribute this to the virtual live format of the 2021 iteration compared to the live, in person format of the 2020 sections. This unexpected increase in enrollment created challenges. The primary challenge was scheduling sufficient preceptors to facilitate the small group workshops. In the live, in person sections, we planned for 1 preceptor per 6-8 enrolled learners. For

Table 5. Comparison of GCP Metrics Spring 2019 - Fall 2021

GCP Metrics	Spring 2019	Fall 2019	Spring 2020	Fall 2020	Spring 2021	Fall 2021*
Format	Live In-Person		Live Online			
Enrolled	208	146	306	194	169	117
Attended All Sessions	117	77	145	106	101	55
Passed Post-Test	81	72	105	78	75	20

* The Fall section of this course was hosted on OpenCourses. It does not close until the end of January 2022, so data reported is not final and is only representative through 12/15/2021.

Figure 7. Good Clinical Practice Fall 2021 Learner Feedback

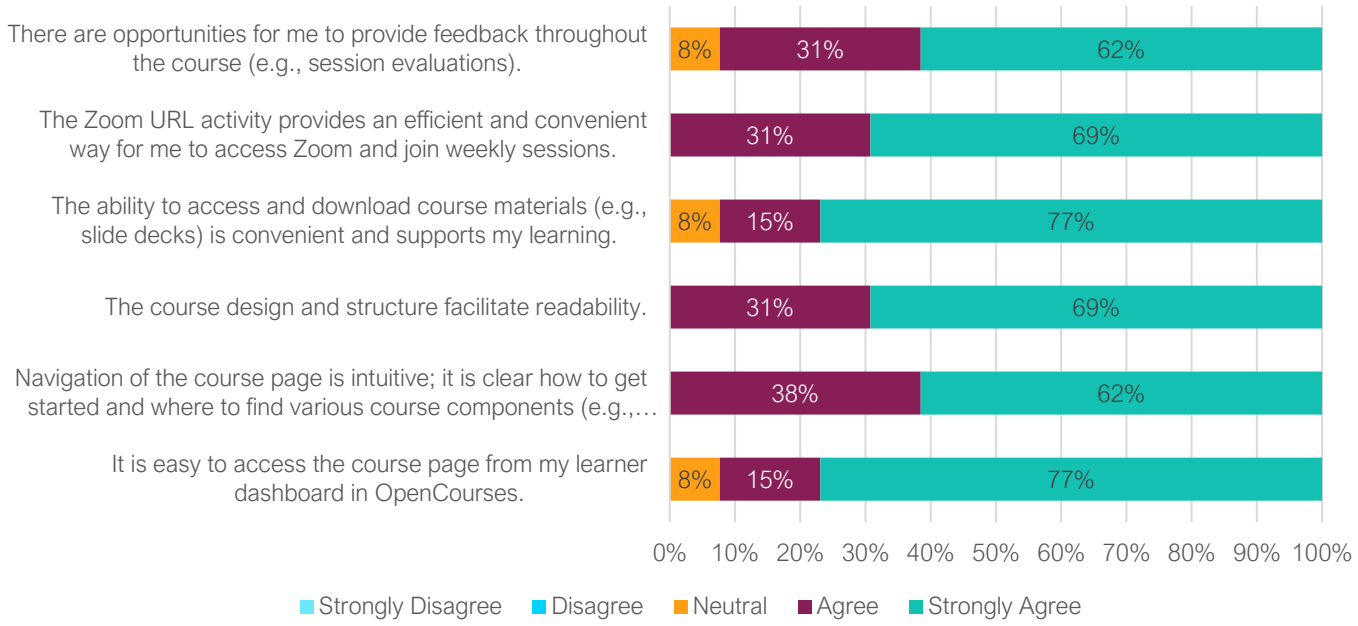


Table 6. Survey Questions and Examples

Question	Examples
Overall, what do you like most about OpenCourses?	That I can go back and re-study things I don't understand. Easy to navigate and find links to zoom/feedback
Overall, what do you like most about the course?	I liked the interactive examples used in the session (polls). I enjoyed multiple presenters on different topics - it kept the presentation engaging. Informative and well-designed. Lots of content I was not aware of. Very relevant information was provided. Presenters were well informed and gave us the opportunity to answer questions.

Note: Examples include responses from several surveys that was administered throughout the course.

Table 7. Conquering the K Metrics for Live Sections

Conquering the K Metrics	2020 Live* (Learn)	2021 Live (Learn)
Enrolled	76	124
Completed (Partial)	61	67**

* These data are cumulative for the two tracks held live in person in February of 2020.

**Estimated based on session attendance counts and not named attendance data.

Table 8. Conquering the K Metrics for 2021 Sections

Conquering the K Metrics	2020 Live (Learn)	2021 Hybrid (OpenCourses)*		
		Didactic	Workshops	Both
Enrolled	124	152	41	25
Completed (Partial)	67**	7 (20)	18	3

* These data are reported through 12/15/21 and include 6 workshops held between October-December.

**Estimated based on session attendance counts.

Table 9. Conquering the K Hybrid Course Feedback

Question	Examples
Didactic Portion: Overall, what do you like most about this course?	Excellent course. Very helpful advice. Clear, helpful guidance and directions towards additional resources.
Workshops: Overall, what do you like most about the workshop?	Excellent course, I can't wait for the next session! This course was fantastic! It was entirely based on what we needed to learn, specific to our questions, and allowed for open discussion. We were able to present materials and receive very targeted feedback which is absolutely invaluable at this level. The facilitator was helpful, kind, respectful, and very willing to continue to assist us. I would recommend all junior faculty considering a K submission attend this course. The course is very time-efficient and I learn a lot about the grant strategizing and writing. Much appreciate. The instructor was clearly invested in teaching us how to succeed at writing a K application. I deeply appreciated his guidance.

the virtual live course, we only had 10 total preceptors for the 2 workshop sessions, which gave a ratio of 1 preceptor per 12-15 learners. Our solution was to have breakout rooms with 6-8 learners, but have preceptors rotate through 3 different breakout rooms during the session. Our intent was to model peer feedback, have learners practice giving peer feedback in the breakout rooms, and have the circulating preceptors facilitate peer feedback for at least 1/3 of the time for each breakout room. While this was our intent, the execution left something to be desired, and we received negative feedback from the learners on the workshop sessions.

Because of this negative feedback, and especially because we know the workshop sessions are the most impactful for learners, we developed a hybrid version of the course that went live in September. This hybrid course included 1) didactic video content recorded during the 2021 virtual live section and posted in September, and 2) small group workshops available twice per month, the first of which was hosted in October. So far, we have hosted 6 workshops in 3 months.

Comparing the hybrid version to the live virtual version in table 8, we do see similar interest (>100 enrolled learners) and similar attrition (50% attendance). On the other hand, if we look at those who have enrolled and/or completed both portions, the numbers are concerningly low (25 enrolled in both, and only 3 completions of both in 3 months). However, the feedback received so far is positive (see table 9) and some learners (see number of partial completes in parentheses in table 8) seem to pick and choose among the didactic content. In su mmary, a more in-depth summative evaluation of the new hybrid version of the Conquering the K course may be needed as completion metrics may not fully account for the success of this course.

User Metrics

With OpenCourses and People (a database of individuals 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 generally available to the whole of the MGB research community.

As shown in figures 8, our users are primarily within MGH, but we are reaching other individuals within the wider system. Additionally, while most our courses are geared toward investigators, we do offer courses aimed specifically at study coordinators and other research staff. This ratio of investigator heavy content is reflected in our audience ratio as seen in figure 9. The data reported in figures 8 and 9 reflect only users of OpenCourses and do not include any potential users who only completed courses in the first half of the year.

Education Programs and Collaborations with Other Teams/Departments

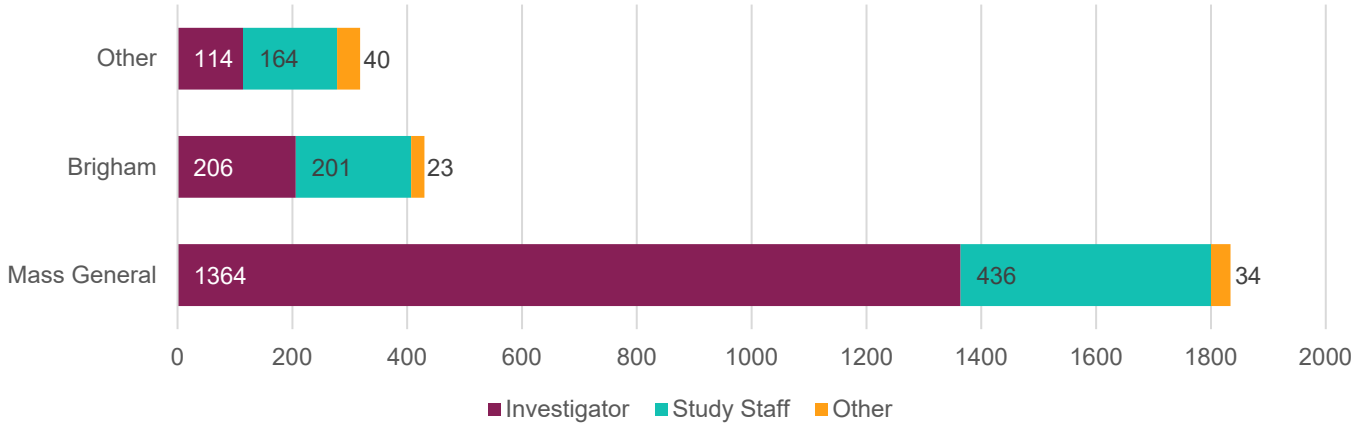
The CCRE values collaboration and transparency. It is also part of our vision to be a leader within the MGB system in educational programming. To these ends, we collaborate with other MGH and MGB stakeholders to produce educational programming.

RCR Program and MGH and MGB research compliance

In 2019, the CCRE took on the responsibility of managing the MGH Responsible Conduct of Research (RCR) Program. Since that time, we have continued to collaborate with MGH Research Compliance and MGB Research Compliance to host a variety of seminars that allow investigators to meet their NIH Responsible Conduct of Research requirements.

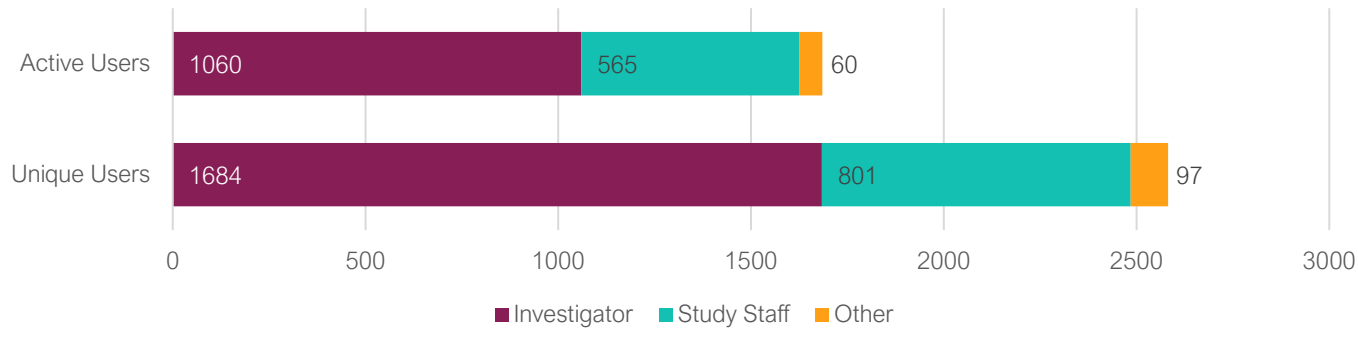
In 2021 we hosted 15 unique and 50 total RCR credit courses, and we plan to host 59 courses in 2022. While the Research Compliance programs provide guidance

Figure 8. User Distrbution by Institution



Other institutions with at least one user include Dana Farber, McLean, Mass Eye and Ear, Mass General Brigham, Newton-Wellesley Hospital, and North Shore Medical Center.

Figure 9. User Distrbution by Role



Active Users are those who have completed at least one course. Most of our users are active: they both sign up for courses and complete them.

on suggested seminar topics, the CCRE takes on the responsibility of identifying and scheduling appropriate speakers and guiding speakers in interactive teaching methods according to NIH requirements. The CCRE also ensure the quality of the learner experience through attendee evaluations which are shared with the speakers. In 2021, this program helped almost 1400 unique learners meet their RCR requirements.

MGH Research Compliance and RITE Committee
In 2021, the CCRE hosted the first convened Research Institute Training and Education (RITE) committee meeting since 2018 to communicate about our new learning management system and new course development process. With the decommissioning of Learn, we assisted MGH research compliance with transitioning to host some of their trainings on OpenCourses. We have been in conversation with other compliance groups within MGH to do the same. We also worked with MGH Biosafety officer, Anne Sallee, to build an on-demand IATA training course. We also host the MGH Research Compliance quarterly discussion group.

Table 10. Responsible Conduct of Research Courses Summary Metrics

RCR Program 2021 Summary	Unique	Total
Courses	15	50
Learners Enrolled	1885	3677
Learners who Completed	1399	2191

Research Information, Security, and Computing (RISC)
We work with the Research Information, Security, and Computing (RISC) group and host their educational offerings. These courses detail how the research community can use the following systems: REDCap, RPDR, and the MGB Biobank. This is a successful collaboration offering 7 unique live, 1 on demand, and 24 total courses and reaching 891 unique learners in 2021.

Table 11. List of Responsible Conduct of Research Courses and Their Metrics

RCR Credit Courses in 2021	Instances	Total Enrolled	Total Completed
Clinical Research Inspections and Audits	2	172	108
ClinicalTrials.gov	10	649	419
Good Clinical Practice in Research	2	287	101
QI Bootcamp for Clinical Researchers and Study Staff	19	1164	791
Academic Medicine, Industry and Collaborative Research in the Era of Emerging Technologies and Precision Health	1	126	91
Managing Conflicts of Interest	1	36	17
Mentor-Mentee Relationships and Responsibilities	1	105	68
Research Integrity	1	44	37
Responsibilities of Scientific Peer Reviews	1	38	23
Responsible Authorship	1	114	0
Responsible Authorship and Publication	1	44	28
The Lab Avoiding Scientific Misconduct	1	121	90
Responsible Data Management	1	103	42
Responsible Conduct of Omics Research	1	87	58
Writing a Clinical Research Protocol	7	587	318
Grand Total	50	3677	2191

Table 12. Research Information, Security, and Computing Courses Summary Metrics

RISC 2021 Summary	Unique	Total
Courses	8	24
Learners Enrolled	1355	2219
Learners who Completed	891	1229

Table 14. Compliance and Education Courses Summary Metrics

C&E 2021 Summary	Unique	Total
Courses	9	76
Learners Enrolled	1984	4614
Learners who Completed	1508	2812

Table 13. List of Research Information, Security, and Computing Courses and Their Metrics

Format	RISC Courses in 2021	Instances	Total Enrolled	Total Completed
Live	Biobank Portal	6	390	206
	Monthly REDCap User Group Meeting	4	126	79
	REDCap eConsent Functionality	2	200	117
	REDCap Survey Features and Functionality	2	256	118
	REDCap: Getting Started	2	217	151
	RPDR	6	790	433
	RPDR Advanced	1	163	96
On Demand	Guide to the Research Patient Data Registry (RPDR) Simulation	1	77	29
	Grand Total	24	2219	1229

Table 15. List of Compliance and Education Courses and their metrics

C&E Courses in 2021	Instances	Total Enrolled	Total Completed
Clinical Research Inspections and Audits	2	172	108
ClinicalTrials.gov	10	649	419
Human Subjects Research Recordkeeping and Record Retention*	10	705	455
IND and IDE Responsibilities for Sponsor-Investigators and Study Staff	6	243	158
Informed Consent Including eConsent*	7	366	189
QI Bootcamp for Clinical Researchers and Study Staff	19	1164	791
Study Team Data Management and Internal QA Monitoring Plans*	10	516	248
Virtual Visits*	6	212	126
Writing a Clinical Research Protocol*	7	587	318
Grand Total	76	4614	2812

* New Course in 2021.

HRA C&E
We work with the MBG Human Research Affairs Compliance and Education (C&E) Office and host their educational offerings. We host several courses every month offered by this group. This team's offerings grew from 4 unique and 22 total courses in 2020 to 9 unique and 76 total courses in 2021. This collaboration also reached 1500 unique learners across MGB this year.

Other Teams within MGB and MGH
We continue to be open to collaborating and engaging with more teams throughout MGH and MGB. We began discussions with the Center for Faculty Development about hosting their courses and events on our OpenCourses platform. While we have not concluded our discussions, we continue to work with them to suggest learning technology solutions that could meet their needs.

Systematic Evaluation of Courses
We are working on implementing a new process of systematic evaluation of all courses. Previous methods of course evaluation included manual surveys, general ratings and comments collection, and individual course data review with limited formal analysis. As evaluation is a systematic process, we are working to conduct evaluation of both courses and our center's performance in planned and purposeful ways. Through our efforts with this implementation, we hope to enhance the decision-making process for improving and refining our programs, processes, courses, and systems.

For our courses, surveys will be administered for all courses subject to evaluation. We hope to collect valuable feedback towards maintaining and improving the quality of our courses, the learner's experience, and the instructor's teaching experience. In addition, course evaluations may be used to:

- Help instructors improve the future of delivery of courses;
- Inform learners about courses and instructors;
- Indicate teaching effectiveness and learner satisfaction;
- Help the CCRE and faculty committees in their decision-making processes.

Overall course evaluation results seek to answer the following key questions for the CCRE:

1. In what areas/aspects and to what extent does the course need to be modified to better meet the expectations and needs of the target audience?
2. In what areas/aspects and to what extent does the course need to be modified to fulfill the intended learning outcomes?
3. In what areas/aspects should the CCRE suggest reasonable next steps and to what extent will those steps promote improvement to CCRE's curriculum?

These key questions will focus and guide the evaluation process. Based on these key questions, our instructional designer has developed a question bank of evaluation questions for evaluating our courses and our center's overall performance. Evaluation findings will be fed into an improvement-focused process that further develops, refines, or revises the course being evaluated. We are working with our SMEs to tailor individual course evaluation surveys from the larger evaluation question bank so that we collect data relevant to each specific course as well as data that can be incorporated into an analysis of the full curriculum. While the development of this evaluation process is still in the early stages, we intend to continue to iterate and improve our efforts toward a systematic evaluation of our center's activities.

Course Management Application
We are working on implementing a course development and management application to ensure systematic quality control of the design, development, implementation, and delivery of courses. This application aims to improve internal consistency and ensure adequate resources necessary to address project goals and timelines are available. In addition, this application will help facilitate the process of working with SMEs; manage our existing curriculum; evaluate learning, performance, and change initiatives; and communicate and report evaluation activities and findings. We envision this application in three sections. The first will be project management for the development of new courses or courses in revision. The second will be program management of existing courses including ongoing formative evaluation. The third will be the formal summative evaluation process resulting in decisions to retire, revise, or maintain the course as is. These stages of the application will use the CCRE's course design guidelines to reflect best practices in 12 major areas and implications for instructional design:

1. Learner Expectations
2. Course Design
3. Use of Multimedia
4. Timing and Pace
5. Course Interactivity
6. Teaching Strategies
7. Evaluation and Feedback
8. Level Difficulty

9. Learner Motivation
10. Learning Outcomes
11. Diversity, Inclusion and Accessibility
12. Resources and Support

Moreover, this application emphasizes three (3) key stages that are present in any meaningful course development process and high-quality learner experience:

- Analysis (determine performance measures)
  - Learning contexts
  - Learners
  - Learning objectives
- Strategy (develop instruction)
  - Organizational strategies
  - Delivery strategies
  - Management strategies
- Evaluation (revise instruction)
  - Formative evaluation
  - Summative evaluation

While this application is currently in the planning stages, we intend to have a pilot or minimally viable product in 2022.

DCR Website

We use our website to communicate with the public as well as our target audiences. In January 2021, we transitioned from the previous TeamSite website to hosting our own website using WordPress. This allowed us more control to quickly maintain our website and curate the content therein. Once we moved to the new website, we turned our static pdf lists of courses for specific roles into a sub-page with links directly to OpenCourses for those suggested courses. The website allows us to dynamically curate content, resources, and courses for our target audiences. Below is a sample of our webpage metrics for November 2021.

Figure 10. WordPress Metrics for November 2021

Pageviews: 1,370	Average Time Spent: 1 min 9 sec
Top 5 Pages: 1. DCR Landing Page 2. Suggested Courses 3. Units and Centers 4. Our Faculty 5. Clinical Research Day 2021	

In 2022, we plan to implement systems integrations between our website and OpenCourses to display our course catalogue and facilitate our target audiences in finding the courses they need.

Advertisement through Constant Contact

Toward the end of 2020, we switched from Lyris to using Constant Contact for our advertisements. Lyris, while provided free of charge by RISC, had several down sides. It required hard coding emails with html, there was no automation for listserv maintenance, and emails were received 24-48 hours after send. Constant Contact, on the other hand, has a means to communicate with the People application via APIs. This allows for scheduled tasks to make daily automatic listserv updates without manual input. Due to this factor, Constant Contact offers a more efficient system for listserv maintenance. In addition, it is very easy to use and create email templates without requiring html coding knowledge, and it sends emails within 10 minutes; there is no delay in outgoing emails. Furthermore, Constant Contact provides meaningful analytics that we can use to hone our advertising strategies. For example, the reporting dashboard can shine insight on our top emailing stats (e.g., open rate, unopened rate, click rate, bounce rate, etc.) over a specified period of time. Below is a summary of our email metrics for 2021 using Constant Contact.

Figure 11. Constant Contact Metrics for 2021

Number of Campaigns: 160	Average Open Rate: 33%
3 Emails per Week	Average Click Rate: 3%
Total Emails Sent: 1,387,214	

In 2022 we plan to revise our advertising strategy to incorporate on demand courses periodically and target specific courses as needed. We are also brainstorming ways to package our courses in ways that make it easy to find beneficial courses or programs to meet the needs of our adult learners.

Clinical Research Day Event and Application

Clinical Research Day is an important event that the DCR and CCRE produce every year to celebrate and highlight clinical research being done at MGH. Not only did we host the event, but we also developed an application to manage the various pieces of the event. This internally developed application housed the submission process, the review process, the event schedule with links, award nominations, award announcements, as well as the abstract and poster

galleries. A full report comparing Clinical Research Day 2017-2021 can be found here.

We have also supported other MGH teams by sharing the application engine with them. The Scientific Advisory Committee used our application to receive abstract/ poster submissions as well as host a poster gallery at their annual meeting. And the Department of Psychiatry used our application to receive nominations for their annual Psychiatry Clinical Excellence Award.

Jamie Quinkert, Assistant Director

In December of 2020, Jamie Quinkert was hired as the new Assistant Director. Their goal for 2021 was to get a sense of the scope of the current DCR curriculum, the scope of various similar curricula, and training and learning trends generally. Their value is as the face of the team. They liaise with various instructors and subject matter experts (SMEs) and other stakeholders in developing, maintaining, and sharing feedback on courses and educational programs. They help shape not only individual courses in discussions with instructors and SMEs but also educational programs and curricula by taking a holistic view of these programs and working to meet the needs of both the audience and stakeholders. They bring their 7+ years of experience in clinical research operations and 8+ years of experience in web labs to this endeavor. With guidance from Teresa on formal instructional design and adult learning best practices, Jamie can suggest concrete steps for instructors and SMEs to take to improve learning experiences for learners.

Future Focus

Technology and Analytics

The CCRE will continue to invest in smart technologies that our small team can leverage to deliver high quality educational opportunities to a wide research audience. In 2021 we pilot tested and implemented several new technologies, including our new learning management system OpenCourses, a new advertising platform Constant Contact, and a new website using WordPress. We plan to continue to assess, build, and implement technologies to serve our needs in 2022. We will prioritize technologies that integrate with our current systems, that are user friendly for us, our SMEs, and our learners, and that allow transparent tracking and meaningful analytics.

Some of the projects we plan to work on in 2022 include reviewing and updating the content and use of our WordPress site, making strategic advertising plans to target specific audiences at specific times, expanding our advertising plans to take advantage of the system resources we have available and target research audiences system-wide, and exploring content packaging strategies to make it easy for our learners to find what they need. We will also focus on building and refining our Course Management Application and evaluation procedures to keep track of our growing curricula and ensure our offerings maintain a high standard of excellence.

OpenCourses

The CCRE has plans to further enhance our educational offerings by integrating with LinkedIn Learning. This integration allows LinkedIn Learning courses and learning paths to be integrated into OpenCourses. With this integration, we can:

- Track user course progress in OpenCourses when learners launch and consume courses within OpenCourses.
- Allow users to search, find, and launch LinkedIn Learning content from OpenCourses.

We are in the process of implementing Security Assertion Markup Language (SAML) authentication in OpenCourses. The process needed to integrate with LinkedIn Learning will be downstream of enabling SAML single sign on.

The CCRE is also tackling many other projects to further enhance OpenCourses for its users. For example, projects include:

- **Auto-generation Course ID Plugin:** This plugin will help OpenCourses administrators manage and keep track of courses in the system.
- **WordPress Integration:** This integration allows viewers to browse our course catalog on our WordPress site, and it also enables registration to courses.
- **Course Application Plugin:** This plugin will serve to iterate and improve on the existing workflow of course enrollment via submitting a course application on OpenCourses.

Tableau

The CCRE runs weekly reports on OpenCourses to view course attendance, activity, and other metrics. Ideally, this project will connect Tableau with OpenCourses to automatically generate what is currently a manual task.

The final dashboard should display a list of courses that happened in the past week, the enrollment, the attendance, and the completion of the courses. Other things to consider are general site metrics: total number of active users in the

past week, total number of new users in the past week, total new enrollments, and so on. The dashboard should be flexible and should be changed as the needs of the CCRE changes.

Curricula Development

Another focus for 2022 will be developing curricula. MGB Human Research has plans to consolidate clinical research regulations and compliance training, and so we will shift our focus to pragmatic training and communities of practice. The units and centers of the DCR engage with the research community on 3 different levels: 1) at one end, they offer one on one consultation services for investigators or study teams who need project-specific help; 2) at the opposite side of the spectrum, many support educational offerings that reach a wide audience within the research community; and 3) in the middle, several support peer networks or small group communities of practice to facilitate social learning. In 2022, we hope to focus on these communities of practice to improve their impact and expand their reach. We also hope to expand and explore different learning activities, content delivery strategies, and methods of learner engagement other than the usual seminar lecture with questions and answers to deliver transformational learning experiences.

In addition to the overall curricula development goals described above, we have several individual courses in development.

- **K to R Transition Course.** We are working to turn our K to R Transition Course into a hybrid course along the same lines as Conquering the K.
- **On Demand Versions of Existing Live Courses.** We have several live courses that we intend to offer as on demand courses between live offerings including Basic Biostatistics (already live), Resources for Global Health Research at MGH (in development), and Introduction to Bioinformatics (in development).
- **Munn Center Grand Rounds.** We are working with the Munn Center to expand the reach of their quarterly grand rounds and advertise it to the general DCR audience.
- **Research Ethics Seminar Series.** The inaugural Research Ethics Seminar Series, a collaborative effort between the DCR's Research Ethics Unit and the Harvard Center for Bioethics, is scheduled for the end of January 2022.
- **PCORI Funding.** A collaboration between the DCR's Patient-centered Outcomes Research Unit and Harvard Catalyst is in the works for a hybrid course on applying for PCORI funding.
- **Mentoring Across Differences.** We are working with Sherri-Ann Burnett-Bowie, MD, MPH and Jessica Haberer, MD, MS to tailor content from an existing mentoring course of theirs into a Mentoring Across Differences Course for a wider audience within the DCR.
- **Comparative Effectiveness Research Unit.** We are also working with James Meigs, MD, MPH to create an on-demand course on working with his Comparative Effectiveness Research Unit.
- **Revision of Existing On-demand Courses.** We also intend to review our current set of on demand courses and prioritize them for revision and updating.
- **Instructional Design Curriculum.** Our Instructional Designer is working on developing a curriculum to provide our faculty, staff, and learners with resources to facilitate a successful teaching and learning experience, as well as provide technology, instructional design, and training support.

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

The Mass General Brigham Biobank at MGH, under the direction of Susan Slaugenhaupt and Jordan Smoller, was devised to be a collaborative effort among patients, clinicians, and scientists to better understand disease, identify novel targets for therapy, and enable personalized medicine by collecting and storing fully consented blood, serum, and plasma samples, linked to electronic medical records and lifestyle and family history survey data, from patients across the institution. Through the Mass General Research Institute, resources were committed to add personnel, space, and equipment to jumpstart the consent and collection program at Mass General. With the additional resources contributed over the past six years, we have seen a dramatic increase in patient recruitment to 131,000+ consented patients—with 64,000 consented at MGH, 4,300 at McLean, 1,500 at Spaulding, and 900 at Mass Eye & Ear. Though the COVID-19 pandemic has temporarily slowed our rate of growth, through the dedicated efforts of the

team, including site-Principal Investigators, Kerry Ressler, MD, PhD (McLean), Ross Zafonte, DO (Spaulding), Lucia Sobrin, MD, MPH (Mass Eye & Ear) and Janey Wiggs, MD, MPH (Mass Eye & Ear), and Mass General-based managers Joe Coletti and Tasha Tchamitchian, the Biobank program has enjoyed great success since the implementation of the strategic plan.

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

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

The Mass General Research Institute continues to be committed to increasing awareness of the Biobank, and now All of Us, to patients and investigators. The Community Advisory Panel (CAP) that launched in 2015 has expanded its membership and has added All of Us to its purview. The CAP continues to be a tremendous success with members contributing valuable input on patient engagement efforts. Biobank sample collection has been accelerated Mass General Brigham-wide by the integration of Sunquest sample collection orders into Epic, which has made contributing a sample to the Biobank significantly easier for our patients, and accelerated sample collection. The MGB Biobank has genotyped or sequenced over 56,000 patient samples to date which has catalyzed research requests by making data freely available to investigators via the Biobank Portal. To date the Biobank has supported over 400 studies with specimens and data. In parallel to the genotyping work, the Biobank continues to return medically actionable genetic results for pathogenic variants within 80 genes (as recommended by the American College of Medical Genetics and Genomics) to Biobank participants. The Biobank provides genetic counseling services to return these results and assist with clinical confirmation. Over 186 medically actionable results have been returned to patients so far.

Since March of 2020 the Biobank has supported the following Covid-19 initiatives:

- Clinical Assessment and Sampling of Individuals with or at Risk for Coronavirus Disease 2019 (COVID-19) in Collaboration with the Mass General Brigham Biobank—Investigators: Xu Yu, MD (MGH) and Jonathan LI, MD (BWH)
- Clinical Assessment and Sampling of Pregnant Women with or at Risk for Coronavirus Disease 2019 (COVID-19), and Healthy Pregnant Controls, in Collaboration with the Mass General Brigham Biobank—Investigator: Andrea Edlow, MD (MGH)
- MGH COVID-19 Sample Repository, in Collaboration with the Mass General Brigham Biobank—Investigator: Marcia Goldberg, MD
- Biorepository for Samples from those at Increased Risk for or Infected with SARS-CoV-2, in Collaboration with the Mass General Brigham Biobank—Investigator: Lindsay Baden, MD (BWH)
- Biorepository for Samples from those at Increased Risk for or Infected with SARS-CoV-2 in Collaboration with the Mass General Brigham Biobank: Prospective SARS-CoV-2 Serological Surveillance of Brigham Health Employees—Investigator: Lindsay Baden, MD (BWH)
- MGB PROTECTS: Mass General Brigham Prospective Repository of Organization-wide Testing for COVID-19 to Track Serology—Investigators: Stephen D. Wiviott, MD (BWH); John Iafrate, MD, PhD (MGH); Scott Weiss, MD (BWH); Lisa A. Cosimi, MD (BWH); Merranda Logan, MD, MPH, CPPS (MGH); Robert J. Birnbaum, MD, PhD (MGH); Ravi Thadhani, MD, MPH (MGB)
- Staff Redeployment to:
  - Moderna Covid-19 Vaccine Clinical Trial
  - Janssen Pharmaceuticals Covid-19 Vaccine Clinical Trial
  - MGH Occupational Health Contact Tracing
  - MGB Personalized Medicine Laboratory for Molecular Medicine

A major focus of the Biobank during 2021 was the reconsenting participants to a new consent form which significantly increases the potential to return research results to participants—which may improve their health.

In addition to being able to return ACMGG monogenic actionable variants, when specimens are sequenced, we will also be able to return approved high polygenic risks scores, pharmacogenetic risks, and information about heredity, ancestry, and traits. During the work from home period previously consented patients were contacted by phone, email, and post. To date over 22,000 patients have reconsented or consented to this new form. Another major focus was relaunching in-person recruitment which resumed in June of 2021.

Goals for this coming year include continued support of Covid-19 research initiatives; consenting and re-consenting patients to the Biobank's new consent form which expands the return of research results; continued expansion of re-integration of Biobank and All of Us with clinical teams throughout Mass General to promote recruitment efforts when appropriate; increased visibility of both Biobank and All of Us within and outside of our institution; rebranding of the Biobank kiosk in the Yawkey building to promote both the Biobank and All of Us programs; and expanding research use of the Biobank data and sample resources.

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.

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 2021, much of the focus of the TRC organization remain focused on continuing COVID-19 related projects that were initiated in 2020, but we were delighted to see a significant re-engagement with industry sponsors on a host of non-COVID projects. Some highlights of this work are presented below.

Accomplishments

The total number of new TRC studies initiated in 2021 was 44, down from the 2020 Covid high of 52, but still substantially more than the pre-COVID number of 29 studies that the TCRC averaged over the first 3 years of full annual operation since the new TCRC facility opened in late 2016. Revenues coming into funds whose studies are utilizing the TRC component of the TCRC rose to $5.1M in direct costs and $8.4M of total costs, substantially more in both categories than were generated in 2019-2020. At the close of the calendar year 2021, there were 74 active studies being conducted in the TRC.

A substantial amount of the TRC activity and revenue was attributable to COVID vaccine studies, the largest of which, the J&J initial vaccination trial, was led by the TRC's one, full-time clinical investigator, Rick Mofsen, DO. The original model for the TRC business plan was built on the concept that committed faculty working as members of the TRC staff would be critical to driving activity and revenue in the facility, and Dr. Mofsen's efforts have validated that concept. The 74 active studies at the end of Q4 2021 is up from 60 in Q4 2020 and 69 at the end of Q4 2019. This increase in study number back to the pre-COVID era value is encouraging in that it suggests a good return of clinical research activity to our White 12 facility. The pace of activity in the TCRC has never seemed greater and that impression is borne out by the study visit numbers in 2021 which were more than twice the number of those in 2020 or 2019 at a total of 2,788 visits.

While the numbers are important parameters by which we can judge the overall activity and value of the TRC to our clinical research community, they do not capture the quality or innovation of the work we facilitate. In the COVID arena, new studies initiated in 2021 began to explore some of the more challenging problems associated with SARS-Cov-2 prevention or complications by investigating the utility of COVID-19 booster vaccinations in patients with autoimmune disease that had responded poorly to initial vaccination (PI - Zachary Renfro-Wallace, MD, MSc, Assistant Professor) or the use of a novel anti-inflammatory peptide for the treatment of Multisystem Inflammatory Syndrome in Children (Mark Siedner, MD, MPH, Associate Professor). Extensions of the initial J&J vaccine trial added studies of the J&J booster program (led by Dr. Mofsen) as well as testing of Moderna's mRNA vaccines in children ages 6 months to < 12 years (Wayne Shreffler, MD, PhD, Associate Professor). All of these trials are likely to contribute major new insights into how healthcare organizations can best treat to prevent, or ease the complications of, SARS-COV-2 infections in patients, young and old, healthy and with pre-existing conditions from around the world.

Thirty-two of the TRC studies approved for conduct in the TCRC in 2021 were not COVID-related. These trials explore the remarkable array of human illnesses that fall within the purview of faculty investigators at MGH. Some of them explore areas of long-standing interest at MGH with very sizable populations of patients, such as ALS, Schizophrenia, Parkinson's, Chronic hepatitis, and Heart failure, while others tackle rarer illnesses that have come to the fore more recently because of advances in medical diagnosis or the advent of potential new therapeutics (Alexander disease (a leukodystrophy disorder), eosinophilic esophagitis, or Canavan disease (degenerative brain disease now being treated with a novel AAV gene therapy). One need only spend a few days in the TCRC to begin to understand the breadth of knowledge and talent of the clinical research community at MGH, but also the chasm in our understanding of so many illnesses that clinical research must bridge in order to improve the lives of the patients who seek help at our institution.

The Translational Medicine group (TMG) of the TRC, which assists investigators at MGH develop novel therapies, often helping to prepare their way into the clinical trial facilities of the TCRC also had a busy year. Led by Yuan-Di Halverson, PhD that team contributed to the development of multiple novel therapeutics for a variety of investigations including: work to develop a gamma secretase modulator for Alzheimer's disease (PI- Rudolph Tanzi, PhD), ketamine intranasal delivery for depression (PI - Maurizio Fava, MD), a novel therapeutic for combined variable immunodeficiency disease (PI - Jocelyn Farmer, MD, PhD), and the use of clavulanic acid as a treatment for obsessive compulsive disorder (PI - Kyle Williams, MD, PhD) . These projects tap into the expertise of the TMG in overcoming obstacles academic investigators commonly encounter in early-stage drug development across a broad array of pre-clinical and early clinical problems.

Other noteworthy contributions of the TCRC /TMG to clinical research at MGH in 2021

- Our nursing director, Kathy Hall, was awarded the first ever Award of Distinction by the Division of Clinical Research on Clinical Research Day for her extraordinary leadership in helping to launch and manage so many of the clinical research studies initiated during COVID
- The long-standing development of a novel SGLT-2 inhibitor by the TMG group on behalf of Theracos, Inc submitted its NDA package for the drug's approval in the fall of 2021. The development of this drug from its initial pre-clinical selection all the way through to the NDA filing was overseen by Dr. Yuan-Di Halvorsen
- The J&J adenovirus vaccine trial to which the TRC contributed more than 300 patients was authorized for use by the FDA. This effort was led by Rick Mofsen, DO, Boris Juelg, MD, PhD and Efren Flores, MD. This effort was coordinated and assisted by the entire MGH TCRC staff including Kathy Hall, Sara Luthern, Lynelle Cortellini, Tony Veilleux, Amanda Griffin, Tong Wu and scores of others as well as tremendous support from the MGH Research Pharmacy (John Vetrano, PharmD, Cheryl Reilly-Tremblay, RPh and their staff)

Adaptations Planned

2021 was the first year that the business model of a TRC investigator, supported fully by the center, could be tested. This model contributed to a substantial growth in the TRC's activity and revenue generation. The success occurred in the context of an explosion in COVID clinical trial work, especially the testing of new vaccines. Assuming the COVID work wanes over time, it will be important to determine in 2022 if this model can remain similarly productive. The TRC plans to hire additional dedicated faculty investigators on a part-time basis in 2022 to determine if that model of employment can work proportionately well.

As highlighted in several prior TRC annual reports, we have continued to struggle with recruitment success and, at the end of 2021, a full-time recruitment coordinator for the

TCRC was hired. With new policies utilizing an "opt-out" approach to contacting patients in the MGB EPIC database system, we are expecting to see better recruitment success through the efforts of this recruiter and new electronic recruitment tools he now has available.

SUPPORT

MGH Research Institute Hits $1 Billion- AGAIN!—Gary J. Smith, MPA, Senior Administrative Director, MGH Research Management

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

During our second year of the COVID-19 Pandemic, research continues to thrive at the MGRI. Research revenues for FY21 again reached an all-time high of $1.197B ($917M direct costs and $280M indirect), a remarkable $184M (18.1%) increase from FY20. Our awarded dollars from the National Institutes of Health (NIH) in FY21 increased from $551M to $601M (8.9% increase). In FY21, MGH jumped from the #12 to #8 spot in NIH funding for all institutions and continues as the #1 ranked independent hospital, a spot we have held for the past 20+ years. The percentage of funding awarded to MGH from the entire NIH extramural grant pool (market share) grew to 1.8%, up from 1.6% the previous fiscal year.

Overall, MGH submitted another record of 4,971 research proposals to all sponsors in FY21, an impressive increase of 5.5% from the prior fiscal year. This is the second year of a significant increase in submissions. We've shown over the past two years that shifting much of our administrative work to remote does not negatively impact our ability to submit grant applications. DHHS success rates for MGH proposals is an impressive 27%, which is higher than the NIH national average of 21%.

Research expenditures from direct DHHS funding (which consists mostly of NIH funding and excludes incoming subcontracts), accounts for 44% of MGH research. DHHS-sponsored research expenditures increased significantly from $442M in FY20 to $524M in FY21. Federal Subcontract (predominately NIH) expenditures were $139M (11% of total research) in FY21, increasing from $103M in the previous year.

Research expenditures for all our other non-NIH sponsor types in FY21 totaled $534M which was a 14.1% increase from FY20. All Other Sponsor (1.8%), Non-Profit (17.7%), Foundations (25.8%), Industry (35.2%) and Other Federal (23.1%) categories saw increases from FY20. Our research activity type has recently shifted to 51% clinical (clinical trials and other clinical research) and 44% basic/fundamental research of the total research portfolio. In past years, the split has been close to 50/50 between clinical and basic research. Training activities make up the remaining 5%.

Our researchers are contributing to the COVID-19 Pandemic in a major way. The MGRI has received $188.8M in research awards since the beginning of the pandemic. 85% of the funding has come from the federal government (49.9% NIH, 35.1% Federal Subcontracts). FY21 COVID-19 research expenditures were $63.2M of which 68% was in clinical related research (20% clinical research, 48% clinical trials).

In aggregate, research activity (direct + indirect dollars) continues to comprise slightly under one quarter (23%) of the total MGH annual operating budget and is distributed across more than 30 departments and centers.

Our financial outlook for FY22 is strong. Early indications (first quarter FY21) show overall research expenditures running on budget and are expected to match or slightly exceed FY21 by fiscal year end. With our early budget performance, along with the significant increase in grant proposals we saw in FY21, we anticipate the financial picture to remain strong in FY22 and beyond for the MGH Research Institute.

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 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 in which scientists can concentrate on their research without having to worry 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 seriously its responsibility to analyze research space utilization using sophisticated metrics to ensure that all research space is used in the most effective manner possible.

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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-three buildings across seven campuses in four cities. The percent allocations amongst the campuses is also similar to last 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 $185 per square foot in Fiscal Year 2020 to $209 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 Cambridge, 5 Longfellow, and Thier.

Fulfilling outstanding space requests remains one of RSMG's most difficult challenges, particularly when there are few if any opportunities to add new space to our current inventory; thus, the only option available is to renovate existing space to make it more efficient. RSMG works with ECOR, RISC, and the research community to better understand the true space requirements and promote space adjacencies amongst collaborative groups. Outstanding space requests from departments with valid funded grants averaged 91,574 nasf over the past five years. In September of this year space requests increased to 41,375 nasf for wet space and 32,570 nasf for dry space, a total of 73,945 nasf. Never static, the current space request total in December 2021 is approximately 76,945 nasf, reflecting new Institution and Department initiatives.

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

In Fiscal Year 2021 with the reopening of research, renovation projects resumed. A total of twenty-seven renovation projects were underway with a total budget of $49,389,101. RSMG saw the completion of seven projects this year, including expansion of research space for The Ragon Institute at 400 Tech Square and addition of research space at 101 Merrimac Street. The completed projects had a total budget of $9,072,445. Multiple projects are expected to be completed in 2022.

Fiscal year 2021 brought the second annual online certification of space, agreements, and people electronically in Insight. The 2020 asset tracking upgrades allowed for 2021 certification of assets via Insight. This enhancement is critical to satisfy compliance with tracking capital equipment purchased with research funds. Since inception of the original Research Space Management Data Base at MGH, RSMG has always kept inventory of capital equipment purchases which was subject to frequent audit. 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 which serves over 75 Units, oversees developer rooms, CO2 tank farms, electronic bulletin boards, and shared copy machines, as well as AV support for all research conference rooms. Monthly safety surveillance rounds are organized and conducted with other key support departments. This year, in collaboration with Environmental Health and Safety, a successful amnesty program was organized that resulted in removing approximately 3,000 plus bottles of chemicals per site. MGH Research Building Management, in collaboration with BWH, McLean, Spaulding, and MEEI, secured competitive pricing for laboratory purchases of -80 freezers offering a significant rebate back to the labs with the expectation to continue this cost saving partnership in the coming years. Collaborative applications such as Zoom and Teams were initiated in conjunction with conference room upgrades with completion by the end of February 2022. Further enhancements will be initiated on the smaller conference rooms in the new fiscal year. New additions for 2022 include conducting safety rounds in all leased lab space, working with the Boston Fire department to improve lab safety and cleanliness, and monthly training for new employees in the proper procedures for use of research autoclaves.

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

On any given day, approximately 150,000 mice, rats, guinea pigs, rabbits, sheep, pigs, non-human primates, and amphibians plus more than 35,000 zebrafish are housed and used within 95,000 square feet dedicated for such purposes on all 3 MGRI campuses. In addition, the MGRI operates two off-site facilities including a BL-2/BL-3 rodent facility that supports the Ragon Institute in Cambridge, MA, and a rodent facility at 65 Landsdowne Street. The MGRI animal program maintains a contractual agreement with Biomere (Worcester, MA) to support our increasing non-human primate housing needs and a collaboration with Tufts University, Cummings School of Veterinary Medicine, North Grafton location to offer relief to our heavily utilized in-house livestock housing 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, including seven (7) ACLAM-boarded veterinarians and a leadership team of 24 mid- and director-level managers, who provide these services throughout the MGRI. In addition, CCM has two (2) veterinary residents in Laboratory Animal Medicine and Management (LAMM), the first residency with an equal focus on clinical medicine and program management in the country. This spring 2022, two (2) additional veterinary residents will be selected to meet the total number of planned participants. This residency is recognized by the American College of Laboratory Animal Medicine (ACLAM) as well as MGH's Graduate Medical Education (GME) Program.

The MGRI animal care and use program has functioned under applicable Emergency Response Plans (ERP) with CCM's ERP serving as the primary guidance to the research community. Detailed descriptions of the ERP-specific personnel safety and animal welfare requirements can be found in the various guidance documents currently published and/or archived on the Animal Program Coronavirus webpage (https://mghresearch.partners.org/coronavirus-animal-research-planning-guide/).

Specific CCM efforts taken in 2021 are noted below:
The MGRI experienced a growing overall population with the rodent census increasing the most during the end of 2020 throughout 2021. CCM provided husbandry, research support and veterinary care to over 150,000 animals housed in 32+K cages/pens daily. The exodus of staff and eligible workers in the Boston/Cambridge area required created a significant "brain drain" as well as staffing shortages which were complicated by COVID positivity surges. With MGH and MGB's support, CCM was able to incentive current staff to bring strong hire candidates our way. The June 2021 implementation of the CCM referral bonus program with HR assistance supported the recruitment of 10 candidates with 5 being successfully hired and retained beyond the 90-day on-boarding.

Several MGB-wide animal program initiatives were conducted in 2021 including improved rodent genotyping and breeding management services through a Transnetyx partnership, the standardization of supplies and practices between MGH, BWH, McLean and MEEI and offering mentoring and leadership to those programs when needed. On-going corporate level efforts include the investigation of a centralized cage processing resource as well as improved capital equipment preventative maintenance and repair agreements for most of the large-scale and bulk equipment.

MGRI prepared for the AAALAC site visit primarily through the establishment and implementation of the ARC community in addition to ECOR's SAR and the IACUC (more documented in the last paragraph of this report). Monthly educational and instructional presentations by CCM subject matter experts offered laboratory leadership with the tools and materials needed to address regulatory compliance concerns and AAALAC accreditation suggestions for improvements. Following the 2021 AAALAC Site Visit, CCM's program, practices, standard operating procedures, visual controls and organization engagement culture were all mentioned in the commendations shared at the site visitors debrief. The longevity of the CCM culture of engagement and empowerment under our lean management umbrella is one of the reasons that the Center endured following the recovery and escalation of census capacity and services at the beginning of 2021. It is also the reason that CCM Leadership is confident in the transition of research staff to assume more CCM-related husbandry and veterinary care tasks compliantly as a part of the CCM ERP Staffing Continuity Plan which is being implemented during the first two months of 2022.

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In Spring of 2021, CCM also conduct a modified strategic planning initiative to look towards the future where manual labor will need to be replace with more automation and staff need to be properly compensated with more opportunity for professional career growth. One key initiative associated with focusing on our staff's needs more is the continued Be Better Program adapted from the MGB United Against Racism. The Be Better Program Task Force identified 2 key initiatives: 1) a reporting system for racial or discriminatory concerns by CCM employees and 2) department-wide trainings on having uncomfortable candid conversation about racism as well as increasing awareness and discovery of unconscious bias and systemic or institutional racism. These initiatives are in additional to on-going weekly to daily conversations to increase awareness and address inequities as well appreciate the benefit of having diverse perspectives "at the table" throughout the entire Center. Over the past year, these efforts have resulted in the promotion of more BIPOC staff to management positions and increased diversity in the Leadership Team. The Be Better Program takes advantage of many basic lean principles of respect and inclusion of everyone in the organization. Program Leadership expects to collect both qualitative and quantitative data for publication related to the work done in the first 3 years of this initiative.

Even during the pandemic, CCM continued to support several key research conduct support initiatives that are noteworthy. These include: 1) Facilitation of key research program improvements that address regulatory agency focused animal welfare concerns while ensuring that the research can be accomplished successful; 2) Provision of sustained-released buprenorphine administration to support appropriate pain management of USDA-regulated species associated with surgical models, 3) expanded breeding program oversight for the Ragon Institute (> 30 lines), 4) establishment of a *C.bovis*-free NSG Rodent Breeding Program for cancer research and 5) increased study conduct for short-term experiments which mimics our competitors (CROs) business model and is an avenue for increased revenue generation outside of per diems (limited by capacity restraints).

Lastly, CCM hosted virtual site visits in 2021 from manufacturing, healthcare, research and laboratory animal leaders and student internship programs most who expressed interest in adopting a lean operations model in their facilities and programs or learning more about careers in lab animal science and biomedical research. In addition, CCM was invited to speak on our Be Better Program launch and success to date. Seminars and webinars on this subject were presented at annual conferences of the American College of Laboratory Animal Medicine, the American Association of Laboratory Animal Science and the Public Responsibility in Medicine and Research and through our on-going affiliation with the Vivarium Operations Excellence Network (http://www.voenetwork.com).

The Institutional Animal Care and Use Committee (IACUC) governs the use of research animals at MGH. The Committee is fully constituted in accordance with regulatory requirements and is comprised of 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. In December 2021 the IACUC lost a respected member of the committee when Dr. Warren Zapol, IACUC Chair, passed away. Dr. Zapol dedicated his career to biomedical research and was committed to the ethical use of animals and the protection of animal welfare while pursuing ground-breaking medical advances. Dr. James S. Allan, Associate Professor of Surgery, assumes the role of IACUC Chair (formerly IACUC Associate Vice-Chair) and is supported by Mark Randolph M.A.Sc., 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.

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

A primary role of the IACUC is the review and approval of IACUC applications. Over 3,000 transactions were processed by the MGH IACUC in the past year, comprised of new protocols, triennial reviews, as well as scientific and study staff amendments. Complete metrics data for the MGH IACUC are available on the Partners Research Navigator website, Research-Analytics-Reporting.

After overseeing the recovery of the animal care and use program during return-to-research in collaboration with the Attending Veterinarian, the IACUC and the OAWA settled into a "new normal" as part of where-we-work. The OAWA staff retains a hybrid work schedule with a rotating on-site presence. The IACUC meets remotely by videoconference while continuing to inspect animal use facilities and

spaces in-person. Adjusting to hybrid work was not just limited to the Office of Animal Welfare Assurance but also our regulatory oversight agencies that inspect our program. The USDA APHIS Veterinary Medical Officer (VMO) reinstated her routine inspections of our program combining in-person visits of the animal use areas with remote document review. We were inspected in June and October of 2021 and received a "clean" inspection report with no non-compliance items identified. In fact, we were commended for the collaboration between the IACUC, CCM and the research community. 2021 was also the year for our AAALAC International site visit. AAALAC International is the accreditation agency for animal care and use programs. The site visit was to be conducted in 2020 but was postponed due to the COVID-19 pandemic. In November, four site visitors were assigned to evaluate our program. New for this cycle, the opening sessions with the site visit team were conducted remotely followed by in-person inspections of the facilities and animal use areas over a three-day period. Immediately following the site visit, the review team shared positive feedback about our program, particularly regarding the structure that is in place to allow the conduct of compliant animal research. They had some suggestions for improvement, mainly focused on the decentralization of our program into the laboratory spaces. We are working collaboratively to address this and look forward to receiving the formal decision about our accreditation status.

Also of note for 2021, IACUC/OAWA partnered with CCM and the research community, continuing the Animal Research Community (ARC) group. The group met monthly throughout the year to review animal research best practices, discuss new tools and resources and review non-compliance examples. A highlight of these sessions were video-based demonstrations on routine research procedures. Based on the positive feedback from much of the community, the ARC group will continue to meet during 2022, still using a videoconference format that provides more flexibility for representatives to attend.

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

In FY21, the Research Institute continued to support IS needs of project teams across MGH and MGB. Misha Pivovarov, Director of Research IT Solitons, 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 FY21. 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 FY21, 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 (OpenCourses); (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 (c) working with MGB information security and network security teams to develop and implement policies, standards, and procedures for enabling secure and friendly computing environment (b) 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 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. Some of our recent feedback:

- "…you have been so helpful and easy to work with which is a big part of what made my job so enjoyable."
- "Great to have your excellent support and guidance for initiating my lab's in vivo studies at the navy yard. I and my lab team enjoyed your training session and site visit. We look towards continuing our collaboration."
- "You're a pleasure to work with and we really appreciate any future offers to talk to the lab once the details are worked out. Thanks as always for making yourself available as a resource."

I believe this type of relationship is key to our success in getting a compliant outcome. As a result, we have been able to accomplish some very important initiatives in FY21. A few examples below:

- *Research Compliance Workplan:* As a result of the Research Compliance Risk Assessment completed in FY20, Research Compliance has been able to work from a risk-based workplan proactively addressing issues that pose the greatest risk to the institution.
- *iLog, MGH's Controlled Substances Database:* Phase I is complete. For the first time, MGH now has a process to track registrations and biennial inventories. Problem registrations and lack of documentation are two of the most cited problems. Using iLog eliminates both of those issues by providing reminder emails to registrants when they are due. By implementing this phase of the project, we were able to identify and correct errors for 41% of the iLog users. Clinical and IND research registrations are being entered now. In FY22, we are working towards Phase II of this project to place better controls in place for purchasing, receipt, and delivery of controlled substances. Build is currently underway to add the other MBG hospitals. Both the DEA and MA DPH consider us the gold standard.
- *Research Misconduct:* In FY21, we saw 5 new cases of research misconduct and closed out 6 federally funded cases. On average, these cases took approximately 2 years from start to finish. 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.
- *Orientation Checklist:* This year we rolled out a new orientation checklist that encompasses and electronically documents the orientation process for new employees. This process systematically provides managers with all of the critical elements in which they need to provide to new employees. The document lives on the Help and Safety App.
- *Lab Safety Checklist:* Implemented this year, is another checklist that provide the tools and links necessary to provide a lab safety orientation and an electronic way to document the training. This checklist lives on the Help and Safety App.
- *Transportation of Biological Specimens:* In January 2021, a memo was distributed by MGB announcing that shuttles could no longer be used to transport biological specimens. Research Compliance worked with key players to operationalize new routes with cargo vans and have created an App to track the biological samples.

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

In FY21, 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. 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 (MGB), along with Keith Jennings, Chief Information Officer for MGH/MGPO and Ye Chin Lee, Vice President, Strategic Research Operations at MGB, CIDH expanded its service capabilities by enlarging

its staff numbers, and appointing two new faculty experts, Areej El-Jawahri, MD, Program Director, Clinical Outcomes Research, and Mike Jernigan, MD. Program Director, Clinical Integration and Quality. Dr. El-Jawahri also serves as Director, Digital Health for the Mass General Cancer Center. 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).

Since launching in FY19, CIDH has secured over $40M for sponsored research collaborations, including an $8.4 million multi-year agreement with AstraZeneca to co-create and clinically validate a patient and clinician facing chronic disease management platform. CIDH's transactions also include five royalty-bearing licenses and equity positions (projected revenue is not included in the total above).

CIDH also secured $4M+ for in-kind hardware and services to support strategic institutional projects. One example is, under the direction of Tom McCoy, MD, Program Director, Data & Analytics, the establishment an architecture to capture and curate inpatient biomedical device data at high frequencies for the purposes of clinical decision support and R&D.

CIDH, in partnership with the Brigham Health Digital Innovation Hub (iHub) 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 and the associated Enterprise teams such as MGB Innovation and Enterprise Data and Digital Health Innovation.

Furthermore, in FY21, 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 (led by Conor O'Brien) restructured CIDH's internal consultation service to provide concrete structured guidance within a set time-frame. This service will be made broadly available to the MGB Research community in FY22. CIDH faculty and staff provided guidance and support to over 1,500 MGH innovators across 90+ MGH and Enterprise departments, divisions, programs, centers and labs.
- CIDH's Strategic Alliances team also worked with MGH inventors looking to bring MGH clinical and care-delivery "know-how" to scale through digital tools. CIDH has shepherded MGH Palliative Care through the exercise of determining the most viable path to scale and commercialize ePAL, a RCT-validated digital therapeutic smartphone application that was launched in the Cancer Center to educate, empower, and improve pain management for cancer patients. At the time of this report CIDH, in partnership with MGB Innovation, is facilitating negotiations with potential external collaborators towards scaling at ePal across MGB, and a broader go-to-market strategy.
- In support of testing and selecting new technologies for MGH's physical sites and the new building, in partnership with MGH Planning, CIDH established the infrastructure to execute on this process (led by Anne Powers). At the time of this report, two initial pilots have launched.

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**.

- In collaboration with MGB Research Management formally launched the Smart and Autonomous Medical Systems CORE led by Dr. Julian Goldman. SaAMs is also a designated Massachusetts eHealth Institute "Sandbox," providing an environment for cybersecurity and interoperability innovation.
- In Q4 of FY21, CIDH Research Acceleration team helped launch two clinical trials in support of the MGH institutional collaboration with AstraZeneca. While the trials concluded in early FY22, early data showed exceptional adherence and promising outcomes.
- A number of MGH labs have experienced a critical shortage of graduate student and post-doctoral researchers in the fields of engineering and computer science. In support of MGH's educational and research mission, CIDH initiated conversations with an academic university facing an equally critical need to provide their engineering and computer science students with experiences in clinical care delivery. At the time of this report, discussions continue to be exploratory.

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**.

- In FY21 the Fern Health collaboration (led by Matt Ross) expanded to include co-creating a software enabled service to support patients suffering from a number of symptoms associated with chronic pain. MGH clinicians (led by Mihir Kamdar, MD) have helped expand the offering to include sleep health, nutrition and many other therapeutic areas. Fern's digital backbone enables our clinical experts to optimize the clinical care experience, while reducing administrative and financial burden to providers, payers and large-employers.
- CIDH continued actively participate in cross-MGB initiatives such as Enterprise Data and Digital Health Innovation's Executive Oversight and Leadership committees, the Innovation Digital Education Academy, and Health Equity Techies (an informal working-group affiliated with MGB's United Against Racism campaign).
- As part of CIDH's annual commitment with the MassChallenge Health Tech startup accelerator program, CIDH established a dedicated advisor relationship with early-stage startup Wolomi, an on-line community dedicating to improving maternal health outcomes for women of color.

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, w**hile diversifying revenue streams** through industry-sponsored research and commercialization.

- CIDH increased its operational support and guidance to key programs in MGH Nursing and Patient Care Services (PCS), assisting in advancing digital health, research and innovation programs in collaboration with MGH Institute for Patient Care, the MGH Center for Innovation in Care Delivery (CICD), and the PCS Technology Advisory Committee.
- CIDH created the framework for the Ether Dome Group for Entrepreneurship "EDGE" (led by Molly Caffrey), a service and dedicated team to support the development of early-stage innovations in digital medicine towards clinical scale and commercialization. At the time of writing this report, CIDH has secured five corporate sponsors willing to provide financial and in-kind support for the program.
- On a weekly basis, promoted innovative research conducted by MGB faculty and collaborators, including publications, awards and presentations. CIDH Strategic Communications (coordinated by Ali Oliveira) launched a new monthly newsletter, "Digital Health Digest," revamped the CIDH website, and created several social media campaigns, resulting in increasing visibility of MGH-led research, and increased the volume of sponsored research collaborations for the greater MGH research community.

Research Program Updates and Initiatives—Harry W. Orf, PhD, Senior Vice President for Research, MGH

Isuggest Surpasses 1,600 Suggestions

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

In 2021, Isuggest received over 130 new suggestions, bringing its total to over 1,600. Of these, over half (890) have been implemented. Since its renewed launch in 2016, Isuggest has been receiving 2-3 new suggestions a week, indicating that the program has effectively reached a steady state where it is known and used routinely across the research enterprise. The success of Isuggest has in large part been due to the continual upgrades to the program to make it more intuitive and user friendly, and to the continued promotion of the "Suggestion of the Month" campaign, where a slide describing a successfully implemented suggestion along with a photo of the suggester is shown at the beginning of every research meeting (ECOR, Research Council, RADG, etc.).

While many of the working groups within the Isuggest structure are functioning well and addressing their suggestions in a timely manner, some were lagging in their responses. To address this issue, new metrics were developed in 2018 to show both the working group leaders and the Isuggest administrative management group which working groups are not operating effectively. Use of these metrics throughout 2021 has resulted in increased attention being paid to previously neglected suggestions.

Research Safety Committee Completes Its Ninth Year
Meeting #36 of the Research Safety Committee (RSC) took place in December, marking the end of nine full years of the committee's existence. Formed in late 2012 and meeting quarterly since its inception, the RSC has a membership of over 70 people, including departmental safety coordinators from every research department and center in the hospital, as well as representatives from Compliance, Environmental Health & Safety (EH&S), Police and Security, and the Research Space Management Group. Task forces are formed on an as-needed basis to work on major safety projects. The committee meetings consist of an incident update from the MGH Director of EH&S, reports from active safety task forces, and presentations on various topics of safety and security of interest to the research community.

Accomplishments of the Committee this past year include: 1) Roll out of a controlled substance database (iLog) that allows us to track permit holders and proactively notify them about renewals and training; 2) Dissemination of the "Help and Safety" app developed by the committee across the entire hospital; 3) Improved (essentially full) compliance with the new, mandatory employee research training survey; 4) Major cleanout of hazardous chemicals and expired substances following a comprehensive review of all our lab facilities and policies by Code Red, a firm commissioned by the Boston Fire Department to inspect our laboratories; 5) Continued bi-weekly meetings of our 200+ COVID Safety Officers, resulting in an exceptional record of zero lab-acquired COVID infections in 2021.

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

Due to COVID and scheduling issues, the federal negotiators have not been able to site visit MGH since 2018. However, their review of our submitted documentation resulted in them agreeing to again hold our onsite and offsite fixed rates for 2021 and 2022 at 68% and 34%, respectively. Overall, we were pleased that the rates held steady given that our research revenues grew while our space and associated indirect costs remained relatively static.

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 Mass General Research Institute (MGRI) and its scientific director, Susan Slaugenhaupt, PhD and ECOR leadership. The office of the Mass General Brigham CAO directly oversees several departments that support a $1.8 Billion research enterprise ($1.18B MGH research) 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 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 Human Research Office (HRO) 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. Research has changed dramatically in the past several years. The single-site study has given way to multi-site (often multi-national) studies. New challenges of risk/benefit analysis that must be addressed include research in genetics, Big Data, data sharing, mobile apps, 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 and the research community. 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.

HRO: The HRO 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 HRO also provides education and support to the research community, maintains policies and procedures, and documentation required by the federal regulations.

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 administrates the ClincalTrials.gov program required for compliance with federal law.

HRA IRB and HRO Activity 10/1/20 - 9/30/21 (FY21)			
Approvals	**Full**	**Expedited**	**Administrative**
Initial protocol review	683	5,675	
Continuing review	1,666	10,683	
Expedited Check-In *(Required every 2 years)*			512
Exempt Check-In *(Required every 3 years)*			2,477
Amendments	330	18,805	
Other Events	121	3,008	
Cede Review to a Non-MGB IRB *(Does not include ceded protocols to Dana Farber)*			562
Column Totals	**2,800**	**38,171**	**3,551**
Grand Total	***44,522**		

*Does not include an additional 36,520 Staff Amendments that are auto approved by the Insight system on submission.

HRA C&E Office Activity 10/1/2020-9/30/2021 (FY21)	
Type of Activity	**Number**
On-site reviews	95
Consultations	283
Presentations/education	84

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 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

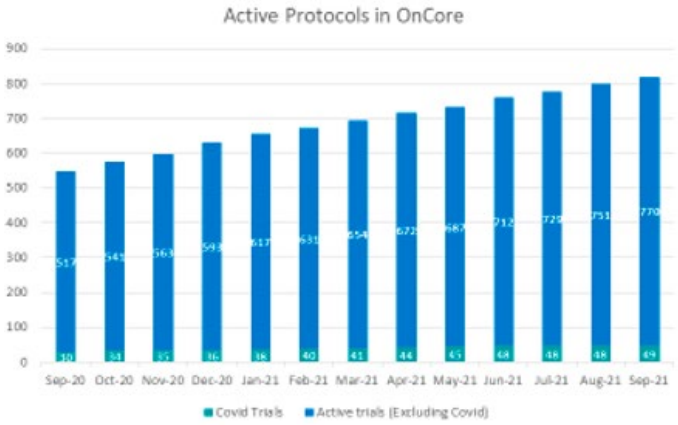
The Mass General Brigham (MGB) Clinical Trials Office (CTO) serves to facilitate, support and expand the conduct of clinical trials at MGB through service excellence and effective collaboration between investigators and industry sponsors. The CTO is responsible for services to the MGH research community including contracting, budget development/negotiation, billing and electronic resources for clinical trials management. These service areas are designed to provide clinical researchers with resources to engage in local, national and international clinical trials initiated by both industry and our investigators. Through participation in these trials, MGH 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 the Hospital's scientific mission.

The Clinical Trials Office had a highly productive year in support of MGH investigators and leadership this year. Overall volume of executed agreements increased significantly between FY20 and 21 (Table) by 18% overall from 2083 to 2451. Of this increase, 27% of the volume was driven by COVID-related projects while the remainder represents growth across numerous therapeutic areas. Research support agreements and subcontracts experienced significant growth, and New clinical trial agreements and amendments achieved solid increases. This productivity has allowed the CTO to increase staffing with the addition of 2 FTEs on the Finance Team, 2 additional paralegal positions and one FTE on the CTMS team. In addition, the CTO received funding to rollout a permanent Central Billing Office. Two FTEs have been hired to begin in January, 2022. Those PIs who participated in the pilot program will be expanded over time.

CTO Executed Agreements Volume (all-MGB)

Agreement Type	FY21	% Change FY21-20	FY20	% Change FY20-19	FY19
Clinical Trial Agreements	395	9%	364	-1%	366
Amendments	665	15%	579	28%	451
Support & Other* Agreements	408	32%	308	29%	239
Confidentiality Disclosure Agreements	695	-5%	731	22%	598
Subcontracts	288	185%	101	-14%	118
Total	2451	18%	2083	18%	1772

FY21 OnCore CTMS



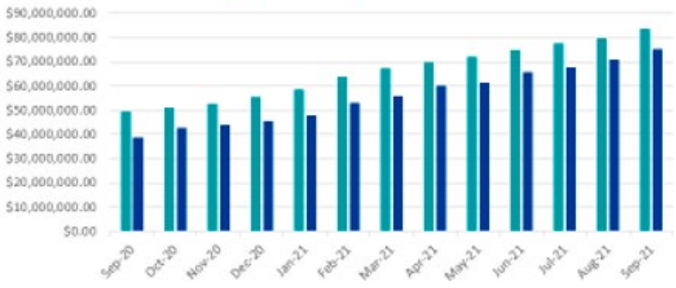
785 Active Users

363 Users Trained

1672 Invoices Created

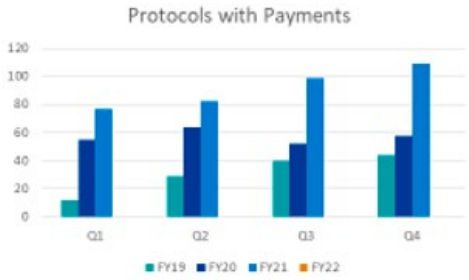
1847 Payments recorded

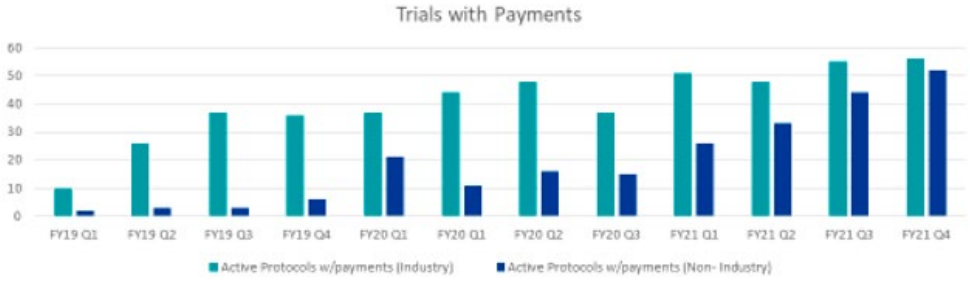
269 Protocols Open to Accrual



FY21 Advarra Payments

Industry	176
Non-Industry	72





Significant advances in FY 21 have been achieved in the area of electronic clinical trial support services. The Advarra OnCore contract has been renewed for an additional 5 years. OnCore utilization has been an area of focus throughout the fiscal year with focus on retraining staff on efficient usage. Monthly reports of clinical trials activity are presented to MGH and MGB leadership highlighting the ability to manage trials in real-time. The integration of OnCore and PeopleSoft resulted in a six-month project with Research Management to reconcile clinical trial funds. This exercise will be adopted into our revenue cycle refinements moving forward.

The MGB research community utilization of Advarra Payments, a real-time subject payment system continued to grow significantly. Advarra Payments in the FY21 Q1 had a significant increase in payments made to study subjects due to the many COVID trials across the organization that leveraged Advarra Patient Payments for subject stipends. 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 continue to work with industry sponsors to bring new clinical trials opportunities to the outstanding investigators at MGH through direct outreach and building on existing relationships between sponsors and CTO and to provide continued efficiency in in core contracting and budgetary services.

Mass General Brigham Research Compliance Office—Heather Cosier, JD, MA, Chief Research Compliance Officer

Heather Cosier, JD, MA was appointed in November 2021, and in January 2022 will begin serving as the Mass General Brigham Chief Research Compliance Officer. Ms. Cosier (formerly of Tufts University) follows Mary Mitchell who retired at the end of 2021 after leading the office for 12 years. Despite the change in leadership, the office continues to be focused on providing system-wide leadership and coordination of research compliance activities for consistency in development, interpretation, application and monitoring of regulations, sponsor policies, and Mass General Brigham research policies. The Research Compliance Office works collaboratively with Mass General Brigham Research Management/Finance, Innovation, Office for General Counsel, and the Office for Industry Interactions; hospital-based Research Compliance and Corporate Compliance offices; hospital Sr. Vice Presidents for Research/Chief Academic Officers and their leadership teams; and the Mass General Brigham offices that manage the human subjects, animal research, and biosafety compliance programs. The MGH Director of Research Compliance (Kele Piper) and her staff are an integral part of all Mass General Brigham Research Compliance activities. For example, Ms. Piper has taken a leadership role in making MGH developed systems and tools available to the greater Mass General Brigham community on the use of controlled substances in research, transporting biological materials among Mass General Brigham Boston and Cambridge locations, and managing and tracking training requirements for new research employees.

International Research Collaborations, "Foreign Interference," and Research Security: International collaborations and responding to federal concerns about "foreign interference" and research security continued as a top compliance priority for a third year. The Mass General Brigham Foreign Collaboration Working Group (WG), a system-wide group of legal, compliance, and research administrators, continued its work during 2020-21. Below is a list of some of the major activities undertaken by the group during the past calendar year.

- Modification of *Insight,* the Mass General Brigham grants management system of record, to assist investigators and hospital grantee institutions in complying with new NIH and other federal agency requirements to disclose "Other Support," domestic and international financial and non-financial support of their research; disclosure of outside activities; participation in foreign talent programs; and reporting of non-Mass General Brigham appointments, both domestic and international, to federal sponsors.
- Coordination of work-flows between Mass General Brigham Research Management and the Office for Industry Interactions for data gathering and review to meet the NIH and grantee institution transparency commitment.
- Throughout the year, periodic meetings with Research Administration and Compliance leadership of Harvard Medical School, Harvard School of Public Health, Broad Institute, MIT, and other Harvard-affiliated hospitals to harmonize Other Support reporting requirements for shared faculty.
- Development of a working relationship with the Boston FBI Office and the US Customs and Border Protection Office at Logan to introduce them to Mass General Brigham research institutions, including MGH, and policies related to sharing and transporting biological materials and data with other institutions both foreign and domestic. This greatly reduced issues for foreign postdocs entering and leaving the US through Logan airport.

- Expansion of the Mass General Brigham Export Control Program through
  - Comprehensive training by outside counsel of hospital Export Control Officers and Research Compliance Staff; Mass General Brigham (three) Research contracting offices; Supply Chain; Clinical Trials Office; Research Information Security staff; and Research Management Pre-Award, Post-Award, and Research Finance staff;
  - License of Visual Compliance to provide hospital Export Control Officers with up-to-date screening of staff, products, and institutions to ensure research collaborations are not established with excluded parties or in OFAC-sanctioned countries without appropriate licenses or other approvals and audit trail of actions taken; and
  - Development of Investigator training to be offered in early 2022.

In addition to the activities listed above, Ms. Mitchell served on several Council of Governmental Relations (COGR) national committee focused on research security/foreign influence and NIH issues bringing a hospital research perspective to these discussions and information back to Boston that was incorporated into Mass General Brigham's research security activities.

Training and Education: A key component of the Mass General Brigham Research Compliance Office's role in supporting the research hospitals is maintenance of a training and education program for investigators, postdoctoral fellows, and research administrators. RCO educational activities in 2021 consisted of:

- Managing and delivering three Mass General Brigham Responsible Conduct of Research (RCR) seminars for 300+ trainees and career awardees across the Mass General Brigham system required to complete this training.
- Offering three specialized RCR seminars at MGH on:
  - Animal Research Compliance
  - Biological Materials
  - Rigor and Reproducibility
- Information seminars at MGH to Research Leadership and a variety of faculty groups on:
  - Federal Agency Requirements Related to "Foreign Influence"
  - Export Controls Requirements
  - Transporting Biological Materials
- Continued oversight of the PI Research Education series to ensure completion of required education by new MGH PIs in Research Misconduct Prevention and Financial Stewardship of Grants and Contracts.

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 1900 scientists in a year, obtaining over 5,500 sets of EHR data in 2021. 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, 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 131,000 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 2.5

million images to hundreds of research projects. In 2021, the MGB Data Enclave was built and offered to researchers thought the Enterprise Data and Digital Healthcare (EDDH) program, enabling secure computation on special data sets from the healthcare system. Over 200 researchers were able to benefit from a special data set built in the Enclave for COVID-19 research during the pandemic. An addition to the Biobank Portal was also built specifically for COVID-19 research on biobank-consented patients during the pandemic.

RISC's patient recruitment strategy encompasses several pathways to optimize the number of patients involved in research. Any Mass General Brigham patient or member of the public can volunteer through Rally, a research portal for patients (rally.partners.org), contacting studies they found by searching for their areas of interest in an online catalog that presents studies in an attractive and informative format. By the end of 2021, over 100,000 people have identified themselves to over 1,500 studies using this system. Additionally-- as of July 6, 2021, all Mass General Brigham patients are eligible to receive research invitations for studies that researchers determine may be a good fit for the patient; research invitations are delivered using electronic outreach tools built into Patient Gateway (or by U.S. mail). Since the start of this initiative, over 300,000 patients have been identified and invited. Patients who do not wish to be contacted directly by researchers may opt out from receiving research invitations by contacting the Research Navigator's office by phone or email; at this time just over 1,600 patients have opted out.

The Health Innovation Platform (HIP) allows the efficient development and deployment of secure, Epic-linked apps into our clinical environment. Using HIP, sophisticated clinical decision support (CDS) apps can be built leveraging RISC capabilities for machine learning and providing high quality data. These apps can then be used to alter clinical workflows and/or improve decision making as well as allowing unique clinical data elements collected through the apps to flow back into research. HIP has been implemented through the Digital Care Transformation program and has helped manage 12,149 lipids and hypertension patients.

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.

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. 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. There are >200 researchers and >100 projects actively utilizing the Data Enclave for research.

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, GitLab and Freezerworks. The Research Applications Support team will help identify the optimal study tool given the investigator's requirements and facilitate the training of personnel in its uses and functions. The institution-wide Electronic Lab Notebook initiative maintained it's 98% PI account activation rate, with the focus on onboarding new PIs into the system. In addition, 20 labs were supported on Freezerworks and >1,300 users are actively using Gitlab. RISC Redcap supports over 28,400 research projects and in FY21 supported 748 COVID specific projects and 744 e-Consent projects.

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. BiobankGenomics 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 Biobank is a data and sample repository that contains DNA, serum, and plasma of consented patients linked to clinical and research data, including genomic data. The Biobank includes samples and data from across Mass General Brigham hospitals and community health centers and enables individual investigators at MGH and across Mass General Brigham to access this resource for research with appropriate IRB approval. It leverages a common electronic health record which spans all of Mass General Brigham. As of January 2022, 130,000+ participants consented and 88,000+ samples have been collected. In addition, the Biobank has supported over $360M in research activities through the distribution of Biobank samples and data as well as through the sample management services, such as DNA extraction services, cell lines, and sample distribution.

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 (56,000+ 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 90,000 participants in New England (as part of the larger goal of 1M+ participants) via a $54M 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 $38M over 4 years.

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

- Next Gen Sequencing services 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, 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 (SeqABoo, 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. Recent work includes a proof-of-concept study for building a scalable genomic data repository to meet the needs of researchers, clinical laboratories, and clinicians.
- 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.
- Assist in the development of the Health Innovation Platform (HIP) and associated apps to improve clinical workflows.

- Support eMERGE development of processes for returning new types of clinical genetic results such as polygenic risk scores to study participants and providers.

Mass General Brigham Innovation—Chris Coburn, Chief Innovation Officer

Mass General Brigham Innovation is the business development unit responsible for the worldwide commercial application of the capabilities and discoveries of Mass General Brigham's 74,000 employees. The Innovation team works to monetize the unique assets of the system, including Massachusetts General Hospital and its Harvard faculty. Its responsibilities include company creation, license transactions, securing research collaborations, technology development funding, venture investing and managing intellectual property including patent prosecution. Mass General Brigham Innovation is the largest academic organization of its kind with 130 staff that includes 2 MDs, 28 PhDs, 21 MBA/MAs, and 16 JDs.

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. Mass General Brigham has over $450 million in capital under management, and Mass General Brigham Ventures (MGBV) has invested in 50 companies, realized 14 successful exits, and produced top quartile venture returns. It raised $251 million in MGBV Fund III, including strategic investment from Eli Lilly, and Fosun Pharma among others. The exclusive focus of the three funds are companies based on technologies developed by MGH faculty and others in the system. Its net internal rate of return equates to top quartile performance in the venture industry and is largely unrivaled in the academic realm.

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 software companies bringing solutions such as data extraction and patient access that are being implemented at MGH and elsewhere in the system.

A system wide Gene and Cell Therapy (GCT) Center strategy and implementation plan is being finalized. This strategy is based on Mass General Brigham's extensive platform of basic research, translational science and world class clinical care. The intent is to position Mass General Brigham as the pre-eminent academic institution to discover, translate, and apply gene and cell therapies (GCT) to improve the lives of patients.

A translational innovation development arm, known as Amplify, was launched in 2021 after an MGH Molecular Biology pilot to enhance and validate technologies with high commercial potential to accelerate them into clinically useful applications.

GCT will be the focus of the annual World Medical Innovation Forum (WMIF) May 2-4, 2022, in partnership with first-time presenting sponsor Bank of America. In this three-day program, CEOs and other industry leaders and top investors along with Mass General Brigham faculty, describe the global state of GCT and outline its challenges and the disruptive opportunity it represents for patients and in the market. Content is aimed at MGH faculty and trainees to give first-hand insights into how commercial innovation priorities are set.

MGH Results

MGH Commercialization Outcomes	FY16	FY17	FY18	FY19	FY20	FY21
Licensing Activity	130	133	198	197	145	**191**
Material Transfer AG	1,067	1,360	1,374	1,537	1,256	**1,452**
New Disclosures	365	311	366	355	384	**362**
Patents Filed (US & Intl)	910	1,091	1,643	1,593	1,483	**1,325**
Patents Issued (US)	126	136	150	165	149	**162**
Patents Issued (Intl)*	311	421	317	464	335	**403**
Royalty & Licensing Inc	$77M	$87.7M	$94.6M	$298M	$143M	**$84.9M**

Totals include the favorable impact of a pathology royalty buyout.

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

Innovator Engagement

Expanding and serving the pool of MGH and other system faculty active in innovation and commercialization is a major priority. The Innovator Community Expansion Initiative (ICEI), was established to increase the output of commercially viable innovation to benefit patients. It focuses on clinicians, early career researchers, women, and other under-represented groups. In 2021, 22 MGH senior diverse faculty participated in workshops with senior industry leaders and investors to gain direct insights into company operations and governance.

As part of this effort, the Commercial Application and Inclusive Leadership program will be held in 2022 with Babson College for new and early career faculty to help grow and diversify the community. Additionally, MESH, originally formed at MGH, has expanded as an innovation and entrepreneurship platform for MGB systemwide. Its Innovation Bootcamp, a custom learning and networking system, has nearly 1200 users and 3000 courses have been viewed 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 oversite of all financial data and reporting. These teams act as stewards who must balance adherence to the rules and regulations governing grants while providing support and guidance to the MGH Investigators and their Department Grant Administrators.

As highlighted across all sections of this report, the MGH Research community had a phenomenal year. The MGH Research community built upon its success from last year, increasing its research revenue by 19% from last year to $1.18B. MGH now accounts for 56% of the $2.1B of research activity across the Mass General Brigham system.

The significant growth in activity occurred across all sponsor types, but was heavily concentrated in DHHS/NIH Federal Awards and subcontracts from Federal Awards. COVID-19 related research was a major driver, with 253 awards in FY21 but growth occurred across all research disciplines.

The overall outlook for research remains very positive for MGH. Proposal submission volume remains strong with 8,948 submissions across MGB, of these 4,997 were submitted by MGH Investigators. New award volume remains strong and MGH received 8 awards greater than $10M in FY21.

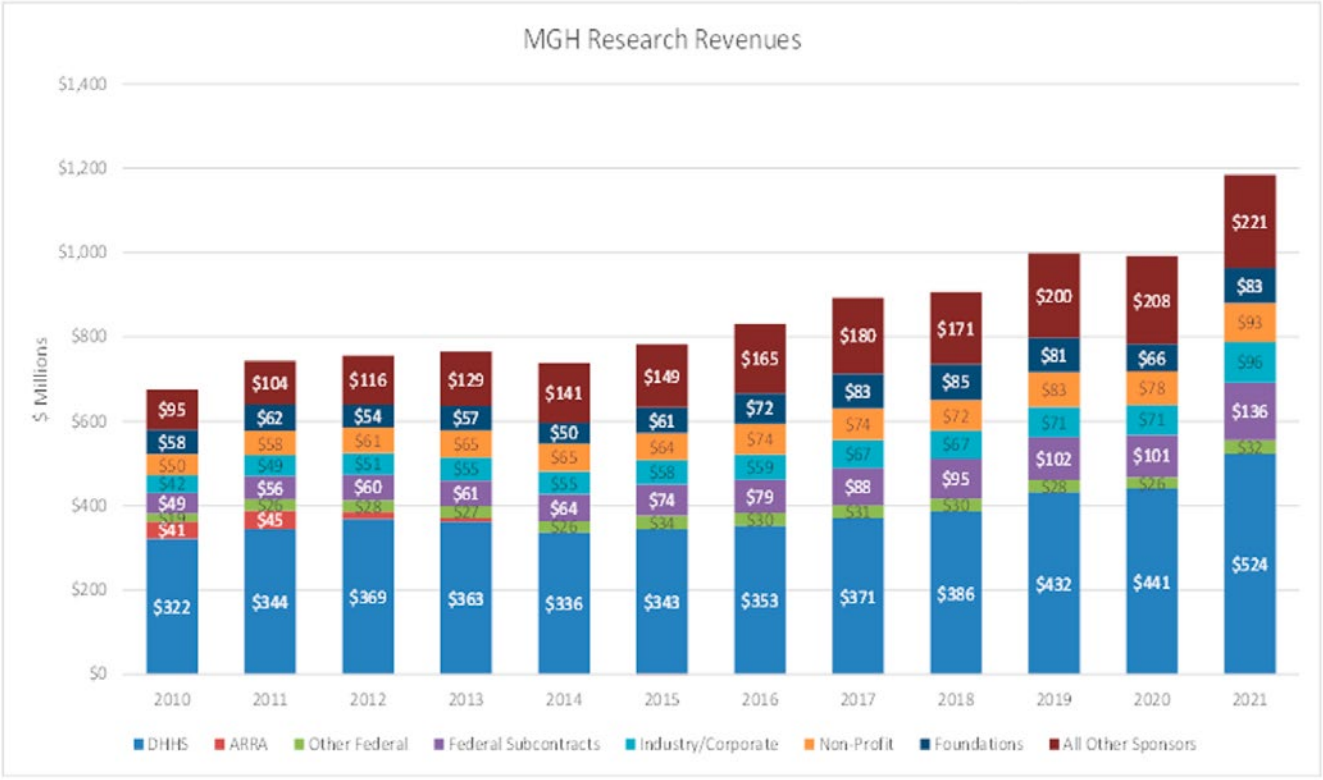
Less enthusiastically, FY21 was notable for a major increase in NIH compliance requirements. These new requirements, requiring disclosure of all domestic and foreign research activities, add additional administrative burden to the investigators and the support teams. These new requirements include providing translated versions of foreign appointment contracts to the NIH, and require electronic signatures from investigators, who must now attest to the accuracy of the information on their Other Support Documentation. Additionally, NIH has increased its scrutiny of this information at the proposal stage, prior to an award, and with the progress reports, often leading to several rounds of questions by NIH officials. Significant efforts were taken over the past year to prepare for the new disclosure and documentation requirements and manage the expectations of the NIH. Improvements have been made to the Insight system to capture the Other Support data elements. Tools and training materials have been created and provided to the Research community to help understand and manage the requirements. The goal remains to minimize the administrative burden on the MGH Investigator community while promoting compliance with the NIH requirements.

Following the trends from previous years, Research contracting activities that require negotiation also increased in volume and complexity. Different data privacy laws, from nations and states, as well as increased information security requirements from sponsors are requiring additional time to review, understand the impact to investigators and the project, and negotiate to protect MGH and the Investigators.

The volume increases with ever expanding federal compliance requirements pushed Research Management to think innovatively, work collaboratively with colleagues and continue to implement process changes to meet the increased demand on services. With the support of Ravi Thadani, MD, MPH, Chief Academic Officer, MGB and Harry Orf, PhD, Senior Vice President of Research, MGH, a streamlined process for Low-Risk Data Use Agreements (DUA) was implemented. This new process allows investigators to manage the completion of the DUA successfully reducing the time the DUA is with Research Management for review to less than two days. Research Management plans to build on the success of this initiative with other agreement types.

Over the next year, improvements to systems and the support infrastructure will continue for the MGH Investigators and the Research community. Research Leadership and Research Management have been proactively ensuring that the needs of the Research community are front and center as MGB transitions from PeopleSoft to Workday as the core system for HR,

MGH Research Revenue Trends



Finance and Supply Chain functions. This major initiative will continue to be a focus for the next several years as processes are redesigned and the new system is rolled out.

Mass General Brigham Office for Interactions with Industry—Christopher Clark, 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:

- 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:

1. 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.

2. 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 2500 consulting and related agreements each year.
3. 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 handles conflicts arising in purchasing and similar types of transactions, and 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 $4M and $5M in funding, each year. This section also coordinates with the hospital Development Offices on gifts from companies to support research projects; last year this section worked on 33 gifts constituting $6.9M.
4. 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.

Over the course of the last year, OII has continued its focus on integration amongst the four substantive sections of the office detailed above in order to enhance efficiency and to provide a better, more seamless experience for investigators and members of the broader community when they interact with our office. Additionally, OII continues the work to implement policy and education with the newest members of the MGB system, especially Mass Eye and Ear and Schepens Eye Institute.

Looking at the Year Ahead—Challenges and Opportunities—Harry W. Orf, PhD, Senior Vice President for Research, MGH

As the previous sections of this report document, significant progress has been made in 2021 despite the continuing challenges presented by the COVID pandemic. As we continue to battle the pandemic into 2022, we are encouraged by an influx of new leadership and science initiatives that will afford us opportunities to strengthen our research enterprise and sustain our standing as a leader in academic medicine and biomedical research.

Jumping into Gene- and Cell-Based Therapy (GCT)
[Portions of text taken from MGB Innovation documents and presentations]
In 2021, Mass General Brigham leadership set a bold ambition to develop a world class Cell and Gene Therapy translational center. A comprehensive plan was written, and work is now proceeding on the next step of this initiative, which is to translate these concepts into detailed strategic and operating plans and a roadmap for implementation.

MGB GCT investigators represent one of the largest and most accomplished academic cohorts in the US. The goal of the Center will be to grow the community of MGB GCT investigators through expert support, dedicated cores, financial awards and, most importantly, to create a vibrant environment that will draw patients, investigators, clinicians, collaborators, investors, and entrepreneurs to MGB. The Center will provide targeted, pre-commercial translational capabilities and funding to advance technologies towards accelerated clinical deployment.

The Center will be a physical space housing central capabilities, labs, and collaboration areas, with the goal of advancing cell and gene therapies across the MGB system. It will do this by applying funding and capabilities (e.g., program management, regulatory, toxicology and manufacturing vendor oversight) to mature a select set of promising technology platforms and therapeutic candidates. The plan is to then capture more value from these assets, which would be returned to fuel and sustain the Center.

Regarding principles for portfolio composition, preference will be given to higher-risk, higher impact opportunities. This takes advantage of the freer nature of academic innovation and tolerance for calculated risk, being informed by deep insights into technologies and patients. The Center will target a mix of therapeutic candidates as well as focus on the maturation of platform technologies (e.g., delivery,

payload), leveraging the differentiating clinical and scientific expertise of GCT investigators across the MGB system.

At the time of writing this report, investigators at all MGB institutions are completing a survey inquiring about their current initiatives and potential interests in GCT. The survey results will be used to refine the areas of initial interest and define the size and scope of the facility. A search of candidate locations is now underway, with the goal of committing to one in 2022. Stay tuned!

The MGH Capital Campaign

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

After a successful launch of the "silent phase" of the campaign, Development officially announced the public launch in late 2021. The response has been strong, with almost $2B of the $3B goal pledged thus far.

The mission of the research component of the campaign is to take new scientific research discoveries as far as we can, as fast as we can—toward new possibilities in prediction, prevention, diagnosis and treatment. This mission focuses on realizing the primary goals upon which the Mass General Research Institute was founded—to provide scientists with the support needed to thrive, and to advance bold scientific inquiry by building community and partnerships. To realize these goals, specific fundraising objectives have been identified in three areas: *People*—MGH Research Scholars, Endowed MGH Research Institute Chairs, and MGH Physician-Scientist Development Award. *Infrastructure*—Research Institute and Thematic Centers. *Programs*—Solution-Driven Research Programs, Programs advancing equity, i.e., Summer Research Trainee Program (populations underrepresented in medicine), and Claflin Distinguished Scholar Awards (women in science). Campaign efforts in research will continue to focus on these objectives in 2022.

The Continuing Need for Research Space

The last two pandemic years have shown us that a significant portion of research work can be conducted remotely. While this is certainly true for dry research space, where computations play a primary part of the work, we have also come to realize that aspects of wet bench work (writing up results, literature searches, etc.) can also be done remotely. These realizations have allowed us to review space use across MGH as well as the entire MGB system. A major "Where We Work (WWW)" project was undertaken to define individual work environments (fully remote, hybrid, or onsite). With hundreds of thousands of square feet of off-campus space leased at expensive rates, consolidating main campus space through "hoteling" and partial remote work affords us the opportunity to reduce our off-campus footprint and save significant rental expenditures. This WWW initiative is being directed by the MGB HR department with full cooperation from the MGH RSMG group.

Despite these dry space consolidation opportunities, the demand for wet research space remains high, reflecting new Institutional and Departmental initiatives. Additionally, as stated previously, our expanding research portfolio has put even higher space demands on our already overcrowded animal housing. Needs for both small and large animal space are becoming critical and several options for contracting with external vendors are being explored. In the wet labs themselves, support space is also becoming extremely tight and options for relocating seldom-accessed freezers offsite are being explored.

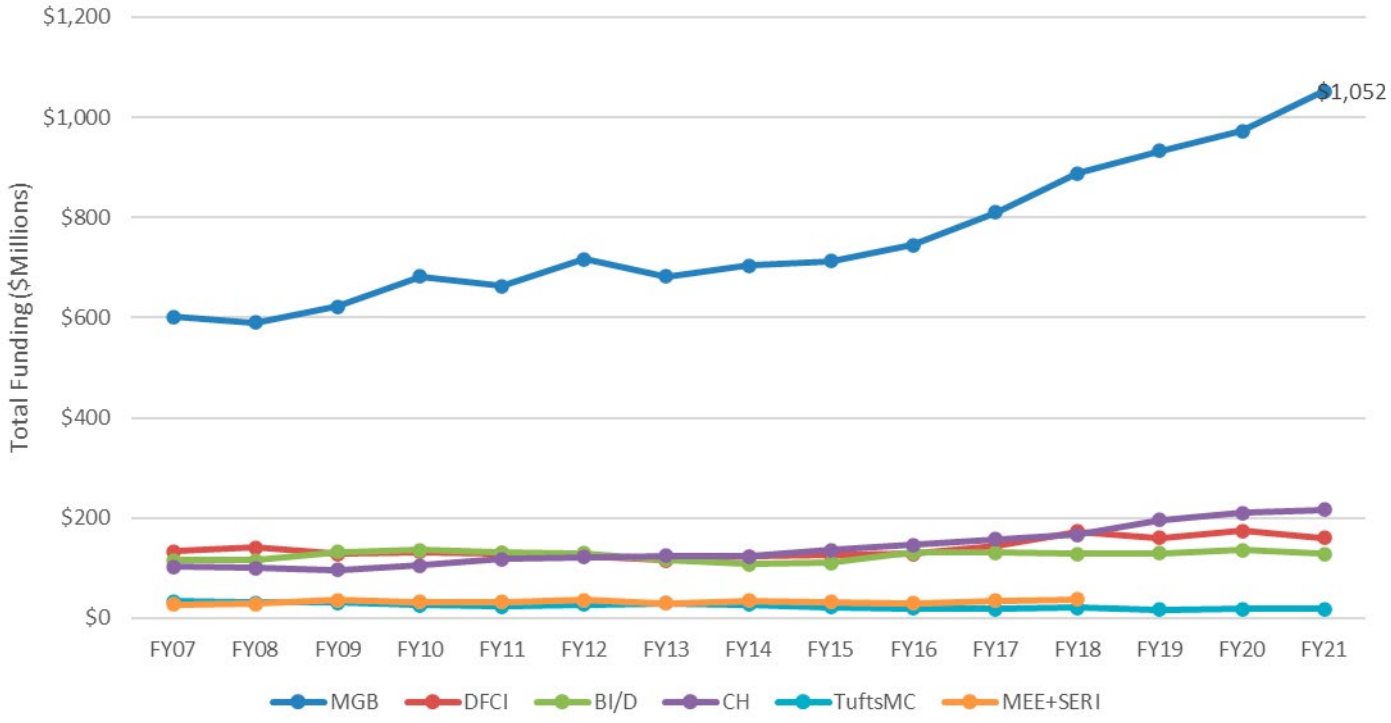
While space metrics put in place last year by RSMG will assist us in consolidating areas of underutilized current space, it along will not come close to meeting the growing wet space demand. Options being explored in 2022 included looking at purchase and/or consolidation of research space, offsite freezer storage and sample management, and offsite animal breeding and cagewash facilities to serve all MGB institutions.

The third consecutive $1 billion research revenue landmark reached in 2021 during the continuing challenges of the COVID pandemic 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 responsible for all of the progress documented in this report and they will continue to rise to the challenges we face in the coming year. On behalf of the entire Mass General Research Institute, I express our appreciation for their determination to persevere through the pandemic and constantly improve and strengthen our research enterprise.

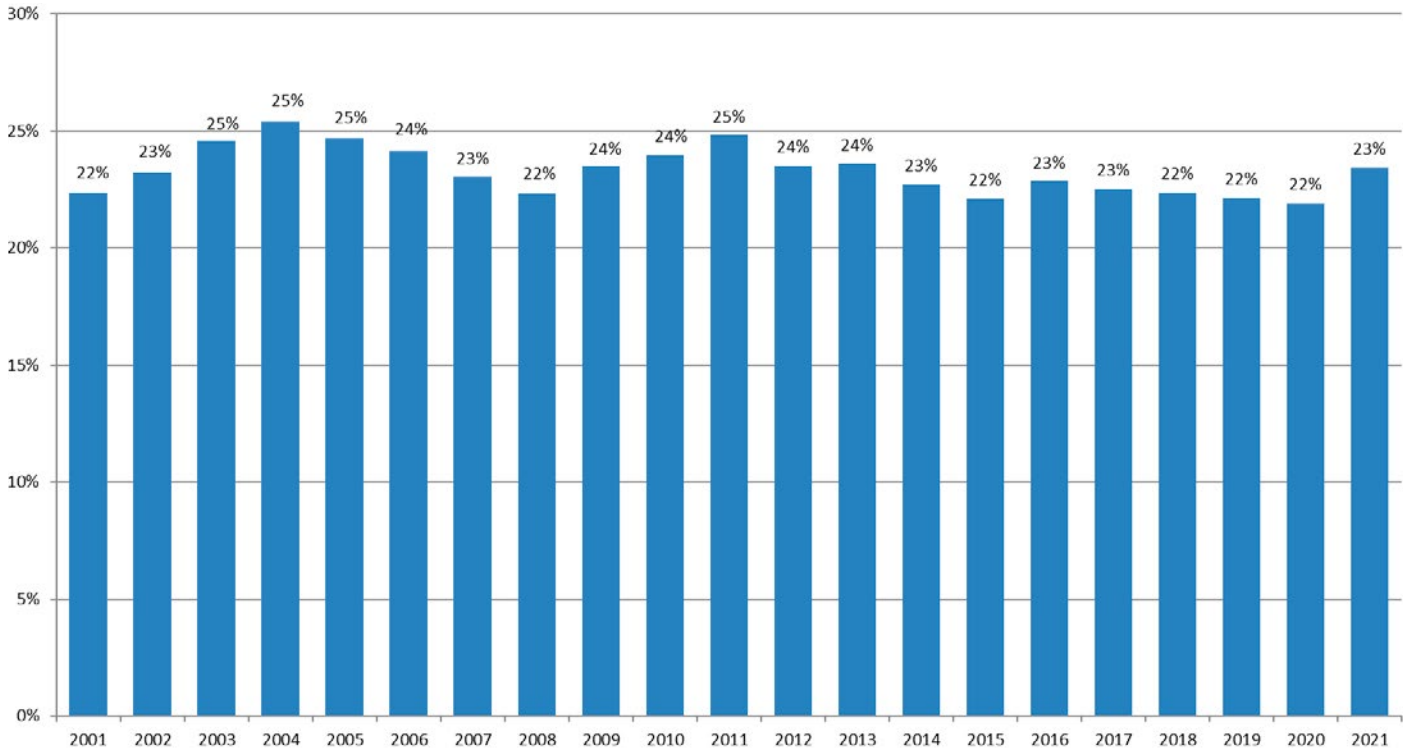
Respectfully submitted,

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

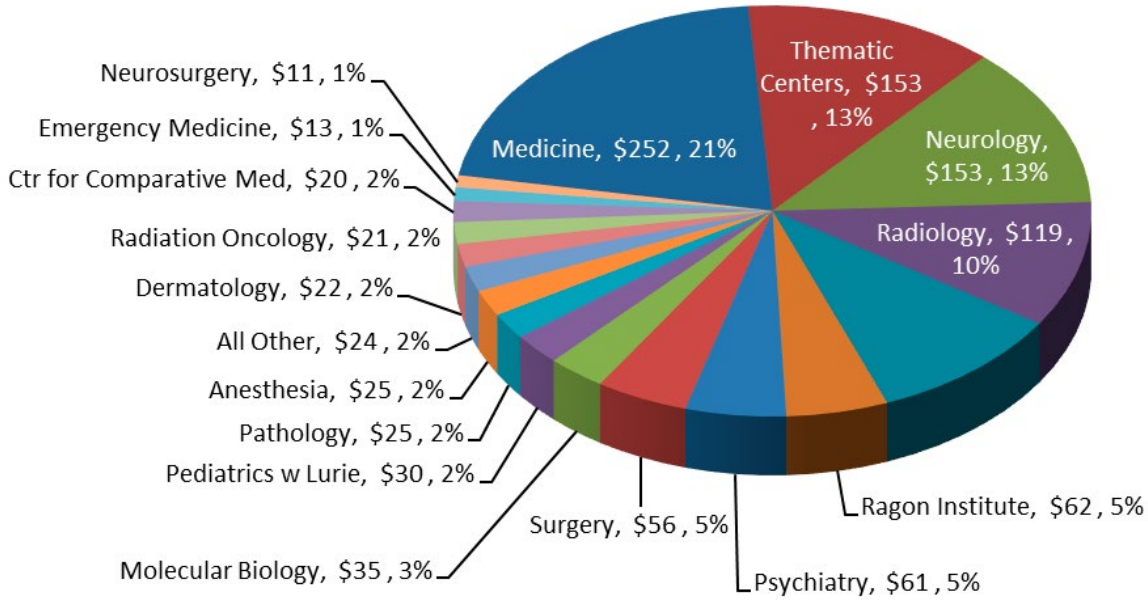
FY2010–FY2020 Top Local Independent Hospitals NIH Extramural Funding



MGH Research Revenue as a Percentage of Total MGH Operating Revenue FY2000-FY2020

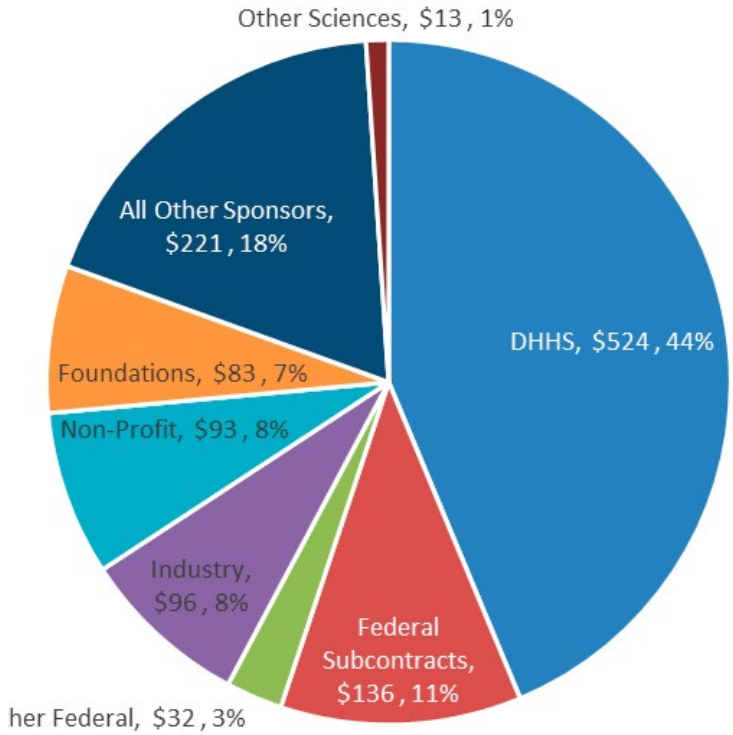


FY2021 MGH Research Expenditures by Department (Direct and Indirect Expenditures, $1,197M) (In millions)



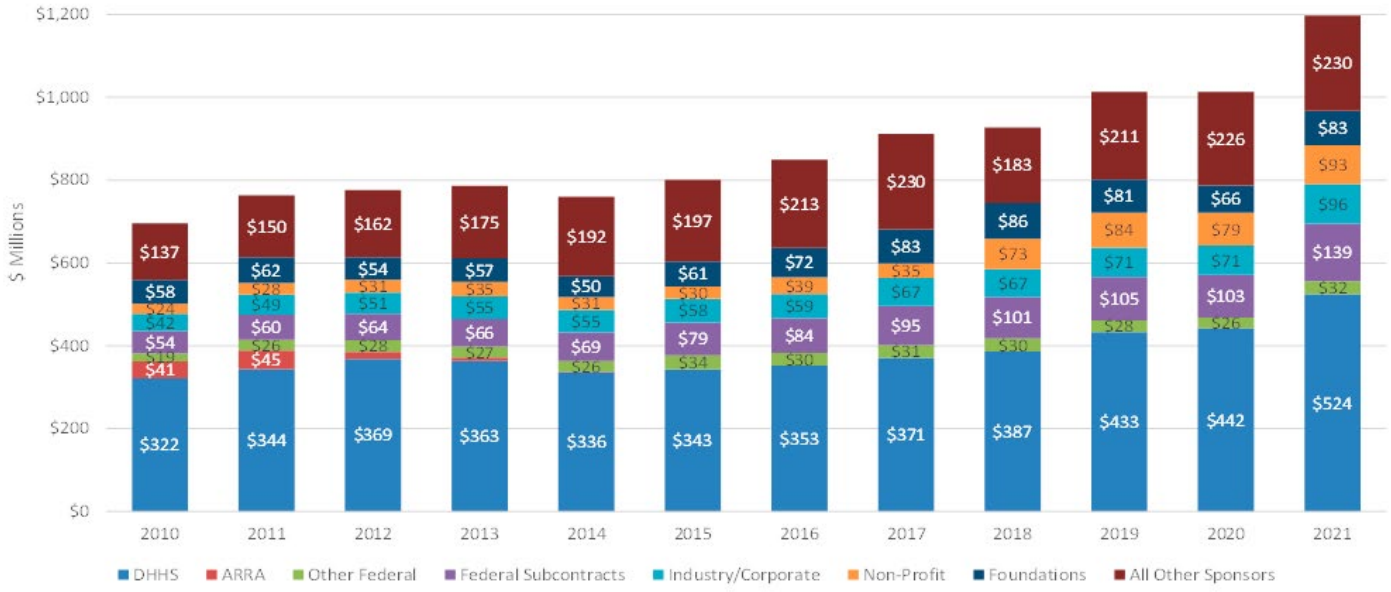
Notes
Based on Full Year FY21 data
Expenditures include ARRA funding and Other Science-1
Surgery includes Pediatric Surgery, Oral Surgery and Urology-2
Other includes Administrative Departments-3

FY21 MGH Total Research Revenue by Sponsor - $1,197M (in millions)



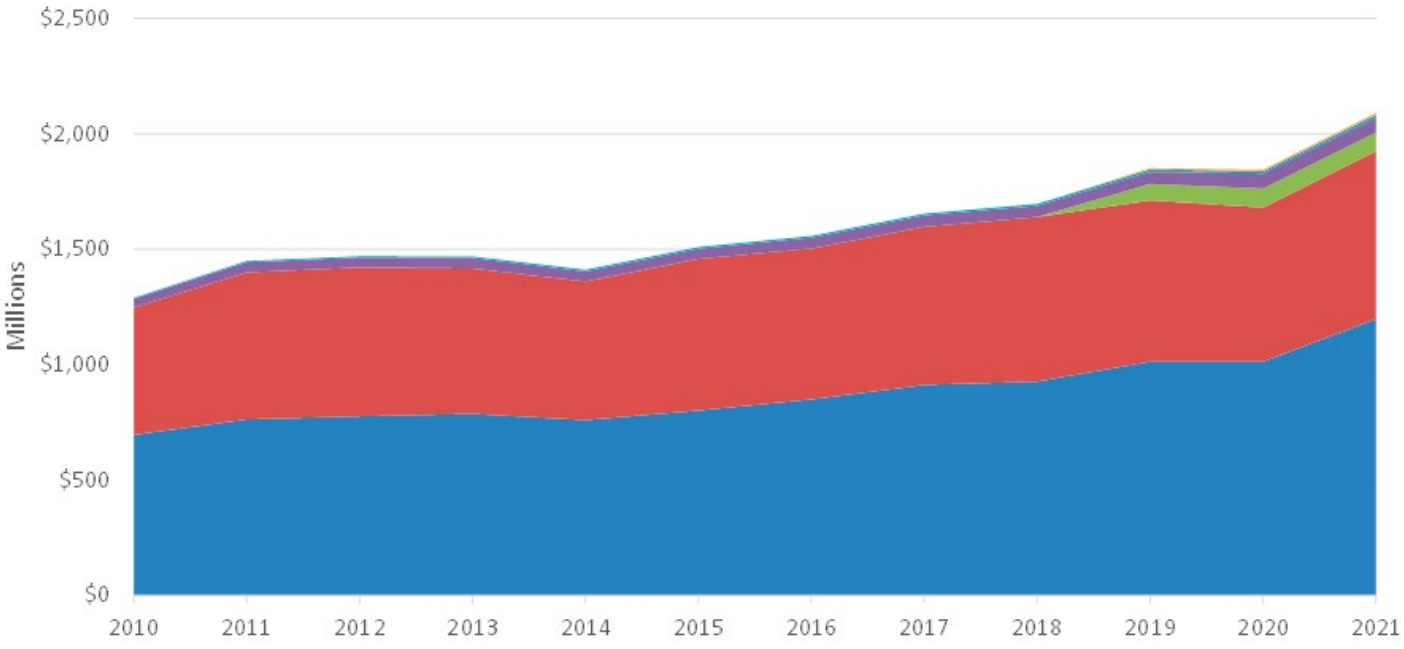
MGH Research Revenue Sponsor Mix

- Total MGH research revenues exceeded $1B for the third straight year, growing 18% from FY20 to FY21 with growth across all external research sponsors.



Mass General Brigham Research Activity

MGB Total Research Activity has grown to $2.1B, up $643M or 44% since 2011



Massachusetts General Research Institute

Executive Report

MASSACHUSETTS GENERAL HOSPITAL Science Activity by Sponsor			
	'Fiscal Year 10/01/20-09/30/21		
Type of Activity	**Direct**	**Indirect**	**Total**
Federal & State	405,663,149	160,953,525	566,616,674
Non-Federal	511,578,418	119,174,234	630,752,652
Total Expenses FY 21	917,241,567	280,127,759	1,197,369,326
Analysis of:			
Federal Activity by Sponsor			
NIH	375,396,640	148,953,758	524,350,398
DOD	16,549,582	9,181,575	25,731,157
DARPA	1,934,043	836,353	2,770,396
NASA	611,240	240,455	851,695
NSF	506,544	283,551	790,095
Other Federal	1,378,183	484,803	1,862,986
Total Other Federal Activity	20,979,592	11,026,737	32,006,329
Subtotal Federal	396,376,232	159,980,495	556,356,727
State	9,286,917	973,030	10,259,947
Total State Activity	9,286,917	973,030	10,259,947
Total Federal and State	405,663,149	160,953,525	566,616,674
Non-Federal Activity by Sponsor			
Industry	71,971,264	29,191,287	101,162,551
Foundations	74,241,517	9,658,676	83,900,193
Subcontracts/Other Nonprofit	150,207,524	49,970,826	200,178,350
MGH Endowment & Gifts	198,707,028	25,465,762	224,172,790
Total Non-Federal Activity	495,127,333	114,286,551	609,413,884
Total Expenses	900,790,482	275,240,076	1,176,030,558
Harvard College	16,451,085	4,887,683	21,338,768
Grand Total	**917,241,567**	**280,127,759**	**1,197,369,326**

Name: Lisa Goers, PhD, Department of Medicine, Division of Infectious Disease
PI: Cammie Lesser, PhD
Category: Humans of MGRI
Title: A Surprising Result

Center for Diversity and Inclusion (CDI)

Programmatic Report

ELENA B. OLSON, JD, EXECUTIVE DIRECTOR

Mission

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

Focus

CDI accomplishes its mission through three focus areas:

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

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 four strategic priority areas:

- Exposing UiM students to academic medicine through programs such as the Summer Research Trainee Program (SRTP) and the Visiting Clerkship Program (VCP).
- Advancing careers and building community amongst UiM physicians, researchers, trainees, and now Patient Care Services (PCS) staff.
- Championing health equity and addressing bias and racism through education, policy and advocacy.
- Driving organizational change at the national, regional, and system level. During 2021, these priorities were supplemented with responding to COVID-19 equity needs.

Though our work has been present and critical for close to three decades, it was the onset of the COVID-19 pandemic that highlighted the importance of those underrepresented in medicine more than ever before. In fact, vital and life-changing initiatives such as the Spanish Language Care Group would not have been possible without the Center for Diversity and Inclusion's ability to activate its diverse clinical and research workforce.

Notable Achievements for the 2021 Year

1. Spanish Language Care Group. While we saw an increase in COVID-19 hospitalizations, we also experienced the widening gap in available linguistic care on the COVID floors as more patients from neighboring communities of color were brought in for intensive care. In response to the staggering numbers, CDI co-led the establishment of the Spanish Language Care Group (SLCG) in collaboration with Surge, the Emergency Department, and the Boston Hope clinical teams. The charge of the SLCG group, which included 51 clinicians and physician-scientists who were native Spanish speakers, included providing in-person and virtual assistance 24 hours a day, 7 days a week. These physicians were tasked with supporting family updates, admissions and discharges, informed consents, family meetings, goals of care, and much more, delivering it with kindness, empathy and care.
2. Community Messengers. Not only were SLCG members available at the bedside for LEP patients, they also provided much needed multilingual messaging to local hard-hit communities by creating videos about COVID 19 safety measures in Spanish and other languages. Many providers joined the MGB Community Messenger team—a group of multi-cultural, multi-lingual clinicians deployed in person on our mobile vans and virtually to educate, inform, and address community-based questions about the virus and the vaccines.
3. Implementation of the MGH Structural Equity Plan/MGH United Against Racism Campaign and expansion of CDI.

   In 2020, MGH established a Structural Equity Plan under the umbrella of the Office for Equity and Community Health which is aligned with the MGB United Against Racism (UAR) Campaign—a system-wide campaign to create and advocate for anti-racist internal and external policies, workforce diversity, equity and inclusion education and discriminatory reporting mechanisms.

   As part of this plan, the scope of CDI has been expanding across the entire workforce continuum via multiple workstreams and incorporating additional subject matter experts, e.g., research, LGBTQ and disability, as well as new leads. This expansion includes a more deliberate focus on the research workforce—including pre- and post- doc students, trainees, and research faculty—as well as PCS staff. As a result, the CDI hired 2 Faculty Co-Directors for Research, an

Administrative Director for Research, a Communications Specialist and Student Project Coordinator in 2021 to implement and support its expansion.

CDI is also driving several other critical initiatives aligned with UAR. This includes policy and practice review to identify and reconcile structural racism and a new Patient Code of Conduct Policy that addresses biased, disruptive and discriminatory behavior by patients, families, visitors and research participants.

4. Awarded 6 Physician/Scientist Development Awards. The Physician/Scientist Development Award (PSDA) was established to enhance research faculty retention and career advancement. Each award is $180,000 plus indirect costs over 3 or 4 years. With funding from Equity and Community Health/CDI and the Executive Committee on Research (ECOR), 6 PSDA applications were funded, increasing the number of awards from 4 in 2020 to 6 in 2021. More UiM researchers will now be able to take advantage of these PSDA funds to help them build a successful research program at Mass General and alleviate debt burden. Oluwaseun Johnson-Akeju, MD, Chief, Department of Anaesthesia, 2011 Physician-Scientist Development Award recipient commented, "The CDI and the Physician-Scientist Development Award have played a key role in helping me become an NIH independent investigator. I am truly grateful to them for helping advance my career." This award continues to provide funding to promising UiM faculty and plays a key role in the path to independence in their research careers. See more details under the Professional Workforce Diversity section below.

5. Provided virtual and onsite experience for Summer Research Trainee Program students and increased the number of participants. The Summer Research Trainee Program (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, nearly 378 students have completed the program with over 149 colleges and universities represented. This year, because of our commitment to increasing the diversity of trainees, SRTP was able to host 29 students for the Summer of 2021, making it the largest SRTP cohort to date, compared to the average cohort of 20 students in past years.

   While two thirds of the students completed the 2021 program in-person, due to the COVID pandemic, a segment of the 2021 summer program was redesigned to provide weekly mentoring career sessions to a small number students and match them to virtual mentors who helped guide students in their research career paths. Participants in this virtual experience stated that the revised program added tangible value to their career decision making and had an impact on their decision to pursue careers in an academic setting. The program, which ran from June to August 2021, allowed UiM undergraduate, medical, graduate and post-baccalaureate students to complete research with MGH faculty preceptors in science labs, clinical sites, health policy and health services settings within 16 departments 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 and social events, in accordance with COVID-19 protocol.

6. Record match of UiM residents to MGH training programs. The recruitment process for residency at MGH during the pandemic shifted from the traditional in-person method to a virtual recruitment effort for the first time in history. MGH saw a 6% increase in all applications, a 17% increase in UiM applications, and a 38% increase in UiM's interviewed compared to 2020. To support recruitment efforts, CDI held 12 virtual receptions, including two joint receptions with Brigham and Women's Hospital (BWH), with tremendous participation by the MGH community and applicants. Out of the 500 attendees, 88% of those who matched at MGH attended at least one CDI reception.

   To address the high cost of living in Boston, CDI, BWH and MGB Graduate Medical Education (GME) created a pilot stipend program for economically disadvantaged residents in need of additional support during their transition to MGH. CDI/GME also offered an additional financial opportunity in the form of a low interest loan program for trainees who needed added monetary support. CDI participated in the virtual SNMA AMEC and LMSA National Conferences helping connect with hundreds of students from around the country.

   As a result of our collective efforts, 67 new UiM residents joined MGH on June 20, 2021. This cohort is the largest in number with a 26% match of UiM's in MGH history, making it our most successful year of residency recruitment and match. Overall, CDI leadership met with Chairs and MGH affiliated residency program directors to help implement diversity and inclusion efforts for trainees and faculty in all MGH departments.

Center for Diversity and Inclusion (CDI)

Programmatic Report

7. The CDI Resident and Fellow Committee. The MGH CDI's Resident and Fellow Committee (RFC) acts as an interdisciplinary forum of UiM residents and fellows with a Board elected by their peers. A unique effort that does not exist across other Harvard teaching hospitals or the country, the RFC is critical to creating a vibrant community of UiM trainees at MGH and in joint MGB training programs. The RFC established a number of career development and networking opportunities for trainees in 2021. RFC members attended after-school workshops with high school students through the Revere High School Power of Know program, collaborated with HUECU on our first Financial Education Series, created a "Virtual Interview Tips" webinar to help support applicants during the unique COVID-19 pandemic restrictions and held several outdoor and virtual social events for the resident and trainees to create connections and build community. CDI and RFC also co-sponsored the first annual EMPOWER, a coalition between HMS SNMA, LMSA and LGBTQIA+ And Allies (LAHMS), bringing together almost 700 middle school through post-collegiate medical students and over 90+ HMS students, alumni and faculty.
8. Chester Pierce Research Society Reinstated. 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 most senior African-American physician-scientist at MGH. CPRS is designed to promote diversity and health equity by featuring the novel research of investigators in the MGH and CDI community.

   Since its inception in 2004, the CPRS has sponsored over 40 talks by Mass General UiM physicians and scientists. The event has been attended by faculty and staff across the Mass General. The CPRS is an opportunity for CDI to recognize and promote UiM faculty, particularly previous recipients of the PSDA and Clinician-Teacher Development Award (CTDA) and their robust research. While the series was on hiatus due to COVID, the program was reinstated with quarterly talks which started in July 2021 with Jose Florez, MD, PhD, Chief of the Endocrine Division and Diabetes Unit in the Department of Medicine and Professor of Medicine, Harvard Medical School and a previous recipient of the CDI sponsored PSDA.
9. Diversity, Equity and Inclusion Education and Training. During our COVID year, CDI also focused on addressing and educating our MGH community on issues of racism, bias and equity through small group conversations and public educational forums. We co-sponsored an expert panel to bring more awareness to Asian xenophobia during the pandemic and explored ways to promote an environment of dignity and respect with the Radiology Diversity and Equity Committee. We co-led and organized the MGH Latino Heritage Month and co-sponsored Juneteenth celebrations, marking the first time Juneteenth was ever celebrated at MGH, as well as the MGB Diversity Summit where we brought in national acclaimed speakers on the topic of structural equity and racism.

Professional Workforce Diversity

We recognize that decisions of faculty recruitment occur at the departmental level, and that the focus must be deliberate if we expect to achieve results. CDI continues to work closely with the Sr. VP for Equity and Community Health to provide more intentional guidance, resources and funding to assist with faculty recruitment, like we have done with our trainee recruitment efforts. Many departments are already in the process of hiring UiM graduates to join our faculty in 2022; and these efforts are assisting with retention.

CDI continues to promote and help advance the careers of many clinical and research faculty through our faculty development award program. With funding from ECOR and the MGPO, CDI sponsored nine faculty development awards in 2021. Since 2004, CDI has awarded 71 faculty development awards totaling over $8 million in funding. The purpose of this program is to increase opportunities for UiM faculty, and who are committed to diversity, inclusion and equity, to advance to senior positions in academic medicine and leadership at MGH.

Under the leadership of the Sr. VP for Equity, there are now two hospital-wide diversity committees, including an Executive Committee on Diversity and Equity and an Equity Leadership Council. CDI serves on both committees and leads many efforts beyond CDI's core mission areas, especially as it relates to the Structural Equity plan, supporting efforts under the UAR campaign. This includes the initiative to review all hospital policies through an equity lens and identifying external policies and providing advocacy to impact equity in our communities.

Name: TJ Danenza, BS
Department: Surgical Photonics & Engineering Laboratory & Facial Nerve Center
PI: Tessa Hadlock, MD
Category: Humans of MGRI
Title: Portraits in a Pandemic

Center for Faculty Development (CFD)

Programmatic Report

MIRIAM BREDELLA, MD, DIRECTOR

Mission/Focus:

The Center for Faculty Development (CFD) aims to serve as a center of excellence on 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 2 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 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 for the Executive Committee on Research (ECOR) within the Mass General Research Institute (MGRI).

In 2021, 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 to 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 implementation of best practices in providing faculty support in the areas of teaching and learning; mentoring; research; writing; promotions and leadership development. Due to the COVID-19 pandemic, all programs continued to be offered virtually via Zoom which allowed the CFD to extend the invitations to all MGB employees and outside institutions. 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 'Leadership Development Program for Researchers' which aims to prepare investigators for challenges inherent in establishing and maintaining a successful research program. This 9-month long program features both 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 second year. Given the success of the program, MGH introduced the 'Anne Klibanski Visiting Scholar Lecture Series' to bring 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 2021 virtual CHADD Mentoring Course, "Mentoring without Borders," was spearheaded and hosted by the MGH CFD, and included innovative elements of small group networking sessions and a virtual interactive social hour.
- In the context of institution-wide efforts to build capacity for high quality mentorship, the CFD sponsored four hours of mentor training for MGH Principal Investigators (PIs) and senior mentors by CIMER, the Center for the Improvement in the Mentored Experiences in Research. CIMER research mentor training (https://cimerproject.org/) is an evidence-based, interactive approach designed to help mentors develop skills for engaging in productive, culturally responsive, research mentoring relationships that optimize the success of both mentors and mentees.
- Monthly hour-long speed mentoring sessions, open to trainees and faculty across MGH, led by pairs of senior mentor leaders: participants ask questions about any aspect of mentoring or being mentored and learn not only from the leaders but also from fellow attendees.
- Creation of new mentorship awards to acknowledge mentors across ranks and populations: Rising Mentor Award, Ally for Women Faculty Award, Outstanding Mentor of Underrepresented in Medicine (UiM)s Award, and Outstanding Research Fellow Mentor Award.

- Grant Writing Course, an 8-session series created by the MGH Science Writing Group and open to all MGH faculty and trainees. This course spanned the entire process, including information on the different NIH funding mechanisms and on when a program officer should be contacted.
- Creation of the CFD Writing Support service, 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.

Strategic Priorities for the Coming Year

- Launch the Office for Senior Faculty Transitions to support faculty as they recognize and adjust to the various changes, new perspectives, and different priorities that accompany growing older. The office will offer resources to help faculty plan for and transition to retirement, including speakers and events on retirement, panels on different roles faculty can transition to, and seminars by professional staff on retirement-related issues. Faculty will be able to schedule individual consultations as well as have access to a community of peer support. (The keynote speaker for the 2022 Mentoring Celebration, Deborah Heiser, is well-known for her work to engage senior citizens in meaningful mentoring.)
- Develop ways to support and celebrate the work of community physicians.
- Provide workshops on how to use social media to support career development.
- Continue expanding and deepening the mentorship culture at MGH through implementing the practice of men allyship for women colleagues, with training by Brad Johnson and David Smith, authors of *Good Guys: How Men Can be Better Allies for Women in the Workplace*.
- 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
  - Coffee and Conversations
  - 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 Series
  - 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.
- 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 Goldberg, MD, Director, Office for Research Careers (ORC), Mary Bouxsein, PhD, Director, Graduate Student Division (GSD), Bakhos Tannous, PhD, Director, Postdoctoral Division (PDD)

The Office for Research Careers (ORC) is one of the four branches that falls under 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 of Microbiology, who was previously the Director of the Postdoctoral Division, until she started her new position. Dr. Bakhos Tannous Associate Professor of Neurology leads the Postdoctoral Division among which the Mass General Postdoc Association (MGPA) falls. Dr. Mary Bouxsein, Professor of Orthopedic Surgery at HMS is spearheading the Graduate Student Division.

Center for Faculty Development (CFD)

Programmatic Report

ORC, GSD and PDD Achievements

- Increased coordination and communication with other MGH departments (i.e., GPS, HR, DCR, CDI, etc.) to support the research faculty at MGH through a more systems-wide approach. This has led to a great number of 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 among the duration of the program.
- Managed two newly created Mentoring Programs:
  - Peer Mentoring Program: This formal program provides mentees focused professional and personal development, while mentors gain valuable mentoring and leadership experience. Mentees are typically trainees who newly joined MGH, while mentors are trainees that have been at the institution for a few years.
  - Peer to Peer Program: A revamped version of the previous Buddy System that connects experienced graduate students with those that recently joined the organization. This provides an opportunity for new graduate students to get a brief introduction to life at MGH and in the greater Boston area.
- Implemented and promoted two onboarding checklists for postdocs and graduate students that will assist them in navigating MGH and the resources available to them.
- 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 junior researchers to utilize as a resource when submitting their first grants.
- Worked with HR to update monthly feeds of MGH faculty and trainees to capture additional information and accurately capture the clinicians, researchers, and trainees at the institution.
- Supported and promoted the internal job database platform that principal investigators and postdocs can utilize to post and seek employment opportunities.
- Processed 70 extension requests for post docs whose research might have been impacted by the ongoing pandemic.
- Conducted a Postdoc Well-Being Survey to understand the well-being of postdocs during the COVID pandemic. The survey also collected information on their level of satisfaction with the current resources and opportunities presented to them by MGH.
  - Results were presented and discussed with several leadership committees across the institution.
- Provided English for Speakers of Other Language (ESOL) classes specifically designed for researchers. A 12-week semester of ESOL divided into four class levels based on their English skill level.
- Increased collaboration with the MGPA to reduce redundancy in programming. Additionally, the MGPA restructured the association to better represent the diverse postdoctoral community at MGH.
  - Frequent communication with the MGPA has allowed for many new initiatives and projects to be discussed and created.
- Continued to offer seminars and workshops targeted specifically to faculty, postdocs, and graduate students (e.g., 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 Appreciation Week
  - Stress Resiliency Program for Trainees

Strategic Priorities—Office for Research Careers (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, shrinking faculty job market, 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.
- Create a grant management series that provides early and mid-career PIs with practical tips on efficiently managing funding:
  - Manage spending on grants (Insight, MicroStrategy, and Budget Documents)
  - Distribution of % effort of lab members and PIs on grants
  - Managing changes in science
- 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—Graduate Student Division (GSD)

- Better identify graduate students conducting research at MGH and ways to support their career advancement and research goals.
- 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.
- Expand Uber program to all graduate students in the Charlestown Navy Yard for travel between classes and their research labs.
- Host programs and events in areas and topics that graduate students highlighted as areas for improvement.
- Collaborate with the Postdoctoral Division and the Mass General Postdoc Association to host combined mentoring programs, events, and networking opportunities and ultimately increase collaboration and communication among the trainees at MGH.
- Foster and promote the peer-to-peer mentoring programs.
- Identify opportunities for MGH faculty to participate in training of graduate student from local institutions other than Harvard.
- Provide examples of successful fellowship applications and provide writing workshops for graduate funding opportunities.

Strategic Priorities—Postdoctoral Division (PDD)

- Utilize results from the 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 that will 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.
- 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 livestream 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.

Center for Faculty Development (CFD)

Programmatic Report

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 2021.
- Implemented a new lecture series "Parenting Series" focused on well-being and work-life balance for MGH faculty and trainee parents.
- Established and met with the new OWC Advisory Committee 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 monthly series "Coffee and Conversation" to create connections among faculty by bringing them together informally to address specific topics of interest and concern.
- Created a "Checklist for Success" for women faculty in collaboration with MGPO leadership and Frigoletto Committee.
- Created and disseminated a survey to build a coaching course tailored for non-clinical, women investigators.
- Established the "Marcela Del Carmen 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.

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 Committee semi-annually to maintain project alignment.
- Meet annually with Department Chairs and leadership.
- Provide updates on key initiatives and outcomes quarterly.

Center for Faculty Development (CFD)

Programmatic Report

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 an Associate 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 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 form for all Departments. Met with all MGH departments to review the Annual Career Conference (ACC) process and compile a unique ACC form for each department. Vetted possible online platforms to be reviewed by senior MGH leadership.
- 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.
- Implemented a new 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.
- Advised faculty and trainees from different departments regarding career advice, CV/cover letter critique, mentorship, and promotion.
- Created a "Women Surgeon List" with the intent to distribute to local primary care providers and increase the number of referrals for women surgeons at MGH.

Strategic Priorities

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

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 at HMS, the Medical Director of the Benson-Henry Institute for Mind Body Medicine at MGH (BHI-MGH), and 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.

Center for Faculty Development (CFD)

Programmatic Report

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.
- 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. Survey results from November 2021 found:
  - 100% of respondents felt that these meditation sessions met their expectations and that they would recommend them to colleagues.
  - Dr. Mehta's meditations were rated an average 4.85 out of 5 for effectiveness and the collective guest leaders were rated 4.64 out of 5.
  - Testimonial: "These have been incredibly helpful and sustaining. I've learned a lot of great techniques. I am now teaching them to my patients. Please continue these sessions indefinitely. It's an invaluable service."
  - Testimonial: "I look forward to them every Monday and Wednesday to start my day. I enjoy the consistency of Monday sessions and then I love knowing Wednesday will be a little different. It keeps it interesting."
- Implemented the Maurizio Fava Lecture Series on Well-Being, which was created to honor Dr. Fava's vision and advocacy for well-being of the MGH community. The OWB hosted two installments of the series in 2021 with Dr. Giovanni Fava and Dr. Susan David.
- 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 $27,642 spread among 53 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.
- Created 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 well-being champions within departments at MGH.

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.

Center for Computational and Integrative Biology

Thematic Center Report

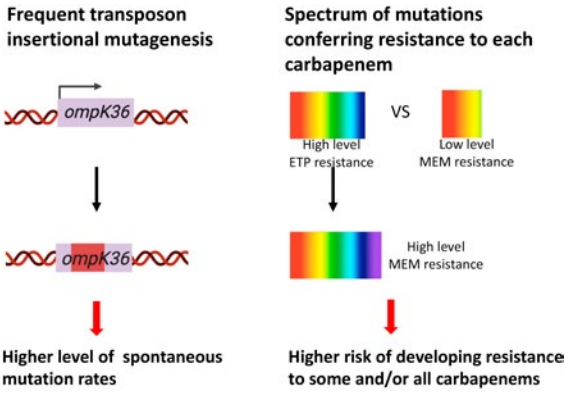


Figure 1: High-level transposon insertional mutagenesis and broader spectrum of resistance-conferring mutations for select carbapenems facilitate the evolution of resistance in clinical isolates.

RAMNIK J. 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, understand and simulate the conditions associated with the emergence of life, 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.

Over the past year, CCIB investigators continued leading and participating in research activities in response to the COVID-19 pandemic. Among these are studies geared toward understanding the molecular mechanisms of SARS-CoV-2/host interactions, including a Hung and Xavier collaboration seeking to answer why some B cells are better than others against SARS-CoV2 *(Cell, DOI: 10.1016/j.cell.2021.04.032)*, and the development of COVID-19 diagnostics, vaccines and therapeutics. Research also continued in key Center areas of focus including mechanisms that influence the propensity to evolve antibiotic resistance, mechanisms of rescuing pathway dysregulation in disease, how the microbiome modulates host susceptibility to disease, and broadening the potential applications of targeted epigenetic editing for research and therapeutics. Advances in these areas are highlighted in the stories below.

Achievements:

Antibiotic resistance is one of the most urgent threats to public health, yet our understanding of how pathogens evolve resistance remains limited. To address this gap, Peijun Ma, PhD, Deborah Hung, MD and colleagues investigated the evolution of carbapenem resistance in *Klebsiella pneumoniae*, a bacterial species that can cause deadly multi-drug-resistant infections. Their study, published in *eLife (DOI: 10.7554/eLife.67310)*, identified multiple factors that facilitate the rise of carbapenem resistance. High-level transposon insertional mutagenesis and the mutational spectrum for each carbapenem play important roles in increased mutation frequencies (Figure 1). The authors propose that defining infecting pathogens at a much higher genetic granularity (beyond species identity and antibiotic susceptibility) can have important implications for diagnosing and treating such infections.

Children born with mutations that make them unable to synthesize Molybdenum cofactor (Moco) suffer lethal neurological and developmental defects. Providing these children supplemental Moco could reverse their symptoms, but the Moco complex is unstable, lasting only minutes in a neutral, aqueous environment when not

bound to a protein. In a 2019 study *(DOI: 10.1038/s41589-019-0249-y)*, the Ruvkun laboratory showed that *C. elegans* can use exogenous, dietary Moco from *E. coli* in addition to synthesizing endogenous Moco. This observation led to a search for the particular form of exogenous Moco that is effectively used by worms. In a study published in *Genes and Development (DOI: 10.1101/gad.345579.120)* this year, Kurt Warnhoff, PhD, Gary Ruvkun, PhD and colleagues show that purified Moco-protein complexes can be ingested by nematodes as part of their diet and can rescue the lethality of Moco-deficient [*moc-1(ok366)*] *C. elegans* feeding on Moco-deficient [*ΔmoaA*] *E. coli* (Figure 2). Protein-bound Moco complexes with this activity were recombinantly expressed and isolated from *E. coli*, red bread mold *Neurospora crassa*, or green algae *Volvox carteri*, or purified from cow's milk. This work demonstrated that protein-bound Moco from plant, animal and bacteria sources is both stable and bioavailable to *C. elegans*. If conserved, these findings may have significant clinical implications as a novel therapy for Moco deficiency.

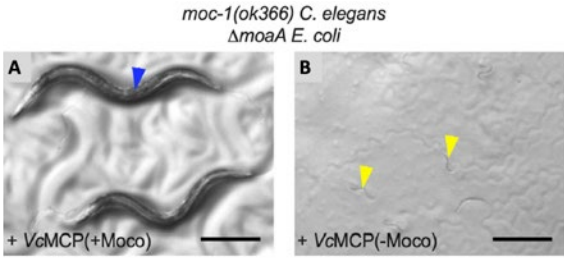


Figure 2: *C. elegans* uses Moco from Moco-containing proteins. *moc-1(ok366) C. elegans* cultured for 72 h on *ΔmoaA E. coli* supplemented with 7.7nmol of Moco bound to Volvox carteri Moco carrier protein (VcMCP) (A) or equivalent amounts of apo-VcMCP (–Moco) (B). Blue arrowhead indicates a fertile adult, while yellow arrowheads denote animals arrested early in larval development. Scalebar, 250 µm.

Two recent studies from the Xavier lab highlight the role of the microbiome in health and disease. In a study published in *Nature (DOI: 10.1038/s41586-021-03832-5)*, Damian Plichta, PhD, Ramnik Xavier, MD and collaborators at the Keio University School of Medicine show that centenarians, or people aged 100 and over, are less susceptible to chronic age-related diseases. Their unique microbiome composition may help support longevity. By analyzing fecal samples from 160 Japanese centenarians, the team found that compared to younger people, the centenarians showed higher levels of intestinal microbes that produce secondary bile acids such as isoalloLCA, which strongly inhibits the growth of some gram-positive bacteria. The findings could help researchers uncover mechanisms and biomarkers of healthy aging. In a separate study published in *Cell Host & Microbe (DOI: 10.1016/j.chom.2021.06.019)*, Drs. Jonathan Wei Jie Lee, Damian Plichta, Ramnik Xavier and colleagues profiled stool and blood samples from patients with IBD before treatment and tracked treatment response. They used modeling and machine learning to identify metagenomic, metabolomic, and proteomic markers that could predict which patients would achieve remission (Figure 3). Biomarkers varied by therapy class, with microbial diversity in the gut being a strong indicator of anti-cytokine therapy success. These response markers could lead to better IBD treatment selection.

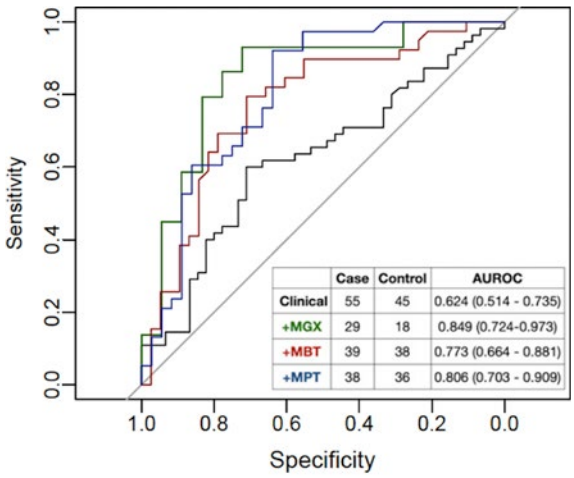


Figure 3: There is an incremental value in each layer of information among patients taking anti-cytokine therapy using random forest classifiers with feature selection and leave-one out cross-validation; a model using only baseline clinical features (black) performed poorly in predicting week 14 remission with an AUC of 0.624. adding metagenomic (green), metabolomic (brown), or proteomic (blue) features significantly increased the predictive value with AUCs of 0.849, 0.773, and 0.806, respectively.

Building on their genome engineering expertise, Esther Tak, ND, J. Keith Joung, MD, PhD and colleagues tackled an important challenge for targeted epigenetic editing technology: how to induce robust long-range activation of human genes using CRISPR-based artificial transcription factors (aTFs). Their findings, published in *Nature Methods, (DOI: 10.1038/s41592-021-01224-1)* confirmed that CRISPR aTF-mediated activation from enhancers is minimal or very inefficient on its own at different loci. Hypothesizing this could be due to inactive gene promoters, they concurrently targeted aTFs to both the distal enhancer and target promoter. This strategy yielded more robust and reliable activation across a variety of genes, cell types and aTF architectures, and allowed the authors to direct enhancer sequences capable of regulating more than one gene to a

specific promoter. Because disease-associated sequence variants are generally more enriched in non-coding regulatory regions than in promoters, they investigated whether they could target and leverage these differences to achieve allele-selective gene activation. Doing this, they successfully expressed one allele preferentially over another at four different genes (Figure 4 shows allele-specific *APOA4* or *APOC3* regulation). Their work has implications for understanding how enhancers function—the finding that enhancer activity is influenced by promoter status may impact how enhancers are identified using CRISPRa screens. In addition, their results illustrate how a single enhancer can differentially regulate multiple promoters within a gene cluster. Finally, allele-selective activation may provide a useful therapeutic approach for haplo-insufficient or dominant-negative human diseases by means such as selectively activating a wild-type over a deleterious mutant allele.

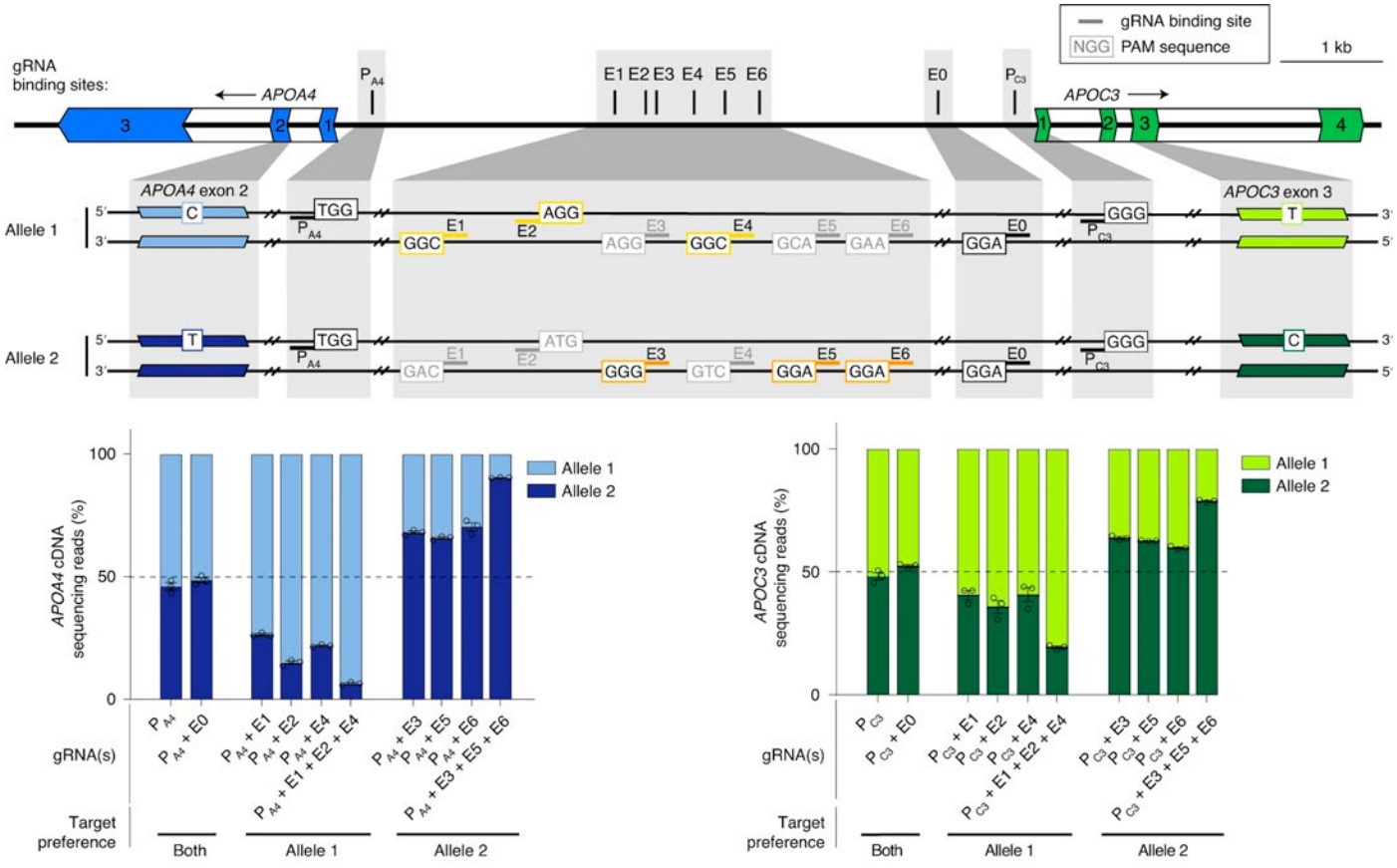
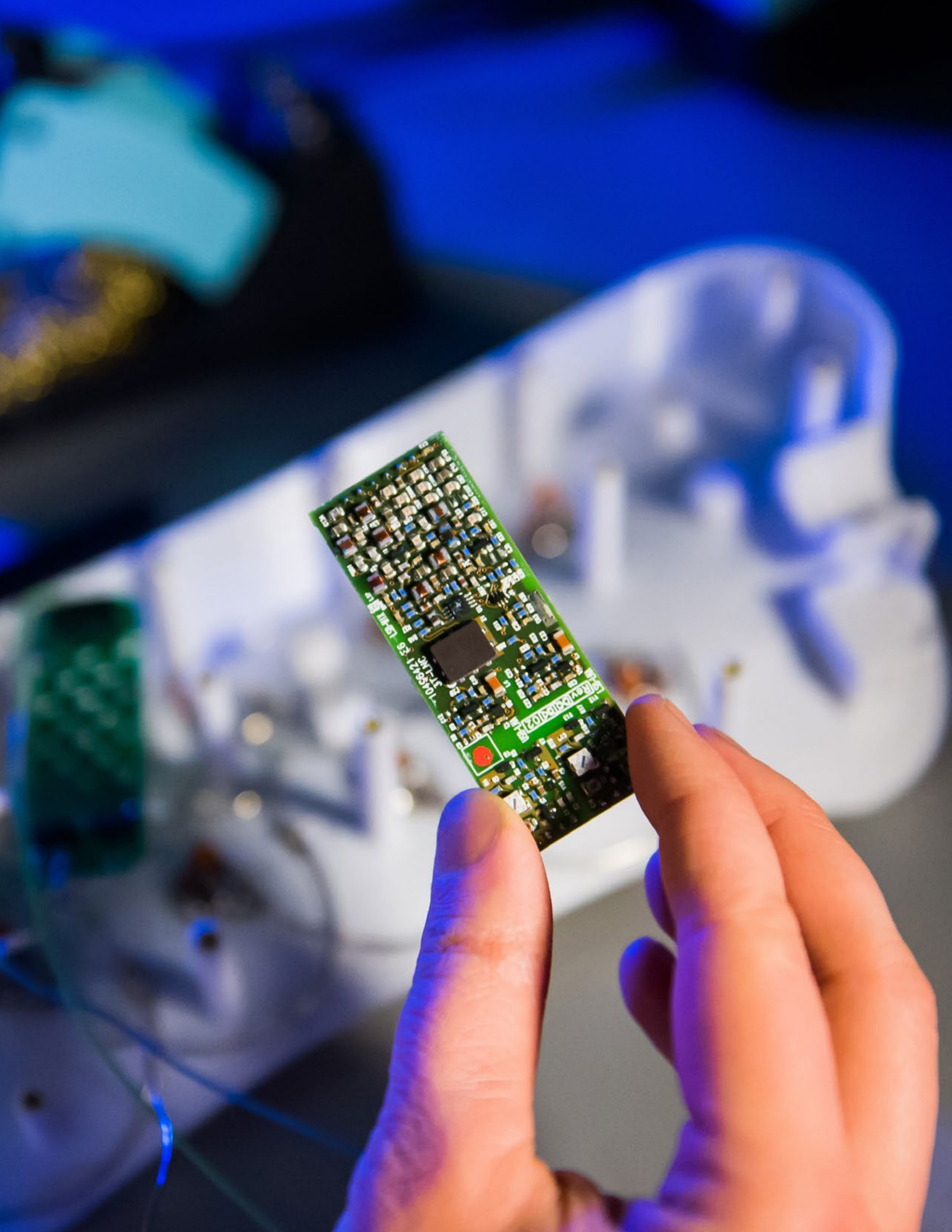


Figure 4: Inducing allele-specific *APOA4* or *APOC3* upregulation in HEK293 cells using heterotopic enhancer activation.



Center for Genomic Medicine

Thematic Center Report

MICHAEL TALKOWSKI, PHD, DIRECTOR

Overview:

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 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**'. 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 (Figure 1).

Leadership

In 2020, MGH completed an international search and **Dr. Michael Talkowski was named 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 succeeds Dr. Sekar Kathiresan and Dr. James Gusella in this role.

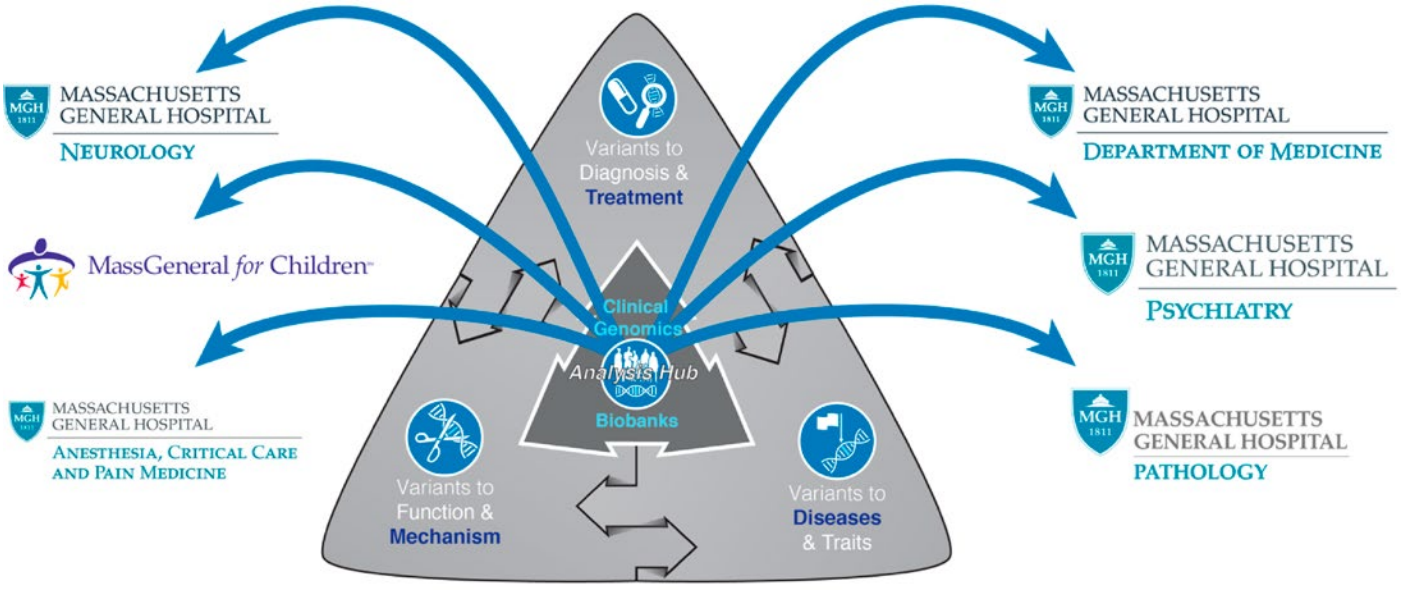


Figure 1: CGM Strategic Vision

Center for Genomic Medicine

Thematic Center Report

Overview

The CGM is a diverse thematic Center comprised of 47 faculty engaged in all facets of genomic medicine. Our programs cut across **seven MGH departments** and include over 400 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.

In 2021, despite myriad 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. At the highest-level summary, the CGM PIs published an astonishing **545** papers in 2021, or ~1 paper per PI per month (Figure 2). These faculty competed for **~$20M** in new funding to CGM, while **increasing our financial portfolio by 9.5% in direct costs and 10.4% in indirect costs**. Our faculty filed numerous patents, started companies, and were recognized with national and international awards of excellence by the genomic medicine community, including **six** CGM Faculty recognized in the 2021 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.

We also significantly increased our administrative capabilities in 2021. We hired a new Sr. Finance Manager from Columbia University, Danajali Ratnayaka, a new administrative coordinator, Piper McCabe, and through an open national search, we selected a new CGM Associate Director, Dr. Alex Soukas, Associate Professor of Medicine, and the Weissman Family MGH Research Scholar. We serviced our community by leading an international **COVID-19 host genetics initiative**, and we re-deployed throughout the MGH to assist clinical activities early in the pandemic. We organized several core committees that drove major infrastructure investments and search committees that led to our hiring of **five new Assistant Professors in the CGM**. 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.

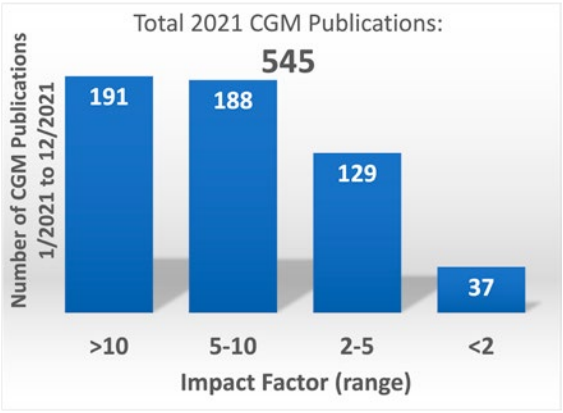


Figure 2: CGM 2021 Publications and Impact

Achievements:

I. Publications

A Few Vignettes from Around the CGM

Mapping the human genetic architecture of COVID-19.
COVID-19 Host Genetics Initiative, Nature. July, 2021.

At the outset of the SARS-CoV-2 pandemic, CGM faculty members in the ATGU, Drs. Benjamin Neale, Mark Daly, and many others helped to form the **COVID-19 Host Genetics Initiative (HGI)** to bring together the human genetics community to study the genetic determinants of COVID-19 susceptibility, severity, and outcomes. In 2021, the flagship paper for the global **HGI** was published in *Nature*. This study sought to answer one of the fundamental mysteries about SARS-CoV-2: why do some individuals develop life-threatening illness while others experience mild or no symptoms? While certain risk factors—age, obesity, and smoking—explained some of the differences, much of the striking variability in outcomes post-infection were inexplicable. Given past findings highlighting the role of human genetic variation in variable response to infection, it was suspected that the genetic profiles of patients played a strong role. By the end of 2020, the consortium had assembled a cohort of nearly 50,000 COVID-19 cases across 19 countries that were collected, genotyped, jointly analyzed, and openly released to the public. The COVID-19 HGI uncovered 13 loci associated to either SARS-CoV-2 Infection and severe COVID19. At six of these loci, protein-altering variants are in linkage disequilibrium with lead variants, including *TYK2* (19p13.2) and *PPP1R15A* (19q13.33). The association peak at *TYK2*, which confers risk for critical illness and hospitalization, implicates the hypomorphic missense variant rs34536443:G>C (p.Pro1104Ala; r 2 = 0.82). This missense variant was previously reported to be protective against autoimmune diseases including rheumatoid arthritis and hypothyroidism. The paper further sought to identify whether lung-specific transcriptomic data from GTEx v821 (n = 515) and the Lung eQTL Consortium22 (n = 1,103) could enlighten on the mechanism by which these genetic variants were influencing COVID-19 outcomes. These analyses uncovered multiple genes, including *FOXP4* (6p21.1), *ABO* (9q34.2), *OAS1/OAS3/OAS2* (12q24.13), and *IFNAR2/IL10RB* (21q22.11), where the COVID-19 associated variants modify gene expression in lung. The *OAS* gene cluster has a role in innate immune responses to viral infection. Overall, these studies establish a definitive genetic basis for susceptibility to COVID-19 infection and disease severity, and were made possible by human geneticists coming together to share data, results, and resources, and underscores the potential influence of coordinated global genomics initiatives to impact human health.

CGM researchers spearhead a collaborative effort to improve diagnosis of rare genetic diseases.

More than 400 million people around the world suffer from diseases caused by alterations in a single gene. These "Mendelian" disorders pose challenges along the spectrum of the genomic medicine cycle, from diagnosis to treatment, and can have devastating consequences to patients and their families. Spearheaded by CGM investigators, a newly expanded Broad Institute Center for Mendelian Genomics will rise to the challenge of addressing monogenic diseases through a collaborative program that will now include CRISPR-based functional modeling of Mendelian variants within the CGM at MGH (Figure 3). The National Human Genome Research Institute announced in July that it would provide $80 million to fund five Mendelian genomics research clinical centers. At the Broad Institute, the center will continue to be led by **Heidi Rehm, PhD**, GMU Director in the CGM, Chief Genomics Officer in MGH Medicine, and Institute Member at the Broad Institute; **Michael Talkowski, PhD**, Director of the CGM, Desmond and Ann Heathwood MGH Research Scholar in MGH Neurology, and Institute Member at the Broad; and **Anne O'Donnell-Luria, MD, PhD**, Assistant Professor of Pediatrics at Boston Children's Hospital and Associate Member at the Broad. The flagship paper for the initial NHGRI CMGs is in press in Genetics in Medicine and a preprint is provided at here. Learn more.

Figure 3: A cross-institutional Mendelian genomics program

TIGER eyes diabetes variants of every stripe.

Genome-wide association studies (GWAS) have identified hundreds of signals associated with type 2 diabetes (T2D). Many of these affect the endocrine pancreatic islets, a tissue central to the pathogenesis of T2D. To gain insight into the molecular mechanisms by which GWAS signals impact the function of pancreatic islets, CGM investigator **Josep Mercader, PhD**, and collaborators created the Translational human pancreatic Islet Genotype tissue-Expression Resource (TIGER), a large expression regulatory variation resource aggregating >500 genomic datasets from human pancreatic islets. The data, made available through the TIGER portal, are expected to facilitate elucidation of molecular mechanisms underpinning T2D and heretofore unappreciated therapeutic inroads. Learn More: Cell Reports and this tweetorial from Dr. Mercader.

Social media impact on mental health.

There is increasing concern about the impact of social media on mental health, particularly in children. Existing studies are primarily cross-sectional—with depression and social media use assessed at the same time—so while they show association, it is not possible to conclude that social media use causes depression or vice versa. Even less is known about the associations with social media use in adults, especially older adults. CGM Faculty member in PNGU and Professor of Psychiatry **Dr. Roy Perlis** is a PI of the covidstates project, an NSF-supported 50-state survey of ~20,000 adults conducted every 4-6 weeks since spring 2020. As part of that study, participants were

asked about a range of behaviors, including social media use, and about mood and anxiety. The study found that, among adults who were not depressed, reporting social media use at one survey wave predicted emergence of depression at a subsequent wave. A key caveat is that the study can only show associations, not causation—but it suggests that the social media use precedes the onset of depression. The work will now help to inform policymakers as they grapple with a range of challenges during covid, including decisions on public policy surrounding regulation of social media. Learn more: covidstates.org and JAMA Network.

Exome sequencing powers gene discovery in schizophrenia.
In a preprint reported last year that is now in press *(Singh et al., Nature)* from the Neale and Daly labs, Singh et al. performed one the largest exome sequencing study to date (24,248 cases and 97,322 controls) and implicate ultra-rare coding variants in ten genes as conferring substantial risk for schizophrenia. These genes are highly expressed in the central nervous system and involved in synaptic functions, and they find significant evidence for an overlap of rare variant risk between schizophrenia, autism spectrum disorders, and severe neurodevelopmental disorders, supporting a neurodevelopmental etiology for schizophrenia.

Initial studies predict diagnostic value of clinical genome sequencing at MGH and beyond.
Two studies from CGM teams demonstrate the value of genome sequencing as a first-tier diagnostic screen. In a study from the Udler and Rehm labs, Brockman, Austin-Tse et al. *(Genet Med 2021 Sep;23(9):1689-1696)* examined 99 individuals who received clinical genome sequencing and standard-of-care testing among 204 participants recruited MGH clinics. In a preprint from the Talkowski lab, Lowther, Valkanas et al. *(bioRxiv)* explored the sensitivity, specificity, and added diagnostic value of genome sequencing to displace conventional approaches in prenatal and pediatric genetic testing. Their analyses of genome sequencing in 6,973 individuals from autism quartet families and trios harboring a fetal structural anomaly on ultrasound revealed that genome sequencing was superior to current diagnostic tests (karyotype, microarray, exome sequencing), with near perfect sensitivity compared to lower resolution technologies.

Preferred population prose.
Over the past decade, genetics publications have increasingly used the term “trans-ethnic” to describe analyses that incorporate multiple ancestrally diverse populations. In *Nature Genetics*, CGM Investigator in ATGU, **Hilary Finucane** and colleagues describe the term as inaccurate, ambiguous, and alienating—and offer a solution. They ask colleagues to stop using “trans-ethnic,” preferring more accurate descriptors such as “cross-population” or “multi-ancestry.” The team suggests researchers should work towards a new consensus on the best terms to use, in part by engaging underrepresented communities

in the discussions. These efforts are but one component of a larger effort to address disparities in genetics. Learn more: *Nature Genetics*.

BMI mediates diabetes risk from cholesterol drug.
Drugs that lower LDL cholesterol modestly increase the risk of type 2 diabetes, and reduced LDL is also associated with weight gain. Whether the effect on diabetes risk is mediated through increased body mass index (BMI) is unclear. In Diabetes Care, CGM investigators **Jordi Merino, PhD, Jose Florez, MD, PhD**, and collaborators used multivariable Mendelian randomization analysis to investigate the interplay between LDL cholesterol, weight gain, and diabetes risk in more than 900,000 people. They found that the diabetogenic effect of lowering LDL cholesterol was partially mediated by increased BMI. This finding advances our understanding of diabetes pathophysiology and help people using these medications take measures to prevent diabetes.

International policies and standards for data sharing across genomic research and healthcare.
The genomics field has yet to uncover many of the causes of rare disease or identify the functional variation underlying common disease. To answer these questions, we will need access to much more data from around the globe, generated in different regions and using different platforms and pipelines. CGM Investigator and GMU Director **Heidi Rehm, PhD** is vice-chair of the Global Alliance for Genomics and Health (GA4GH), which is a policy-framing and technical standards-setting organization, enabling the responsible sharing of genomic and health data. This past month, Rehm led the publication of GA4GH's marker paper, along with over 200 authors, which outlines the organization and its strategic goals and frameworks. The paper highlights many technical standards and policy frameworks that have been developed by eight Work Streams and implemented across 24 Driver Projects. The paper is part of a special issue of Cell Genomics where members of GA4GH published multiple papers covering their work of developing open-source interoperable standards and policy frameworks and implementing these in programs internationally. Learn more: Cell Genomics.

Baby teeth may one day help identify kids exposed to early life stress.
Exposure to maternal psychosocial stressors during the prenatal and perinatal periods can have major long-term mental and physical health consequences for children. In spite of this, no validated and inexpensive biomarkers are available to identify children who have been exposed to said stressors. By examining exfoliated baby teeth and epidemiological survey data in a prospective cohort study, CGM investigator in PNGU **Erin Dunn, ScD, MPH**, and colleagues determined that the width of a growth mark in teeth, called the neonatal tooth line, was significantly associated with exposure to maternal perinatal psychosocial factors, including maternal depression, psychiatric problems, and maternal prenatal anxiety or

depression. This work was featured in multiple press releases because of its potential transformative impact on the field. Learn more: Press Release and JAMA Network.

Deep learning suggests novel therapeutic targets for existing compounds.
A manuscript in *Nature Communications* from the CGM investigators **Susan Slaugenhaupt, PhD**, and **Michael Talkowski, PhD**, led by CGM Instructors **Dadi Gao, PhD**, and **Elisabetta Morini, PhD**, in MGH Neurology, show that novel machine learning approaches can predict response to pharmacological modulation, strongly supporting the use of *in silico* approaches to expand the therapeutic potential of drugs that modulate splicing.

Recessive genome-wide meta-analysis illuminates genetic architecture of type 2 diabetes.
Genome-wide association studies (GWAS) of complex traits performed using models with additive allelic effects may miss loci with recessive effects, leaving potentially important genes undiscovered. CGM Investigators **Jose Florez, MD, PhD**, and **Josep Mercader, PhD** led the largest GWAS meta-analysis to date using a recessive model for type 2 diabetes, identifying 51 loci associated with a substantially higher risk of type 2 diabetes.

Electronic health record-based meta-analysis provides insights on the genetic architecture of non-alcoholic fatty liver disease.
Non-alcoholic fatty liver disease (NAFLD) is a complex disease with incompletely understood genetic underpinnings. CGM investigator **Amit Khera, MD**, and colleagues performed a genome-wide meta-analysis of 4 cohorts of electronic health record-documented NAFLD, identifying susceptibility loci for NAFLD, and reinforcing positive genetic correlations between NAFLD and cardiometabolic diseases. The work is a paradigm for genetic discovery using the richness of clinical data available in electronic health records.

Serum- and glucocorticoid-induced kinase drives insulin resistance by inhibiting AMP-activated protein kinase.
A hallmark of type 2 diabetes is resistance to insulin's glucose-lowering effects. In this study in *Cell Reports*, members of the **Soukas** lab identify the insulin-activated serum- and glucocorticoid-regulated family of protein kinases (SGK) as a driver of insulin resistance in the setting of consumption of an unhealthy, high-fat diet. Targeting SGK may help to treat or prevent type 2 diabetes.

Cross-disorder genomics data analysis elucidates a shared genetic basis between major depression and osteoarthritis pain.
Osteoarthritis (OA) and major depression (MD) are two debilitating disorders that frequently co-occur and affect millions of the elderly each year. In this work by CGM's **Phil H. Lee** and **Smoller** groups within PNGU, cross-disorder investigation of OA and MD using genome-wide association data indicates significant positive genome-wide genetic correlations. Further, Mendelian randomization (MR) analysis identified a bidirectional causal effect between OA and MD, indicating genetic variants affecting OA risk are, in part, shared with those influencing MD risk.

Cerebral small vessel disease and depression among intracerebral hemorrhage survivors.
Intracerebral hemorrhage (ICH) is an acute manifestation of cerebral small vessel disease (CSVD). CSVD-related imaging findings are associated with increased depression incidence in the general population. In this study in *BMC Neurology*, Members of the **Rosand** and **Biffi** groups at CGM found that CSVD-related markers were associated with depression risk both pre- and post-ICH, and that survivors of cerebral amyloid angiopathy-related lobar ICH were more likely to be diagnosed with depression before ICH, less likely to achieve remission of depressive symptoms, and less likely to benefit from antidepressant therapy.

Dystonia-specific mutations in THAP1 alter transcription of genes associated with neurodevelopment and myelin.
The dystonias are a group of complex neurologic disorders characterized by sustained involuntary muscle contractions and twisted postures. In a functional genomics study led by Dr. Aloysius Domingo in the American Journal of Human Genetics from the CGM's **Talkowski** laboratory and the **Bragg** laboratory, both core faculty in the MGH Neurology Collaborative Center for X-linked Dystonia Parkinsonism, characterized the impact of variants in the *THAP1* gene, which encodes a transcription factor linked to a monogenic form of dystonia. Neural stem cells engineered to carry either THAP1-dystonia mutations exhibit dysregulated expression of genes related to neurodevelopment and myelin, and analysis of brains of mice with Thap1 disruption confirms the presence of structural myelin defects. This work highlights the potential role of neuron-glial interactions in dystonia pathogenesis.

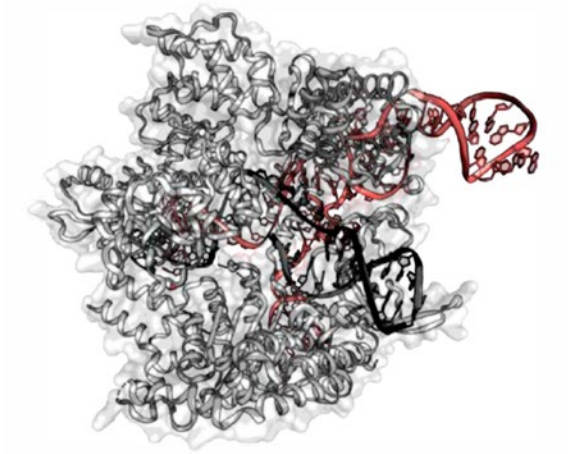


Figure 4: Goodman Fellow Awardee leads CRISPR innovations in CGM.

II. MGH Awards

Dr. Ben Kleinstiver: 2021 Howard M. Goodman Fellow
Ben Kleinstiver was a 2021 recipient of the ECOR Howard M. Goodman Fellowship. Ben is a biochemist and genome editor whose interests include protein engineering and genome editing technology development, with the long-term goal of translating these technologies into molecular medicines. Within the CGM at MGH, the Kleinstiver laboratory develops scalable methods for molecular engineering to accelerate the development of CRISPR technologies. The major goals of the research in his laboratory are to address limitations of existing technologies, to develop new capabilities that will help solve important research questions at the forefront of the genome editing field, all with the hope of providing safe and effective treatments for patients. Since starting in the CGM, the Kleinstiver laboratory has developed new CRISPR-Cas enzymes and base editors that can, for the first time, access the entire genome (Walton et al., Science 2020), has developed scalable methods for protein engineering and characterization *(Walton et al. Nature Protocols 2021)*, and has forged collaborations with research groups in the CGM to develop pre-clinical models to explore therapeutic approaches for various diseases (Figure 4).

2021 Celebration of Science Recognition Awards to CGM Faculty
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 2021, ECOR provided Celebration of Science Recognition Awards for the most competitive nominations that were not selected. The awards were announced at the 2021 SAC meeting and four of these prizes were CGM nominations. The awardees included one paper from the Kleinstiver laboratory and three papers from the genome aggregation database (gnomAD) project. Links to these papers are included below, to learn more about the MGH awardees, project leaders, and a brief description of each paper click here.

Unconstrained genome targeting with near-PAMless engineered CRISPR-Cas9 variants
Walton et al., 2020, Science. Russel Walton on behalf of the Kleinstiver Lab

The mutational constraint spectrum quantified from variation in 141,456 humans
Karczewski et al., 2020, Nature. Konrad Karczewski on behalf of the MacArthur, Daly, and Neale Labs

A structural variation reference for medical and population genetics
Collins et al., 2020, Nature. Ryan Collins & Harrison Brand on behalf of the Talkowski Lab

Evaluating drug targets through human loss-of-function genetic variation
Minikel et al., 2020, Nature. Eric Minikel on behalf of the MacArthur Lab

III. Community

During the 2020-2021 academic year, the CGM launched an open international search in genomic medicine. Our search produced almost 100 outstanding candidates, and three new faculty were ultimately selected. These candidates included Dr. Melina Claussnitzer, Assistant Professor of Medicine in the MGH Endocrine Division. Melina is already a leading the field in variant to function studies. She will spearhead the pursuit of scalable quantitative biology studies in the CGM. Dr. Kaitlin Samocha was selected as an Assistant Professor in Medicine to join the GMU in the CGM, and Dr. Elise Robinson was selected as an Assistant Professor in Psychiatry to join PNGU in the CGM. Elise leads autism research in the Psychiatric Genomics Consortium and the NeuroDev project, which is seeking to define the genetic etiology of neurodevelopmental disorders and diagnose patients in Africa.

These amazing scientists join two earlier searches in 2020 that included new CGM faculty Alicia Martin in the ATGU and Myriam Udler in the MGH Diabetes Unit (Figure 5). These new faculty will spearhead CGM initiatives for years to come, and our internal MGB search currently in process will bring new faculty into our genomic medicine community in 2022.

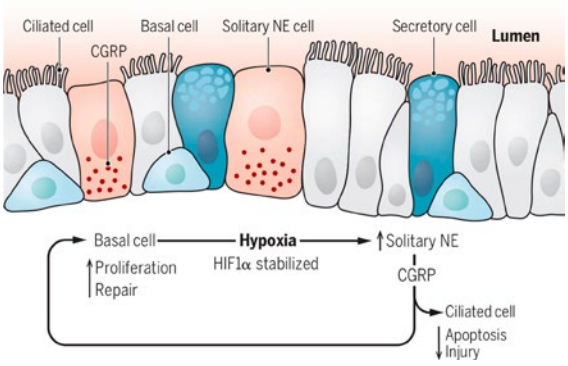
Figure 5: Five new CGM faculty will lead genomic medicine at MGH.

IV. Training

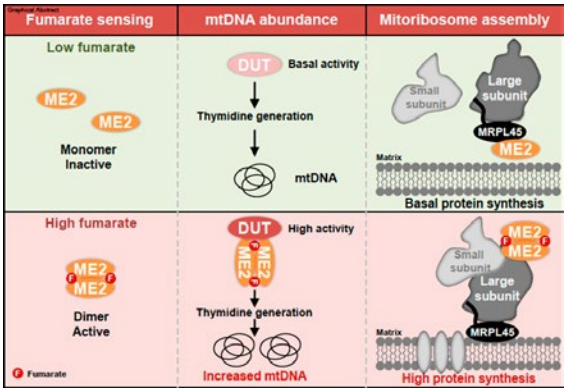
The primary training initiative in the CGM that was formerly spearheaded by Drs. Kathiresan and Smoller was the pursuit of an NHGRI Institutional Research Training Grant (T32) program: **"MGB Training Program in Precision and Genomic Medicine"**. The T32 program was awarded in 2019 and Dr. Heidi Rehm has assumed the MPI role with Dr. Smoller. This CGM T32 initiative has engaged 43 faculty within its program from throughout the MGB community and is in its **fourth** annual call for new trainees in Precision and Genomic Medicine. The CGM Genomic Medicine Seminar also continued remotely and increased in frequency to a weekly seminar to promote greater interaction and engagement given the isolation of the pandemic for many. The seminar hosted local, national, and international speakers in genomic medicine, including an invited seminar with Elena Olson, JD from the MGH Center for Diversity and Inclusion to engage the CGM community in a discussion around the CDI structural equity plans at MGH.

Center for Regenerative Medicine

Thematic Center Report



Identifying stem cells that directly sense hypoxia and respond by differentiating into solitary NE cells that secrete a protective peptide that mitigates hypoxic injury.



This image shows how the Krebs cycle intermediate fumarate links metabolism to mitobiogenesis through binding to malic enzyme 2 (ME2).

DAVID SCADDEN, MD, DIRECTOR

Mission and Focus:

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

4 Key Scientific Achievements in 2021:

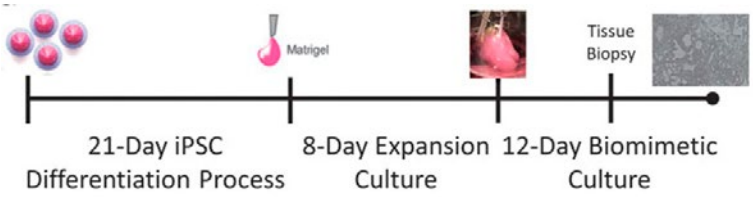
1. **Defined that airway stem cells respond to hypoxia by differentiating into neuroendrocrine cells:** Rajagopal lab: *Shivaraju et al., Science 371(6524):52-57 January 1, 2021*

   Neuroendocrine (NE) cells are epithelial cells that possess many of the characteristics of neurons, including the presence of secretory vesicles and the ability to sense environmental stimuli. The normal physiologic functions of solitary airway NE cells remain a mystery. We show that mouse and human airway basal stem cells sense hypoxia. Hypoxia triggers the direct differentiation of these stem cells into solitary NE cells. Ablation of these solitary NE cells during hypoxia results in increased epithelial injury, whereas the administration of the NE cell peptide CGRP rescues this excess damage. Thus, we identify stem cells that directly sense hypoxia and respond by differentiating into solitary NE cells that secrete a protective peptide that mitigates hypoxic injury.

2. **Defined how new mitochondria are made in response to increased metabolic activity.** Scadden lab: *Wang et al. Cell Metabolism 33(5):1027-1041 May 4, 2021.*

   We found that the Krebs cycle intermediate fumarate links metabolism to mitobiogenesis through binding to malic enzyme 2 (ME2). Mechanistically, fumarate binds ME2 with two complementary consequences. First, promoting the formation of ME2 dimers, which activate deoxyuridine 5'-triphosphate nucleotidohydrolase (DUT). DUT fosters thymidine generation and an increase of mtDNA. Second, fumarate-induced ME2 dimers abrogate ME2 monomer binding to mitochondrial ribosome protein L45, freeing it for mitoribosome assembly and mtDNA-encoded protein production. Methylation of the ME2-fumarate binding site by protein arginine methyltransferase-1 inhibits fumarate signaling to constrain mitobiogenesis. Notably, acute myeloid leukemia is highly dependent on mitochondrial function and is sensitive to targeting of the fumarate-ME2 axis. Therefore, mitobiogenesis can be manipulated in normal and malignant cells through ME2, an unanticipated governor of mitochondrial biomass production that senses nutrient availability through fumarate.

3. **Defined how to make human lung alveolar cells from iPSC.** Ott lab: *Becerra et al. Tissue Engineering 27;12:639-648. December 21, 2021.*

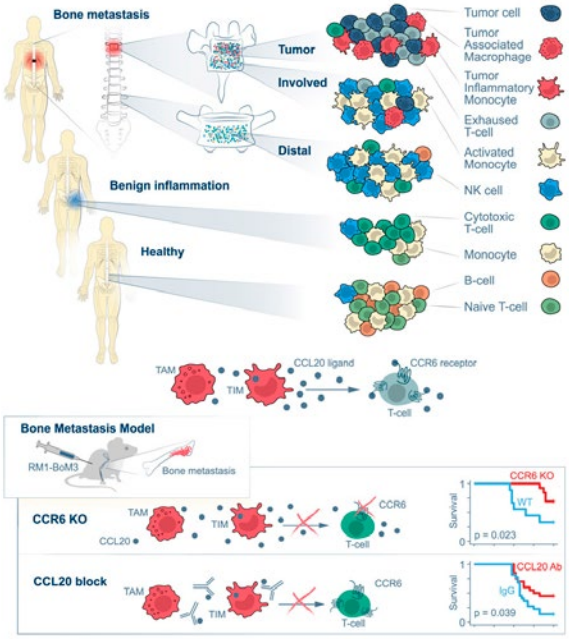


A scalable method for human alveolar cell differentiation for human lung regeneration bioengineering or for commercial cell production.

We developed a novel culture method for induced pluripotent stem cell-derived alveolar epithelial cell (AEC) expansion with enhanced proliferative capacity and reduced resource requirements compared with previously described methods. This method is scalable for human whole-lung regeneration bioengineering or could be automated for commercial cell production.

4. **Defined the tumor microenvironment in human prostate bone metastases and that modifying the CCL20-CCR6 axis in it improves survival in a syngeneic mouse model.** Sykes lab: *Kfoury et al. Cancer Cell: 39(11):1464-1478. Novermber 8, 2021.*

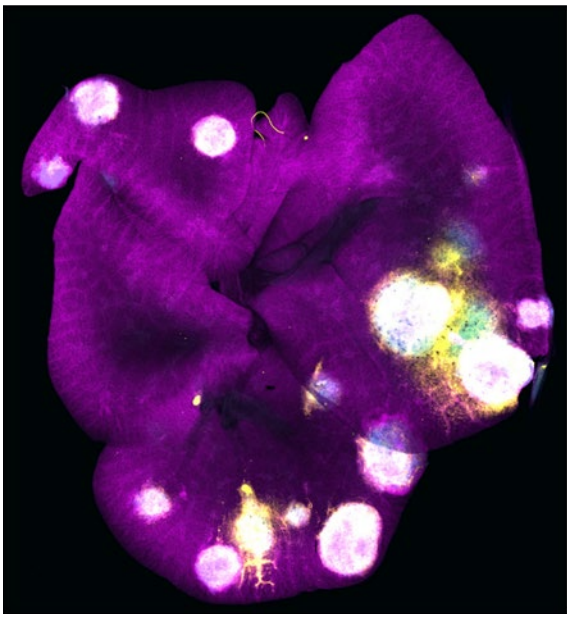
In a multi-disciplinary collaboration between the Sykes lab, Scadden lab, Kharchenko lab (HMS) Neurosurgeon, Dr. John Shin (MGH) and Oncologist Dr. Phil Saylor (MGH) bone marrow samples from patients with prostate cancer bone metastases, as well as control patients, were collected fresh for an analysis of the complex tumor and bone marrow microenvironments (upper panel). There was expansion of the TAM (Tumor Associated Macrophages) and TIM (Tumor Inflammatory Monocytes) populations specifically within the tumor fractions, and these populations showed overexpression of the CCL20 chemokine. The secretion of CCL20 from myeloid cells leads to T-cell suppression by signaling through the CCR6 receptor (middle panel). In a model of bone metastatic prostate cancer, abrogation of the CCL20-CCR6 axis, both by genetic knock-out as well as by neutralizing antibody approaches, suppressed tumor growth and improved animal survival (bottom panel).



Distinctive immune microenvironment in prostate bone metastases defined with molecular targets to modify it shown in animal models.

Center for Systems Biology

Thematic Center Report



Opening the doors for a Trojan Horse in cancer therapy. New imaging techniques for simultaneously tracking delivery and action of the widely used chemotherapy, nanoparticulate albumin-bound paclitaxel (nab-paclitaxel, yellow), revealed how oncogenic KRAS signaling controls albumin-drug uptake in a genetically engineered mouse model of lung adenocarcinoma (cyan). Tumor uptake of albumin-bound drug (shown as white) and corresponding efficacy could be enhanced by manipulating nutrient signaling via targeting the insulin-like growth factor 1 receptor (IGF1R). *Li, R., T. S. C. Ng, S. J. Wang, M. Prytyskach, C. B. Rodell, H. Mikula, R. H. Kohler, M. A. Garlin, D. A. Lauffenburger, S. Parangi, D. M. Dinulescu, N. Bardeesy, R. Weissleder, and M. A. Miller. Therapeutically reprogrammed nutrient signalling enhances nanoparticulate albumin bound drug uptake and efficacy in KRAS-mutant cancer. Nature Nanotechnol 2021;16: 830-839*

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

Achievements:

Bone marrow acts up in cardiovascular disease.
It is now all but certain that in addition to bad cholesterol, inflammation is the other main driver of coronary heart disease. Heart attacks happen when an inflamed buildup of lipids clogs the blood supply through a coronary artery. White blood cells, which usually defend us against infection, are the main drivers of this vessel wall inflammation. Many of these cells can be found in a plaque, where they arrive after being born in the bone marrow and a quick journey through the blood stream. Since white blood cells that destroy the artery are quite short lived, it is important study their "just in time" production by blood stem cells, a process also called hematopoiesis.

In patients with heart disease, white blood cells are more numerous. But what leads to their increased bone marrow output is still not clear. Rohde et al. discovered that the bone marrow vasculature is also affected by cardiovascular disease. While it almost seems obvious that systemic vascular disease impacts bone marrow vessels just as it does heart vessels, this was not known to occur. High blood pressure, atherosclerosis and acute myocardial infarction changed the bone marrow blood vessel number, structure and function. These milestones of coronary heart disease also affected the vasculature's release of factors that regulate blood cell production and migration. As a consequence, more white blood cells were available in the body, and this increase, called leukocytosis, propels inflammation everywhere, including in the arteries and the heart. This study will

allow examination of how to reduce blood cell production to normal values, thereby cooling off inflamed plaques anywhere in the body.

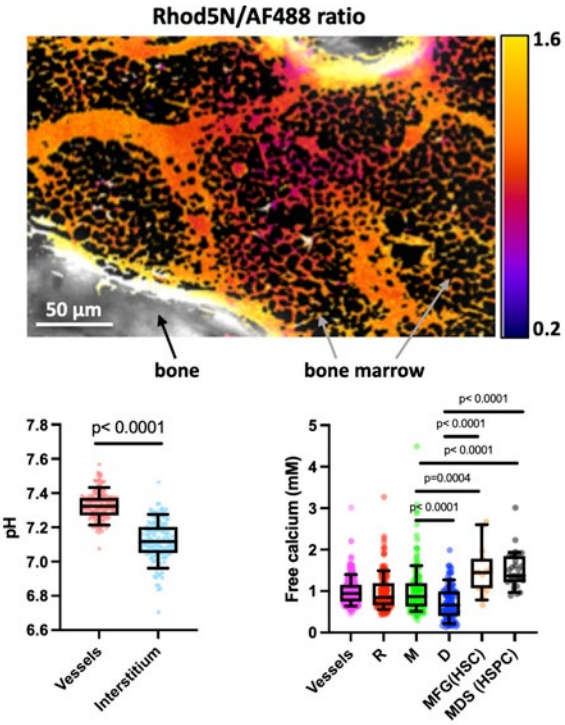
Rohde, D., K. Vandoorne, I.-H. Lee, J. Grune, S. Zhang, C. S. McAlpine, M. J. Schloss, R. Nayar, G. Courties, V. Frodermann, G. Wojtkiewicz, L. Honold, Q. Chen, S. Schmidt, Y. Iwamoto, Y. Sun, S. Cremer, F. F. Hoyer, O. Iborra-Egea, C. Muñoz-Guijosa, F. Ji, B. Zhou, R. H. Adams, J. D. Wythe, J. Hidalgo, H. Watanabe, Y. Jung, A. M. van der Laan, J. J. Piek, Y. Kfoury, P. A. Désogère, C. Vinegoni, P. Dutta, R. I. Sadreyev, P. Caravan, A. Bayes-Genis, P. Libby, D. T. Scadden, C. P. Lin, K. Naxerova, F. K. Swirski, and M. Nahrendorf. 2021. Bone marrow endothelial dysfunction promotes myeloid cell expansion in cardiovascular disease. *Nature Cardiovascular Research 2021; in press*

A molecule that may help prevent Alzheimer's disease.
Communication within the glial cell ecosystem is essential for neuronal and brain health. McAlpine et al found that astrocyte-sourced interleukin-3 (IL-3) programs microglia to ameliorate the pathology of Alzheimer's disease (AD) in humans and mice. Upon recognition of ß-amyloid (Aß) deposits, microglia increase their expression of IL-3Rα—the specific receptor for IL-3—making them responsive to IL-3. Astrocytes constitutively produce IL-3, which elicits transcriptional, morphological, and functional programming of microglia to endow them with an acute immune response program, enhanced motility, and the capacity to cluster and clear aggregates of Aß and tau. These changes restrict AD pathology and cognitive decline. Our findings identify IL-3 as a key mediator of astrocyte–microglia cross-talk and a node for therapeutic intervention in AD.

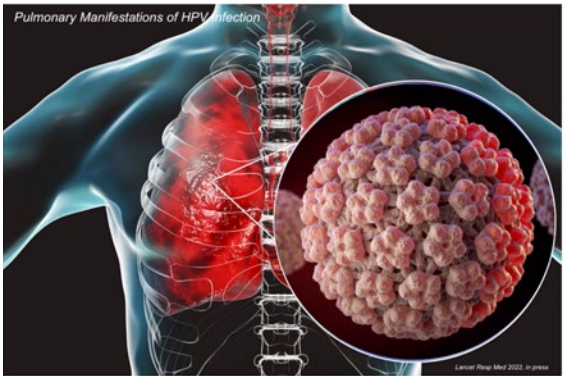
McAlpine, C. S., J. Park, A. Griciuc, E. Kim, S. H. Choi, Y. Iwamoto, M. G. Kiss, K. A. Christie, C. Vinegoni, W. C. Poller, J. E. Mindur, C. T. Chan, S. He, H. Janssen, L. P. Wong, J. Downey, S. Singh, A. Anzai, F. Kahles, M. Jorfi, P. F. Feruglio, R. I. Sadreyev, R. Weissleder, B. P. Kleinstiver, M. Nahrendorf, R. E. Tanzi, and F. K. Swirski. Astrocytic interleukin-3 programs microglia and limits Alzheimer's disease. Nature 2021;595: 701-706.

Widening the safety margin of cancer immunotherapies
Immune checkpoint blockade (ICB) has revolutionized cancer therapeutics; however, in many cases, ICB is limited by immune-related adverse events (irAEs). Thus, a better understanding of the immune responses that lead to irAEs and how they are distinguished from antitumor immunity is needed. Here, Siwicki et al. used anti-CD40 therapy as a mediator of TH1-induced antitumor immunity in mouse tumor models. They found that liver-resident Kupffer cells induced neutrophil-mediated liver toxicity by producing IL-12 and responding to IFN-γ. Inhibition of the neutrophil response limited liver toxicity while retaining the antitumor efficacy of anti-CD40. Similar data were found in patients treated with anti–PD-1 and anti–CTLA-4. Together, these data suggest that the toxicity of ICB can be inhibited without negatively affecting antitumor immunity.

Siwicki, M., N. A. Gort-Freitas, M. Messemaker, R. Bill, J. Gungabeesoon, C. Engblom, R. Zilionis, C. Garris, G. M. Gerhard, A. Kohl, Y. Lin, A. E. Zou, C. Cianciaruso, E. Bolli, C. Pfirschke, Y. J. Lin,



Novel bone marrow imaging in the Lin lab. Contrary to expectation that the bone marrow is highly enriched in calcium, the interstitial [Ca2+] is not much higher than the intravascular [Ca2+] (about 1 mM), with no observable spatial gradient away from the endosteal surface. The interstitial [Ca2+] varies with the stage of bone remodeling. Cavities undergoing bone deposition (D-type) have the lowest [Ca2+] whereas cavities undergoing bone resorption (R-type) have levels comparable to intravascular [Ca2+]. Hematopoietic stem cells (HSCs) and progenitor cells (HSPCs) reside in locations with slightly elevated [Ca2+]. *Quantification of bone marrow interstitial pH and calcium concentration by intravital ratiometric imaging. Yeh et al, Nature Communications, 2022, in press*



Human papillomavirus (HPV) types 6 and 11 can infect the epithelium that lines the respiratory tract. Up to 8.9% of recurrent respiratory papillomatosis (RRP) patients have lung involvement that carries a 32-fold lifetime risk of malignant transformation. RRP is associated with a high morbidity and those with pulmonary involvement have a higher mortality rate due to the limited understanding of the biological factors driving the disease course and, correspondingly, limited treatment options. The Pai lab is identifying prognostic molecular biomarkers to predict which patients are at highest risk for developing pulmonary disease and/or invasive cancer. Furthermore, given the multi-focality of pRRP, novel systemic therapeutic approaches are actively being evaluated in the clinical trial setting. *Sara I. Pai, I. Wasserman, Y.D. Ji, M. Gilman, Y.P. Hung, W.C. Faquin, M. Mino-Kenudson, and A. Muniappan. Pulmonary Manifestations of Chronic HPV Infection in Patients with Recurrent Respiratory Papillomatosis. Lancet Respiratory Medicine 2022, in press.*

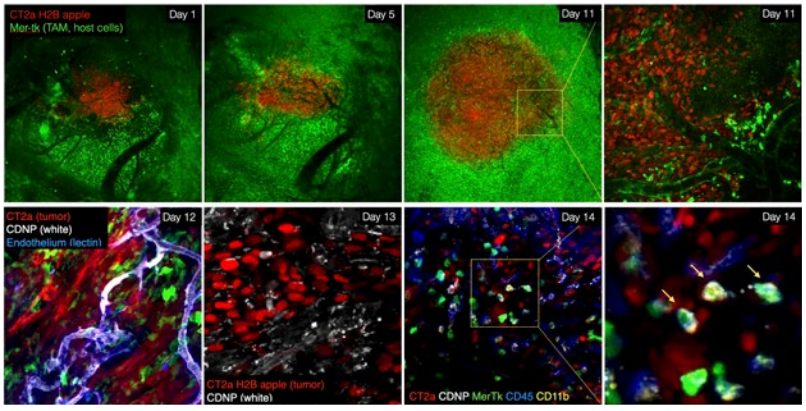
C. Piot, J. E. Mindur, N. Talele, R. H. Kohler, Y. Iwamoto, M. Mino-Kenudson, S. I. Pai, C. deVito, T. Koessler, D. Merkler, A. Coukos, A. Wicky, M. Fraga, C. Sempoux, R. K. Jain, P. Y. Dietrich, O. Michielin, R. Weissleder, A. M. Klein, and M. J. Pittet. Resident Kupffer cells and neutrophils drive liver toxicity in cancer immunotherapy. Science Immunol 2021;6: eabi7083.

Five-minute marijuana test

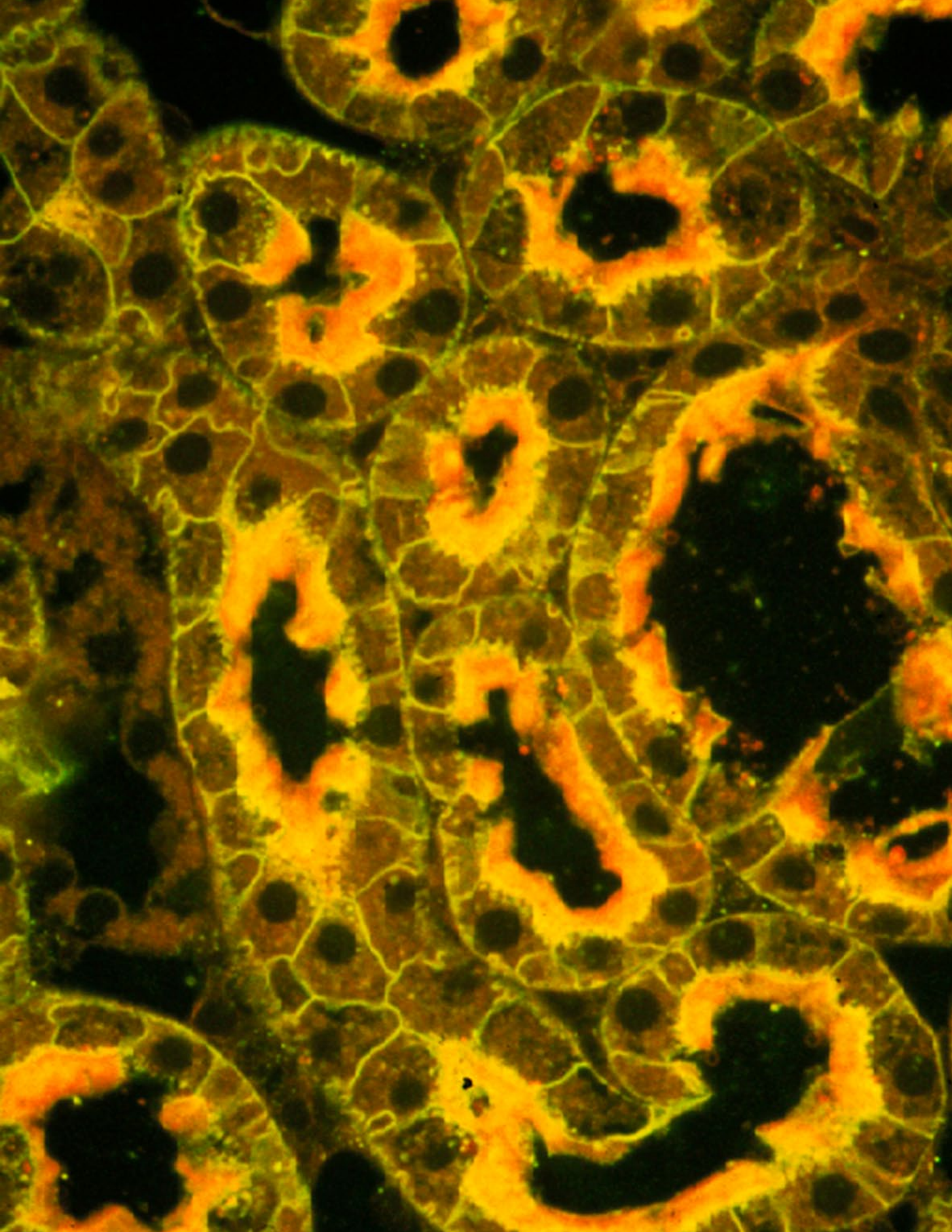
Smoking marijuana impairs cognitive/motor functions and increases the risk of vehicular accidents. Quantifying recent marijuana use remains difficult due to the low sensitivity (binary results) of rapid kits, and long turn-around of laboratory-based tests. In the paper published in Science Translational Medicine, CSB investigators describe a new sensor, EPOCH (express probe for on-site cannabis inhalation), for on-site marijuana testing. EPOCH integrates novel engineering features such as a radial membrane for molecular capture and transmission optics-based signal processing, all contained in a compact cartridge. The sensor quantifies tetrahydrocannabinol (THC), marijuana's main psychoactive substance, at the level below the regulatory guideline within 5 minutes. In a pilot field testing, EPOCH identified recent (<12 hours) marijuana users by detecting THC in saliva samples.

Yu, H., H. Lee, J. Cheong, S. W. Woo, J. Oh, H. K. Oh, J. H. Lee, H. Zheng, C. M. Castro, Y. E. Yoo, M. G. Kim, J. Cheon, R. Weissleder, and H. Lee. A rapid assay provides on-site quantification of tetrahydrocannabinol in oral fluid. Science Transl Med 2021;13: eabe2352.

For a complete list of 2021 publications, please see here: https://csb.mgh.harvard.edu/publications?year=2021



Serial *in vivo* multicolor imaging of glioblastoma therapy with novel IL12 inducing nano constructs. CT2a-H2B-mApple glioblastoma cells (red) were implanted intracranially in Mer-Tk-GFP mice (green host cells). Note the tumor growth and perivascular host cells infiltration on day 11. At that point, a pacific blue labeled cyclodextrin nanoconstruct (white) was injected systemically to locally induce IL12 in myeloid cells. On Day 14, a new click chemistry-based technology (SAFE-IVM) was used to stain for up to 12 immune cell markers in living mice. The drug carrying nano construct (white) primarily accumulated in triple positive cells staining for CD11b (yellow), CD45(blue) and Mer-Tk(green), i.e. myeloid derived tumor associated macrophages. From *Weissleder lab (unpublished)*



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. If fulfilling our mission leads us beyond photomedicine…that's OK. Major research themes include: advanced live microscopy, point-of-care optical diagnostics, light-activated cancer treatments, wound repair and healing, trauma interventions, photobiomodulation (light-stimulated metabolic changes), melanoma genetics and treatment strategies, bio-inspired optical technologies, 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 >240 full time personnel. Wellman Center spent $42M on research during FY 2021; we submitted 91 grant applications. Our core strength is the intellectual diversity of 31 excellent faculty (6 professors, 6 associate prof, 7 assistant prof, 11 Instructors, 1 lect) who aim for real impact. There are also 12 affiliated faculty. Our faculty have responded directly to the pandemic, co-leading an MGB innovation center (Professor, Gary Tearney, MD, PhD), inventing better vaccination strategies (Professor, Mei Wu, MD, PhD), and volunteering.
- *Innovation.* Wellman is the birthplace of many inventions and discoveries now in widespread use. In 2021, we were a leading source of MGH royalty income; there were 31 new invention disclosures, 91 new US and international patents were issued, and 6 startup companies were formed based on Wellman inventions.
- *World Health.* We are pursuing collaborative research on problems from every continent including Antarctica (where some whales are mysteriously dying), with emphasis on environmental change, trauma, malnutrition, child health, infection and cancer in developing countries.
- *Education.* We offer CME and special courses, a regular seminar and 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). There are 76 postdoctoral fellows, and a wide range of students from multiple universities.
- *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.

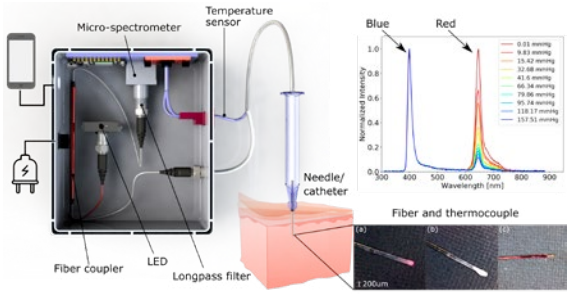
- *Magic.* The “Magic Wand” initiative was launched at MGH to support clinician-driven, problem-driven collaborative research. The MW initiative, supported by philanthropy and led by Lilit Garibyan, MD, PhD, and colleagues, will support a dozen early stage research teams during 2022-2023.

A Sample of 2021 Research Highlights

Wellman Center published over 150 research papers in 2021, a pace of about 3/week. Here are several highlights:

Achievements:

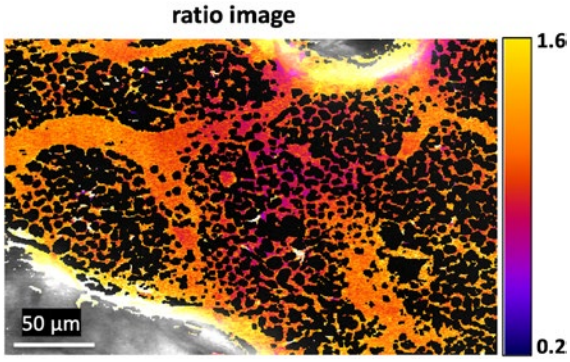
Directly Sensing Tissue Hypoxia
Hypoxia is a major cause of mortality and morbidity, in every organ system. For example, Compartment Syndrome insidiously causes sudden death of muscles, due to limited blood supply after over-use injury, surgery, or trauma. With DOD support, Conor Evan, PhD’s lab has synthesized a bright, rapid, non-toxic oxygen-sensing phosphor material that is being incorporated into practical devices. A small fiber optic implant (operated by smartphone) was built and validated *in vivo* in swine to detect compartment syndrome. This will launch clinical studies and commercialization. Witthauer L, Cascales JP, Roussakis E, et al.



"Portable oxygen-sensing device for the improved assessment of compartment syndrome and other hypoxia-related conditions." ACS Sensors 6:1 (2020); 43-53.

Tracking Unlabelled Molecules In Tissue
Rapid tracking and imaging of a drug based on its molecular structure is possible in tissue using a new strategy for detecting Raman scattering. Called ‘sparse spectral sampling stimulated Raman scattering’ (S4RS), a novel tunable laser rapidly tunes to the specific vibrational signature of molecules of interest. Supported by FDA, this new approach will allow direct evaluation of bioequivalence for generic and new drugs. *Pence IJ, Kuzma BA, Brinkmann M, Hellwig T, Evans CL. "Multi-window sparse spectral sampling stimulated Raman scattering microscopy." Biomedical Optics Express 12, no. 10 (2021): 6095-6114.*

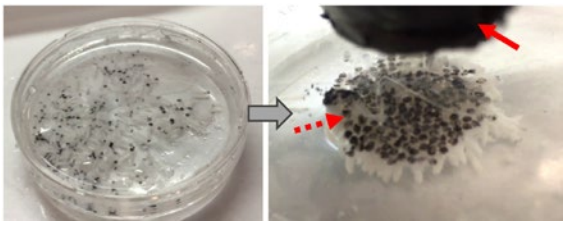
Where Is Calcium in the Bone Marrow Microenvironment?
Bone stores 99% of our calcium, a key signaling molecule, and bone marrow is a dynamic, rich source of stem cells—but almost nothing is known about calcium gradients in bone marrow. The lab of Charles Lin, PhD used *in vivo* multiphoton microscopy of fluorescent Ca^{2+} probes to image bone marrow cavities undergoing deposition (D-type) or resorption (R-type). Surprisingly, interstitial Ca^{2+} levels in bone marrow were similar to intravascular levels, at ~1mM. Hematopoietic stem cells reside in high-Ca^{2+} niches (~1.5mM), while D-type cavities have the lowest Ca^{2+} level.



In the figure, Ca^{2+} level is false color-coded to the concentration scale (mM) shown; bone is seen in the lower left, and marrow cells are seen grouped into cavities. *Yeh SC, et al “Quantification of bone marrow interstitial pH and calcium concentration by intravital ratio metric imaging.” Nature Communications (accepted).*

Wellman Center for Photomedicine

Thematic Center Report



In the figure, freshly harvested MSTCs (at left) self-align and pack to create a live skin construct (at right), when a magnetic coating (black dots, dashed arrow) on their epidermal surface interacts with an external magnet (solid arrow). *Fuchs C, Pham L, Wang Y, Farinelli W, Anderson RR, Tam J. MagneTEskin—reconstructing skin by magnetically induced assembly of autologous micro tissue cores. Sci Adv. 2021 Oct 8; 7(41):eabj0864. doi:10.1126/sciadv.abj0864.*

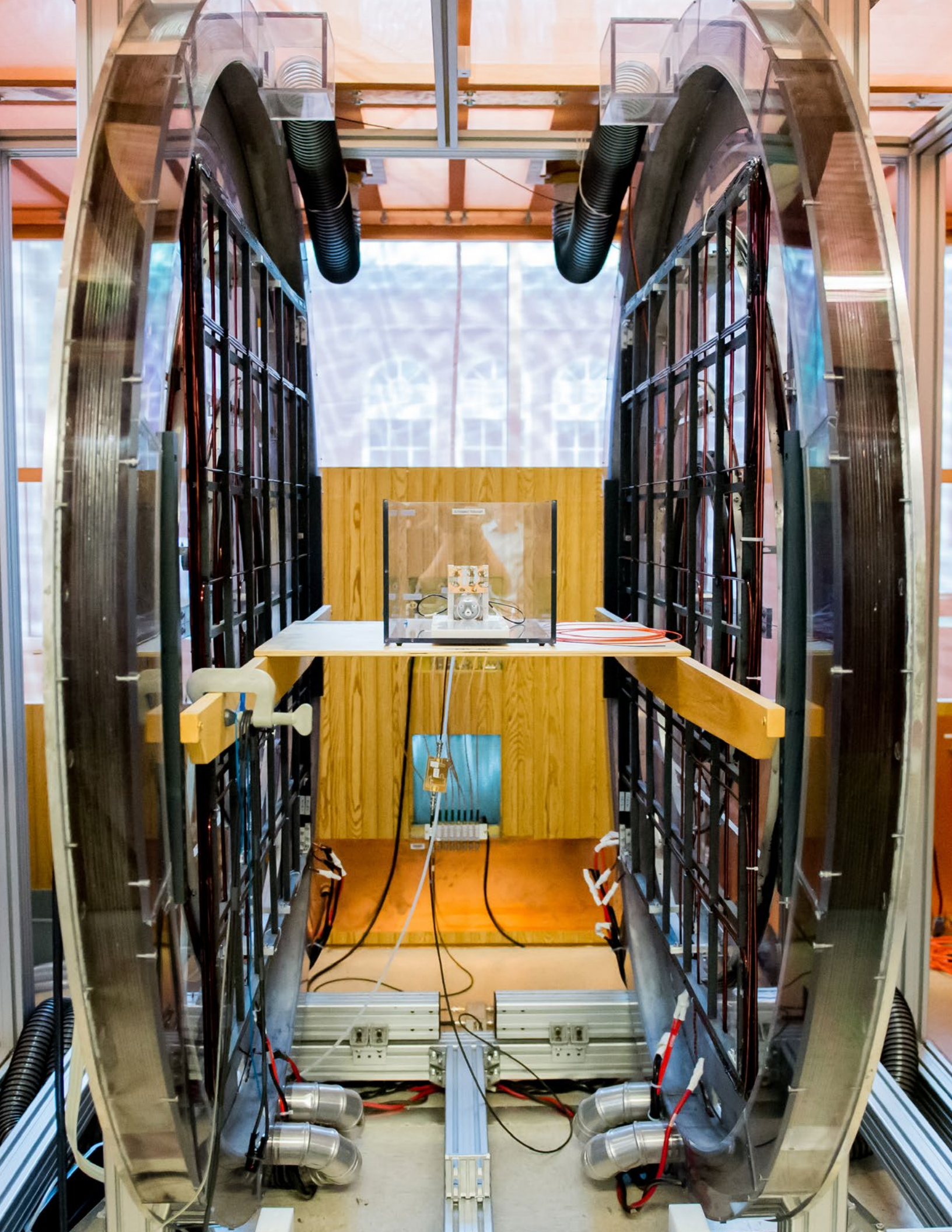
The figure shows an OCT-TE capsule and the briefcase-sized portable imaging system.

Healing Wounds by "Copying" the Skin

Skin wounds are a medical and socioeconomic burden that has bedeviled the regenerative medicine field for decades. Rox Anderson, MD's lab previously invented a device and method that improves wound healing by harvesting autologous micro skin tissue cores (MSTCs) without the donor site morbidity of conventional skin grafts; this was commercialized for clinical use and is close to FDA clearance. But can MSTCs really be used to reconstruct skin? Magnetic fields were used to assemble harvested MSTCs in their natural epidermal-dermal orientation, producing constructs that highly resemble natural skin structure. Beyond a practical new way for skin grafting, the work revealed how dermal tissue morphology affects the course of wound remodeling.

Tethered-Capsule Microscopy of the Esophagus

Dong, J., C. Grant, B. Vuong, N. Nishioka… G.J. Tearney Feasibility and Safety of Tethered Capsule Endomicroscopy in Patients With Barrett's Esophagus in a Multi-Center Study. Clin Gastroenterol Hepatol, 2021. S1542-3565(21)00109-9. Screening patients with Barrett's esophagus (BE), a common pre-cancerous metaplasia, is difficult and expensive. An alternative was demonstrated in a multicenter clinical trial using tethered-capsule Optical Coherence Tomography (OCT-TE), technology invented in Gary Tearney's lab. Unsedated patients swallowed the device, operated by either physicians or nurses who are not expert in OCT-TCE, to rapidly and safely evaluate microscopy of the esophagus, and accurately recapitulate endoscopic findings. This is an important step toward widely available screening and surveillance of BE patients.



Anesthesia, Critical Care and Pain Medicine

Department Report

Julia Rosenbloom, MD, anesthesiologist, was awarded the Physician/Scientist Development Award (PSDA) from the Mass General Center for Diversity and Inclusion (CDI).

OLUWASEUM JOHNSON-AKEJU, MD, 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 research activities have national and international reputations and encompass a broad range of disciplines with active research units focused in the areas of cardiac and pulmonary pathophysiology, molecular and system neuroscience, pharmacology, pain neurobiology, neuroimaging, stem cell research, genetics, comparative outcome research, biomedical engineering, new drug and medical device development, and clinical research.

    i. DACCPM has over 155 research staff, including MD and/or PhD investigators, post-doctoral fellows, graduate students, administrative and supporting staff, and another 60 research staff with non-employee status.

    ii. Laboratories and clinical research units are mainly located in the main MGH campus and the MGH-East research facility at the Charlestown Navy Yard.

    iii. Despite the unprecedented challenges of the COVID-19 pandemic, research activities at DACCPM continue to grow and are currently supported by over 109 grants, including 57 NIH grants as of FY 2020. During 2021, the number of grant applications remain steady at 150 and total grant awards from NIH were increased by 10% as compared to those of 2020.

    iv. In 2021, the DACCPM faculty published 371 journal articles and numerous books/book chapters.

2. There are three long-term strategic research priorities at DACCPM.

    i. **Expanding a premier research team:** We have 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 M.D. and/or Ph.D. investigators, and supplemental salary support for basic science and clinical researchers. During 2020, 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.

    ii. **Strengthening a research platform that promotes integration between basic science and clinical research:** During 2020, we re-organized our research leadership structure by installing four Research Directors under the leadership of Vice Chair for Research and Innovation and 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. For example, we have set up competitive intra-departmental clinical research funding mechanisms that provide financial support for clinical research, and have established an innovative Anesthesia Research Center (ARC), 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.

iii. **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.

Katarina Ruscic, MD, PhD, was selected as a DACCPM recipient of the 2021 Eleanor Shore Award. This is a one-year award sponsored by Harvard Medical School and the MGH DACCPM.

Lorenzo Berra, MD, received the 2021 A. Clifford Barger Excellence in Mentoring Award.

Highlights in Research, honors, and Awards in 2020:

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 2021.

1. **DACCPM Research Retreat:** In the middle of this pandemic, the department organized an online Research Retreat in the early Spring of 2021. Over 25 speakers presented their research projects, including presentations by early stage investigators, basic science, pain and neuroscience, statistics, medical engineering, QA and education research, and clinical and translational research. Over 90 participants joined the research retreat.
2. **Novel Findings on a Cellular mechanisms of Hypoxia:** Fumito Ichinose, MD, PhD, William T. G. Morton Professor of Anesthesia, Harvard Medical School, and his collaborators reported novel

Anesthesia, Critical Care and Pain Medicine

Department Report

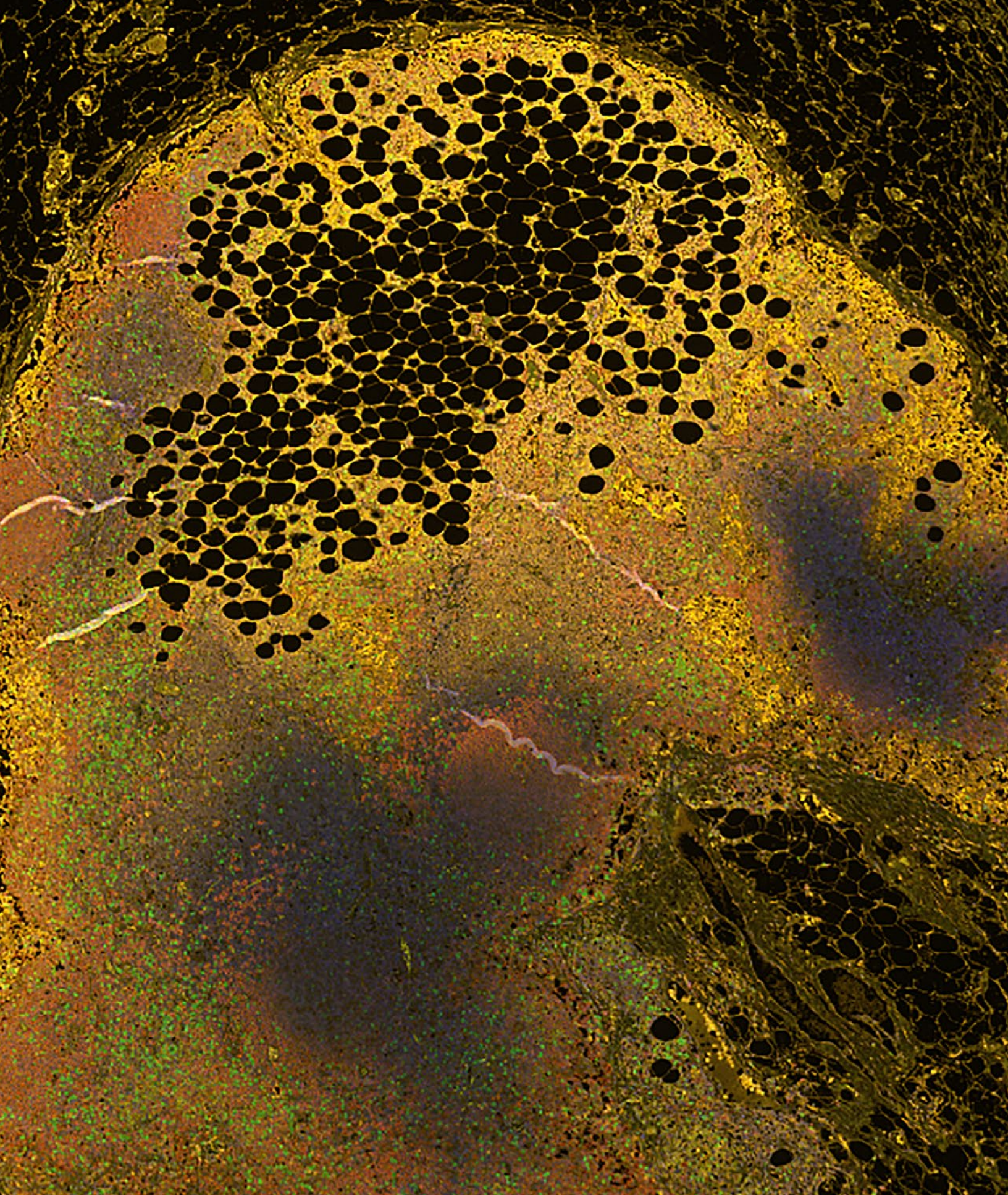
Emery Brown, MD, PhD, Named Among 1,000 Inspiring Black Scientists in America. Emery Brown, MD, PhD, director of the Mass General Neuroscience Statistic Research Lab, the Warren M. Zapol Professor of Anesthesia at Harvard Medical School, and practicing anesthesiologist, was named to Cell Mentor's list of 1,000 inspiring Black scientists in America.

findings on a cellular mechanism of hypoxia. The mammalian brain is highly vulnerable to oxygen deprivation, yet the mechanism underlying the brain's sensitivity to hypoxia is incompletely understood. Hypoxia induces accumulation of hydrogen sulfide, a gas that inhibits mitochondrial respiration. Here, we show that, in mice, rats, and naturally hypoxia-tolerant ground squirrels, the sensitivity of the brain to hypoxia is inversely related to the levels of sulfide: quinone oxidoreductase (SQOR) and the capacity to catabolize sulfide. Silencing SQOR increased the sensitivity of the brain to hypoxia, whereas neuron-specific SQOR expression prevented hypoxia-induced sulfide accumulation, bioenergetic failure, and ischemic brain injury. Excluding SQOR from mitochondria increased sensitivity to hypoxia not only in the brain but also in heart and liver. Pharmacological scavenging of sulfide maintained mitochondrial respiration in hypoxic neurons and made mice resistant to hypoxia. These results illuminate the critical role of sulfide catabolism in energy homeostasis during hypoxia and identify a therapeutic target for ischemic brain injury. These findings are published in *Nat Commun 2021 May 25;12(1):3108. doi: 10.1038/s41467-021-23363-x.*

3. **Honors and Awards:** In 2021, numerous faculty members in our department received honors and awards for contributions to their respective research fields. Several are highlighted as follows.

    i. **High-Dose Inhaled Nitric Oxide Safe, Effective For Non-Intubated Covid-19 Patients**
    Researchers at Mass General, including **Lorenzo Berra, MD,** anesthesiologist and medical director for Respiratory Care at Mass General, and **Bijan Safaee Fakhr, MD,** anesthesia research fellow, initiated a study that investigated the effectiveness and safety of inhaling 160 ppm nitric oxide (NO) gas twice daily for 30 minutes in 29 spontaneously breathing, non-intubated hospitalized patients with mild to moderate COVID-19-induced pneumonia.

    ii. A study and publication in Communications Biology from the lab of **Zhongcong Xie, MD, PhD**, were featured on massgeneral.org. Co-lead authors **Feng Liang, MD, PhD**, and **Yuanlin Dong, MD**, along with Dr. Xie, senior author, report on findings that provide new insights on tau protein spreading and how it contributes to the brain changes of Alzheimer's disease. The hope is that this work will lead to more research on anesthesia, tau proteins and Alzheimer's disease pathology that will ultimately improve care for patients.



Name: Daniel Ruiz Torres, MSc, Cancer Center
PI: Shannon Stott, PhD, and Daniel Faden, MD
Category: A Closer Look
Title: Heading the War Against Cancer

Cancer Center

Department Report

DANIEL HABER, MD, PHD, DIRECTOR

Overview:

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.

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 support for fundamental discoveries on the origin and progression of cancer, which we believe to be the centerpiece of our successful research and translational enterprise. We are also committed to teaching and training the next generation of cancer researchers, within a diverse and inclusive research community.

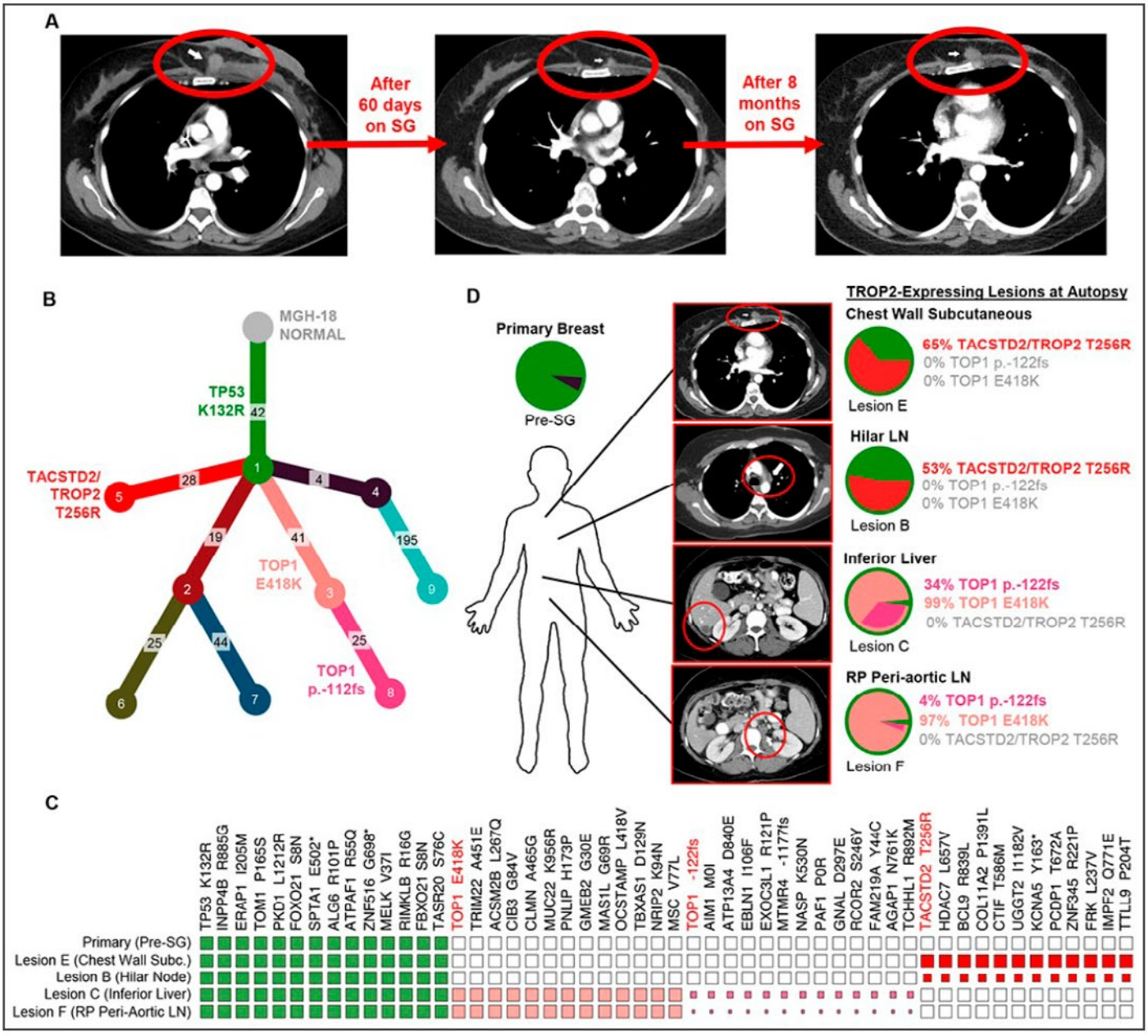
Our research highlights from 2021 include major discoveries and observations from investigators within the multi-departmental Center for Cancer Research (CCR) and the Division of Hematology Oncology (Department of Medicine), both of which are administered through the Cancer Center. David Ryan, MD is Clinical Director of the Cancer Center and Chief of Hematology/Oncology; Lee Zou, PhD and Raul Mostoslavsky, MD, PhD are the co-Scientific Directors; and Keith Flaherty, MD is Director of Clinical Research. Total annual research expenditures for CCR and Hematology/ Oncology in FY21 were $118 million (including industry clinical trials contracts). In 2021, the MGH Cancer Center enrolled 2,817 patients on 790 clinical trials (1,126 patients on therapeutic/ interventional trials), 46% (516) of which were early Phase I/II trials of first-in-human drugs.

Achievements:

The events of the past two years and the COVID-19 pandemic have greatly impacted our clinical and research communities, despite these challenges, our researchers have been able to uphold our scientific excellence and productivity. Our *highlighted accomplishments* for 2021 demonstrate our strong culture of collaboration and collegiality, as demonstrated by multiple co-authored manuscripts and cross-laboratory team science. The highlights are grouped into four thematic areas:

Fundamental Mechanisms of Tumorigenesis

Lee Zou, PhD and Li Lan, MD, PhD developed an assay to assess the effect of local transcription on Homologous Recombination (HR) and DNA repair. They found that transcription enhances HR



Multiple independent parallel mechanisms of acquired resistance to the antibody-drug conjugate Sacituzumab Govitecan, as assessed by the analysis of independent breast cancer deposits within a single patient (MGH rapid autopsy program). From *Coates J.T. at al; Cancer Discovery, PMID: 34404686, 2021.*

in a sequence- and orientation-dependent manner, through the formation of DNA-RNA hybrids. *(Ouyang J. et al; Nature, PMID: 33981036, 2021)*. Shyamala Maheswaran, PhD, Michael Lawrence, PhD and Daniel Haber, MD, PhD, found that the orphan nuclear receptor NR4A1 regulates replication stress in cancer cells, through an unusual mechanism: NR4A1 binds across the gene body and 3' UTR of immediate early genes (IEGs), restraining their transcriptional elongation at baseline, but releasing this inhibition and allowing a burst of IEG expression upon replication stress. Suppression of NR4A1 and deregulation of IEGs in cancer cells triggers massive mitotic catastrophe, an example of "non-oncogene addiction" with therapeutic implications *(Guo H et al; Mol Cell, PMID: 34624217, 2021)*. Raul Mostoslavsky, MD, PhD, and Nir Hacohen, PhD showed that the NAD+-dependent histone deacetylase sirtuin 6 is a robust tumor suppressor in squamous cell carcinomas, acting as a modulator of glycolysis in these tumors. *(Choi J et al; Nature Metabolism, PMID: 33619381, 2021)*.

Molecular Therapeutics

In a randomized phase 3 trial, Aditya Bardia, MD, MPH and his colleagues evaluated the antibody drug conjugate (ADC) Sacituzumab Govitecan (SG), as compared with standard chemotherapy in patients with refractory metastatic triple-negative breast cancer (TNBC), and showed that progression-free and overall survival were significantly longer with the ADC. This study led to the FDA approval of SG for the treatment of TNBC *(Bardia A et al; N Engl J Med, PMID: 33882206, 2021)*. Leif. Ellisen, MD, Aditya Bardia, MD, MPH, and their colleagues demonstrated resistance mechanisms to Sacituzumab Govitecan (SG), the first antibody–drug conjugate (ADC) approved for triple-negative breast cancer. Their findings highlight the role of parallel genetic alterations in either antibody binding targets or pathways targeted by the chemotherapy payload in mediating resistance to ADCs *(Coates J.T. at al; Cancer Discovery, PMID: 34404686, 2021)*. Ryan Corcoran, MD, PhD, Rebecca Heist, MD, MPH and Aaron Hata, MD, PhD identified the mechanisms by which cancer cells acquire resistance to the novel KRAS-G12C inhibitors. By using tumor biopsies and the MGH rapid autopsy program, they sampled multiple drug resistant tumor lesions in patients treated with these inhibitors, demonstrating convergent mechanisms of drug resistance, focused on RAS-MAPK reactivation, and including a novel KRAS Switch-II Pocket mutation. *(N. Tanaka et al; Cancer Discovery, PMID: 33824136, 2021)*. In two First-in-Human clinical trials, Justin Gainor, MD and his colleagues reported the activity of the highly potent RET inhibitor Pralsetinib in RET-fusion-positive non-small-cell lung cancer *(Gainor J. et al; Lancet Oncol, PMID: 34118197, 2021)*. Dr. Keith Flaherty described the activity of the pan-AKT inhibitor Capivasertib in patients with an AKT1 E17K-mutated tumors. *(Kalinsky K et al; JAMA Oncol, PMID: 33377972, 2021)*.

Cancer Immunology

Taking advantage of single cell RNA sequencing of colorectal tumors from patients treated with immune checkpoint inhibitors (ICB), Dr. Hacohen and his colleagues identified gene expression programs embedded within multicellular immune cell "hubs" as highly predictive of clinical response. By defining the biological significance of these immune hubs, as opposed to single immune cell infiltrates in tumors, this study points to a new dimension in spatial transcriptomics as a molecular marker to guide cancer therapy *(Pelka K et al; Cell, PMID: 34450029, 2021)*. Genevieve Boland, MD, PhD, Keith Flaherty, MD and their colleagues studied tumor samples over nine years from a patient with metastatic melanoma with complete clinical response to ICB followed by delayed recurrence and death. Their phylogenetic analysis revealed co-evolution of seven lineages with multiple convergent, but independent resistance-associated alterations. *(Liu D et al; Nature Medicine, PMID: 33941922, 2021)*. David Langenau, PhD and Marcela Maus, MD, PhD, established an immunocompromised zebrafish model that allows for real-time single-cell visualization of T cell-based immunotherapies *in vivo*, and showed that EGFR-targeted immunotherapies can be used as a powerful approach to kill rhabdomyosarcoma cells. *(Yan C et al; J Exp Med, PMID: 34415995, 2021)*.

Digital Health and Palliative Care

Areej El-Jawahri, MD, created a self-administrated mobile app, DreAML, to provide supportive clinical information, psychoeducation and self-care for patients with Acute Myeloid Leukemia (AML), as they navigate through their own personal journey of cancer care. The mobile app was granted breakthrough designation by the FDA and has been licensed for commercial development. In a randomized clinical trial of patients with AML, Areej El-Jawahri, MD and Jennifer Temel, MD also showed that integrated palliative and oncology care led to substantial improvements in quality of life, psychological distress, and end of life care. (*El-Jawahri A et al; JAMA Oncol, PMID: 33331857, 2021)*.

The Consortia for Improving Medicine with Innovation & Technology

Department Report

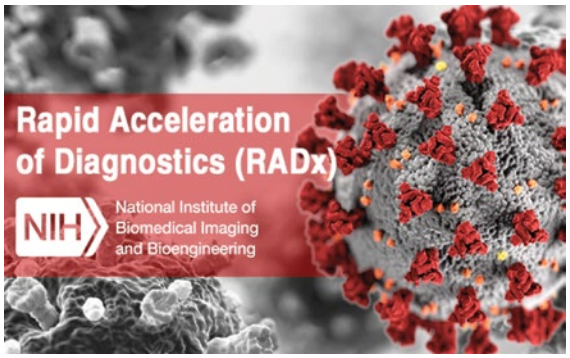
JOHN A. PARRISH, MD, CEO

Overview:

The Consortia for Improving Medicine with Innovation & Technology (CIMIT, http://cimit.org/) was founded in 1998 by Massachusetts General Hospital, Brigham and Women's Hospital, Massachusetts Institute of Technology, and Draper Laboratory 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 the 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 where they will directly impact patient care.

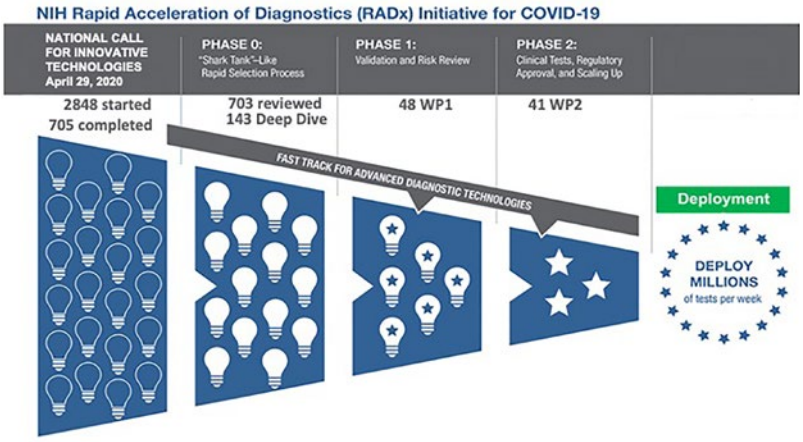
In 2021, CIMIT continued to leverage its processes to: provide extramural support for The Rapid Acceleration of Diagnostics Tech program (RADx Tech), act as the Coordinating Center for Point-of-Care Technologies Research Network (POCTRN), hold several Commercialization Readiness Assessment and Accelerator for Solutions in Healthcare (CRAASH) courses, further enhance the Guidance and Impact Tracking System (GAITS) platform, stand up the NIH Blueprint MedTech Pilot program, and collaborate with Yale University on the BRIDGE-U program.

Achievements:



Rapid Acceleration of Diagnostics Program (RADx Tech)
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 29, 2020, over 824 applications have been evaluated and 44 projects have moved into Phase 2 increasing the overall COVID-19 testing capacity in the U.S. by approximately 1 billion. RADx Tech supported companies can currently produce ~7M tests and test products per day, hold 35 FDA Emergency Use Authorizations, and have produced the first over-the-counter test for at-home use. These milestones include projects from both RADx Tech as well as RADx Tech II, launched in June 2021, which aimed to further accelerate validation, manufacturing scale up, and commercialization of innovative COVID-19 testing capabilities.

In April 2021, the IEEE Open Journal of Engineering in Medicine and Biology published the special issue, *RADx Tech: A New Paradigm for Medtech Development* (https://www.embs.org/ojemb/special-issue-radx-tech/), highlighting the insights, lessons learned, and critical components that helped transform COVID-19 diagnostic testing.



Additionally, as part of the RADx Tech program, CIMIT and MIT collaborated to develop WhenToTest.org (http://whentotest.org). 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.

Finally, in October of 2021, 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 two over the counter, at-home COVID-19 tests.

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 appropriate point-of-care diagnostic technologies though collaborative efforts that simultaneously merge scientific and technological capabilities with clinical need. Additionally, the Network provides parallel educational activities that advance evidence-based medical practice in point-of-care testing in primary outreach, and low-resource environments, including global health settings.

In 2021, CIMIT has continued as a Coordinating Center for Year 4 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.

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

The Consortia for Improving Medicine with Innovation & Technology

Department Report

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.

Yale U-BRIDGE
In July 2021, CIMIT collaborated with Yale University to support the BRIDGE-U program to advance research utilization in Liberia's health sector. The program aims to foster entrepreneurship in the healthcare sector in Liberia by working with local community partners in Liberia at iLab and the University of Liberia's College of Health Sciences to offer an innovation seminar series curriculum on translation of health innovations to the marketplace and fostering academic and entrepreneurial collaboration in the health sector.

CIMIT's CRAASH Program
In 2021, CIMIT continued to conduct CRAASH programs (https://www.craash.org) in support of NIBIB and in support of CIMIT's collaborators in Europe. Two courses with EIT Health (https://wildcard.eithealth.eu) and Biocat in Barcelona (https://www.moebio.org/en/program/craash-barcelona). The NIBIB program was delayed and is being kicked-off in January of 2022.

Some notable successes stemming from prior year programs are:

- iLoF (intelligent lab on a fiber): iLoF has developed a cloud-based library of optical fingerprints, powered by photonics and AI, to provide non-invasive tracking, screening and stratification for drug discovery, adapted to each clinical trial needs. In 2021 it closed a Series-A investment round and was recognized as one of the top 150 digital health start-ups worldwide by CB Insights.
- S4DX (Smart 4 Diagnostics): A Munich based start-up that closes the preanalytical data gap between blood collection and lab analysis and enables a new quality standard for diagnostic decision making. In 2021 It closed Series-A investment round with collaborator Sarstedt as strategic partner.
- ABtrace: A healthtech startup founded by a NHS doctor in London, Abtrace uses machine learning to learn from patients' health records and suggests tests proactively. In 2021 it £2.1 seed million funding to transform how GPs detect and treat long-term health conditions.

CRAASH is a program that facilitates the acceleration of healthcare innovations emerging from academic labs or start-ups into commercialization and clinical practice. It is based on the iCorp 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

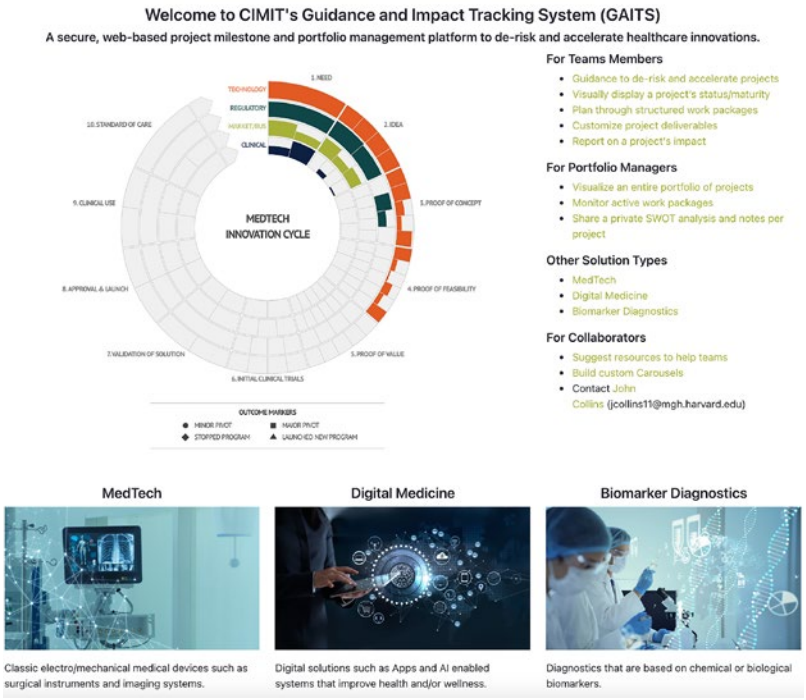
commercialization roadmap based on data from actual customers and other stakeholders. Teams also receive 1:1 mentoring from successful healthcare entrepreneurs and group coaching from commercialization experts and investors.

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 2021. 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 core set of deliverables at each milestone in four domains critical to success in healthcare innovation: Clinical, Market/Business, Regulatory/Approvals, and Technology.

In August of 2021, several key improvements were rolled out on the GAITS platform including a streamlined deliverable/requirement status, an upgraded deliverable/requirement form, updated work package sections, as well as the roll out of updated portfolio manager functions. In addition, NIBIB supported creating a new Solution Type for IVDs and NCI supported creating a Therapeutics Solution Type. Both will be available in early 2022.

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 ½ from outside the U.S.



Dermatology

Department Report

DAVID E. FISHER, MD, PHD, CHIEF

Overview:

MGH Dermatology provides clinical care to a large population of patients while simultaneously representing one of the most distinguished historically important contributors to the modern field of skin biology and cutaneous medicine. Faculty at MGH Dermatology dating back to the 1800s included many innovators for whom clinical conditions are named and through whom the modern discipline of dermatology has been derived. The Department is particularly proud that it housed the first female physician at MGH, Dr. Loretta Cummings, a Dermatologist working in the Department in the early 1900s. Dr. Cummings bequeathed a portion of her estate to the MGH Dermatology Department, and the proceeds of that fund are currently used to support an annual research award pertaining to a female-related dermatologic study.

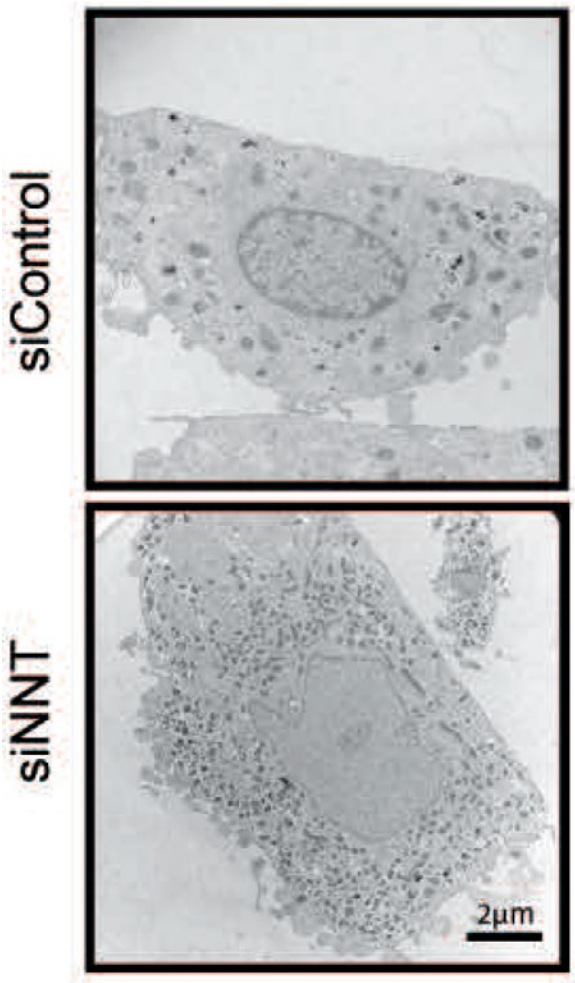
The greatest challenge to MGH Dermatology during 2021 involved the ongoing COVID epidemic, which severely challenged clinic operations as well as laboratory research, teaching and community outreach activities. Multiple faculty members carried out COVID-related research activities, with **Esther Freeman, MD, PhD**, becoming a national and international leader in cutaneous manifestations of COVID—and director of an international registry of COVID skin manifestations. But all members of the clinical care enterprise at MGH Dermatology worked extra hard providing additional clinic opportunities for patients—in person or virtually—to help meet the needs of our patient population.

The department's core missions remain focused upon the delivery of outstanding clinical care, research, education, and community outreach. The department supports and nourishes close collaborations with faculty colleagues across nearly all departments at MGH, as well as numerous colleagues at other academic institutions. MGH Department has a global dermatology interest with faculty representation on WHO dermatologic leadership (Dr. Esther Freeman). Care of the homeless population remains a high priority for which the department commits resources in a program spearheaded by **Jennifer Tan, MD**. Annually, MGH Dermatology delivers care in approximately 90,000 patient visits. Despite the extreme stress imposed by COVID during 2021, the Department reached very close to this patient volume, through the extraordinary efforts of its entire clinical and support staff. Patient care is provided at MGH main campus as well as multiple community care centers and MGH-Northshore in Danvers. In collaboration with MGH Pathology, an outreach community-based Dermatopathology Lab is one of the busiest across New England.

In addition to providing general medical dermatologic care, the department provides additional specialty dermatologic care in topics including 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 was the first of its kind in the US and recently celebrated its 50-year anniversary. Aside from the Clinical Service, the MGH Dermatology Department contains multiple research-oriented programs. These include the Clinical Trials Unit (CURTIS: Clinical Unit for Research Trials In Skin) and the Cutaneous Biology Research Center (CBRC). CURTIS typically runs 10-20 ongoing clinical trials, with a combination of Industry Sponsored and Investigator Initiated investigations. The Cutaneous Biology Research Center was founded over 30 years ago and currently houses 14 Principal Investigators who carry out cutting edge research in this highly distinguished Center. During the past year Jian Shu, PhD, from the Broad Institute and the Whitehead Institute (MIT), joined CBRC and set up his lab, studying multiple single cell resolution analytics. The Center has attracted substantive federal grant support as well as industry funding that includes a longstanding deep collaborative skin research program with Shiseido Cosmetics from Japan. This collaboration represents one of the largest industry-academic collaborations in modern history. The faculty at CBRC lead research laboratories studying topics including melanoma, non-melanoma skin cancers, hair, cryobiology, itch, stem cells, inflammatory pathways, drug discovery, UV radiation, pigmentation, epigenetics, cancer immunotherapy, laser biology, targeted therapy, metabolomics, RNA biology in skin, and developmental/differentiation pathway control. Strong collaborations exist with the MGH Cancer Center (in which several CBRC faculty hold joint appointments) as well as collaborations with MGH Dermatopathology and numerous additional departments. Additional research faculty whose academic home is in Dermatology include many researchers in the Wellman Center for Photomedicine, an MGH Thematic Center that has made seminal contributions to the current practice of dermatology largely through the development of devices used in the diagnostic or therapeutic aspects of medicine (including dermatology).

During 2021 faculty members from the Department of Dermatology published 304 scholarly articles and gave 245 speaking engagements. During this period MGH Dermatology held 93 active NIH awards comprising over $33M. 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 multimillion-dollar Program Project Grant on Melanoma, which is highly collaborative with investigators across Harvard Medical School. The Department also hosts numerous visiting trainees including specific initiatives to enhance diversity representation in the field of Dermatology and skin research. Finally, MGH Dermatology particularly prides itself on close interactions and collaborations with most departments across



Electron micrographs reveal striking increase in differentiated (pigmented) melanosomes within melanocytes after genetic knockdown of the NNT gene.

the hospital—in clinical care initiatives, research projects, medical education and community outreach.

Achievements:

Schiferle EB, Cheon SY, Ham S, Son HG, Messerschmidt JL, Lawrence DP, Cohen JV, Flaherty KT, Moon JJ, Lian CG, Sullivan RJ, and Demehri S. Rejection of benign melanocytic nevi by nevus-resident CD4+ T cells. Sci Adv. 2021 Jun;7(26). PMID: 34162549.*

This publication examined skin moles (called nevi) and identified a striking role of the immune system in controlling the survival of these pigmented lesions, which may rarely transform into melanoma or alternatively regress and disappear.

Rambhatla, R., Jamgochian, M., Ricco, C., Shah, R., Ghani, H., Silence, C., Rao, B., Kourosh A. S. Identification of Skin Signs in Human Trafficking Survivors. 2021 Intl J. of Women's Dermatol.

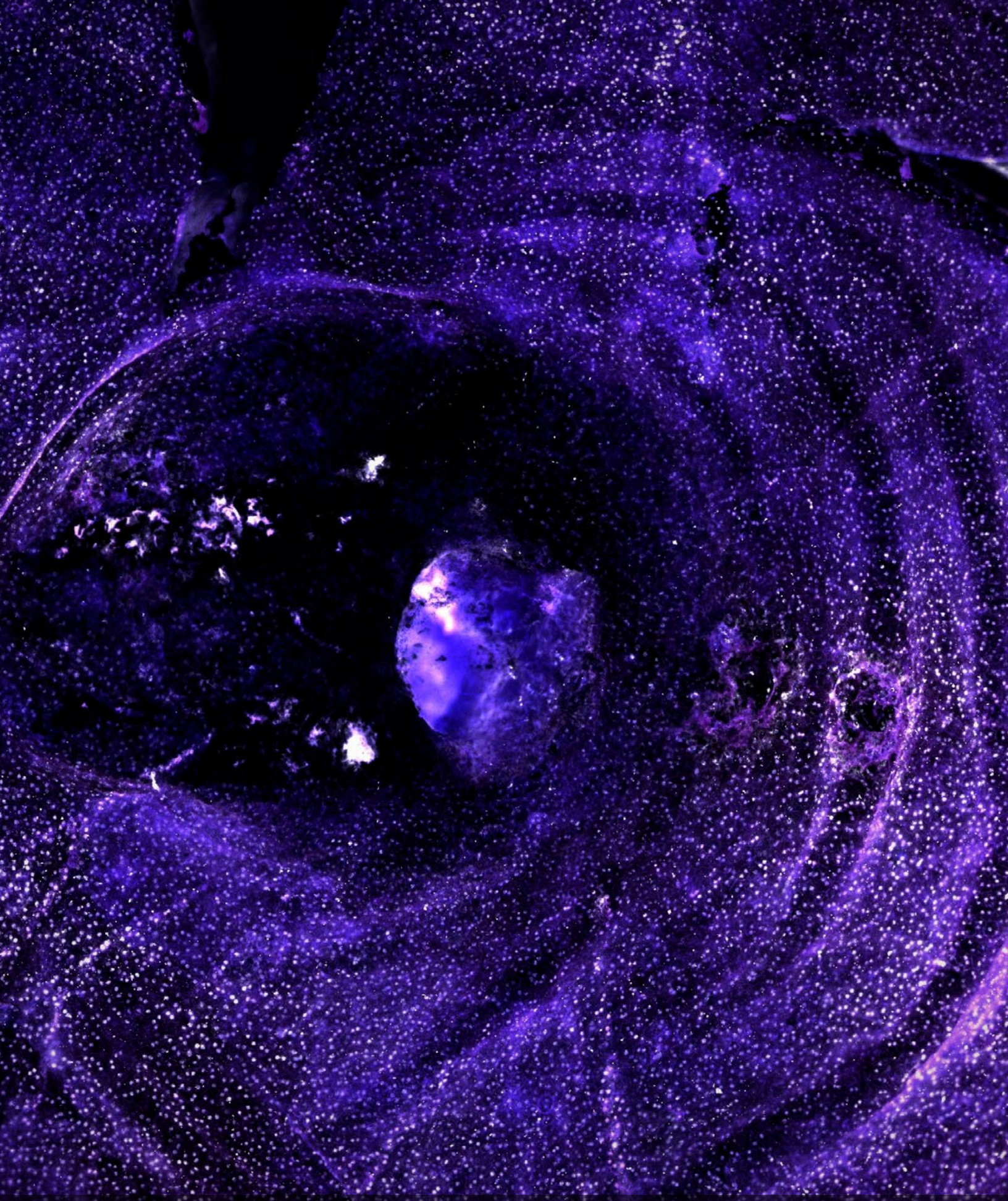
This study represents the intersection of academic work with a vital community public health initiative. It conveys what has been learned from tattoos that were removed from human trafficking survivors as part of a pro-bono tattoo removal program (which has previously won Harvard Medical School's Dean's Community Service Award).

Blumenthal KG, Freeman EE, Saff RR, Robinson LB, Wolfson AR, Foreman RK, Hashimoto D, Banerji A, Li L, Anvari S, Shenoy ES. Delayed Large Local Reactions to mRNA-1273 Vaccine against SARS-CoV-2. N Engl J Med. 2021 Apr 1;384(13):1273-1277. PMCID: PMC7944952.

This study describes clinical cutaneous features associated with mRNA vaccines against COVID-19.

Allouche J, Rachmin I, Adhikari K, Pardo LM,.....Ruiz-Linares A, Fisher DE, Roider E*. NNT mediates redox-dependent pigmentation via a UVB- and MITF-independent mechanism. Cell. 2021 Aug 5;184(16)4268-4283. PMCID: PMC8349839*

This study identified a novel pathway controlling skin pigmentation, present in human populations, and potentially manipulatable using small molecules.



Name: Hui (Jasmine) Zhang, BS, Dermatology, Cutaneous Biology Research Center
PI: Alexander Marneros, MD, PhD
Category: A Closer Look
Title: Eyes that See the Stars

Emergency Medicine

Department Report

MICHAEL VANROOYEN, MD, MPH, CHIEF

Overview:

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 COVID-19 pandemic of 2020 touched essentially all of these areas of investigation, which was validating to our research program mission in that we, as a matter of routine, address constantly evolving emergent and emerging critical illness challenges in our research efforts. Our clinical research team was well-equipped to pivot to COVID-19 research in 2020 and is continuing to contribute significantly in answering relevant clinical and research questions in 2021. We have actively participated in large, multicenter COVID-19 clinical trials since the onset of the pandemic, yet our contributions to scientific research in 2021 have begun to reflect a view beyond COVID-19, into a time of new challenges for our practice environment.

Our contributions include over 300 peer-reviewed publications in 2021 by over 30 contributing faculty. We are proud of our accomplishments and highlight several of these works below.

Goals for 2021:

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, clinical research coordinators, and now a clinical research nurse.
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. This is particularly relevant given our multiple MGH research collaborations, contribution to MGH COVID-19 Biorepository and clinical trials, and the overall contribution of the MGH emergency department research infrastructure to collaborators within MGH, Harvard, and external academic community.
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 2021:

1. *Integrated omics endotyping of infants with respiratory syncytial virus bronchiolitis and risk of childhood asthma. Raita Y, Pérez-Losada M, Freishtat RJ, Harmon B, Mansbach JM, Piedra PA, Zhu Z, Camargo CA, Hasegawa K. Nature Commun. 2021 Jun 14;12(1):3601. doi: 10.1038/s41467-021-23859-6.*

   The Emergency Medicine Network (EMNet) continued in 2021 to publish impactful work, including demonstration of its increasing footprint in clinical translational research. This work, by Kohei Hasegawa, MD, MPH, MS and co-authors, highlights the importance of an integrated clinical, microbiological, and immunological approach to elucidating distinct subtypes (endotypes) of disease that have clinical relevance. Using simple clinical data, nasal pathogen- and microbiome-specific data, and transcriptomic and metabolomic data reflective of the host immune response, this study identified distinct endotypes of among infants with RSV bronchiolitis that had differential outcomes, risks of developing subsequent asthma and recurrent wheeze, with distinctive underlying biological traits. These bronchiolitis endotypes have implications on identifying infants at risk for severe disease and those who may respond to certain therapies over

others. This work also provides a model for how to approach other acute diseases that may represent a heterogeneous mix of disease subtypes under the surface.

2. *Patient characteristics associated with the successful transition to virtual care: Lessons learned from the first million patients. Zachrison KS, Yan Z, Sequist T, Licurse A, Tan-McGrory A, Erskine A, Schwamm LH. J Telemed Telecare. 2021 Jun 13:1357633X211015547. Doi: 10.1177/1357633X211015547.*

   As a necessity during the COVID-19 pandemic, virtual care has evolved immensely. The scope of virtual care has spanned all specialties of medicine, but the real implication and nature of this novel modality of care delivery are not fully understood. In this work, Kori Zachrison, MD and co-authors explore patient characteristics in over 500,000 patients that successfully transitioned to virtual care in various ambulatory settings. They found that those utilizing virtual care were more frequently older, English-proficient, those with behavioral health visits and for COVID-19 care, and those with high frequency of visits. Another publication by Dr. Zachrison and co-authors in JAMA Network Open reported that the majority of ambulatory visits were substituted with virtual care visits during the first months of the pandemic, and that in-person visits have since returned to about 75% original levels, with the exception of behavioral health visits that have remained almost entirely virtual. These are all important findings that will help inform the optimal patient populations for virtual care and develop strategies to overcome barriers to its access.

3. *Racial and ethnic disparities in emergency department restraint use: A multicenter retrospective analysis. Carreras Tartak JA, Brisbon N, Wilkie S, Sequist TD, Aisiku IP, Raja A, Macias-Konstantopoulos WL. Acad Emerg Med (IF: 3.45; Q1). 2021 Sep;28(9):957-965. Doi: 10.1111/acem.14327.*

   The increasing burden of psychiatric illness in our emergency department is a daily challenge and is reaching the point of crisis. As Wendy Macias-Konstantopoulos, MD, MPH, MBA and co-authors highlight in this multi-institutional study, this phenomenon is not unique to MGH and is an issue across the MGB system and beyond. The COVID-19 pandemic has only exacerbated the lack of resources widely available beyond MGH to care for this patient population. This impactful study demonstrates the unfortunate need for physical restraints in patients with acute psychiatric illness and its differential use in male sex, Black/African American race, Hispanic ethnicity, and those with Medicaid insurance, when controlled for other factors. The presence of race and socioeconomic bias in administering physical restraints may indicate inherent bias amongst clinicians that warrants larger consideration and has led to directed educational efforts for all ED clinicians, staff, and security within MGB hospitals. A correlated study in 2021 by MGH pediatric emergency physician Dr. Foster in J of Pediatrics demonstrated a 268% increase over the last 5

years in pediatric ED visits for mental health and a 370% increase in the use of pharmacologic restraints in this population, with a similar preferential administration in male, black and Hispanic demographics.

4. *Longitudinal proteomic analysis of severe COVID-19 reveals survival-associated signatures, tissue-specific cell death, and cell-cell interactions. Filbin MR, Mehta A, …Goldberg MB. Cell Rep Med. 2021 May 18;2(5):100287. Doi: 10.1016/j.xcrm.2021.100287.*

   Lastly, many of our publications in 2021 reflect the department's tremendous contribution to multidisciplinary translational research that was accelerated during the COVID-19 pandemic. This work, by Michael Filbin, MD, MS and co-authors, represents a collaboration between the MGH Departments of Emergency Medicine and Medicine (Division of Infectious Diseases and MGH Center for Cancer Immunotherapy), and the Broad Institute that details proteomic signatures that predominate during severe COVID-19 illness, death, and recovery. Serial blood samples throughout hospitalization were obtained from over 300 severely-ill COVID-19 patients enrolled during the first pandemic surge. This cohort represents the largest single-center sample repository of severe COVID-19 with a full complement of single cell RNA sequencing, proteomics, viral load data, and detailed antibody response profiling. The cohort has provided a rich resource for investigators at MGH, Harvard, and beyond, and has yielded numerous impactful scientific discoveries and publications.

Medicine

Department Report

KATRINA A. ARMSTRONG, MD, PHYSICIAN-IN-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.

Acheivements:

The pandemic has underscored the social vulnerabilities that many individuals in the US face daily. **The Division of General Internal Medicine** has an active research portfolio focused on minoritized populations. **Jocelyn Carter, MD, MPH, Anne Thorndike, MD, MPH**, and colleagues conducted a randomized controlled trial to determine if pairing hospitalized patients with community health workers (CHWs), who may address patients' unmet psychosocial and clinical care needs following discharge, would reduce 30-day readmission rates compared to usual care (1). This team demonstrated that pairing inpatient adults with CHWs reduced readmissions and missed outpatient visits 30 days post-discharge. Compared with participants in the control group, participants in the intervention group were less likely to be readmitted within 30 days (odds ratio [OR], 0.44; 95% CI, 0.28-0.90) and to miss clinic appointments within 30 days (OR, 0.56; 95% CI, 0.38-0.81. Reducing preventable readmissions is a central priority for the Centers for Medicare & Medicaid Services and principal health care stakeholders. These types of interventions may be particularly beneficial to patients who experience social barriers to post-discharge care.

As the incoming Chair of the US Preventive Services Task Force (USPSTF), **Michael Barry, MD**, oversees the development of evidence reviews and guidelines for this influential group. In 2021, the USPSTF began operational steps to create preventive care recommendations to address the harmful effects of racism (2). The USPSTF proposes to consider the opportunity to reduce health inequities when selecting new preventive care topics and prioritizing current topics; seek

evidence about the effects of systemic racism and health inequities in all research plans; summarize the likely effects of systemic racism and health inequities on clinical preventive services in USPSTF recommendations. By changing the methods of developing evidence-based recommendations, with a partner and public input in the activities to implement the advancements.

Substance use has increased exponentially during the pandemic, requiring new approaches to treatment. **Danielle Fine, MD**, and **Travis Baggett, MD, MPH**, conducted a retrospective cohort study in the Boston Health Care for the Homeless Program to evaluate treatment retention and mortality in an office-based addiction treatment (OBAT) program designed specifically for individuals experiencing homelessness with opioid use disorder (OUD) (3). Continuous retention in the OBAT program was 45.2% at 1 month, 21.7% at 6 months, and 11.3% at 12 months. Continuous buprenorphine adherence was 41.5% at 1 month, 17.6% at 6 months, and 10.2% at 12 months, and continuous opioid abstinence was 28.3% at 1 month, 6.1% at 6 months, and 2.9% at 12 months. The all-cause mortality rate was 29.0 deaths per 1000 person-years, with 51.8% dying from a drug overdose. Past-month OBAT program attendance was associated with lower mortality risk (adjusted hazard ratio, 0.34; 95%CI, 0.21-0.55). In this large cohort of treatment-seeking homeless individuals with OUD, mortality rates were high, with a substantial burden of deaths caused by drug overdose. OBAT program retention was low, particularly within the first month of follow-up, but program attendance was associated with reduced mortality irrespective of buprenorphine adherence and opioid abstinence. Interventions aimed toward promoting increased OBAT program attendance among people experiencing homelessness are needed.

In this collaboration spanning an interdisciplinary team of physicians, scientists, economists, and policymakers from over 30 countries, and including MGH faculty across the **Divisions of Endocrine, Infectious Diseases, and General Internal Medicine**, the authors characterized the relationship between body mass index (BMI) and diabetes risk across 57 low- and middle-income countries (LMICs), totaling nearly 700,000 participants and spanning 6 world regions (4). This is relevant because LMICs are home to 79% of the estimated 463 million adults living with diabetes today. BMI is the most widely used clinical tool to diagnose obesity, a key risk factor for diabetes, but studies that have informed BMI thresholds for diabetes screening have been largely conducted in high-income countries. Given that BMI is an important and affordable clinical tool to diagnose overweight and obesity, understanding its relationship to diabetes risk in areas of the world with the highest projected burden of diabetes is critically important, particularly in lower resource contexts. The authors found substantial variability in the association between BMI and diabetes risk across 57 LMICs, as well as between women and men. They also found that the risk of diabetes emerged at younger ages in some regions and at lower BMI cutoffs than those currently recommended in global diabetes screening guidelines. The impact and potential implications of this work stem from three key findings: 1) there is considerable sex- and geographic- variability in the relationship between BMI

and diabetes risk in LMICs, 2) the risk of diabetes emerges at lower BMI thresholds in LMICs than currently recommended in diabetes screening guidelines, and 3) the risk of diabetes emerges at younger ages in certain regions, primarily Sub-Saharan Africa, than the age recommended for the initial screening of diabetes risk by the World Health Organization. These findings contribute to the literature on anthropometric tools and their clinical utility in assessing diabetes risk in LMICs and could inform BMI cutoffs to tailor screening efforts for diabetes in these settings. The results also highlight the importance of the inclusion of populations from diverse backgrounds in research studies and challenge the assumption that well-established biological relationships, in this case between BMI and diabetes risk, hold true across all diverse populations. Lastly, despite the international focus of this work, these findings could have implications for our understanding of diabetes risk and its assessment through anthropometric tools in the U.S., where the burden of diabetes is also growing fastest in non-European ancestry populations.

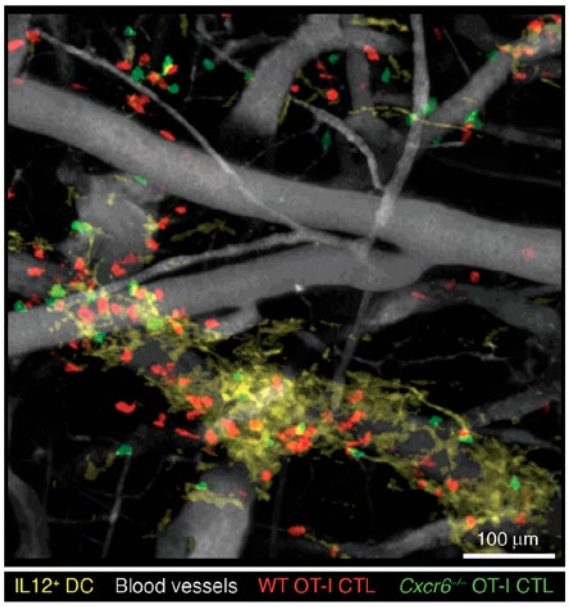
Nonalcoholic fatty liver disease (NAFLD) is a common comorbidity among people living with HIV that has a more aggressive course than NAFLD among the general population. In a recent randomized placebo-controlled trial (Clinical Trials Registry Number: NCT02196831), a collaborative team involving members of the **Gastroenterology and Endocrine Divisions** demonstrated that the growth hormone-releasing hormone analog tesamorelin reduced liver fat and prevented fibrosis progression in HIV-associated NAFLD over 1 year. As such, tesamorelin is the first strategy that has shown to be effective against NAFLD among the population with HIV. The first study *(JCI Insight)* leveraged paired liver biopsy specimens from this trial to identify hepatic gene pathways that are differentially modulated by tesamorelin versus placebo (5). Using gene-set enrichment analysis, the authors found that tesamorelin increased hepatic expression of hallmark gene sets involved in oxidative phosphorylation and decreased hepatic expression of gene sets contributing to inflammation, tissue repair, and cell division. Tesamorelin also reciprocally up-and down-regulated curated gene sets associated with favorable and poor hepatocellular carcinoma prognosis, respectively. Notably, among tesamorelin-treated participants, these changes in hepatic expression correlated with improved fibrosis-related gene score. In the follow-up study *(Sci Rep)*, the authors performed a focused assessment of 9 plasma proteins corresponding to top leading-edge genes within differentially modulated gene sets (6). Tesamorelin led to significant reductions in vascular endothelial growth factor A (VEGFA), transforming growth factor beta 1 (TGFB1), and macrophage colony-stimulating factor 1 (CSF1) versus placebo. Among tesamorelin-treated participants, reductions in plasma VEGFA and CSF1 correlated with a decline in NAFLD activity score. Decreases in TGFB1 and CSF1 were associated with reduced gene-level fibrosis score. Tesamorelin suppressed key angiogenic, fibrogenic, and pro-inflammatory mediators. The authors conclude that their findings inform our knowledge of the biology of pulsatile growth hormone action and provide a mechanistic basis for the observed clinical effects of tesamorelin on the liver. In particular,

CSF1, a regulator of monocyte recruitment and activation, may serve as an innovative therapeutic target for NAFLD in HIV.

Chronic rejection is the leading cause of organ transplant loss, and the high burden of immunosuppression is associated with significant side effects such as infection and cancer. The PD-1: PD-L1 signaling is a major inhibitory pathway that plays a critical role in regulating the immune response. So far, no therapeutic strategies have been applied to enhance PD-1 signaling to promote immune regulation in transplantation. A recent study led by the Riella Lab in the **Division of Nephrology** investigated whether overexpression of PD-1 on T cells (PD-1 Tg) could promote long-term graft survival. Using an approach to overexpress PD-1 on T cells, they showed that T cell-specific overexpression of PD-1 promoted tolerance in an MHC-fully mismatched murine cardiac transplant model combined with a single dose of costimulation blockade (7). PD-1 overexpression on T cells also protected against chronic rejection in a single MHC II mismatched cardiac transplant model. At the same time, it still allowed the generation of an effective immune response against an Influenza A virus. Notably, Treg cells from PD-1 Tg mice were required for tolerance induction and presented higher ICOS expression than wild-type mice. Furthermore, the survival benefit of PD-1 Tg recipients required ICOS signaling and donor PD-L1 expression. Overall, these results indicate that the modulation of the PD-1:PD-L1 axis could be a promising strategy to induce tolerance in organ transplantation.

Immune checkpoint inhibitors have transformed the treatment landscape for patients with solid tumors; however, their use can lead to organ-specific autoimmunity, termed 'immune-related adverse events.' These events have been associated with prolonged survival in patients on immune checkpoint inhibitor therapy, but prior analyses have been confounded by immortal time bias. Thyroiditis is a well-defined and common immune-related adverse event that can occur soon after initiation of immune checkpoint inhibitor therapy. The authors investigated whether immune-mediated thyroiditis was associated with overall survival while correcting for immortal time bias. In a real-world observational study of 6596 patients receiving immune checkpoint inhibitors, we performed time-varying Cox proportional hazards model and conditional landmark analysis and found that thyroiditis was associated with a decreased risk of death (adjusted hazard ratio (HR) 0.80, 95% CI 0.71-0.89, P<0.001). Conditional landmark analyses by cancer type showed that the association between thyroiditis and improved overall survival was strongest in patients with lung cancer (HR 0.56, 95% CI 0.40–0.79, p<0.001) (8). In a second analysis, they found that developing thyroiditis early in the course of immune checkpoint inhibitor therapy is a novel risk factor for acute and chronic kidney function decline after immune checkpoint inhibitors (9).

In the **Division of Rheumatology, Allergy, and Immunology** and the **Center for Immunology and Inflammatory Diseases**, the lab of **Thorsten Mempel, MD PhD**, studies how T cells and other immune cells interact and communicate with each other to regulate immune responses. In a study published in *Cell* (10) they describe how



CTL survival niches in tumor tissue. Multiphoton intravital micrograph of a mouse melanoma demonstrating the CXCR6-dependent accumulation tumor-specific cytotoxic T cells (red WT and green *Cxcr6*$^{-/-}$) around perivascular clusters of IL-12-expressing dendritic cells (yellow). Modified from *Di Pilato M. et al., Cell, 2021.*

regulatory T cells (Treg) use the protein CTLA-4 to detach so-called co-stimulatory molecules from the surface of dendritic cells. While this impairs the dendritic cells' ability to activate effector T cells, it also restricts the activation of Treg themselves. The latter likely represents a self-control mechanism to limit Treg immune-suppressive activity and prevent them from "over-regulating" useful immune responses against pathogens. Importantly, certain forms of cancer immunotherapy that block the function of CTLA-4 with the intent to increase the function of anti-tumor effector T cells may inadvertently also release Treg from this form of self-control, increase immune-suppression, and thereby reduce the efficacy of this form of therapy in patients.

The **Mempel lab** published another study in *Cell* (11), where they showed how tumor-infiltrating cytotoxic T cells survive their own battle with cancer. Using intravital imaging of tumors in mice, they observed how the chemokine receptor CXCR6 allows CTL to enter survival niches surrounding tumor blood vessels. CTL are attracted to these niches by specialized dendritic cells that not only express the CXCR6 ligand CXCL16 but also express critical activation and survival factors for CTL, including the cytokine IL-15. This allows CTL to proliferate and expand in these perivascular niches and gain strength for their subsequent cytotoxic interactions with cancer cells that are essential for the ability of the immune system to control and often reject tumors altogether. In parallel, collaborative studies published in *Nature Biomedical Engineering* they could also demonstrate that engineering therapeutic CAR T cells to express CXCR6 enabled them to reject pancreatic cancer in mice. This suggests a novel strategy to make CAR T cell therapy, which so far only works for hematological cancers, effective against solid human cancers.

In a complementary study published in *Immunity* (12), the lab of **Andrew Luster, MD, PhD**, found that another chemokine receptor CXCR3 and its ligand CXCL10 that they had previously shown to be important for the CTL response to tumors, also plays an important role in the differentiation and heterogeneity of CTL in response to chronic antigen stimulation as seen in tumors and chronic infection. CD8+ T cells responding to tumors and chronic infection adopt an altered differentiation program that provides some restrain on pathogen replication yet limits immunopathology. This adaptation is imprinted in stem-like cells and propagated to their progeny. Understanding the molecular control of CD8+ T cell differentiation in chronic infection has important therapeutic implications. The **Luster lab** found that the chemokine receptor CXCR3 was highly expressed on viral-specific stem-like CD8+ T cells and that one of its ligands, CXCL10, regulated the persistence and heterogeneity of responding CD8+ T cells in spleens of mice chronically infected with lymphocytic choriomeningitis virus. CXCL10 was produced by inflammatory monocytes and fibroblasts of the splenic red pulp where it granted stem-like cells access to signals promoting differentiation and limited their exposure to pro-survival niches in the white pulp. Consequently, functional CD8+ T cell responses were greater in *Cxcl10*$^{-/-}$ mice and were associated with a lower viral set point. In addition, CXCL10 inhibition improved the durability of functional T cell responses in chronically

infected mice treated with anti-PDL1, suggesting a novel therapeutic approach to improve checkpoint blockade therapy.

Alexandra-Chloe Villani, PhD co-led a study published in *Nature* (13) that generated single-cell atlases of 24 lung, 16 kidney, 16 liver, and 19 heart autopsy tissue samples and spatial atlases of 14 lung samples from donors who died of COVID-19 to investigate how the SARS-CoV-2 virus interferes with the function of cells and their genetic programs. Integrated computational analysis uncovered substantial remodeling in the lung epithelial, immune, and stromal compartments, with evidence of multiple paths of failed tissue regeneration, including defective alveolar type 2 differentiation and expansion of fibroblasts and putative TP63^{+} intrapulmonary basal-like progenitor cells. Viral RNAs were enriched in mononuclear phagocytic and endothelial lung cells, which induced specific host programs. Spatial analysis in lung distinguished inflammatory host responses in lung regions with and without viral RNA. Analysis of the other tissue atlases showed transcriptional alterations in multiple cell types in heart tissue from donors with COVID-19 and mapped cell types and genes implicated with disease severity based on COVID-19 genome-wide association studies. This foundational dataset elucidates the biological effect of severe SARS-CoV-2 infection across the body, a key step towards new treatments, and the cell atlas is freely and openly available, providing a resource for other scientists to explore and use in future studies.

Exercise is the only known physiological driver of the birth of new cardiomyocytes (cardiomyogenesis) in the adult mammalian heart. In the **Division of Cardiology, Haobo Li, PhD**, working with **Anthony Rosenzweig, MD**, and others, set out to identify the pathways responsible. Dr. Li identified a set of cardiac long noncoding RNAs, termed lncExACTs, that are dynamically regulated in the heart in response to exercise (14). Cardiac lncExACT1 increases in human and experimental disease but decreased with exercise. Antisense inhibition of lncExACT1 using chemically modified oligonucleotides similar to some FDA-approved medicines was sufficient to induce an ‘athlete’s heart’ phenotype in mice *in vivo*, including induction of cardiomyogenesis, as well as protecting against pathological stress and heart failure. Dr. Li also elucidated the responsible downstream mechanisms which include novel mediators of cardiomyocyte proliferation and the Hippo/Yap signaling pathway. In addition to the insights provided, these studies suggest a tractable target that can be manipulated to recapitulate many of the cardiac benefits of exercise.

Cardiovascular complications are common in COVID-19 and associated with disease severity and mortality. **Jason Roh, MD, MHS**, working with Dr. Rosenzweig and others performed a plasma proteomics study in COVID-19 patients with and without cardiovascular involvement (15). Despite age-matching subjects, the senescence-associated secretory phenotype, a marker of biological aging, emerged as the most upregulated process associated with cardiac involvement. Of the almost 5000 analytes measured, follistatin-like 3 (FSTL3), an indicator of senescence-promoting Activin/TGFß signaling and a stress-cardiomyopathy related protein,

was the most significantly upregulated protein associated with the heart failure biomarker, NTproBNP (ß=0.4;padj=4.6x10-7). ADAMTS13, a vWF-cleaving protease whose loss of function causes microvascular thrombosis and TTP, was the most downregulated protein associated with myocardial injury (ß=-0.4;padj=8x10-7). Mendelian randomization of ADAMTS13 cis-pQTLs supported a causal role in myocardial injury. Key findings were confirmed in a validation cohort. Key findings were supported by data in the hamster model, which displayed evidence of thrombosis and myocardial injury. Collaborative studies with Dr. Dan Barouch at BIDMC in a hamster SARS-CoV-2 infection model confirmed many of the key findings and demonstrated that COVID can induce expression of senescence genes even in young animals, suggesting a bidirectional interaction with cellular aging: Aging increases the risk of serious COVID infection and COVID infection induces biological aging.

Investigators in the **Division of Infectious Diseases** conducted important studies into critical questions relating to the clinical aspects and pathogenesis of COVID-19. In the wake of reports that SARS-CoV-2 vaccination was occasionally complicated by anaphylaxis or other allergic reactions, **Erica Shenoy, MD, PhD**, was a leader in the development of the after-vaccination symptom survey and clinical decision support tool used by MGB employees. In collaboration with **Kimberly Blumenthal, MD, (Allergy)** and investigators in Infection Control, Occupational Health, and Informatics, Dr. Shenoy described delayed large, localized skin reactions after Moderna vaccination ("Moderna arm") and how this is not a contraindication to receiving subsequent doses (16). **Marcia Goldberg, MD, Roby Bhattacharyya, MD, PhD, Nir Hacohen, PhD (Cancer Center), Michael Filbin, MD, MS (Emergency Medicine), Arnav Mehta, MD, PhD (Cancer Center)**, and a team of others collected and analyzed the plasma proteome of 306 COVID-19 infected patients who presented to the MGH Emergency Department. They described the role of circulating immune cells and tissue cells in inflammation, disease severity, and survival of COVID-19 and proposed a model in which interactions among myeloid, epithelial, and T cells drive tissue damage (17). Using this extensive dataset, **Daniel Leisman, MD, Marcia Goldberg, MD**, and others found that alveolar and endothelial injury likely contribute at different times to disease progression in severe COVID-19, with alveolar injury markers rising early and endothelial injury markers rising later and associating with cardiorenovascular injury and 28-day outcome (18).

A subset of individuals with HIV ("elite controllers") survives long-term without the development of AIDS, maintaining very low or undetectable levels of HIV RNA in the absence of antiretroviral therapy. Insights into the immune mechanisms that enable these individuals to suppress HIV might suggest strategies for therapeutic interventions for HIV-infected individuals who do not control the virus. Using samples from the Ragon Institute HIV controller cohort, **Boris Julg, MD, PhD**, and **Galit Alter, PhD** (Ragon) identified and characterized a novel class of HIV-infected cell targeting monoclonal antibodies with enhanced Fc-functionality (19). In addition, they mapped the HIV-specific antibody repertoire in 22 HIV controllers

from this cohort, analyzing >12,000 HIV-1 envelope-specific single memory B-cells. Using this approach, they found that in individuals with particularly broad antibody responses that were able to neutralize different HIV strains, antibodies were highly mutated and consisted primarily of large clones (20); understanding this antibody evolution will help pave the way for future vaccine design.

Based on his experience as director of the Respiratory Illness Clinic (RIC) during the initial COVID-19 phase, **Michael Dougan, MD, PhD**, from the **Division of Gastroenterology**, focused on early treatment of patients with mild and moderate COVID-19 in addition to his regular investigations on the side effects of immunotherapy (21). As part of the BLAZE-1 consortium, he led the study investigating the efficacy of Bamlanivimab plus Etesevimab, two neutralizing monoclonal antibodies originally isolated from convalescent plasma obtained from patients infected with SARS-CoV-2. This phase 3 randomized trial showed that when Bamlanivimab plus Etesevimab was given within 3 days of demonstrated infection, treatment reduced Covid-19–related hospitalization and death from 7.0 in the control group to 2.1% in the treatment group. This work, published in the NEJM, not only demonstrates the importance of early treatment to prevent severe disease, but highlights the adaptability of researchers in our division to respond to the global pandemic.

In a study published in *Cell Host & Microbe,* **Ramnik Xavier, MD, PhD**, and **Ashwin Ananthakrishnan, MBBS, MPH**, utilized stool microbiome analysis combined with serum metabolomics and proteomics profiling in patients undergoing anti-cytokine or anti-integrin therapy for moderate-to-severe inflammatory bowel disease to assess biomarkers predictive of remission (22). Importantly, both individual microbiome species and serum metabolites were unique to indicate clinical remission on specific therapies. These results can now be used to aid in selecting the most appropriate therapeutic for individual patients and to identify novel therapeutic targets for patients with IBD.

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Molecular Biology

Department Report

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 16 faculty, 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 physiology and disease (Mootha), and mitochondrial membrane structure and proteins (Mootha, Chao).
- Plant biology, signaling, and pathogen defense (Sheen). Immune signaling pathways, host-pathogen interaction (Ausubel, Hung, Ruvkun, Sheen, Xavier).
- Cytoskeletal assembly, dynamics, and transport (Subramanian), macromolecular assembly dynamics (Chao).
- Chemical biology (Hung, Szostak). Synthetic biology, chemical evolution, and protocells (Szostak).
- V(D)J recombination (Oettinger), innate and adaptive immunity (Xavier).
- Synapse formation, transmission, and trafficking (Kaplan).
- miRNA and RNAi pathways. Aging in *C. elegans*. Search for extraterrestrial life (Ruvkun).
- Clinical gastroenterology, inflammatory bowel disease, Crohn's disease, celiac disease and ulcerative colitis, gut microbiome (Xavier).
- Pathophysiology and somatosensory defects in Autism Spectrum Disorder (Orefice).

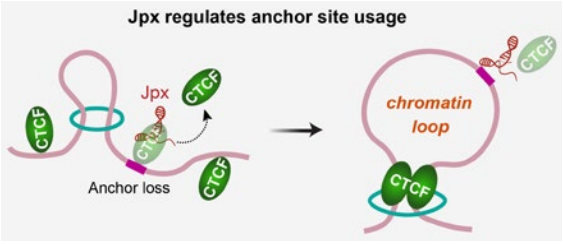
Achievements:

The Department of Molecular Biology is excited to welcome a new Junior Fellow, Margarete Diaz Cuadros, who will start her research program in June 2022. Margarete joins us after completing her PhD in Olivier Pourquié's laboratory at BWH and the Harvard Stem Cell Institute. For her doctoral studies, Margarete developed an *in vitro* system for the study of the somite segmentation clock in paraxial mesoderm-like cells, derived from human and mouse pluripotent stem cells. She described, for the first time, the dynamic properties of the human segmentation clock and its oscillations; characterized the role of major signaling pathways (FGF, Wnt, Notch, Yap) in regulating the segmentation clock *in vitro*; and investigated the role of metabolism in regulating the species-specific tempo of the segmentation clock. The Department looks forward to hosting Margarete over her first several years as a Principal Investigator.

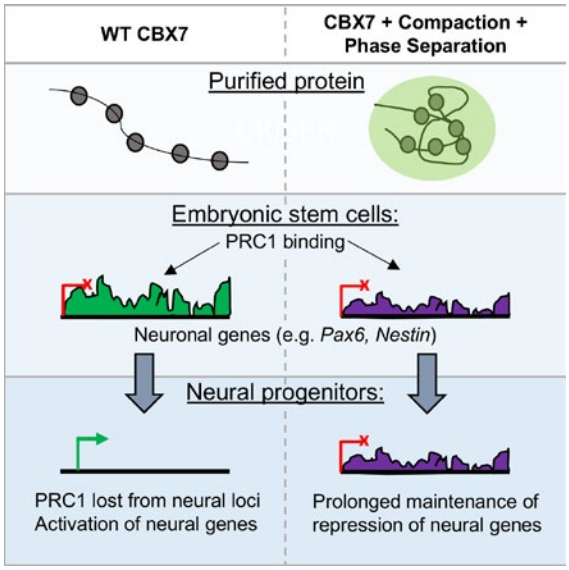
Presented below are two recent research highlights from the department, showcasing our strengths in chromatin dynamics and gene regulation.

Oh HJ, Aguilar R, Kesner B, Lee HG, Kriz AJ, Chu HP, Lee JT. Jpx RNA regulates CTCF anchor site selection and formation of chromosome loops. Cell. 2021 Nov 25:S0092-8674(21)01327-1. doi: 10.1016/j.cell.2021.11.012. PMID: 34856126.

In order to fit inside a cell's nucleus, chromosomes have to be folded in an organized fashion. At a most basic level, chromosomes are first organized into loops of that bring together long-range contacts for proper gene regulation. It is known that loops form and dissociate in a very dynamic way in order to respond to environmental changes. A complex of cohesins and CTCF is required to hold the loops together. But how a cell regulates which loops form at any given time is not known. In this article, we have identified a surprising player in the regulation of loop formation—a noncoding RNA (Jpx) that was previously thought to be involved only in X chromosome inactivation (the counting of X chromosomes and induction of Xist RNA). The Lee lab shows that Jpx is produced from the X chromosome but diffuses all over the nucleus to engage ~5000 target sites across the genome. When Jpx RNA is depleted, ~900 genes become misregulated. The Lee lab shows that Jpx activates genes by controlling the binding of the key looping protein, CTCF. When Jpx comes into contact with CTCF, CTCF is evicted—thereby disrupting formation of the chromosome loop. During cell differentiation, Jpx is upregulated 10-fold—this change leads to a dramatic change in chromosome looping patterns and altered expression of hundreds of cell differentiation genes. In this paper, Oh et al report on the first RNA that specifically controls chromosome looping and provide a mechanism by which an RNA can control how CTCF selects loop anchor sites.



Jpx RNA regulates chromosome looping throughout the genome by releasing CTCF from chromatin, thereby determining where CTCF binds, how anchor sites are selected, and how genome architecture is regulated.

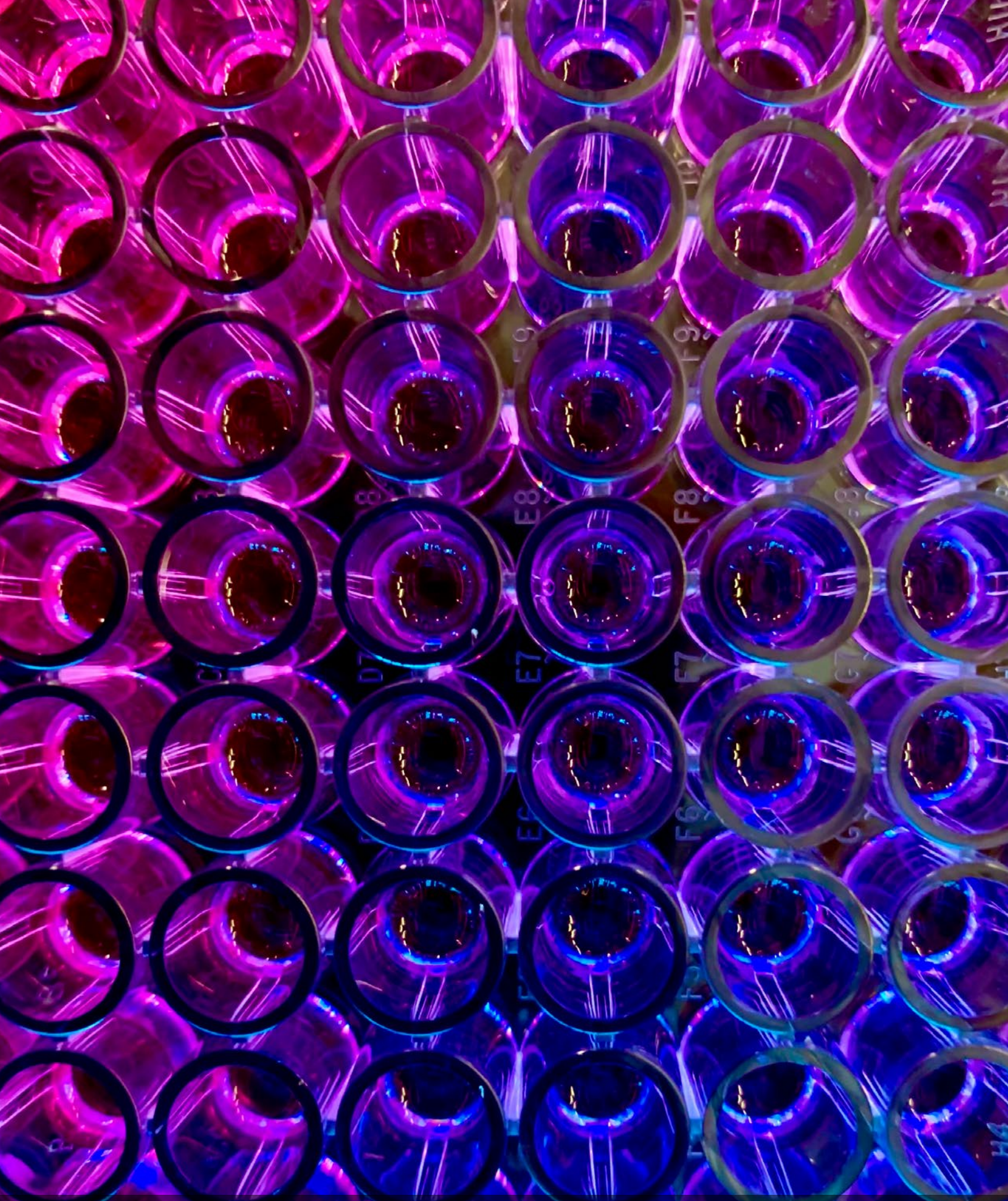


Addition of the compaction and phase separation domain into CBX7 creates droplets of compacted chromatin *in vitro* (top panel). In pluripotent ES cells genes necessary for neuronal lineages are kept in a repressed state by binding of PcG components (middle panel). When pluripotent cells are provided a signal to differentiate along a neuronal lineage, this repressive complex is removed from key neuronal genes in WT cells to allow differentiation. It is maintained on neuronal genes in the gain-of function mutant cells and cells do not differentiate but instead maintain a pluripotent phenotype (bottom panel). This shows that this domain can drive maintenance of repression.

Jaensch ES, Zhu J, Cochrane JC, Marr SK, Oei TA, Damle M, McCaslin EZ, Kingston RE. A Polycomb domain found in committed cells impairs differentiation when introduced into PRC1 in pluripotent cells. Mol Cell. 2021 Nov 18;81(22):4677-4691.e8. doi: 10.1016/j.molcel.2021.09.018. PMID: 34637753.

Proper development of mammals requires that gene expression patterns in differentiated tissues be maintained during every cell division across the lifetime of the organism. One key aspect is the maintenance of genes in a 'silent' or repressed state when expression would be deleterious to a given cell type. A set of genes responsible for maintaining repression, called the Polycomb-Group (PcG), was discovered using flies in 1947 and subsequently identified and studies in mice and in humans. Defects in PcG function cause developmental abnormalities and can also be drivers in cancers such as prostate and glioblastoma. One recent model for maintaining a repressed state is the placement of repressed genes into a phase separated droplet inside the cell nucleus that concentrates all components of the PcG repressive machinery on the gene. This increased concentration of components increases the likelihood that the repressive machinery will re-assemble on the gene after every cell division.

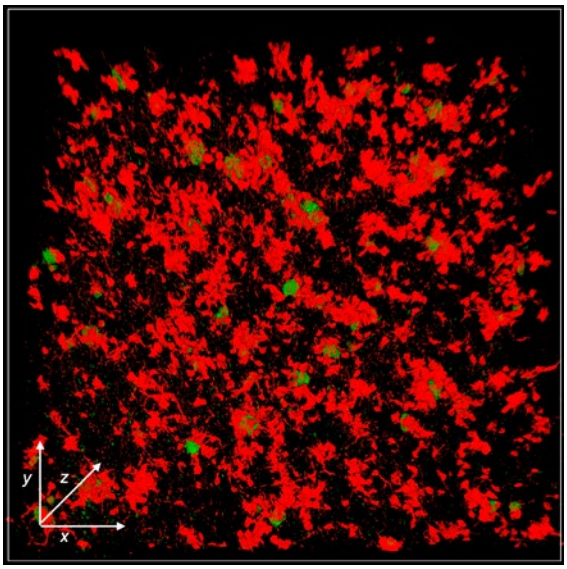
The Kingston group has identified a functional domain in a family of four PcG genes called 'CBX' that both compacts the chromatin on the repressed gene into a tight ball and causes phase separation of the gene into droplets. The domain is found in the CBX2, CBX4 and CBX8 genes that are expressed in stable differentiated cell lineages in mammals. This domain is not found in CBX7, the paralog in the PcG that is expressed in pluripotent cells. This paper explores the hypothesis that the lack of compaction and phase separation activity in CBX7 is essential for the fluid ability of pluripotent cells to differentiate into multiple different lineages. The domain responsible for compaction and phase separation was inserted into CBX7 using CRISPR-Cas9. The resultant 'gain of function' CBX7 was shown to generate compacted chromatin that formed droplets, and the pluripotent cells that expressed this protein were no longer capable of differentiating properly into multiple lineages. This supports the hypothesis that compaction of genes into droplets blocks their ability to transit from a repressed state to an active state on cell division and thereby plays a key role in proper development.



Name: Markus Schweiger, MSc, Neurology
PI: Bakhous Tannous, PhD
Category: A Closer Look
Title: Beauty in the Simple Things

Neurology

Department Report



This image is of the brain of a mouse with Alzheimer's disease. Brain immune cells called microglia (red) are clustering beta-Amyloid plaques (green).

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's research revenue continues to grow, securing over $178M in research funds annually. Our greatest asset in achieving our goals is our talented faculty. Last year we promoted 13 gifted postdoctoral fellows to Instructors and had 17 faculty promotions.

As the pipeline for new potential therapies for neurologic disease is growing there is an unmet demand for clinical trial specialists/ experts. Therefore, during this past year our department created the Associate Chief for Clinical Therapeutic Research, a position that we have successfully filled with James Berry, MD, MPH. Serving as a new key member of the neurology executive leadership team, Dr. Berry will work in collaboration with division directors, vice chairs and physician investigators through the department to set the vision for clinical therapeutic research and lead therapy development.

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 on the 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 second-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.

This year the program engaged 30 students underrepresented in neurology across 16 MGH neurology labs (including those of faculty members underrepresented in neurology) under the leadership

of Nicte Mejia, MD, MPH. In addition, Dr. Mejia and Clay Turner, MD, MSc, received CPIP funding to lead a multidisciplinary team in the development of a quality improvement project called **MGB United Against Racism** that aims to implement a patient-centered community health worker intervention to more effectively support acute ischemic stroke survivors in the most marginalized communities across Massachusetts.

Furthermore, Dr. Mejia was honored with the American Neurological Association inaugural Audrey S. Penn Lectureship Award recognizing efforts related to the MGH Youth Neurology Education and Research Program.

Lastly, we have launched the *MGH Neurology Pathways from Community College (CC) to Neuroscience Career Program*. This is an important gap and opportunity as the U.S. CC population includes 56% women, 50% people of color, and 36% first generation students. This new and exciting initiative aims to develop meaningful partnerships with the 15 community colleges across Massachusetts to foster the career development of students interested in Neuroscience.

The program offers the "Visiting Neuroscientist Program" for MGH neurology neuroscientists to visit CC classrooms to engage in interactive discussions focused on science and career development. More importantly, the program creates a mechanism for CC students interested in neuroscience to engage in flexible paid mentored research opportunities at MGH neurology with a strong emphasis on workforce development.

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 seven Transformative Scholars to date, three of which have already attained Career Development Awards.

The **MGH Neurology Grant Reviews Program** is a new voluntary peer-review program in our department to help faculty improve the science section of their NIH R01 and R21 grant proposals prior to submission. The overarching goals are to improve the odds of success in getting grant proposals funded, retain qualified investigators and enhance the collegial interactions and mentoring between our department's junior and senior investigators.

The organizers of this program are Dora Kovacs, PhD, Elizabeth Klerman, MD, PhD, and Steven Greenberg, MD, PhD. This is also the second 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.

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Over the years the department has established several centers and cores, and their 2021 achievements are highlighted below.

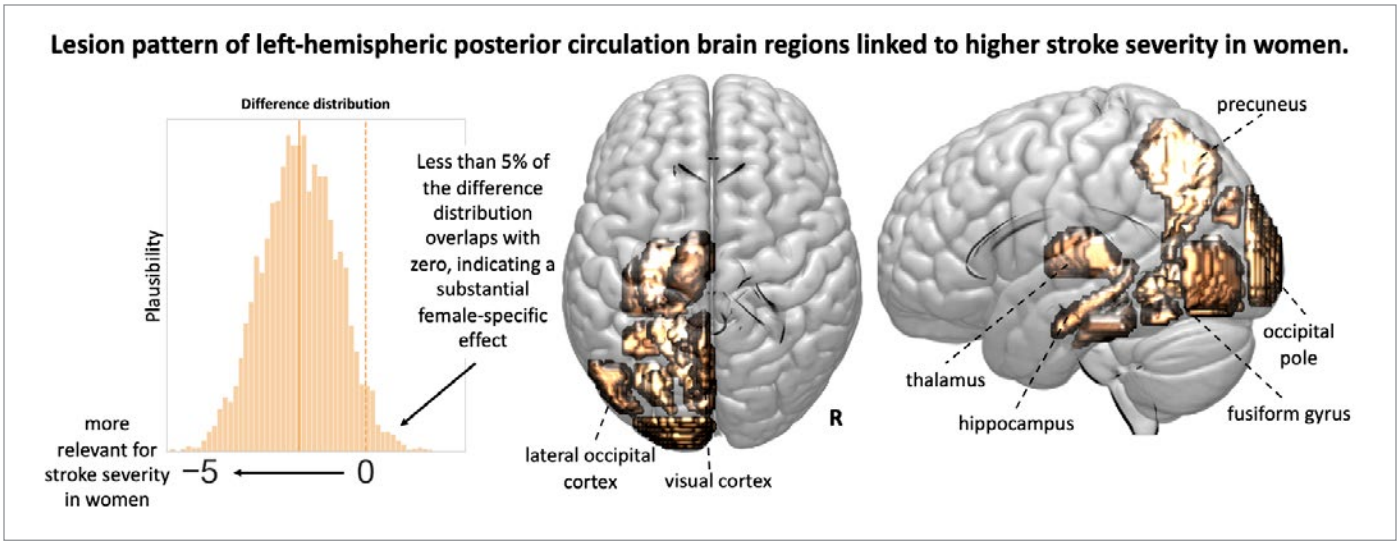
McCance Center: TheMcCance Center for Brain Health serves as an **incubator for cutting-edge neuroscience research** that is leading to the discovery of indicators of brain health, as well as interventions to preserve and promote brain health, and prevent brain disease. The center had some notable highlights in the past year, including:

1. **COVID-19 and Brain Health.** The McCance Center has been the fulcrum around which the efforts to understand and treat the neuropsychiatric symptoms associated with post-acute sequelae of COVID-19 infection (PASC) have evolved. The center's COVID-19 Brain Health Clinic has become a model for the MGB PASC clinical program and the center's leadership was instrumental in the Greater Boston PASC Consortium securing the competitive NIH grant, "ADVANCE: Boston COVID-19 Recovery Cohort (BCRC)" and one of the leading sites for "RECOVER Initiative: REsearching COVID to Enhance Recovery."
2. **Implementation of the McCance Brain Care Score™ in Primary Care.** To address the urgent need for a tool to assess and improve the care for our brain in the primary care setting, the center is partnering with practices both within and external to MGB to integrate the McCance Brain Care Score™ into routine practice.
3. **Human Sleep Project.** The center is harnessing sleep data to discover indicators of brain health and to develop interventions that modify these sleep-derived indicators.
4. **Clinical Trials.** The McCance Center is conducting clinical trials of lifestyle interventions and natural products that have potential to promote brain health.

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 Clinical and Translational Research Unit (CTRU) is the major stakeholder in the IBC and co-locates the program with the Institute for Innovation in Imaging (i3); the CTRU will be used to conduct research studies that focus 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 2021, we were able to complete construction, and purchased the required equipment for the center.

Outpatient Sleep, Circadian and Activity Rhythms (OSCAR) Core is a new core that provides the scientific expertise and technical support to facilitate the rigorous collection, processing and analysis of outpatient sleep, actigraphy and circadian rhythms data for human studies. Currently Core users include Neurology, Psychiatry, and Anesthesiology/Genetics.

Healey & AMG Center: The Sean M. Healey & AMG Center's mission is to discover life-saving therapies for people worldwide affected by amyotrophic lateral sclerosis (ALS). Accelerating the path to effective treatments for ALS, the Center is leading the first ALS Platform



Acute ischemic stroke affects men and women differently. This figure illustrates the lesion pattern of left-hemispheric posterior circulation brain regions that explained a higher acute stroke severity explicitly in women, but not in men in a large hospital-based cohort of 1,058 acute ischemic stroke patients.

Trial where multiple treatments are tested in parallel using a shared infrastructure. Enrollment for the first four experimental treatments being tested through this innovative trial design completed in 2021. As a companion to the HEALEY ALS Platform trial, a multi-center Expanded Access Protocol (EAP) program was established in 2021 to connect more people at more centers to the selected therapies, this program is currently offering access to 75 people with ALS across 8 centers nationwide.

Center for Value-Based Population Healthcare and Sciences: The brand-new Center for Value-Based Population Healthcare and Sciences integrates state-of-the-art research and clinical care to develop and implement healthcare delivery models that improve patient experience and key outcomes in neurology care. After being formally established in December 2021, this center is already working on two multi-center quality improvement networks: ELHS (Epilepsy Learning Healthcare System) and PASSION (Post-Acute Symptomatic Seizure Investigation & Outcomes Network). In addition to these systems, the center is actively looking for collaboration opportunities within MGB-specific departments, clinics and labs, where these value-based systems can be utilized. Ultimately, the center will distribute lessons and techniques learned through these systems by educating the next-generation of QI and value-focused clinicians and researchers.

Clinical Data Animation Center (CDAC): The Clinical Data Animation Center supports researchers and companies in the advancement of patient care by bringing clinical data to life through machine learning and artificial intelligence. This past year, CDAC partnered with the MGH McCance Center for Brain Health and Center for Neurotechnology and Neurorecovery (CNTR), focusing on two large initiatives that are interrelated:

1. Human Sleep Project—A multi-institutional collaboration led by CDAC and the McCance Center with aims to establish a comprehensive repository of sleep data and associated clinical

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Often critically ill patients are too sick to be transported to a traditional MRI suite for brain imaging. With the portable MRI, we have successfully brought imaging to the patient's bedside. Due to its ease of use, there are also many other potential settings where the device can be used, including in the Emergency Room in collaboration with Dr. Josh Goldstein and in the outpatient clinic. (Left to Right: Dr. Matt Rosen, Dr. Taylor Kimberly)

variables as well as new tools leveraging recent advances in data science to develop robust sleep-based biomarkers of brain and cardiovascular health and mortality.

2. Brain Data Science Platform (BDSP)—A collaboration between CDAC, CNTR, and the McCance Center working together to create the world's largest research repository of neurophysiology data and a platform that supports Big Data Science.

Departmental Strategic Research Priorities

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

Achievements:

We are proud to share the Department published more than 1,513 papers in FY21, with many in high profile journals! Of the 1,500 published, 350 were high impact publications with the several NEJM articles and the strongest concentration in Neurology, JAMA Neurology, Alzheimer's & Dementia and Stroke.

Breakthroughs in Research and Therapeutics

Astrocyte-derived interleukin-3 reprograms microglia and limits Alzheimer's disease. Communication within the glial cell ecosystem is essential for neuronal and brain health. The influence of glial cells on the accumulation and clearance of ß-amyloid (Aß) and neurofibrillary tau in the brains of individuals with Alzheimer's disease (AD) is poorly understood, despite growing awareness that these are therapeutically important interactions. Here we show, in humans and mice, that astrocyte-sourced interleukin-3 (IL-3) programs microglia to ameliorate the pathology of AD. Upon recognition of Aß deposits, microglia increase their expression of IL-3Rα—the specific receptor for IL-3 (also known as CD123)—making them responsive to IL-3. Astrocytes constitutively produce IL-3, which elicits transcriptional, morphological, and functional programming of microglia to endow them with an acute immune response program, enhanced motility, and the capacity to cluster and clear aggregates of Aß and tau. These changes restrict AD pathology and cognitive decline. Our findings identify IL-3 as a key mediator of astrocyte–microglia cross-talk and a node for therapeutic intervention in AD.

Cameron S. McAlpine, Joseph Park, Ana Griciuc, Eunhee Kim, Se Hoon Choi, Yoshiko Iwamoto, Ma´te´ G. Kiss, Kathleen A. Christie, Claudio Vinegoni, Wolfram C. Poller, John E. Mindur, Christopher T. Chan, Shun He, Henrike Janssen, Lai Ping Wong, Jeffrey Downey, Sumnima Singh, Atsushi Anzai, Florian Kahles, Mehdi Jorfi, Paolo Fumene Feruglio, Ruslan I. Sadreyev, Ralph Weissleder, Benjamin P. Kleinstiver, Matthias Nahrendorf, Rudolph E. Tanzi, Filip K. Swirski. Astrocyte-derived interleukin-3 reprograms microglia and limits Alzheimer's disease. Nature. 2021 Jul;595(7869):701-706.

Plasma IL-12/IFN-γ axis predicts cognitive trajectories in cognitively unimpaired older adults. Immune dysregulation is implicated in neurodegeneration and altered cytokine levels are seen in people with dementia. However, whether cytokine levels are predictive of cognitive decline in cognitively unimpaired (CU) elderly, especially in the setting of elevated amyloid beta (Aß), remains unclear. We measured nine cytokines in the baseline plasma of 298 longitudinally followed CU elderly and assessed whether these measures were associated with cognitive decline, alone or synergistically with Aß. We next examined associations between cytokine levels and neuroimaging biomarkers of Aß/tau/neurodegeneration. Higher IL-12p70 was associated with slower cognitive decline in the setting of higher Aß (false discovery rate [FDR] = 0.0023), whereas higher IFN-γ was associated with slower cognitive decline independent of Aß (FDR = 0.013). Higher IL-12p70 was associated with less tau and neurodegeneration in participants with higher Aß. Immune dysregulation is implicated in early-stage cognitive decline, and greater IL-12/IFN-γ axis activation may be protective against cognitive decline and early-stage AD progression.

Hyun-Sik Yang, Can Zhang, Becky C. Carlyle, Sherri Y. Zhen, Bianca A. Trombetta, Aaron P. Schultz, Jeremy J. Pruzin, Colleen D. Fitzpatrick, Wai-Ying W. Yau, Dylan R. Kirn, Dorene M. Rentz, Steven E. Arnold, Keith A. Johnson, Reisa A. Sperling, Jasmeer P. Chhatwal, Rudolph E. Tanzi. Plasma IL-12/IFN-g axis predicts cognitive trajectories in cognitively unimpaired older adults. Alzheimer's & Dementia. 2021 Jun 23;10.1002/alz.12399.

Whole-genome sequencing reveals new Alzheimer's disease-associated rare variants in loci related to synaptic function and neuronal development. Genome-wide association studies have led to numerous genetic loci associated with Alzheimer's disease (AD). Whole-genome sequencing (WGS) now permits genome-wide analyses to identify rare variants contributing to AD risk. We performed single-variant and spatial clustering-based testing on rare variants (minor allele frequency [MAF] ≤1%) in a family-based WGS-based association study of 2247 subjects from 605 multiplex AD families, followed by replication in 1669 unrelated individuals. We identified 13 new AD candidate loci that yielded consistent rare-variant signals in discovery and replication cohorts (4 from single-variant, 9 from spatial-clustering), implicating these genes: FNBP1L, SEL1L, LINC00298, PRKCH, C15ORF41, C2CD3, KIF2A, APC, LHX9, NALCN, CTNNA2, SYTL3, and CLSTN2. Downstream analyses of these novel loci highlight synaptic function, in contrast to common AD-associated

variants, which implicate innate immunity and amyloid processing. These loci have not been associated previously with AD, emphasizing the ability of WGS to identify AD-associated rare variants, particularly outside of the exome.

Dmitry Prokopenko, Sarah L Morgan, Kristina Mullin, Oliver Hofmann, Brad Chapman, Rory Kirchner, Alzheimer's Disease Neuroimaging Initiative (ADNI); Sandeep Amberkar, Inken Wohlers, Christoph Lange, Winston Hide, Lars Bertram, Rudolph E Tanzi. Whole-genome sequencing reveals new Alzheimer's disease-associated rare variants in loci related to synaptic function and neuronal development. Alzheimer's & Dementia. 2021 Sep;17(9):1509-1527.

Genome-encoded cytoplasmic double-stranded RNAs, found in* C9ORF72 *ALS-FTD brain, propagate neuronal loss. Triggers of innate immune signaling in the CNS of patients with amyotrophic lateral sclerosis and frontotemporal degeneration (ALS/FTD) remain elusive. We report the presence of cytoplasmic double-stranded RNA (cdsRNA), an established trigger of innate immunity, in ALS-FTD brains carrying *C9ORF72* intronic hexanucleotide expansions that included genomically encoded expansions of the G_4C_2 repeat sequences. The presence of cdsRNA in human brains was coincident with cytoplasmic TAR DNA binding protein 43 (TDP-43) inclusions, a pathologic hallmark of ALS/FTD. Introducing cdsRNA into cultured human neural cells induced type I interferon (IFN-I) signaling and death that was rescued by FDA-approved JAK inhibitors. In mice, genomically encoded dsRNAs expressed exclusively in a neuronal class induced IFN-I and death in connected neurons non-cell-autonomously. Our findings establish that genomically encoded cdsRNAs trigger sterile, viral-mimetic IFN-I induction and propagated death within neural circuits and may drive neuroinflammation and neurodegeneration in patients with ALS/FTD.

Steven Rodriguez, Asli Sahin, Benjamin R Schrank, Hawra Al-Lawati, Isabel Costantino, Eric Benz, Darian Fard, Alefiya D Albers, Luxiang Cao, Alexis C Gomez, Kyle Evans, Elena Ratti, Merit Cudkowicz, Matthew P Frosch, Michael Talkowski, Peter K Sorger, Bradley T Hyman, Mark W Albers. Genome-encoded cytoplasmic double-stranded RNAs, found in C9ORF72 *ALS-FTD brain, propagate neuronal loss. Science Translational Medicine. 2021 Jul 7;13(601):eaaz4699. doi: 10.1126/scitranslmed.aaz4699.PMID: 34233951*

Identifying Medicare beneficiaries with dementia. No data exist regarding the validity of International Classification of Disease (ICD)-10 dementia diagnoses against a clinician-adjudicated reference standard within Medicare claims data. We examined the accuracy of claims-based diagnoses with respect to expert clinician adjudication using a novel database with individual-level linkages between electronic health record (EHR) and claims. In this retrospective observational study, two neurologists and two psychiatrists performed a standardized review of patients' medical records from January 2016 to December 2018 and adjudicated dementia status. We measured the accuracy of three claims-based definitions of dementia against the reference standard. From an eligible population of 40,690 fee-for-service (FFS) Medicare beneficiaries, aged 65 years and older, within the MGB

Accountable Care Organization (ACO), we generated a random sample of 1002 patients, stratified by the pretest likelihood of dementia using administrative surrogates. We evaluated the accuracy (area under receiver operating curve [AUROC]) and calibration (calibration-in-the-large [CITL] and calibration slope) of three ICD-10 claims-based definitions of dementia against clinician-adjudicated standards. We applied inverse probability weighting to reconstruct the eligible population and reported the mean and 95% confidence interval (95% CI) for all performance characteristics, using 10-fold cross-validation (CV). Beneficiaries had an average age of 75.3 years and were predominately female (59%) and non-Hispanic whites (93%). The adjudicated prevalence of dementia in the eligible population was 7%. The best-performing definition demonstrated excellent accuracy (CV-AUC 0.94; 95% CI 0.92-0.96) and was well-calibrated to the reference standard of clinician-adjudicated dementia (CV-CITL <0.001, CV-slope 0.97). This study is the first to validate ICD-10 diagnostic codes against a robust and replicable approach to dementia ascertainment, using a real-world clinical reference standard. The best performing definition includes diagnostic codes with strong face validity and outperforms an updated version of a previously validated ICD-9 definition of dementia.

Lidia M V R Moura, Natalia Festa, Mary Price, Margarita Volya, Nicole M Benson, Sahar Zafar, Max Weiss, Deborah Blacker, Sharon-Lise Normand, Joseph P Newhouse, John Hsu. Identifying Medicare beneficiaries with dementia. Journal of the American Geriatrics Society. 2021 Aug;69(8):2240-2251. doi: 10.1111/jgs.17183. Epub 2021 Apr 26.PMID: 33901296.

Novel genetic variants in MAPT and alterations in tau phosphorylation in amyotrophic lateral sclerosis post-mortem motor cortex and cerebrospinal fluid. Although the molecular mechanisms underlying amyotrophic lateral sclerosis (ALS) are not yet fully understood, several studies report alterations in tau phosphorylation in both sporadic and familial ALS. Recently, we have demonstrated that phosphorylated tau at S396 (pTau-S396) is mislocalized to synapses in ALS motor cortex (mCTX) and contributes to mitochondrial dysfunction. Here, we demonstrate that while there was no overall increase in total tau, pTau-S396, and pTau-S404 in ALS post-mortem mCTX, total tau and pTau-S396 were increased in C9ORF72-ALS. Additionally, there was a significant decrease in pTau-T181 in ALS mCTX compared controls. Furthermore, we leveraged the ALS Knowledge Portal and Project MinE data sets and identified ALS-specific genetic variants across MAPT, the gene encoding tau. Lastly, assessment of cerebrospinal fluid (CSF) samples revealed a significant increase in total tau levels in bulbar-onset ALS together with a decrease in CSF pTau-T181:tau ratio in all ALS samples, as reported previously. While increases in CSF tau levels correlated with a faster disease progression as measured by the revised ALS functional rating scale (ALSFRS-R), decreases in CSF pTau-T181:tau ratio correlated with a slower disease progression, suggesting that CSF total tau and pTau-T181 ratio may serve as biomarkers of disease in ALS. Our findings highlight the potential role of pTau-T181 in ALS, as decreases in CSF pTau-T181:tau ratio may

reflect the significant decrease in pTau-T181 in post-mortem mCTX. Taken together, these results indicate that tau phosphorylation is altered in ALS post-mortem mCTX as well as in CSF and, importantly, the newly described pathogenic or likely pathogenic variants identified in MAPT in this study are adjacent to T181 and S396 phosphorylation sites further highlighting the potential role of these tau functional domains in ALS.

Petrozziello T, Amaral AC, Dujardin S, Farhan SMK, Chan J, Trombetta BA, Kivisäkk P, Mills AN, Bordt EA, Kim SE, Dooley PM, Commins C, Connors TR, Oakley DH, Ghosal A, Gomez-Isla T, Hyman BT, Arnold SE, Spires-Jones T, Cudkowicz ME, Berry JD, Sadri-Vakili G. Novel genetic variants in MAPT and alterations in tau phosphorylation in amyotrophic lateral sclerosis post-mortem motor cortex and cerebrospinal fluid. Brain Pathology. 2021 Nov 14;e13035. doi: 10.1111/bpa.13035.

Outcome after acute ischemic stroke is linked to sex-specific lesion patterns. Acute ischemic stroke affects men and women differently. In particular, women are often reported to experience higher acute stroke severity than men. We derived a low-dimensional representation of anatomical stroke lesions and designed a Bayesian hierarchical modeling framework tailored to estimate possible sex differences in lesion patterns linked to acute stroke severity (National Institute of Health Stroke Scale). This framework was developed in 555 patients (38% female). Findings were validated in an independent cohort (n = 503, 41% female). Here, we show brain lesions in regions subserving motor and language functions help explain stroke severity in both men and women, however more widespread lesion patterns are relevant in female patients. Higher stroke severity in women, but not men, is associated with left hemisphere lesions in the vicinity of the posterior circulation. Our results suggest there are sex-specific functional cerebral asymmetries that may be important for future investigations of sex-stratified approaches to management of acute ischemic stroke.

Anna K. Bonkhoff, Markus D. Schirmer, Martin Bretzner, Sungmin Hong, Robert W. Regenhardt, Mikael Brudfors, Kathleen L. Donahue, Marco J. Nardin, Adrian V. Dalca, Anne-Katrin Giese, Mark R. Etherton, Brandon L. Hancock, Steven J. T. Mocking, Elissa C. McIntosh, John Attia, Oscar R. Benavente, Stephen Bevan, John W. Cole, Amanda Donatti, Christoph J. Griessenauer, Laura Heitsch, Lukas Holmegaard, Katarina Jood, Jordi Jimenez-Conde, Steven J. Kittner, Robin Lemmens, Christopher R. Levi, Caitrin W. McDonough, James F. Meschia, Chia-Ling Phuah, Arndt Rolfs, Stefan Ropele, Jonathan Rosand, Jaume Roquer, Tatjana Rundek, Ralph L. Sacco, Reinhold Schmidt, Pankaj Sharma, Agnieszka Slowik, Martin Söderholm, Alessandro Sousa, Tara M. Stanne, Daniel Strbian, Turgut Tatlisumak, Vincent Thijs, Achala Vagal, Johan Wasselius, Daniel Woo, Ramin Zand, Patrick F. McArdle, Bradford B. Worrall, Christina Jern, Arne G. Lindgren, Jane Maguire, Danilo Bzdok, Ona Wu, MRI-GENIE and GISCOME Investigators and the International Stroke Genetics Consortium, Natalia S. Rost. Outcome after acute ischemic stroke is linked to sex-specific lesion patterns. Nature Communications. 2021 Jun 2;12(1):3289. doi: 10.1038/s41467-021-23492-3.

Assessment of brain injury using portable, low-field magnetic resonance imaging at the bedside of critically ill patients.
Neuroimaging is a key step in the clinical evaluation of brain injury. Conventional magnetic resonance imaging (MRI) systems operate at high-strength magnetic fields (1.5-3 T) that require strict, access-controlled environments. Limited access to timely neuroimaging remains a key structural barrier to effectively monitor the occurrence and progression of neurological injury in intensive care settings. Recent advances in low-field MRI technology have allowed for the acquisition of clinically meaningful imaging outside of radiology suites and in the presence of ferromagnetic materials at the bedside. Researchers performed an assessment of brain injury in critically ill patients in intensive care unit settings, using a portable, low-field MRI device at the bedside. This was a prospective, single-center cohort study of 50 patients admitted to the neuroscience or coronavirus disease 2019 (COVID-19) intensive care units at Yale New Haven Hospital in New Haven, Connecticut, from October 30, 2019, to May 20, 2020. Patients were eligible if they presented with neurological injury or alteration, no contraindications for conventional MRI, and a body habitus not exceeding the scanner's 30-cm vertical opening. Diagnosis of COVID-19 was determined by positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction nasopharyngeal swab result. Point-of-care MRI examinations were performed on 50 patients (16 women [32%]; mean [SD] age, 59 [12] years [range, 20-89 years]). Patients presented with ischemic stroke (n = 9), hemorrhagic stroke (n = 12), subarachnoid hemorrhage (n = 2), traumatic brain injury (n = 3), brain tumor (n = 4), and COVID-19 with altered mental status (n = 20). Examinations were acquired at a median of 5 (range, 0-37) days after intensive care unit admission. Diagnostic-grade T1-weighted, T2-weighted, T2 fluid-attenuated inversion recovery, and diffusion-weighted imaging sequences were obtained for 37, 48, 45, and 32 patients, respectively. Neuroimaging findings were detected in 29 of 30 patients who did not have COVID-19 (97%), and 8 of 20 patients with COVID-19 (40%) demonstrated abnormalities. There were no adverse events or complications during deployment of the portable MRI or scanning in an intensive care unit room. This single-center series of patients with critical illness in an intensive care setting demonstrated the feasibility of low-field, portable MRI. These findings demonstrate the potential role of portable MRI to obtain neuroimaging in complex clinical care settings.

Kevin N Sheth, Mercy H Mazurek, Matthew M Yuen, Bradley A Cahn, Jill T Shah, Adrienne Ward, Jennifer A Kim, Emily J Gilmore, Guido J Falcone, Nils Petersen, Kevin T Gobeske, Firas Kaddouh, David Y Hwang, Joseph Schindler, Lauren Sansing, Charles Matouk, Jonathan Rothberg, Gordon Sze, Jonathan Siner, Matthew S Rosen, Serena Spudich, W Taylor Kimberly. *Assessment of brain injury using portable, low-field magnetic resonance imaging at the bedside of critically ill patients. JAMA Neurology. 2020 Sep 8;e203263. doi: 10.1001/jamaneurol.2020.3263.*

Neurosurgery

Department Report

BOB S. CARTER, MD, PHD, CHIEF

Overview:

Massachusetts General Hospital's Department of Neurosurgery is one of the nation's leading neurosurgery centers, treating around 70-90 patients a day, and we perform more than 4,000 neurosurgical procedures each year. This unique scale fuels a research enterprise that focuses on bringing cutting-edge science and technology to bear on the most difficult problems in the field of neuroscience. Indeed, across the diverse areas of neurosurgery practice (tumor, cerebrovascular, functional/epilepsy, spinal disorders, peripheral nerve, trauma and pediatrics), a vision for integrating research into our centers is a hallmark of the department.

Some Notable Achievements:

Advancing CNS diagnostic technology

Ganesh Shankar, MD, PhD, an assistant professor in Neurosurgery, has pursued rapid molecular diagnostics under the auspices of his K08-funded laboratory. Diagnosing primary central nervous system lymphoma (PCNSL) frequently requires neurosurgical biopsy due to nonspecific radiologic features and the low yield of cerebrospinal fluid (CSF) studies. Dr. Shankar's team characterized the clinical evaluation of suspected PCNSL (N =1007 patients) and designed a rapid multiplexed genotyping assay for MYD88, TERT promoter, IDH1/2, H3F3A, and BRAF mutations to facilitate the diagnosis of PCNSL from CSF and detect other neoplasms in the differential diagnosis. Among 159 patients with confirmed PCNSL, the median time to secure a diagnosis of PCNSL was 10 days, highlighting the urgent need for better diagnostics. Among 86 archived clinical specimens, a targeted genotyping assay accurately detected hematologic malignancies with 57.6% sensitivity and 100% specificity (95% confidence interval [CI]: 44.1% to 70.4% and 87.2% to 100%, respectively). MYD88 and TERT promoter mutations were prospectively identified in DNA extracts of CSF obtained from patients with PCNSL and glioblastoma, respectively. The testing had a rapid turnaround, with results within 80 minutes. Across 132 specimens, hallmark mutations indicating the presence of malignancy were detected with 65.8% sensitivity and 100% specificity (95% CI: 56.2%-74.5% and 83.9%-100%, respectively). This targeted genotyping approach offers a rapid, scalable adjunct to reduce diagnostic and treatment delays in PCNSL. The manuscript describing these finding, entitled "A rapid genotyping panel for detection of primary central nervous system lymphoma" was published in *Blood* in 2021.

Global Neurosurgery

Recognizing the value in training and empowering global neurosurgeons from resource limited settings, **Brian Nahed, MD, MSc**, and **Myron Rolle, MD**, created the Harvard–Massachusetts General Hospital International Observership Program (IOP) in

partnership with the Congress of Neurological Surgeons. The IOP will provide the opportunity for a senior resident, fellow or junior neurosurgery consultant from a resource-limited setting to participate in a fully sponsored, highly curated series of global neurosurgery educational opportunities both clinical and public health related over six months in Boston. The recipient will advance his/her public health practice of global neurosurgery through the engagement of Harvard Catalyst Biostatistics courses, editorial meetings at the Journal of Global Neurosurgery, Anti-Racism/Anti-Colonialism workshops, and weekly lectures through the Center for Surgery and Public Health and the Program in Global Surgery and Social Change. Additionally, the recipient will strengthen their clinical acumen through offerings at the MGH Department of Neurosurgery including participating in simple and complex operations, grand round lectures, intensive care unit and ward rounding, outpatient clinics, educational activity sessions, and specialty specific conferences. The recipient will be responsible for a longitudinal project to be presented at the end of the IOP to the clinical and public health cohorts. Ultimately, the IOP aims to strengthen the global neurosurgical skills necessary to make a lasting impact in the lives of the most vulnerable populations around the world and MGH Neurosurgery is proud to play an active role in that process.

Immunotherapy for brain tumors

Our major commitment to the study of immunotherapy was underscored in 2021 by the recruitment of two new faculty members: **Bryan Choi, MD, PhD**, and **Gavin Dunn, MD, PhD**.

Dr. Bryan Choi joined the junior faculty at MGH in the summer of 2021. Dr. Choi is a graduate of Harvard College and Duke University School of Medicine. With a long-standing interest in immunotherapy for malignant brain tumors, Dr. Choi has pioneered, even in his early career, new approaches to chimeric antigen receptor T cell therapy for glioma. Working with **Marcella Maus, MD, PhD**, during his fellowship at MGH, he has developed new strategies for improving the local delivery of T-cell engaging molecules in the glioma microenvironment, work published in *Nature Biotechnology* in 2017. His subsequent 2019 paper entitled “CRISPR-Cas9 disruption of PD-1 enhances activity of universal EGFRvIII CAR T cells in a preclinical model of human glioblastoma” further highlighted a new strategy for rendering Chimeric Antigen Receptor T-cells resistant to the immunosuppressive glioma microenvironment. An outstanding surgeon and proponent of resident education, Dr. Choi published a well-considered editorial in JNS on the impact of COVID-19 on resident education in 2021. Dr. Choi has been awarded a K12 award as he initiates his independent research career here in the MGH and Harvard/DFHCC community. His clinical efforts will focus on neurosurgical oncology as a member of the Pappas Brain Tumor Center at MGH. Alongside collaborators in the Mass General Cancer Center and the Department of Neurosurgery,

he will spearhead our efforts in developing a new bench-to-beside CAR T-cell therapy program.

Dr. Gavin Dunn, a nationally recognized leader in the study of CNS Immunology and Immunotherapy, was recruited to the senior faculty from the Departments of Neurological Surgery, Pathology and Immunology at Washington University. Dr. Dunn will be returning to his roots at MGH where he completed his neurosurgical training. His NIH R01-funded research focuses on the immunobiology of malignant glioma with the goal of translational and clinical trial efforts in the treatment of this disease and has provided many foundational observations in the field over the last decade. Typified by his manuscript "Characterization of the Genomic and Immunologic Diversity of Malignant Brain Tumors through Multisector Analysis," published in *Cancer Discovery* in 2022. Despite success systemic cancers, targeted or immune-based therapies have shown limited efficacy against primary brain malignancies, including glioblastoma. Focusing on intratumoral heterogeneity of GBM, which has been implicated in treatment resistance, Dr. Dunn's team profiled the immunogenomic state of 93 spatially distinct regions from 30 malignant brain tumors through whole-exome, RNA, and T-cell receptor sequencing. Their analyses identified differences between primary and secondary (metastatic) malignancies, with gliomas displaying more spatial heterogeneity at the genomic and neoantigen levels. In addition, this spatial diversity was recapitulated in the distribution of T-cell clones in which some gliomas harbored highly expanded but spatially restricted clonotypes. By comparing the impact of spatial heterogeneity on genomic and immunologic characteristics of gliomas and brain metastases, these findings suggest that gliomas harbor significantly greater intratumoral heterogeneity of genomic alterations, neoantigens, and T-cell clones than brain metastases, indicating the importance of multisector analysis for clinical or translational studies

Dr. Dunn's laboratory will continue a world-leading focus on understanding the molecular and cellular basis of the immune response to glioblastoma in preclinical and translational settings as well as clarifying the relationships between glioma genomics and immunogenicity, an area termed cancer immunogenomics. As a clinical translation of his work, Dr. Dunn has launched a novel clinical trial of personalized vaccine for GBM. At Mass General, Dr. Dunn will lead a new CNS Neuro-Oncology Immunotherapy program in the Department of Neurosurgery in close collaboration with the MGH Cancer Center's Immunotherapy Program and the Division of Neuro-Oncology. Dr. Dunn's efforts will synergize with the historical and existing efforts in the Department by **William Curry, MD, Samuel Rabkin, PhD, Robert Martuza, MD**, and **Bob Carter, MD, PhD,** and the MGH Cancer Center in CNS viral immuno-oncology, immune microenvironment studies, and CAR-T cell therapy to create one of the nation's most comprehensive efforts in CNS onco-immunotherapy.

Nursing

Department Report

The Dorothy A. Jones Endowed Research Award Recipient: Jennifer Cahill, PhD, RN, Nurse Scientist, The Munn Center for Nursing Research. Her study will explore, " Development and testing of a pediatric version of the Functional Health Pattern Assessment Screening Tool (FHPAST-P)."

GAURDIA BANISTER, PHD, EXECUTIVE DIRECTOR, INSTITUTE FOR PATIENT CARE, DIRECTOR, YVONNE L. MUNN CENTER FOR NURSING RESEARCH

Overview:

During the past year, nursing research and related scholarship continues to advance within the Yvonne L. Munn Center for Nursing Research and across the entire Mass General community. Although some research activities were put on hold due to the COVID 19 pandemic, many initiatives began to resume virtually and in person during the Spring and Summer months of 2021. The Munn Center Nurse Scientists continued to facilitate the development of research investigations, participate on Mass General committees, engage in interdisciplinary research activities (e.g., submission of a HRSA Grant with Dr. Elyse Park), promote grant development, and support research implementation. Dr. Gaurdia Banister, Executive Director of the Institute for Patient Care and Director of the Munn Center was formally appointed as a member of the Executive Committee on Research (ECOR) and is a visible nursing presence within this group. In addition, the Munn Center partnered with the MGH Research Institute and the Division of Clinical Research on a Science Slam, a fun, informal science communication event where researchers are challenged to explain their science in layman's terms in three minutes or less.

The Munn Center Nurse Scientists completed a research study entitled *"Nurse Sensitive Clinical Indicators During Covid 19"* funded by the Connell-Jones Endowed Chair for Nursing and Patient Care Research. Currently, the faculty are in the process of submitting a manuscript detailing the outcomes of their investigation and conclusions within a nursing framework. The focus of this nursing inquiry will offer researchers continued opportunity to mine existing data as well as advance nursing research related to health promotion and health care equity/inclusion within underserved communities.

Strategic Goals 2021-22

GOAL 1: Facilitate nurses' participation in the development of nursing knowledge that aligns with the goals of Mass General and Nursing & Patient Care Services.

GOAL 2: Foster opportunities within the Mass General Research Institute to enhance the unique contributions of nursing science.

GOAL 3: Partner with academic, clinical settings and industry to improve the health and well-being of the communities we serve.

- Strengthen ties with academic partners.
- Share nursing research resources across practice settings external to Nursing & Patient Care Services

GOAL 4: Expand the impact of nursing science through the acquisition 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:

Accomplishment Highlights

2021 Inaugural Recipient of The Dorothy A. Jones Endowed Research Grant Award

The Dorothy A. Jones Endowed Nursing Research Grant Award is designed to advance the work of nursing science at Mass General and beyond through the generous contributions of Mrs. Frances Foster, APRN, MS, FNI. Funding provided by The Dorothy A. Jones Endowed Nursing Research Award is designed to support doctorally prepared nurse scientists advancing a program of research that focuses on clinical reasoning and the use of the Functional Health Pattern Assessment Framework (Gordon, 1994) to identify patient (family, community) responses to illness. Nurse designed interventions used to promote health and wellness outcomes for patients across health care settings are also encouraged. In addition, proposals that support nurse-guided interdisciplinary partnerships (IOM, 2015) will be included for review and potential funding.

The inaugural recipient of The Dorothy A. Jones Endowed Nursing Research Award is Dr. Jennifer Cahill, Nurse Scientist in the Munn Center. Dr. Cahill's research to date has focused on children with cancer and their responses and experiences living with this illness. With her new grant funding, Dr. Cahill will explore the *Development and Testing of a Pediatric Version of the Functional Health Pattern Assessment Screening Tool (FHPAST-P).*

According to Dr. Cahill, *"the holistic assessment of the pediatric patient is a critical component of the nursing process requiring sophisticated nursing skills."* A validated and reliable tool that captures essential information about the patient facilitates clinical decision making, guides nursing care and optimizes patient outcomes. This project aims to develop and test a focused pediatric nursing assessment framework derived from Gordon's Functional Health Assessment framework that will reflect a nurse-sensitive approach to understanding the impact of health and illness on children.

The Connell Nursing Research Scholars (CNRS) Program

This year marked the appointment of Dr. Debra Lundquist, Nurse Scientist and Clinical Research Nurse in the Termeer Center for Targeted Therapies as the 10th CRNS Nurse Scholar. With the support of the CRNS program, Dr. Lundquist will now have additional protected time and resources to continue advancing her program of research around the cancer survivorship experience for patients who have participated in clinical research trials. Dr. Lundquist will also be mentored by an external nurse researcher and distinguished scholar, Dr. Betty Farrell over an 18-month period and will work on extending her scholarship and seeking external funding to support her nursing research at MGH. A video is available on the Munn Center website (https://www.mghpcs.org/munncenter/index.asp) that highlights the many accomplishments that have been realized from the generous support of the Connell Family for other CRNS recipients. The video showcases presentations provided by five former CNRS Nurse

The Connell Nursing Research Scholar: Debra Lundquist PhD, RN, Nurse Scientist and Clinical Research Nurse in the Termeer Center for Targeted Therapies.

Nursing

Department Report

The Connell-Jones Endowed Chair Diversity Research Scholars. From Left to Right: Luis Brigida, RN, Termeer Center; Rosebud Mayanja-Sserebe, RN, GYN, Philips 22; Emma Chong, RN, Cardiology, Ellison 110; Claudia Guillen, CNP, Medicine, Chelsea Health Center; Joanna Karanja, RN, Neuro ICU, Lunder 6; Ashley Kariuki, RN, Surgery, White 7; Jhoana Yactayo, RN, Medicine, Ellison 12; Rute Teixeira, CNP, Pediatric Urology.

The Massachusetts General Hospital Nurses" Alumni Association (MGHNAA) Grant Recipient: Marie Borgella DNP, RN, Nurse Director, Bigelow 7 for her project," Improving the age-friendliness of a general medical inpatient unit and impact on patient readiness for discharge; a quality improvement project."

Scholars who discuss the meaning of the CNRS award and its impact on advancing nursing research and resulting knowledge and overall impact of research findings on patient care and nursing practice.

The Connell-Jones Endowed Chair Diversity Research Scholars Program

The Connell-Jones Endowed Chair Diversity Research Scholars (DRS) Program is designed to encourage, educate, and attract racially diverse nurses to pursue a research trajectory designed to achieve health equity, eliminate health disparities, and improve the health of racially diverse communities. Research Scholars enrolled in the program are exposed to research environments that foster their spirit of inquiry. Through participation in didactic research training and mentorship with leading academic, ethnically diverse researchers in their respective area of interest, the scholars explore questions of importance to the nurse scientist. DRS have the opportunity for exposure to, and an expanded awareness of, a research environment internally at Mass General, Mass General Brigham locations and at external academic sites. The DRS Program aims to provide a comprehensive experience to help increase the likelihood that scholars will ultimately consider research as a future career. Applications for the next Diversity Research Scholars (DRS) Program will occur during the Spring of 2022.

The goals of the Diversity Research Scholars Program are to create opportunities for:

- Exposure to successful racially diverse researchers and scholars at Mass General and external academic sites who will provide guidance with elucidating career paths in research.
- Mentorship 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.
- Participation in regular meetings with racially diverse researchers and scientists and the program director.

- Participation in didactic sessions through the MGH Research Institute and affiliated institutions that are designed to enhance and facilitate learning about the research process (i.e., ethical and regulatory aspects of human subject research) and principles and practice of clinical research, including research methods.

Last summer, eight Connell Diversity Research Scholars were competitively selected from within the Mass General nursing community to participate in an eight-week Nursing Research Institute. The program, under the leadership of Dr. Gaurdia Banister and facilitated by a diverse cohort of nationally recognized nurse scholars, designed an innovative virtual curriculum, that explored diversity, equity, and inclusion within the framework of nursing research. Evaluation of the experience by scholars and mentors suggested that the experience was both personally and professionally transformative and enhanced interest in seeking opportunities to advance their knowledge about research overall and explore research questions that were sensitive to the health care challenges within diverse, underserved populations.

Nursing Research Day
Nursing Research Day occurred virtually on the afternoon of September 30, 2021. The program included a lecture by a renown nurse scientist and the presentation of research grants and nursing research poster awards.

Dr. Rosa Gonzalez-Guarda, PhD, MPH, RN, CPH, FAAN, an Associate Professor at Duke University School of Nursing and the Faculty Lead for the Population Health Research Area of Excellence in the school's Center for Nursing Research served as the keynote speaker. Her presentation was entitled: *Nursing's Role in Leading and Improving Health Equity through Research: Lessons Learned from Addressing Health Disparities among Latinx Immigrants in the US.* In addition, Dr. Katherine Rosa presented the results of her research supported by the Jeanette Ives Erickson Research Institute Grant. The study focused on the development and psychometric evaluation of the RELATE Scale designed to measure healing and the nurse patient relationship.

The Virtual Poster Showcase featured 40 posters that demonstrated the incredible work of MGH nurses in Evidence Based Practice, Original Research, and Quality Improvement. The posters are available for viewing on the Munn Center website https://intranet.massgeneral.org/npcs/munncenter/Research-Day-Virtual-Showcase-2021.asp

The award recipients were also recognized during at this important celebration. Those who received an award and accompanying grant to support their research were:

The Massachusetts General Hospital Nurses' Alumni Association (MGHNAA) Grant
The 2021 recipient of the Massachusetts General Hospital Nurses' Alumni (MGHNAA) Grant was Marie Borgella, DNP, RN, Nurse Director, Bigelow 7 for her project, "Improving the age-friendliness of

The National Institute for Occupational Safety and Health (NIOSH) Grant Recipient: Patricia S. Crispi PhD, RN, NPD-BC (Right), Professional Development Specialist, The Norman Knight Nursing Center for Clinical and Professional Development for her study, " Exploring Relationships Between Health-Promoting Self-Care Behaviors Among Nurses and their Perceived Incidence of Presenteeism."

Her mentor is Jane Flanagan, PhD, RN, ANP-BC, AHN-BC, FAAN, (Left) Nurse Scientist, The Yvonne L. Munn Center for Nursing Research.

Nursing

Department Report

Munn Center Predoctoral Research Grant recipients

Principle Investigator: Christopher DePesa, RN, MS, TCRN, PhD(c), Clinical Nurse Manager Emergency Department, Newton-Wellesley Hospital (Employed at MGH at the time award was granted) for his study, " Emergency Nurse Efficiency as a Measure of Emergency Nurse Performance."

Principle Investigator: Patricia Railsback Masson, RN, MSN, PhD(c), Sr. Regional Director, Mass General Network Development and Integration for her study, " Factors Influencing Blood Pressure Control Among Hypertensive Adults at Risk for Stroke."

Principle Investigator: Tara M. Tehan, MSN, MBA, RN, NE-BC, PhD(c), Nurse Director, MGH Neuroscience Intensive Care Unit for her study, "A Feasibility Study to Reduce the Symptoms of Post-Intensive Care Syndrome in Family Members."

a general medical inpatient unit and impact on patient readiness for discharge: A quality improvement project."

This funding opportunity, supported by the **MGH School of Nursing Nurses Alumni Association**, provides two years of funding ($3000) to nurses enrolled in a Master of Science in Nursing or Doctor of Nursing Practice (DNP) Program who are developing projects to advance nursing science and improve outcomes for the nursing workforce, patients, or families.

The National Institute for Occupational Safety and Health (NIOSH) Grant

The 2021 recipient of the National Institute for Occupational Safety and Health (NIOSH) grant was Patricia S. Crispi PhD(c), RN, NPD-B, Professional Development Specialist, Norman Knight Nursing Center for Clinical and Professional Development for her study, "Exploring Relationships Between Health-Promoting Self-Care Behaviors Among Nurses and their Perceived Incidence of Presenteeism."

This grant is supported by OSHA (*"Be Well - Live Well"* initiative) and focuses on workforce safety and health promotion. This grant is led by a Nurse Scientist with a team interested in studying strategies that can foster a healthy work environment. The $8,000 grant is given to promote research initiatives among nurses with a focus on health promotion and workforce safety.

2021 Munn Center Research Grants

The 2021 recipients of the Munn Center Research Grants were:

Principal investigator: Lisa Carter, RN; mentor, Jane Flanagan, PhD, RN, ANP-BC, AHN-BC, FAAN, and team members, Amy Greenblatt, RN, MSN; Martin Lantieri, RN, MSN ; and Karen Regan, Director, Transplant Patient Ambassador Program, for their study, "Healing from liver transplant surgery: The patient's story."

Principal investigator: Erin Sinclair, RN, BSN; mentor, Virginia Capasso, PhD, CNP, ACNS, CWS, FACCWS, for her study, "Effect of an algorithm on improving delivery of enteral nutrition to critically ill patients: A pilot study."

The 2021 recipients of the Munn Predoctoral Research Grant 2021 were:

Christopher DePesa, RN, MS,TCRN, PhD(c), Clinical Nurse Manager Emergency Department, Newton-Wellesley Hospital, (Employed at MGH at the time award was granted), "Emergency Nurse Efficiency as a Measure of Emergency Nurse Performance."

Patricia Railsback Masson, RN, MSN, PhD(c), Sr. Regional Director, Mass General Network Development and Integration, "Factors Influencing Blood Pressure Control Among Hypertensive Adults at Risk for Stroke."

Tara M. Tehan, MSN, MBA, RN, NE-BC, PhD(c), Nurse Director, MGH Neuroscience Intensive Care Unit, "A Feasibility Study to Reduce the Symptoms of Post-Intensive Care Syndrome in Family Members."

The Munn Research Grants are supported by the Senior Vice President for Patient Care and Chief Nurse and the leadership of the Department of Nursing. Studies focusing on original research are initiated by Mass General nurses for the purpose of advancing nursing science and improving outcomes for patients and families. The intent is that the studies support and advance Patient Care Services annual strategic goals and the professional practice model. Completed studies are featured as presentations throughout the year at quarterly Munn Center Nursing Research Grand Rounds.

2021 Poster Awards
The winners of the 2021 Nursing Research Poster Awards were:

Alyssa Baldino, BSN, RN, Michelle Gorski, BSN, RN, Erin Sinclair, BSN, RN, Jessica Witchey RD, and Virginia Capasso PhD, CNP, ACNS-BC, CWS, ***won in the category of Evidence-Based Practice*** for their poster, "Effect of an algorithm on improving delivery of enteral nutrition to critically ill patients: An evidence-based practice project."

Christina L. Burke, RN and Anne-Marie Barron, PhD, RN, PMHCNS-BC, FAAN, ***won in the category of Original Research*** for their poster, "Exploring the experiences and perspectives of bone marrow transplant nurses in relation to integrating humor in their practice."

Meg Soriano, RN, MBE, Corey McEwen, PharmD MS, Julie Cronin, DNP, RN, OCN, NE-BC, Brianne McGree, NP, and Matt Lei, PharmD, BCOP ***won in the category of Advanced/Mid-Career Nurse Researcher*** for their poster, "Transition of a chemotherapy treatment for lymphoma patients from the inpatient to ambulatory setting."

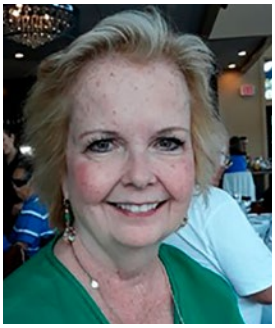
Christina Swanberry, MSN, RN, CCRN-K, SCRN, Stacey Savage, MSN, RN, CEN, CPEN, TCRN, Peter Hedberg, MD, Lukas Kolm, MD, Pamela Poulin, MSN, RN, CENP, and Betty Peterson ***won in the category of Quality Improvement*** for their poster, "Reducing door-to-CT times for anticoagulated head strikes at a level III trauma center: A quality improvement initiative."

Pamela Quinn, DNP, RN, NPD-BC, ***won in the category of Emerging Scholar*** for her poster, "Improving nurse confidence and proficiency of peripheral intravenous catheterization through education."

Forty posters were accepted for presentation during Nursing Research Day. They were evaluated and awardees were selected by an interdisciplinary team of judges.

Scholarship and Dissemination
The Munn Center continues to participate in generating relevant research and evidence to support magnet criteria, highlighting how nursing knowledge, discovery and a creative spirit of inquiry are fully embedded within the culture of Mass General Nursing. Many scholars have disseminated research findings globally and share nursing knowledge that impacts patient care outcomes. Over the past year, many scholars published research findings in high impact journals. Examples include:

The Association of Distinct Social Determinants of Health with Added Sweetener Knowledge and Consumption in a U.S. Sample of People



Munn Center Research Grants

Top row, left to right: Amy Greenblatt, RN, MSN, AGCNS-BC; Lisa Carter, ARN, BSN, Principle Investigator; Marty Lantieri, RN, MSN, CNL-BC, NE-BC, Nurse Director Blake 6.

Top row, left to right: Karen Regan, Director, Transplant Patient Ambassador Program; Mentor Jane Flannagan, PhD, RN, ANP-BC, AHN-BC, FAAN for their study, " Healing from liver transplant surgery: The patient's story."

Nursing

Department Report

Munn Center Research Grants

Left to Right: Principle Investigator, Erin Sinclair, RN, BSN, Michelle Gorski, RN, BSN; Mentor, Virginia Capasso, PhD, CNP, ACNS, CWS, FACCWS; Jessica Witchey, RD, LDN and Alyssa Baldino, RN, BSN from the Cardiac Intensive Care Unit (CICU) for their study, “Effect of an algorithm on improving delivery of enteral nutrition to critically ill patients: A pilot study.”

Living with HIV. Kileel EM, ***Dickins KA****, Zheng H, Fitch KV,* ***Looby SE****. AIDS Behav. 2021 Nov 3. doi: 10.1007/s10461-021-03508-1. Online ahead of print.*

Findings From a Provider-Led, Mindfulness-Based, Internet-Streamed Yoga Video Addressing the Psychological Outcomes of Breast Cancer Survivors. ***Flanagan JM****, Post K, Hill R, Winters LN. Holist Nurs Pract. 2021 Sep-Oct 01;35(5):281-289. doi: 10.1097/HNP.0000000000000465.PMID: 34407026*

Developing a pilot lifestyle intervention to prevent cardiovascular disease in midlife women with HIV. Raggio G, Goodman G, Robbins GK, ***Looby SE****, Labbe A, Psaros C. HIV Res Clin Pract. 2021 Feb;22(1):1-13. doi: 10.1080/25787489.2021.1883957. Epub 2021 Feb 21. PMID: 33616022*

Silva, R. D. C. G. E., & ***Jones, D. A.*** *An integrative review of comprehensive nursing assessment tools developed based on Gordon's Eleven Functional Health Patterns. International journal of nursing knowledge.*

Ford, A. R., Smith, D. L., & ***Banister, G. E.*** *(2021). Recruitment and retention of occupational therapy practitioners and students of color: A qualitative study. American Journal of Occupational Therapy, 75(1), 7501205150p1-7501205150p8.*

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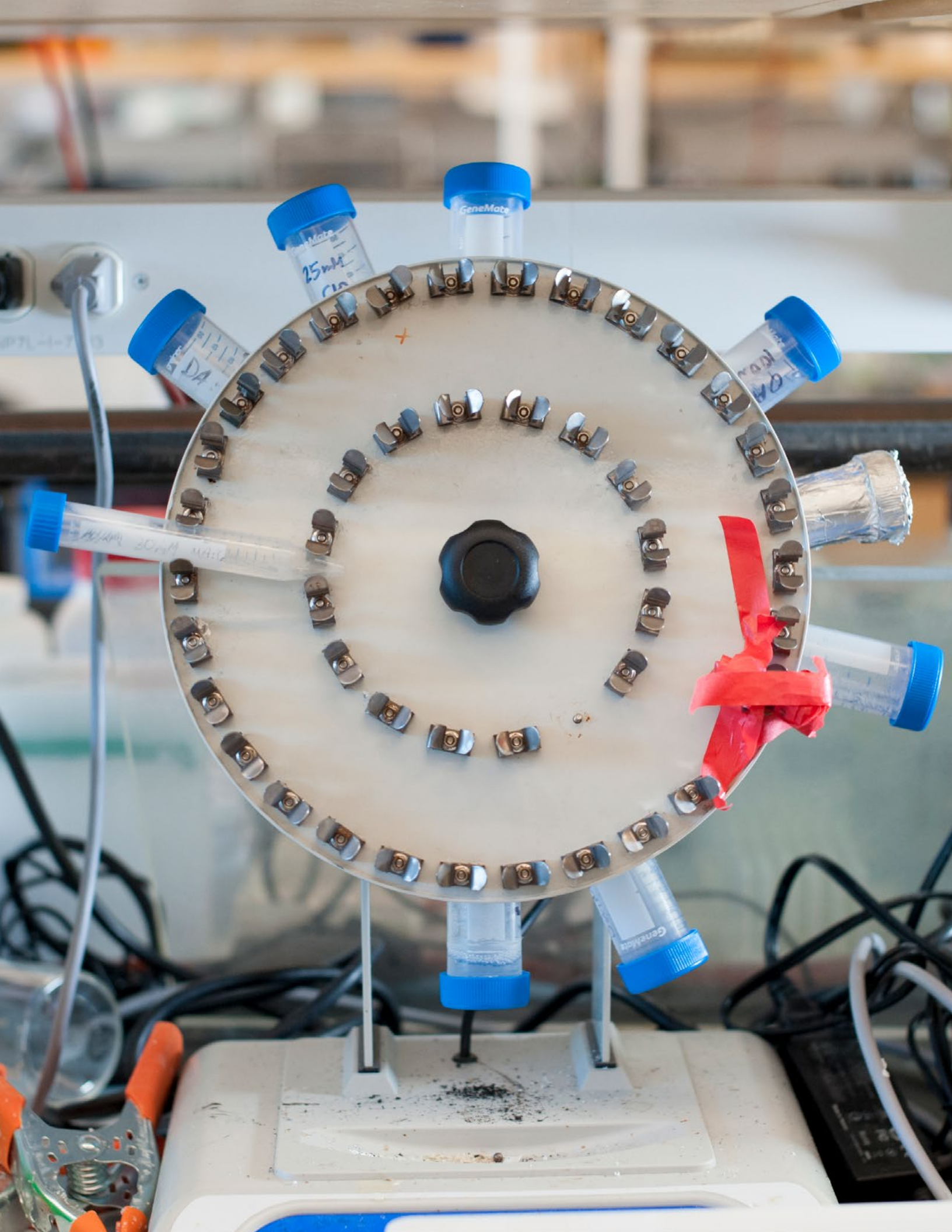
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Obstetrics and Gynecology

Department Report

JEFFREY L. ECKER, MD, CHIEF

Overview:

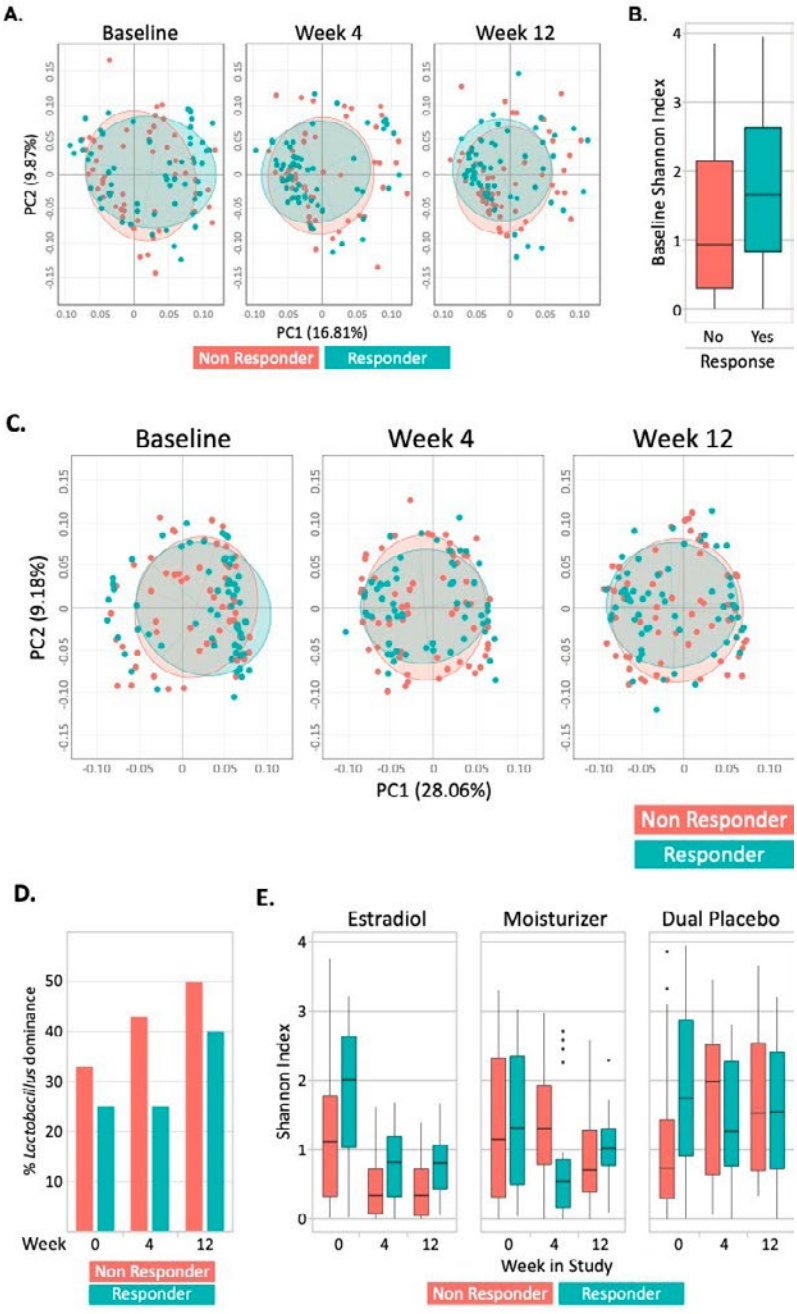
Research in Obstetrics and Gynecology at MGH

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

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

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

Mass General Global OB/GYN integrates three core missions to address the unmet promise of reproductive health care for all women throughout the world by providing care, bolstering education and trainings, and conducting innovative research. We strive to ensure that our efforts are guided by 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.



(A) Beta diversity represented by Principle Coordinate Analysis plots. Each dot represents the bacterial community in a single participant and data is shown across three timepoints; baseline, week 4 and week 12. Axes are the coordinates of maximal variability in the multivariate data with PC1 and PC2 explaining 16.81% and 9.87% of the variation, respectively. The bacterial community was similar between responders (n=58 and 58 at weeks 4 and 12, respectively) and non-responders throughout the trial (n=60 and 59 at weeks 4 and 12). (B) Responders had a higher median Shannon index (α -diversity) at enrollment compared to non-responders (p = 03). (C) There were no significant association between the profile of metabolites and responder status throughout the trial. (D) There was no statistically significant difference in the proportion of women with *Lactobacillus* dominance between responders and non-responders at any visit. (E) The Shannon index decreased significantly throughout the trial, especially in the estrogen and moisturizer arms, but was not associated with responder status. Responders were defined as women who had a >2-point decrease in most bothersome symptom (MBS) severity over 12 weeks of treatment and non-responders were defined as women who had <1-point decrease.

Postpartum woman at Mbarara Regional Referral Hospital with wireless physiologic monitor on left arm.

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. *Mitchell CM*, *Ma N, Mitchell A, Wu MC, Valint DJ, Proll, S, Reed SD, Guthrie KA, LaCroix AZ, Larson J, Pepin R, Raftery D, Fredricks DN, Srinivasan S. Association between postmenopausal vulvovaginal discomfort, vaginal microbiota and mucosal inflammation: Vaginal microbiome and treatment response in postmenopausal women. AJOG 2021 Mar 3. [EPub ahead of print] PMID 33675793*

AJOG at a Glance:

A. Why was this study conducted?

- We performed this study to identify microbial, immune or metabolic markers associated with response to topical treatment for genitourinary syndrome of menopause.

B. What are the key findings?

- We found no association between treatment response and vaginal microbial community diversity or richness, *Lactobacillus* dominance, vaginal fluid metabolites or soluble immune markers.
- Women randomized to vaginal estrogen had the greatest decrease in microbial diversity and altered vaginal fluid metabolites, whether symptoms improved or not.

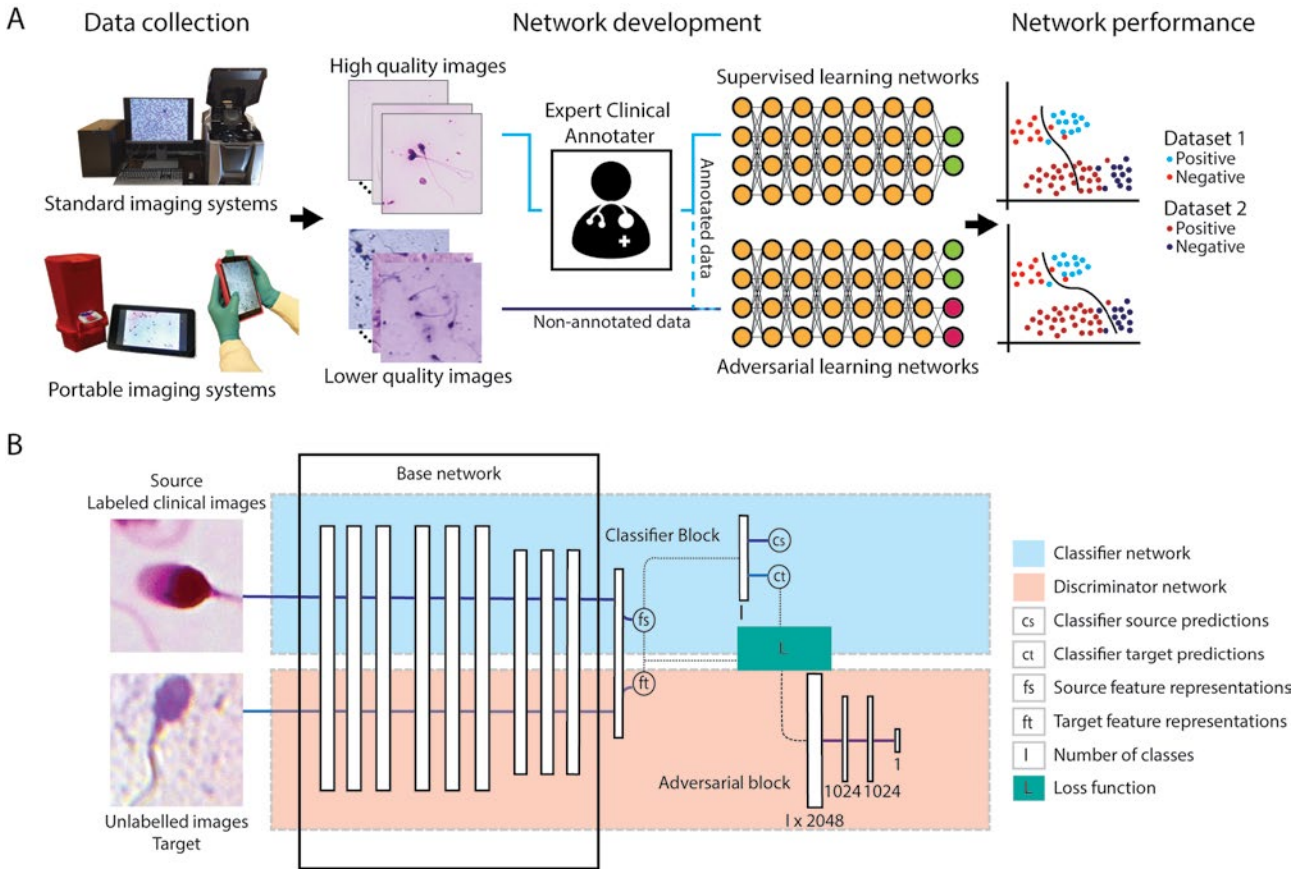
C. What does this study add to what is already known?

- Our results suggest that the biological markers used to define treatment response for vaginal estradiol may not be useful markers for symptom improvement

Abstract:

Introduction: Half of all postmenopausal women report symptoms of vulvar, vaginal or urinary discomfort with significant impact on sexual function and quality of life; underlying mechanisms leading to symptoms are poorly understood. To examine the possibility that the vaginal microbiota and/or mucosal immune response contribute to the severity of bothersome vaginal symptoms we conducted a substudy of samples from a randomized trial of vaginal treatment for genitourinary syndrome of menopause (GSM) to compare these features between women whose symptoms improved vs. those who did not.

Methods: This is a secondary analysis of samples collected in a 12-week randomized trial of treatment with vaginal estradiol or moisturizer versus placebo for moderate-severe postmenopausal symptoms of vaginal discomfort. We randomly selected 20 women in each arm with ≥2-point decrease in most bothersome symptom (MBS) severity (responders) and 20 matched controls with ≤1-point decrease (non-responders). At 0, 4, 12 weeks, we characterized



vaginal microbiota (16S rRNA gene sequencing), vaginal fluid metabolites (broad-based metabolomic profiling), vaginal fluid soluble immune markers (MesoScale Discovery), pH and vaginal maturation index (VMI). We compared responders versus non-responders at baseline, and across all visits using linear mixed models to evaluate associations with microbiota, metabolites and immune markers, incorporating visit and participant-specific random effects while controlling for treatment arm.

Results: Women (n=120) were mean age 61 years and primarily White (92%). At enrollment no significant differences were observed between responders and non-responders in age, MBS type or severity, microbiota composition or diversity, *Lactobacillus* dominance, metabolome or immune markers. There was a significant decrease in diversity of the vaginal microbiota in both responders and non-responders ($p<0.001$) over 12 weeks. While this change did not differ by responder status, diversity was associated with treatment arm: more women in the estradiol arm (63%) had *Lactobacillus*-dominant, lower diversity bacterial communities than women in the moisturizer (35%) or dual placebo (23%) arms ($p=0.001$) at 12 weeks. Metabolome, VMI and the measured immune markers were not associated with responder status over the 12 weeks but varied by treatment arm.

Fig. 1 Schematics of the use of adversarial domain adaptive neural networks for medical image analysis. **a,** Supervised learning networks for medical image analysis are limited to fully expert-annotated datasets for training and are generally unable to adapt to unseen distributions of data collected using different imaging systems used in different clinical settings. Clinical expert staff may not be able to reliably annotate medical images obtained through portable point-of-care optical systems that are usually of lower quality compared with bulky and expensive benchtop microscopes. However, adversarial learning networks can be used to utilize standardized annotated image datasets obtained from one distribution (source) to adapt themselves with unannotated data obtained from a different distribution (target) towards a substantially more generalized neural network. **b,** Schematic of the general framework of the adversarial domain adaptive medical neural networks (MD-nets). The base network layers can be replaced using any regular custom neural network architecture. Additional elements for pseudolabelling can be added to enable the network to achieve adaptation in the absence of source data.

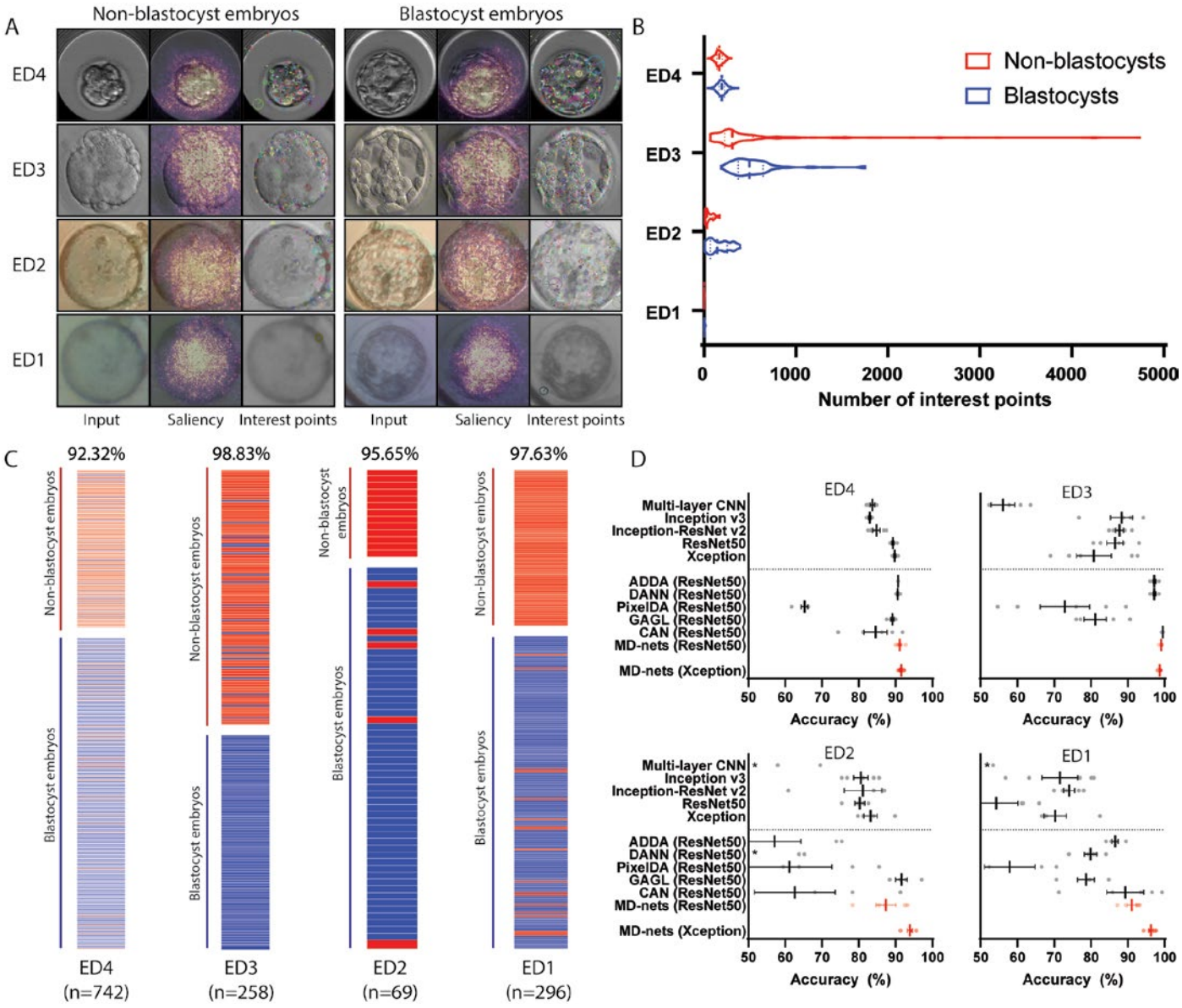


Fig. 2 Comparison of supervised CNNs and domain adaptation methods for the morphological analysis of human embryo images. a, The embryo image datasets were collected from a clinical time-lapse system (ED4), various clinical brightfield inverted microscopes (ED3), a portable 3D-printed imaging system (ED2) and a 3D-printed smartphone-based imaging system (ED1). The overlaid saliency maps help to visualize pixels that are most utilized by the MD-nets in their decision-making. The interest points are examples of strong features of different embryo images identified by the SIFT algorithm. b, The distribution of feature points in non-blastocyst and blastocyst-stage embryo images collected from ED4 (n = 251 and n = 491), ED3 (n = 141 and n = 117), ED2 (n = 13 and n = 56) and ED1 (n = 99 and n = 197). The dashed lines represent the median and dotted lines represent quartiles. c, The performance of MD-nets in evaluating embryo images collected using different imaging systems on the basis of their developmental stage. The red bars represent non-blastocysts and the blue bars represent blastocysts. d, The performance of MD-nets in embryo image classification compared to different supervised learning models trained with only the ED4 dataset (source) and unsupervised domain adaptation strategies implemented with ResNet-50, when tested on target test datasets of ED4 (n = 742), ED3 (n = 258), ED2 (n = 69) and ED1 (n = 296). The dotted line separates the domain adaptation methods from the supervised models. Each result represents the average of five random initialization seeds and the error bars represent the s.e.m. The asterisks indicate performance averages of below 50%. The dots represent the individual performance values of each model.

Comment: Postmenopausal vaginal symptom severity was not significantly associated with vaginal microbiota or mucosal inflammatory markers in this small study. Women receiving vaginal estradiol experienced greater abundance of lactobacilli and lower vaginal pH at end of treatment.

2. ***Boatin AA****, Ngonzi J, Wylie BJ, Lugobe HM, Bebell LM, Mugyenyi G, Mohamed S, Martinez K, Musinguzi N, Psaros C, Metlay JP, and Haberer JE. Wireless versus routine physiologic monitoring after cesarean delivery to reduce maternal morbidity and mortality in a resource-limited setting: protocol of type 2 hybrid effectiveness-implementation study. BMC Pregnancy Childbirth. 2021 Feb 12;21(1):124. PMID: 33579213.*

Abstract:
Women in sub-Saharan Africa have the highest rates of morbidity and mortality during childbirth. Despite significant increases in facility-based childbirth, quality gaps at the facility have limited reductions in maternal deaths. Infrequent monitoring of women around childbirth is a major gap in care that leads to delays in life-saving interventions. Simple increases in staffing will not overcome this gap, thus necessitating new strategies. This research project is investigating using a simple wireless monitor to improve the detection of complications immediately after childbirth and allow clinicians to provide life-saving interventions when needed. Using a hybrid clinical effectiveness-implementation design, women delivered by cesarean in Mbarara, Uganda have been recruited to wear a wireless physiologic monitor for 24 hours after delivery and their clinicians recruited to use the monitoring system, including the receipt of text message alerts should women develop abnormalities in physiologic signs. Women wearing the monitor and a control group without monitoring have been followed to assess in-hospital rates of morbidity and mortality s. Clinical adoption and implementation is assessed with the RE-AIM implementation framework and semi-structured interviews. To date, over 1200 women have been enrolled into the intervention arm, and 2000 into the control group. The study will be completed in February 2022.

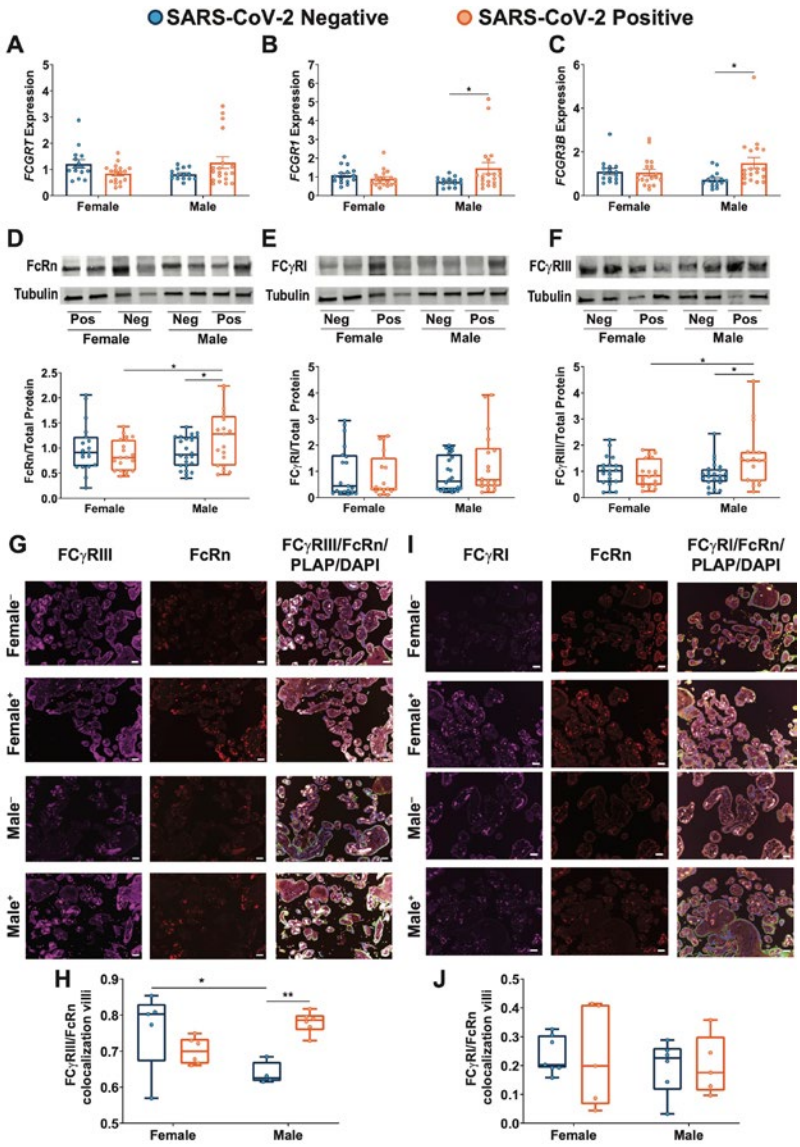
3. *Branda JA, Tsibris AM, Kuritzkes DR,* ***Petrozza JC****, Bormann CL, Hadi Shafiee H. Adaptive adversarial neural networks for the analysis of lossy and domain-shifted datasets of medical images. Nat Biomed Engin. 2021 Jun 10;5:571-585.*

Abstract:
In machine learning for image-based medical diagnostics, supervised convolutional neural networks are typically trained with large and expertly annotated datasets obtained using high-resolution imaging systems. Moreover, the network's performance can degrade substantially when applied to a dataset with a different distribution. Here, we show that adversarial learning can be used to develop high-performing networks trained on unannotated medical images of varying image quality. Specifically, we used low-quality images acquired using inexpensive portable optical systems to train networks

for the evaluation of human embryos, the quantification of human sperm morphology and the diagnosis of malarial infections in the blood, and show that the networks performed well across different data distributions. We also show that adversarial learning can be used with unlabeled data from unseen domain-shifted datasets to adapt pretrained supervised networks to new distributions, even when data from the original distribution are not available. Adaptive adversarial networks may expand the use of validated neural-network models for the evaluation of data collected from multiple imaging systems of varying quality without compromising the knowledge stored in the network.

4. *Bordt EA, Shook LL, Atyeo C, Pullen KM, De Guzman RM, Meinsohn MC, Chauvin M, Fischinger S, Yockey LJ, James K, Lima R, Yonker LM, Fasano A, Brigida S, Bebell LM, Roberts DJ, Pépin D, Huh JR, Bilbo SD, Li JZ, Kaimal A, Schust D, Gray KJ, Lauffenburger D, Alter G,* ***Edlow AG****. Maternal SARS-CoV-2 infection elicits sexually dimorphic placental immune responses. Science Translational Medicine. 2021, e-pub 10/19, Vol 13 Issue 617.* https://www.science.org/doi/10.1126/scitranslmed.abi7428

Abstract:
There is a persistent bias toward higher prevalence and increased severity of coronavirus disease 2019 (COVID-19) in males. Underlying mechanisms accounting for this sex difference remain incompletely understood. Interferon responses have been implicated as a modulator of COVID-19 disease in adults and play a key role in the placental antiviral response. Moreover, the interferon response has been shown to alter Fc receptor expression and therefore may affect placental antibody transfer. Here, we examined the intersection of maternal-fetal antibody transfer, viral-induced placental interferon responses, and fetal sex in pregnant women infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Placental Fc receptor abundance, interferon-stimulated gene (ISG) expression, and SARS-CoV-2 antibody transfer were interrogated in 68 human pregnancies. Sexually dimorphic expression of placental Fc receptors, ISGs and proteins, and interleukin-10 was observed after maternal SARS-CoV-2 infection, with up-regulation of these features in placental tissue of pregnant individuals with male fetuses. Reduced maternal SARS-CoV-2–specific antibody titers and impaired placental antibody transfer were also observed in pregnancies with a male fetus. These results demonstrate fetal sex-specific maternal and placental adaptive and innate immune responses to SARS-CoV-2.

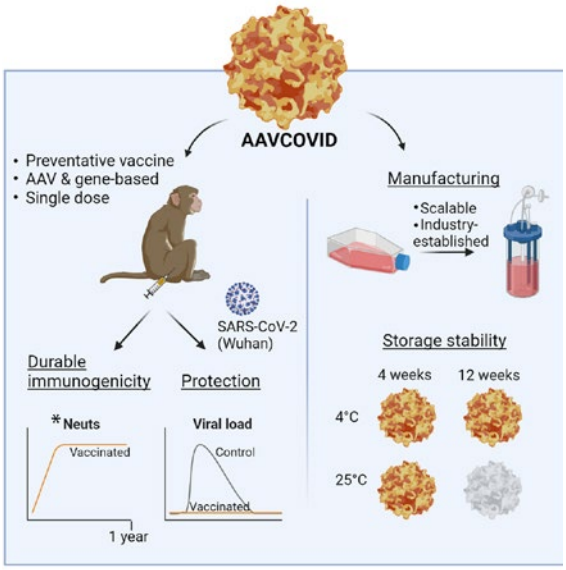


Sexually dimorphic regulation of placental FC receptor gene and protein expression in the setting of maternal SARS-CoV-2 infection.

(A to C) RT-qPCR analyses of male or female placental expression of FCGRT (A), FCGR1 (B), and FCGR3B (C) in placental biopsies from SARS-CoV-2–negative (blue) or SARS-CoV-2–positive (orange) pregnancies (n = 15 to 18 per group). Expression shown is relative to reference genes YWHAZ and TOP1. Bar plots in (A) to (C) indicate means ± SEM. (D to F) Representative immunoblots and quantification of fetal female or fetal male expression of FcRn (D), FCγRI (E), and FCγRIII (F) in placental biopsies from SARS-CoV-2–negative (blue) or SARS-CoV-2–positive (orange) pregnancies (n = 19 per group). Neg and Pos on Western blot designates SARS-CoV-2–negative and SARS-CoV-2–positive pregnancies, respectively. For box and whisker plots in (D) to (F), the box extends from the 25th to 75th percentile, the whiskers depict minimum and maximum, and horizontal line depicts the median. (G) Placental tissue sections from SARS-CoV-2–positive and SARS-CoV-2–negative mothers were stained for FCγRIII (purple), FcRn (red), and placental alkaline phosphatase (PLAP; green), a trophoblast marker, and 4',6-diamidino-2-phenylindole (DAPI, blue). (H) Box and whisker plots showing FCγRIII/FcRn colocalization in placental villi (n = 4 to 6 per group). (I) Placental tissue sections from SARS-CoV-2–positive and SARS-CoV-2–negative mothers were stained for FCγRI (purple), FcRn (red), and PLAP (green), a trophoblast marker, and DAPI (blue). (J) Box and whisker plots showing FCγRI/FcRn colocalization in placental villi (n = 5 to 7 per group). Scale bars, 100 μm (G and I). For box and whisker plots in (H) and (J), the box extends from the 25th to 75th percentile, the whiskers depict minimum and maximum, and horizontal line depicts the median. Differences across groups were assessed by two-way ANOVA followed by Bonferroni's post hoc analyses. *P < 0.05 and **P < 0.01.

Ophthalmology

Department Report



Schematic demonstrating preclinical studies for the AAV-COVID vaccine. AAV-COVID vaccine delivers SARS-CoV-2 spike antigen as a gene via AAV. Results demonstrated protection from viral challenge in non-human primates, durable immunogenicity, cross-reactivity with emerging variants, a scalable production method, and room-temperature stability for 1 month. *Neuts = neutralizing antibody titers.

Adapted from *Zabaleta et al., Cell Host & Microbe, 2021 29:1437-1453.*

JOAN W. MILLER, MD, FARVO, CHIEF

Overview:

The research mission of the Mass Eye and Ear/Mass General 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 an important focus.

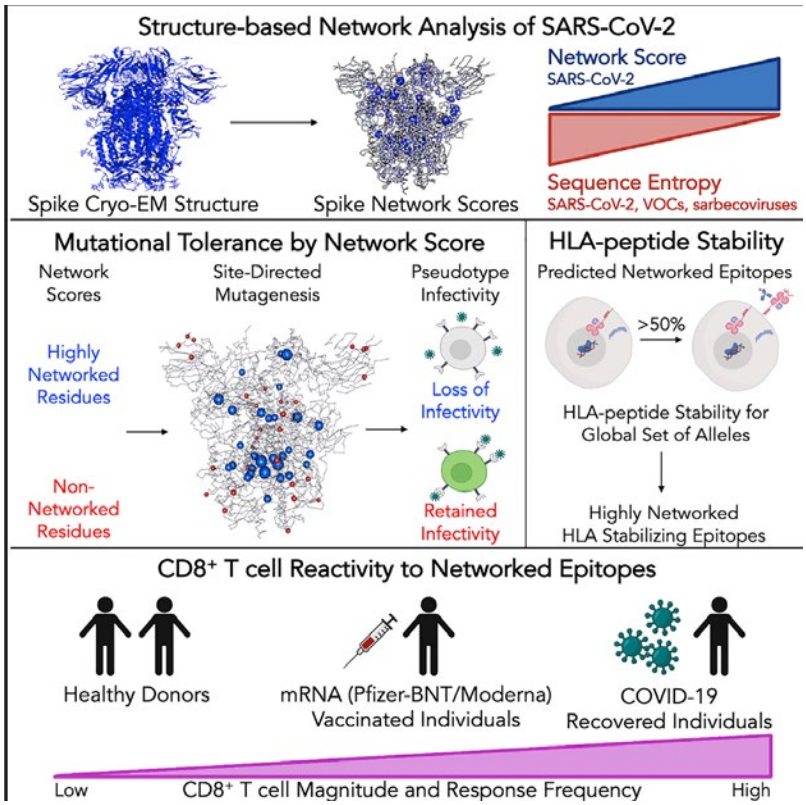
The department's commitment to translational medicine extends into gene-based therapies, with Mass Eye and Ear serving as a lead site for the first-in-human, CRISPR-based gene editing clinical trial for any disease, developed for the treatment of retinal degeneration associated with Leber congenital amaurosis (LCA). A pioneer in big data research, the department recently established the Clinical Data Science Institute, which leverages big data to build stronger health profiles and predictive models that will ultimately improve the diagnosis and treatment of eye diseases. As part of this effort, Mass Eye and Ear is one of four academic groups selected nationwide and awarded unique access to the American Academy of Ophthalmology's Intelligent Research in Sight (IRIS®) Registry. Department faculty are using this comprehensive eye disease and condition database to answer large-scale questions about ophthalmic disease. As we continue to pursue these promising research areas, we are confident that treatment breakthroughs and cures are imminent for many blinding diseases.

Highlighted accomplishments for the Department of Ophthalmology in 2022 are grouped thematically below:

Achievements:

Diversity, Equity, and Inclusion

This past year, we reinforced the department's commitment to diversity, equity, and inclusion (DEI), and launched new initiatives. We recently combined our department-wide efforts into the EYE



Schematic demonstrating structure-based network analysis studies for SARS-CoV-2. Structure-based network analyses identified regions in the SARS-CoV-2 proteome that are mutually constrained and bear CD8+ T cell epitopes that are also conserved in new variants and other SARS-like coronaviruses. These epitopes elicited a stronger CD8+ T cell response in COVID-19 recovered individuals over mRNA vaccine recipients and represent a framework for a broad T-cell-based coronavirus vaccine.

From *Nathan et al., Cell, 2021 184:4401-4413.*

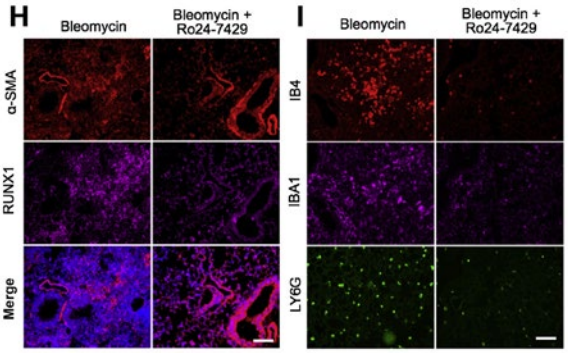
CAN Program. This program is a multi-tiered approach to improve diversity in our faculty ranks by starting with school-aged children and encouraging them to believe "EYE CAN do anything." It has incorporated initiatives like unconscious bias training in the residency selection process, mentorship programs for under-represented college students, combined research, clinical observership, and scholarly work for under-represented medical students, and leadership development for residents, fellows, and faculty.

In the summer of 2021, the department launched the Harvard Ophthalmology Research Scholars Program, conceived and directed by **Joseph F. Arboleda-Velasquez, MD, PhD,** and **James Chodosh, MD, MPH**. This immersive eight-week experience in ophthalmology paired seven first-year medical students from underrepresented in medicine (UIM) and disadvantaged groups with both research and clinical faculty. The scholars conducted research and gained clinical experience in ophthalmology, with the opportunity to publish their work at the end of the program.

In the fall of 2021, the Harvard Retinal Imaging Laboratory Undergraduate Minority Mentorship Program, led by **John B. Miller, MD**, expanded in class size from 16 to 21 participants. In this program, URiM undergraduate pre-medical students at Harvard College are matched with mentors to help support their career development and interest in ophthalmology.

Ophthalmology

Department Report



Antifibrotic and anti-inflammatory effect of RUNX1 inhibition. Immunohistochemistry on paraffin sections of mouse lung with bleomycin-induced fibrosis. Mice treated with RUNX1 inhibitor (Ro24-7429) showed reduced infiltration of inflammatory cells, specifically neutrophils (LY6G) and macrophages (IB4, IBA1).

Adapted from *O'Hare et al., Am J Pathology, 2021 191(7):1193-1208.*

Annual Quality and Outcomes Report

The Mass Eye and Ear/MGH Department of Ophthalmology continues to lead the nation in defining appropriate ophthalmology measures, collecting data, and publishing its quality and outcomes data with complete transparency. This commitment is part of our overarching goal to improve the care and experience of each and every patient. Led by **Alice C. Lorch, MD, MPH**, the eleventh edition of the Quality and Outcomes Report was published in February of 2021. In line with the renewed commitment of the department to focus on DEI, Mass Eye and Ear will begin analyzing our quality and outcome data by race, ethnicity, and other socio-economic determinants when possible to better understand and identify healthcare disparities affecting health outcomes.

COVID-based Research

In the second year of the COVID-19 pandemic, researchers from the Mass Eye and Ear/Mass General Department of Ophthalmology continued to pursue innovative initiatives towards vaccine development and identification of potential treatment-strategies and novel therapeutic targets.

A collaborative international research group led by **Luk Vandenberghe, PhD**, reported that a novel, gene-based COVID-19 vaccine leveraging a unique adeno-associated viral vector (AAV) was highly effective in eliciting neutralizing antibody responses and cellular immunity from a single dose *(Zabaleta et al., Cell Host & Microbe, 2021 29:1437-1453)*. Furthermore, the AAV-COVID vaccine was stable at room-temperature storage conditions for up to one month, facilitating potential future distribution of the vaccine. These research findings represented the first peer-reviewed study demonstrating preclinical effectiveness of the AAV-COVID vaccine and maintenance of peak level immunity for at least 11 months from a single-dose immunization, with currently unpublished longer-term data suggesting even longer immunity.

Previously developed to study human immunodeficiency virus (HIV), structure-based network analysis identifies viral epitopes that are constrained or restricted from mutation. Changes in mutationally constrained epitopes are rare, as they can cause the virus to lose its ability to infect and replicate, essentially rendering it unable to propagate itself. In response to the COVID-19 global pandemic, a team of research collaborators including co-first authors **Elizabeth J. Rossin, MD, PhD**, and **Anusha Nathan**, an MD/PhD student at Harvard Medical School, applied the principles of structure-based network analysis to SARS-CoV-2 to identify 53 mutationally constrained SARS-CoV-2 epitopes that can be recognized by T cells *(Nathan et al., Cell, 2021 184:4401-4413)*. These highly networked epitopes could be used in T cell vaccine development with the potential to provide long-lasting, broad protection against new and emerging variants of SARS-CoV-2 and other SARS-like coronaviruses.

Pulmonary fibrosis can arise from unknown causes, or as a consequence of infections, including SARS-CoV-2. In fact, pulmonary fibrosis develops in an estimated 30% of COVID-19 patients with

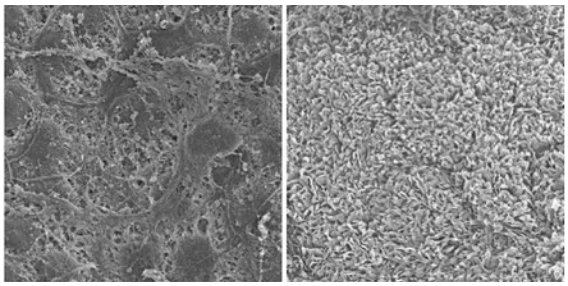
acute respiratory distress syndrome. Research studies from **Leo A. Kim, MD, PhD, Joseph F. Arboleda-Velasquez, MD, PhD,** and colleagues found evidence for involvement of the transcription factor RUNX1 in pulmonary fibrosis. In a preclinical mouse model of bleomycin-induced lung injury, treatment with a RUNX1 inhibitor, Ro24-7429, blunted downstream mediators of fibrosis and inflammation, with preservation of lung structures similar to those in controls *(O'Hare et al., American Journal of Pathology, 2021 191(7):1193-1208)*. Moreover, RUNX1 inhibition reduced expression of ACE2 and FURIN, two proteins that play critical roles in lung uptake of SARS-CoV-2, in mice and human lung epithelial and vascular endothelial cells *in vitro*. These findings suggest that RUNX1 inhibition may provide a promising new approach to treating or preventing lung damage in COVID-19.

Big Data and the IRIS Registry

In 2013, the American Academy of Ophthalmology established the Intelligent Research in Sight (IRIS®) Registry, the nation's first electronic health record-based comprehensive eye disease and condition registry. Clinical researchers can use this 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 72 million unique patients and over two billion unique diagnoses. Mass Eye and Ear was one of the four academic groups selected nationwide and awarded unique access to the IRIS® Registry. Led by co-principal investigators **Joan W. Miller, MD**, and **Alice C. Lorch, MD, MPH**, researchers and clinician scientists in the department have been using this database to answer large-scale questions about ophthalmic disease in the U.S.

A research team led by **Tobias Elze, PhD**, investigated age, gender, and laterality at the onset of various subtypes of retinal vascular occlusions (RVO). Results from this study confirmed increased risk of RVO with age, as well as identifying RVO subtype-specific differences related to gender and right-eye versus left-eye onset preference *(Li et al., Ophthalmology Retina, 2021 May 12: S2468-6530(21)00163-9)*. These findings may improve our understanding of the etiology of different subtypes of RVO and the relationship between the subtypes with structural and anatomical asymmetries of the vascular system.

Nazlee Zebardast, MD, MSc, led a study investigating trends surrounding minimally invasive glaucoma surgery (MIGS) usage in the US, as there is limited evidence around the long-term safety or effectiveness of MIGS. The results of this study identified a significant increase in MIGS use over the studied 6-year period, with the proportion of iStent procedures almost tripling (from 14% to 40%) during the study period *(Yang et al., Ophthalmology Glaucoma, 2021 4(6):558-568)*. These results highlight the need for trials comparing safety and outcome of MIGS versus traditional glaucoma surgical approaches.

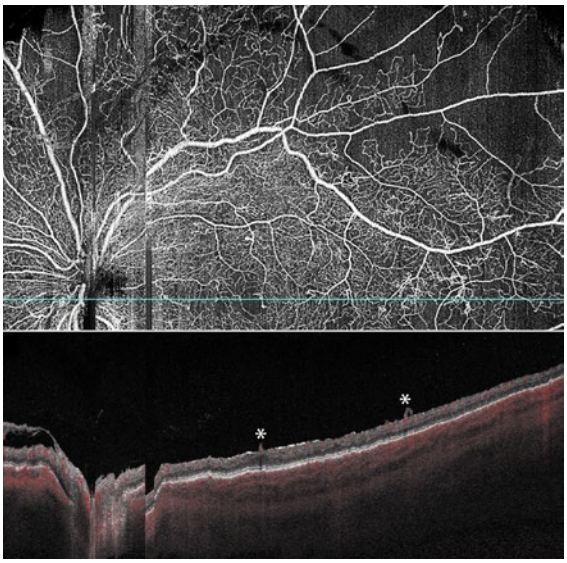


Representative scanning electron microscopy of RP mouse RPE-flat mounts. In the control eye (left panel), RPE cells are largely devoid of microvilli. The contralateral eye of the same mouse received AAV-Nrf2 (right panel). RPE are indistinguishable from wild type mice with a full complement of microvilli processes that interdigitate with photoreceptors.

From *MGH Advances in Motion:* https://advances.massgeneral.org/ophthalmology/journal.aspx?id=2035

Ophthalmology

Department Report



Representative widefield SS-OCTA images of an eye with proliferative diabetic retinopathy showing vitreous hemorrhage during follow-up at 28 days. Whole retina slab (top panel) and Corresponding B-scan (bottom panel). Asterisk (*) indicates presence of a forward neovascularization, which is characterized morphologically by traversing the posterior hyaloid face into the vitreous.

From *Cui et al., Ophthalmology, 2021 128:1312-1324.*

Jia Yin, MD, PhD, MPH, and colleagues analyzed patterns of chemical and thermal ocular burns in the US with the goal of learning more about the incidence and longer-term visual outcomes of ocular burn injuries. Ocular burns are an infrequent yet potentially blinding condition that accounts for 12-22% of all ocular traumas. Thus, the data set in the IRIS database provided opportunity to investigate a large sample size of patient data. Despite the perception that young men are at greater risk, results from this study determined that ocular burns affect both sexes at similar rates, and that the mean age of the patents was older than previously reported *(Anchouche et al., Ocular Surface, 2021 21:345-347)*. Additional analyses found an overall increase in the number of new cases in recent year, and that while ocular burns can result in significant short-term visual morbidity, that the vast majority of cases yield no significant long-term loss of visual acuity or increase in intraocular pressure.

Clinical Trial Updates

In the 2021 Department of Ophthalmology report, we featured two cutting-edge clinical trials—the first in-human use of CRISPR-Cas9 gene-editing and transplantation of cultivated autologous epithelium stem cells (CALEC)—aimed at treating ophthalmic disorders with the goal of improving and restoring vision. In the last year, exciting updates have occurred in both of these exciting and promising areas:

Michael Kalberer became a pioneer in September 2020, as the second person in the world to receive CRISPR-Cas9 gene editing therapy delivered *in vivo* to treat his rare form of an inherited retinal disorder, Leber congenital amaurosis (LCA). CRISPR-Cas9 genome editing therapy targets a genetic mutation in the *CEP290*gene, which causes LCA and results in significant vision loss and potentially blindness. Since receiving gene therapy, Michael has reported some small, but meaningful, changes in his vision, including distinguishing between different colors. Additionally, CRISPR-Cas9 gene therapy has proven to be safe and effective, with no serious adverse events observed in any of the patients treated with the experimental gene therapy. **Eric A. Pierce, MD, PhD**, and **Jason I. Comander, MD, PhD**, leaders of the BRILLIANCE Phase 1/2 clinical trial, suggest these results are very promising, as the early signs of efficacy indicate positive biological activity and potential clinical benefit by improving visual function.

In July 2020, Nick Kharufeh's left eye was severely damaged following a fireworks malfunction at a neighborhood party. After examination, Nick was determined to be a good candidate for CALEC transplantation. **Ula V. Jurkunas, MD**, leader of the team of researchers from Mass Eye and Ear, Boston Children's Hospital, and Dana-Farber Cancer Institute who developed CALEC procedure, took a small biopsy of stem cells from the limbus of Nick's healthy eye and expanded them in tissue culture. The stems cells were grown on a membrane substrate until ready for transplantation. Following extensive removal of scar tissue, Dr. Jurkunas transplanted the CALEC sheet onto the cornea of Nick's damaged eye. Three-weeks following CALEC transplantation, Nick had remarkable improvement in his peripheral and central vision in his damaged eye. The results from Nick's treatment suggest that CALEC transplantation holds great

promise in safely and effectively treating those who have lost vision from corneal burns and infections.

Influences of Polygenic Risk on Glaucoma Penetrance
As the progression of vision loss is relatively slow, glaucoma often does not come to clinical attention until the vision loss is largely irreversible. Glaucoma is a highly heritable disease—to date, over 127 independent common risk variants for primary open-angle glaucoma (POAG) have been identified in multiethnic populations. Of these mutations, the *MYOC* (myocilin) p.Gln368Ter variant is the most common rare mutation among populations of European ancestry. A team of researchers led by **Nazlee Zebardast, MD, MSc**, and **Janey L. Wiggs, MD, PhD**, conducted a population-based study in an effort to understand the true population-wide penetrance and characteristics of glaucoma among individuals with the *MYOC* p.Gln368Ter variant. Results from the study found that one in four individuals with the *MYOC* p.Gln368Ter mutation demonstrated evidence of glaucoma, a substantially higher penetrance than was previously estimated *(Zebardast et al., Ophthalmology 2021 128:1300-1311)*. Further, nearly 70% of these cases went undetected, and a large portion of p.Gln368Ter carriers, including those with disc-defined glaucoma, had intra-ocular pressure within the normal range. These results have important clinical implications by demonstrating that glaucoma occurs across a range of IOPs in this at-risk population and support the usefulness of polygenic risk score (PRS) in optimizing risk stratification for patients with this mutation.

Nrf2 Protein May Slow Retinal Pigment Epithelium Degeneration
A regulator of response to oxidative stress, the transcription factor Nrf2 has been shown to rescue cone photoreceptors and slow vision loss in mouse models of retinal degeneration. Located between the choroid and the retina, the retinal pigment epithelium (RPE) is also damaged in these models and susceptible to oxidative stress. Loss of RPE is common in retinal disease, such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD), and is a key cause of vision loss. A research team led by **David M. Wu, MD, PhD**, and **Constance Cepko, PhD**, modified an adeno-associated virus (AAV)—the same type of vector used in human gene therapy applications—to overexpress Nrf2 selectively in RPE cells to reverse RPE cell loss from oxidative damage. Study results showed that RPE cells receiving AAV-Nrf2 gene therapy appeared structurally similar to those of wild type mice. Furthermore, although the expression of AAV-Nrf2 was localized to the RPE, protection extended beyond to the overlying cone photoreceptors that are critical for central vision *(Wu et al., JCI Insight, 2021 6(2):e145029)*. In untreated RP mice, RPE cells were damaged and the regularly spaced array of cone photoreceptors was disrupted. In RP mice treated by AAV-Nrf2, the RPE layer is intact, which in turn, kept the cone layer intact as well. Visual testing of these mice also showed treatment with AAV-Nrf2 resulted in vision rescue compared to controls. These findings suggest that the RPE plays a potential role in RP retinal degeneration and that Nrf2 gene therapy targeted to the RPE may prevent both anatomical and functional damage.

Genomic-Metabolomic Associations and Age-related Macular Degeneration

While it is well established that genetic risk factors play a role in AMD and genome-wide association studies have linked more than 7,000 single nucleotide polymorphisms (SNPs) to AMD risk, these studies are unable to determine their role in disease development and progression. Metabolites are downstream of the genetic transcription process and are closely related to disease phenotypes. Previous studies from **Deeba Husain, MD, Joan W. Miller, MD**, and collaborators identified distinct plasma metabolomic profiles in patients with AMD compared to controls, and that these profiles differ across different stages of the disease. In follow-up to these studies, the research team analyzed genomic-metabolomic associations in patients with and without AMD, identifying 28 highly significant SNP-metabolite associations corresponding to five metabolites and two genes: *ASPM* and *LIPC (Laíns et al., Ophthalmology Science, 2021 1(1):100017)*. Polymorphisms in the *ASPM* gene were associated with branched-chain amino acids; polymorphisms in the *LIPC* gene were associated with phosphatidylethanolamine metabolites—which are glycerophospholipids. These findings indicate that the *LIPC* gene and the glycerophospholipid metabolic pathway may play an important role in AMD, representing a new potential therapeutic target for this disease.

Widefield Swept-Source Optical Coherence Tomography Angiography (SS-OCTA) Imaging Predicts Vitreous Hemorrhage in Proliferative Diabetic Retinopathy

Traditional imaging methods used to monitor patients with proliferative diabetic retinopathy, such as color fundus photography and fluorescein angiography are limited in their ability to capture the morphology of the retinal vasculature and the relationship with surrounding tissues that may signal development of vitreous hemorrhage, a common vision-threatening result of proliferative diabetic retinopathy. **John B. Miller, MD**, and colleagues have been investigating the use of widefield swept-source (SS) optical coherence tomography angiography (OCTA), which can determine number, location, and morphological features of new blood vessels and their relationship with vitreoretinal interface changes. Through the use of widefield SS-OCTA, the research team identified imaging biomarkers related to neovascularization that may predict occurrence vitreous hemorrhage in patients with proliferative diabetic retinopathy *(Cui et al., Ophthalmology, 2021 128:1312-1324)*. These results suggest that widefield SS-OCTA is a safe and non-invasive tool with the ability to significantly improve clinical management and prognosis of retinal diseases, with clinicians better able to anticipate timely interventions like anti-VEGF injections or laser photocoagulation.

Wearable Devices Reduce Collision Risk

People who have visual impairments are at a significantly higher risk for collision and falls. Commonly used mobility aids like long canes and guide dogs can offer benefits, but come with limitations in effectiveness and costs, respectively. While some electronic

devices are marketed direct-to-consumer and claim to warn wearers of surrounding objects, there is little evidence of their effectiveness in actual daily mobility settings. **Gang Luo, PhD, Shrinivas Pundlik, PhD**, and **Alex Bowers, PhD**, led one of the first randomized-controlled trials to look at the potential benefits of the devices at home and outside of a controlled lab environment. The results of this study found that a wearable computer vision device can reduce collisions for both people who are blind and those who are visually impaired using a long cane and/or guide dog by 37 percent, compared to using other mobility aids alone *(Pundlik et al., JAMA Ophthalmology, 2021 139(9):998-1005)*. These findings provide evidence of the benefit of a collision warning device in reducing contacts in mobility outside of a laboratory setting.

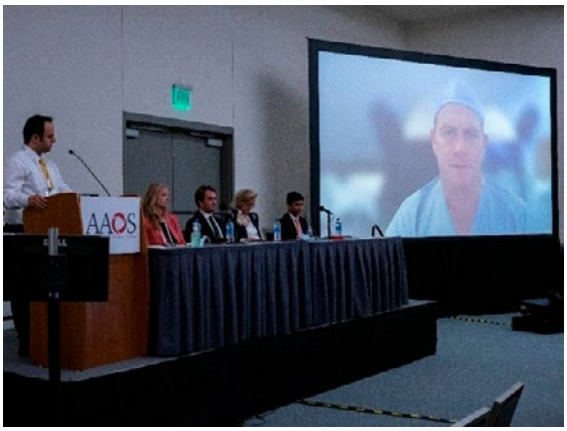
Ophthalmology Innovation

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

- **Kera Therapeutics**, founded in 2020, is focused on the preclinical development of therapeutics for corneal cell loss. Kera exclusively licensed technology from Mass Eye and Ear arising from work led by **Reza Dana, MD, MSc, MPH**.
- **GelMEDIX, Inc.**, founded in 2020, is focused on the preclinical development of novel bioadhesives platform to provide new solutions for ocular drug delivery. GelMEDIX exclusively licensed technology from Mass Eye and Ear and the University of California at Los Angeles arising from work led by **Reza Dana, MD, MSc, MPH**.
- **Affinia Therapeutics** was founded in 2019 to develop next generation AAV gene therapy vectors based on technology from **Luk Vandenberghe, PhD**, of Mass Eye and Ear, and Lonza. Affinia raised $110 M Series B funding in May 2021.
- **Akouos** was founded in 2017 to develop gene therapies to treat hearing loss using technology from **Luk Vandenberghe, PhD**, of Mass Eye and Ear. Akouos was granted Orphan Drug designation by the European Union in August 2021 for their gene therapy to treat otoferlin gene-mediated hearing loss.

Orthopaedics

Department Report



SORG team members and PIs at AAOS March 2021 holding a special symposium on AI in orthopaedic.

MITCHEL HARRIS, MD, CHIEF

Spine

Overview:
The orthopedic spine service is committed to providing outstanding clinical care to the patients of the Massachusetts General Hospital. We have made great strides towards our goal of expanding access to our services through reorganization and hiring of new providers. In addition, we have rekindled efforts towards our goal of establishing a virtual spinal center through collaboration with providers outside of the orthopedic spinal service.

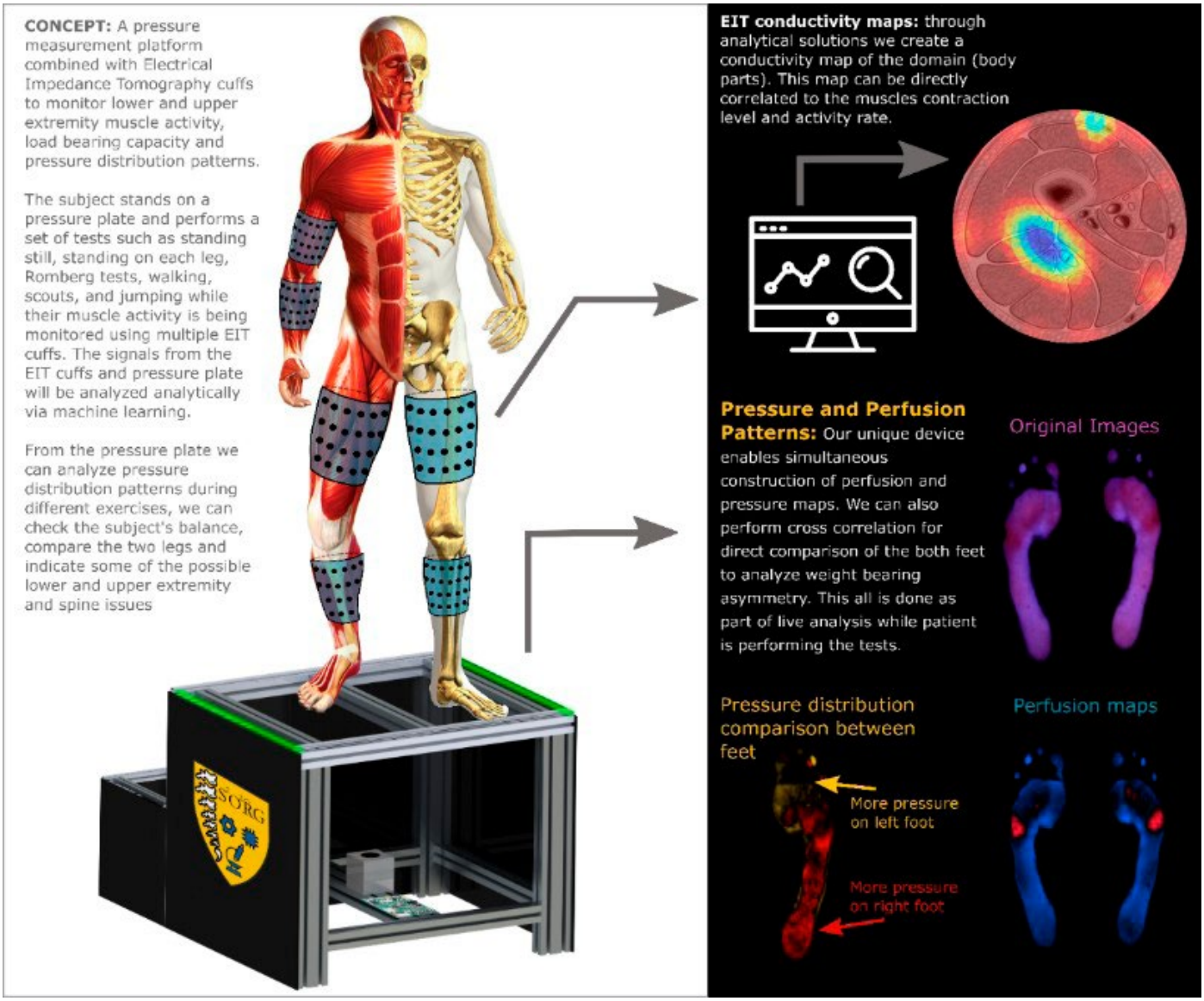
Research is a key component in our effort to provide outstanding clinical care for our patients. Our research program is broad in its reach and its depths reach the fundamental aspects of clinical medicine. The research efforts are guided by clinically relevant questions harvested from the clinical service. Here again, our strength is derived from the integration of clinically relevant questions and close collaboration with scientists from the fields of engineering or biology.

Achievements:

Research Topic: Cannabinoids after Orthopaedic Surgery?
The opioid epidemic is a public health crisis, and it is imperative to find alternative forms of pain management following surgery. Medical marijuana has emerged as an option but its effect on bone healing after orthopaedic surgery is unknown. Harold Fogel, MD from MGH Orthopaedic Spine Surgery and Ara Nazarian, DrSc. Vice-Chair of Research at BIDMC, have teamed up to investigate the effects of cannabinoids after spine fusion in a rat model. Their preliminary research demonstrates that cannabinoids have no adverse effect on the rate of spinal fusion in rats and may in fact have osteoinductive properties for bone healing. Additional studies are underway to further investigate this topic.

Skeletal Oncology Research Group (SORG)

Overview:
The mission of SORG is to improve patient outcomes through integrating concepts of engineering and clinical sciences with artificial intelligence. SORG is a world-renowned research groups that has been responsible for development of several widely used AI-based predictive algorithms in different areas of orthopaedic. SORG is also powering the CPAI and manages the orthopaedic registries of Mass General Brigham. CPAI or Center for Artificial Intelligence is the SORG's sister lab that focuses on development of biomedical devices, wearables, and orthopaedic implants. For the orthopaedic registries MGB, SORG uses its experience in developing AI algorithms to improve quality of care throughout the orthopaedic departments of the MGB.



SORG and CPAI are built on honesty, trust, and diversity. It is crucial for us to create a comfortable and joyful environment for all SORG members that nourishes imagination, creativity, innovation, and scientific courage. This is why in SORG and CPAI with more than 25 engineering and clinical postdocs, research fellows, PhD, master and undergraduate students, we are proud to have a group consisting of people from **12 different countries, 4 races, more than 60% female and 52% international researchers**. We believe in international inter and multi-disciplinary research. Therefore, we are partnering with the Foot and Ankle Research Group (FARIL) at MGH and collaborating with several different labs and universities outside MGH including, Biomedical Engineering Departments at Tufts University, University of Cambridge, MIT, Purdue University, University of Utrecht, Amsterdam UMC, Flinders University, National Taiwan University, University of

Iowa, University of Maryland, and Northeastern University. During 2021 SORG and CPAI members have published more than 40 peer reviewed journal papers, patented 7 ideas, presented their work in world class conferences and symposiums, and have won several awards including the best poster in the engineering and mathematic section of AAAS/Science annual meeting.

Achievements:

AI-based decision support systems: There is no doubt that AI is becoming a great part of healthcare system in the next 10 years. However, asking the right clinical questions and building trust in AI algorithms has been a challenge that we at SORG are trying to answer. We use different approached in AI and statistics such as deep learning, natural language processing, and regular linear and non-linear machine learning algorithms to answer some of the most important questions in orthopaedic. In 2021 our group was invited by several journals and conferences to talk about how we believe the AI in orthopaedic must evolve and what are the gaps and unmet needs in the system and the science. We were invited to publish special issues in *The Spine Journal*, and the *Seminars in Spine Surgery*. We also held a special topic symposium at the American Association of Orthopaedic Surgeons (AAOS), where we discussed different approaches in healthcare AI.

Multi-disciplinary research: In a partnership with the FARIL and the great support from the Orthopaedic Department leadership at MGH we have started a state-of-the-art facility located at Weston, MA to bring the true multi-disciplinary research into life. We have developed an amazing innovative culture by bringing up a large group of more than 50 talented researchers from different areas of clinical sciences, engineering, and computer science together. This partnership is capable of performing research in basic and translational science including, cadaveric research, electromechanical research and development, cellular and molecular research, heavy computing including Finite Element Analysis and Machine Learning. **We are aiming to solve some of the most challenging problems in orthopaedics.**

This effort has been already successful in many fronts. Even with the limitations from the pandemic and the short time since this group has been conceived, we have published several papers, patented multiple devices and wearables, have won several awards and raised more than $750k in donation and $100k from industry. An example of our accomplishment has been development of a novel optical pressure mapping device to assess patient balance and progress assessment. Moreover, we are integrating this device with our recently developed Electrical Impedance Tomography cuffs for muscle and tendon monitoring. Our research on these devices has been one of the top three finalists of the *Science* annual meeting poster competition that will be concluded in Feb 2022.

Orthopaedic Registries: In 2021 SORG was selected by the leadership of the Orthopaedic Departments at MGH and BWH to

manage the orthopaedic registries of the MGB. One of the main focuses of the registries is to integrate with the AAOS national registries. SORG is managing the creation of these large registries for all the hospitals in the MGB system. During the 2021 we have been hard in work for development of the foundation required for development of image and text base machine learning algorithms. In a collaboration with the Laboratory of Medical Imaging and Computation directed by Synho Do, PhD at the Radiology Department we have developed and validated a platform for annotations of image-based healthcare data (MarkIt) and text-based data (an in-house developed software). These software will be used to develop AI-based registries that can interpret image and text-based data.

Oncology

Overview:
The Musculoskeletal Oncology Service is part of the Department of Orthopaedic Surgery, The Sarcoma Care Center and the Cancer Center. The mission of our service is to provide the highest level of clinical and compassionate care to patients with benign and malignant primary bone and soft tissue tumors of the extremities, pelvis, and spine. We also provide care to patients with metastatic disease originating from different primary sites that affects or involves the bone. Our main goal is to do our best to save the lives of patients affected with primary sarcomas of the bone or soft tissue through multidisciplinary care while helping them to maintain function, mobility, and quality of life. The same principles guide our management of patients with benign bone and soft tissue neoplasms. In patients with metastatic disease, our objective is to maintain function, mobility, quality of life, and as much independence as possible.

Achievements:
In terms of research, our mission is to execute studies that will help or improve the clinical care of our patients. Our pillars of research include the following:

- Assessment of the use, radiologic advantages, and impact in the management of oncologic patients with the use of carbon fiber implants or intramedullary polymer devices for bone fixation.
- Evaluation of the use of custom-made implants in orthopaedic oncology to improve function through reconstructions with custom-made implants that are unachievable with traditional reconstructive solutions.
- Standardization of clinical care and research through a comprehensive network for the care of amputees with oncologic and non-oncologic limb loss.
- Creation of AI interactive calculators designed to predict and quantify the prognosis of oncologic patients in terms of overall survival, local recurrence risk, and metastatic disease risk. Through these tools, we aim to help the patients and team of clinicians to make decisions in terms of treatment.

- Translational research with microRNA, using this tool to identify differences at the molecular level between conditions that have a divergent clinical course or presentation. This past year, we researched the differences in terms of microRNA expression in patients with osteosarcoma of the extremities sustaining pathologic fractures vs. those who did not. Currently, we are starting a project for which we received an award from the Musculoskeletal Tumor Society. The focus of this project is to compare the differences between conventional osteosarcoma and extra-skeletal osteosarcoma.
- Projects focusing on the reduction of periprosthetic joint infections with different technologies such as calcium sulfate beads in combination with antibiotics.
- Development of new surgical and multidisciplinary techniques in order to improve local control and reduce local recurrence rates in the treatment of soft tissue and primary bone sarcomas.

Our division had different rewarding accomplishments during this past year. Since January of last year, our division has published 35 articles in peer-reviewed journals with many more in review or on the path to publication. Despite the limitations and cancellations due to COVID-19, the members of our division continue to actively participate in regional, national, and international webinar conferences. The visibility of our division has increased by the recognition of one of our members as one of the 100 most influential Hispanic researchers in the U.S. Our division received an award through the Musculoskeletal Tumor Society (MSTS) mentoring program that is supporting now one of our microRNA translational studies. Through contributions from patients and families, we raised 25,000 USD that are being invested in starting new translational research with the pathology department.

Pediatrics

Achievements:
Adolescent idiopathic scoliosis (AIS) is a complex 3D spinal deformity that affects 2-4% of all populations worldwide and represents 90% of all scoliosis. Treatment options for AIS are limited, with fusion surgery representing the only definitive treatment over the past 50 years for severe and progressive curves. Though fusion surgery is relatively safe and effective in correcting and controlling scoliosis, this comes at great cost, as fusion is maximally invasive and profoundly non-physiologic, eliminating growth, motion, and function of the spine.

Anterior vertebral tethering (AVT) is a minimally invasive alternative to fusion surgery for AIS that offers the potential for definitive scoliosis treatment with preservation of growth, motion and function of the spine. In contrast to a rigid, multi-level instrumented spinal fusion, flexible correction of spinal deformity with AVT may also reduce the future risk of additional surgeries for adjacent segment degeneration. Evidence in support of this novel procedure has steadily accumulated over the past two decades, following an arc of translational research from bench to bedside.

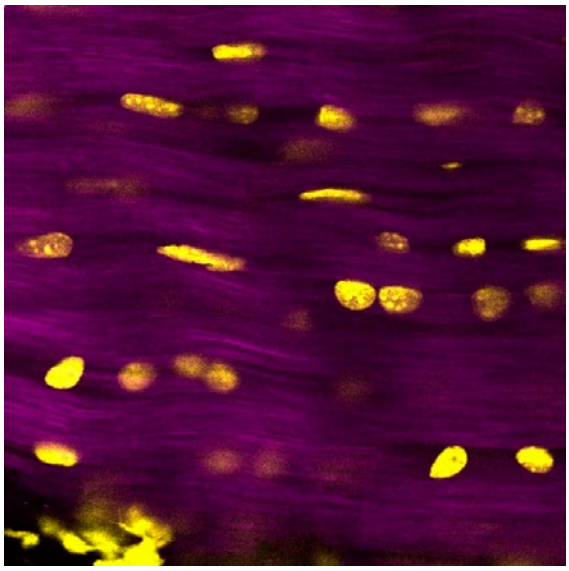
Before performing the first successful, endoscopic AVT procedure for AIS in 2010, we had the benefit of a decade of basic science research and preclinical testing of various fusionless scoliosis surgery strategies, demonstrating their safety and efficacy in creating, correcting and controlling scoliosis in animal models. Since 2010 we led the field in pioneering AVT as a safe and effective treatment alternative to fusion for AIS, culminating in FDA approval of a first-of its-kind tether device in 2019. Our work has not only established appropriate indications for this novel surgery but optimized techniques for performance of this minimally-invasive spinal procedure. Over the past decade we have performed tether procedures on approximately 170 patients with definitive treatment in over 90% and no major medical or surgical complications.

Since performing the first FDA approved AVT procedure in New England in Dec 2019 at MGH, we have established MGH as the busiest scoliosis tether center in the country. The surgical team of Drs. Grottkau, Lawlor and Braun represents a center of excellence for minimally-invasive fusionless scoliosis surgery that provides patients, from around the country, and as far away as Viet Nam, with superior outcomes and minimal complications. Our 10 year tether results were recently presented at the Fifty-sixth Annual Scoliosis Research Society Meeting in St Louis, MO, Sept 2021. This 10 year data, which represents the first series of AVT patients ever treated and the longest follow-up available in any study, is currently being submitted for publication in JBJS. Additional retrospective studies include analysis of correction of the rib prominence after AVT, analysis of correction of trunk shift after AVT, complications and additional procedures 2-12 years after AVT, outcomes in immature vs more mature AIS patients after AVT, and prediction of outcomes using ideal vs acceptable surgical indications. The paper involving analysis of rib prominence correction after AVT has been accepted for presentation at the Pediatric Orthopaedic Society of North America meeting in Vancouver, May 2022.

Though multiple retrospective studies, currently underway at MGH, promise to provide unique insights into this novel procedure, our greatest research effort at this time involves a prospective analysis of all treatment options available for severe and progressive scoliosis in children. This prospective study will not only allow for a better understanding of the ideal indications for tethering and fusion but will help define a more accurate risk profile for each procedure. This prospective study will likely set the stage for a larger, more definitive, multicenter NIH tether study centered at MGH.

Musculoskeletal Genetics & Regenerative Biology Laboratory (MGRBL)

Jenna Galloway, PhD, Director of the MGRBL received the 2021 Stepping Strong Innovator Award in collaboration with Miho Tanaka, MD, for harnessing single cell RNA-sequencing technology for the development of new tendon regenerative medicine strategies. Traumatic injuries to tendons are devastating and impact a patient's mobility and quality of life. Current treatment options are limited



Human hamstring tendon with nuclei visualized with Hoechst (yellow) and collagen fibrils (purple) by second harmonic generation multiphoton imaging (Grinstein, M; Tanaka, M and Galloway, JL).

to repair or reconstruction of the injured structure to restore joint function. However, complete integration of surgical repair and restoration of full function can be clinically challenging as tendon tissues are not capable of complete regeneration and are often limited by degeneration that is associated with the original injury. Tendon regenerative medicine strategies aim to target endogenous stem or progenitor cells to improve repair outcomes or use isolated progenitor cells for tissue engineering approaches to create a better engineered tissue with optimal healing potential. This award will support the use of single cell RNA-sequencing technology to establish a pipeline for the isolation of tendon progenitors and identification of pathways that could be targeted for their activation. Successful completion of these goals would provide a framework for new innovative therapies for tendon and ligament injuries.

Publication: *Tsai SL, Nödl MT, Galloway JL. Bringing tendon biology to heel: Leveraging mechanisms of tendon development, healing, and regeneration to advance therapeutic strategies. Dev Dyn. 2021 Mar;250(3):393-413. doi: 10.1002/dvdy.269. Epub 2020 Nov 21. PMID: 33169466; PMCID: PMC8486356.*

Arthroplasty

Overview:
The MGH Arthroplasty service has a rich heritage. Arthroplasty of the hip is an operation that was pioneered at MGH by Dr. Smith-Peterson, inventor of the Cup arthroplasty, an early approach to hip replacement. Doctor Smith-Peterson's mantle was inherited by Dr. William Harris who developed the most commonly used bearing surface for hip arthroplasties worldwide.

The mission of the Arthroplasty service is to provide outstanding clinical care, perform cutting edge research and maintain the premier teaching service in the Harvard orthopedic community.

This mission is fulfilled daily by talented clinicians who perform almost 1000 arthroplasty surgeries per year, allied scientists who publish over 200 papers annually in peer reviewed journals and teachers who garner awards for guiding medical students, residents, and fellows. While our focus on providing compassionate and competent clinical care reigns foremost in our efforts, we continue to advance the frontiers of knowledge in joint replacement.

Achievements:
Two of our recent efforts have included development of a uniquely modified bearing surface for hip replacements that has been shown to withstand wear for decades, and adoption of robotic-assisted surgery for joint replacement to improve alignment and motion with a further benefit of allowing more quantitative analysis of results. We continue to work collaboratively with industry and national professional organizations to advance and streamline our approaches to meet the highest standards of patient care and technical advancement.

Acute Surgical Management of Vascular Injuries in Hip and Knee Arthroplasties

With an increasing number of total hip and knee arthroplasties being done at surgical centers and vascular surgeons often not immediately available in this setting, it is critical for orthopaedic surgeons to be comfortable with the acute surgical management of vascular injuries. Although they are fortunately uncommon in primary total hip and knee arthroplasties, damage to a major artery or vein can have potentially devastating consequences. Surgeons operating both in a hospital and an ambulatory surgical setting should be familiar with techniques to gain proximal control of massive bleeding because the principles can be helpful in primary and revision arthroplasties. In this study, we review the vascular anatomy around the hip and knee and the surgical management of these potentially catastrophic complications.

Bioengineering Laboratory, Department of Orthopaedic Surgery, Massachusetts General Hospital

At the Bioengineering Laboratory, Department of Orthopaedic Surgery, Massachusetts General Hospital, we have a very long and proud tradition of excellence in innovative research in order to optimize or improve the outcomes of patients with failing hip and knee replacements. The clinical translational research program at the Bioengineering Laboratory was recently highlighted with a total of **42 accepted abstracts** presented at the 2021 Orthopedic Research Society (ORS) Annual Meeting and the American Academy of Orthopaedic Surgeons (AAOS) Annual Meeting.

Our current focus of research is to visualize and quantify the kinematics of the hip and knee prosthesis after it's been implanted in the patients, while the patients perform functional activities including walking, rising from a chair or stair climbing. Utilizing this technology, we have better understood the in-vivo kinematics of total knee arthroplasty. We demonstrated substantial variability in in-vivo kinematics during functional tasks across subjects, alongside the importance of mimicking native knee kinematics in order to optimize patient satisfaction and outcomes. In the case of total hip arthroplasty, we better understood the importance that the position or optimal position to which the hip implant components should be placed may differ from the standard information that was used in the past. We learnt the importance of considering or taking into consideration a much more functional orientation such as when a patient is standing up, which does take into consideration any spine or pelvic movement. In the coming years, we will try to get an even deeper understanding of how we can actually make this information translate into optimizing the component orientation in patients with a total hip arthroplasty.

Besides the analysis of in-vivo hip and knee implant kinematics, the Bioengineering Laboratory has a long-standing track record for clinical research in order to improve patient outcomes. The analysis on patient, implant and surgical factors through retrospective analysis of large patient cohorts has resulted in many peer-review publications in order to share with the community our findings on the latest

treatment strategies for patients with failing hip and knee implant. This work encompasses the multitude of clinically relevant complications for patients with hip and knee arthroplasty including periprosthetic joint infection, aseptic loosening, dislocation and adverse local tissue reactions. The mission of the Bioengineering Laboratory is to continuously improve the treatment algorithms for patients with adverse local tissue reactions in order to optimize patient outcomes.

As the Director of the Bioengineering Laboratory, Dr. Kwon's expertise in metal-on-metal hip replacements has been recognized nationally by many of our academic societies and has led to his selection by the American Academy of Orthopaedic Surgeons (AAOS), American Association of Hip and Knee Surgeons (AAHKS) and The Hip Society to serve as the Chair on the national Metal-on-Metal Taper Corrosion Task Force in 2020. This task force is charged with formulating evidence-based guidelines for all orthopaedic surgeons in North America in treating patients with metal-on-metal taper corrosion hips. The Boards of all three Orthopaedic Societies, namely the American Association of Hip and Knee Surgeons (AAHKS), American Academy of Orthopaedic Surgeons (AAOS), and the Hip Society have ratified the task force's proposed whitepaper. These national Consensus statements have been published in the Journal of Bone and Joint Surgery.

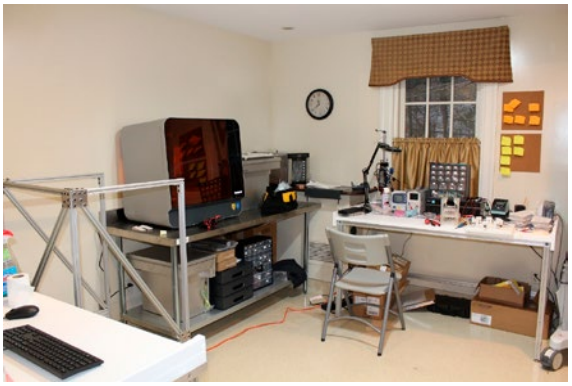
The three stories FARIL lab building, outside view.

Foot & Ankle Research and Innovation Laboratory (FARIL)

Overview:
Foot & Ankle Research and Innovation Lab (FARIL) was formally established in 2019. In 2019 and 2020, the main focus of FARIL was to conduct cadaver studies and retrospective studies while we were working on our visibility, raising funds for studies, increasing the number of researchers, and the quality of research projects. We were benefiting from world-class clinicians and scientists, we had a three-floor building with more than 15,000 square feet capacity to run our center, and we had all the potentials to turn into a big center, but not unleashed. The mission, call it the dream, of FARIL, was to turn into one of the biggest foot and ankle, and even orthopaedic research and innovation centers in the world. Although during the past two years we were struggling with COVID 19, trying hard to fulfill the dream did not stop. In order to cope with the condition, we refined our mission, our focus, and our strategic priorities. We called it "The Vision, The Dream".

In 2021, we refined our mission and strategies. Our focus turned into expanding our fields of interest and our collaborations. We decided not to work as separate silos in the department, but to work as a team. This way, all could benefit from each other's potentials and not do the same thing in parallel which was a waste of resources. Thus, we started fruitful collaborations with the spine, the hand, the arthroplasty, sports. Among these collaborations, the Surgical oncology research group (SORG) team became our tag team. Our strategic priorities then became the following:

1. Opening up our huge lab space for all our collaborators who want to perform a funded study
2. Applying for grants and funding opportunities
3. Increasing the number and the quality of publications, development of innovative devices, and techniques
4. Collaborating with medical companies for study support, fundraising, and manufacturing our inventions and prototype ideas
5. Applying for seed funds, incubator funds, entrepreneurship funds
6. Expanding our fields of interest by including studies on a) Artificial intelligence in orthopaedics, b) social determinants of health, c) using portable ultrasound, d) using the modern weightbearing CT scan, e) using a modern needle arthroscope, f) orthopaedic education via social media and entertainment, g) developing biomedical devices, h) research on patient-reported outcome measurement systems (PROMS)
7. Expanding our collaborations with research centers in the US and around the world starting with the University of Pennsylvania, Toledo, the Netherlands, India, England, and Canada.
8. Increasing the number of researchers including undergraduate students and graduate MDs and related PhDs.



Biomedical engineering room, 3D printer, and engineering devices.

Top: City-wide foot and ankle journal club.
Bottom: Orthopaedic registry weekly meeting.

Achievements:

- **Receiving grants, funds, and being accepted in entrepreneurship programs:** In 2021, we were successful in winning two grants. The first was the grand grant of $50K paid by the American foot and ankle orthopaedic society (AOFAS) on a project entitled “the use of AI in prediction of VTE in foot and ankle patients” and the other was the National Science Foundation (NSF) ICORPS grant of $50K on a project entitled “Automated musculoskeletal image interpretation system, **AMISS**”. The latter was completely paid to the applicants to spend courses of entrepreneurship and conduct customer discovery for one of our AI products. With the help of our great team, we could raise a great number of philanthropic funds as well and we are going to add a clinical research coordinator to our team while we will spend it on expansion and improvements. In 2021, we also received a sum of about $50K from industries for research while we got approval for a sum of more than $100K research funds from two other companies as well. We got accepted to be a part of the Harvard Innovation lab for 3 consecutive semesters to move forward with one of our innovations named “**FIXUS**” which is an AI-based image interpretation system. At the end of the year, we also got selected for the MESH incubator powered by Mass General Brigham and Harvard.
- **Improving the publications, public scientific and educational content:** Compared to 2020 with 12 published peer-reviewed papers, in 2021 our team published 32 peer-reviewed papers in highly visible world-renowned journals. Despite COVID hit, our team has presented more than 20 abstracts in different national and

Orthopaedics

Department Report

A cadaver experiment involving sports surgeon and researchers from FARIL.

Top: sitting space with modern computers for researchers. Bottom: The media recording room for creating videos and podcasts. All the equipment was provided in collaboration with SORG team.

international conferences, virtually or in person. One of our studies became a finalist for Roger Mann Award at AOFAS. We also agreed to take part as guest editors in an upcoming issue of the Asia-pacific foot and ankle surgery journal. We have also submitted more than 5 patents to the MGH patent office in 2021. Currently, we have more than 33 ongoing projects on different aspects of orthopaedic surgery. In collaboration with Harvard Global orthopaedic Collaborative (HGOC), we have developed and published more than 20 educational videos and helped in the coordination of educational conferences for low-income and low-resource African countries. All the videos are available online on the HGOC YouTube channel. All these were done to appreciate the value of the common good and to help democratize knowledge and expertise around the world.

- **Improving the lab facility, equipment, and environment:** Collaborating with other divisions and other departments has helped us a lot in improving our huge lab space. Knee and sports surgeons, spine, foot and ankle, hand and upper extremity, have started or are planning to start conducting their projects there. Becoming tag-teams with the SORG group has led to turning our center from a pure cadaveric lab with a maximum of 2 or 3 persons working there daily into a place that is filled with a minimum of 10 and a maximum of 30 people a day. All researchers, undergraduate and graduated students from around the US and around the world, keen to learn and do research; keen to dream! We also hold journal clubs for foot and ankle surgeons from all around Boston twice a year. This collaboration also brought us different capabilities which are managed by us and SORG team together and all can benefit from them. Now we have a) the processing power for AI projects, b) an engineering room for developing medical devices and prototyping, c) 3D printer, d) virtual reality instruments, e) portable ultrasound and radiographic imaging equipment, f) a cozy conference room and media room for creating videos and podcasts, g) a fully equipped cadaver lab with arthroscopes, need arthroscope, giant freezers, and numerous instruments. Other than the arthroscopy devices and the cadaver lab, all these improvements happened in 2021. The environment of the lab is super friendly, people feel comfortable, and amid the distance and hard commuting, they tend to come there in person to work on their projects almost every day.
- **Improving national and global outreach:** One of our greatest achievements was partaking in the leading team for developing the MGB Orthopaedic Registry system. We started collaborations not only with the MGB system but also outside Massachusetts and the US. To improve the quality of our educational content we got approval from Dr. Nabil Ebraheim, the chief of orthopaedic surgery in Toledo who has millions of followers on social media to use his educational videos in our educational platform called "Orthomind". We are using social media including Instagram (@faril_mgh), LinkedIn (www.linkedin.com/in/faril), twitter (@FARIL_MGH), and a website (faril.mgh.harvard.edu) to promote our work globally. In a research project named "Delta collaboration" we got approval from

Dr. Kennedy from NYU and Dr. Kerkhoffs from Amsterdam, the Netherlands, to collaborate on a project funded by a big orthopaedic company with an amount of $700K. We planned to introduce our first FARIL Ambassador, to teach, train, and conduct inter-central studies with us and with our affiliation in another country. Four of our students got accepted into medical schools around the US who are still working with us remotely. Another couple of researchers from FARIL are working with us from Japan. We have started collaborating with orthopaedic surgeons from Groningen, the Netherlands, and Melbourne, Australia on several AI projects. I the upcoming year, collaborations with London Imperial College will start as well. Via HGOC, as mentioned above, we have conducted educational courses and conferences in Lybia, sub-Saharan Africa, Oman, and Malawi. We have planned to conduct the next one in Africa as well in order to educate providers in limited-resource settings.

Trauma

Overview:
The MGH Orthopaedic Trauma Service is a member of the Harvard Medical School Orthopedic Trauma Initiative, an inter-institutional effort between four core institutions: Massachusetts General Hospital, Brigham & Women's Hospital, Beth Israel Deaconess Medical Center, and Children's Hospital. It is our mission to improve the clinical, functional, and quality of life outcomes of patients with traumatic musculoskeletal injuries through novel and innovative clinical research. The Initiative has a history of successful research collaborations with investigators from many medical and surgical specialties, including emergency medicine, general surgery, endocrinology, physical therapy, biomechanics, and psychometrics.

Achievements:

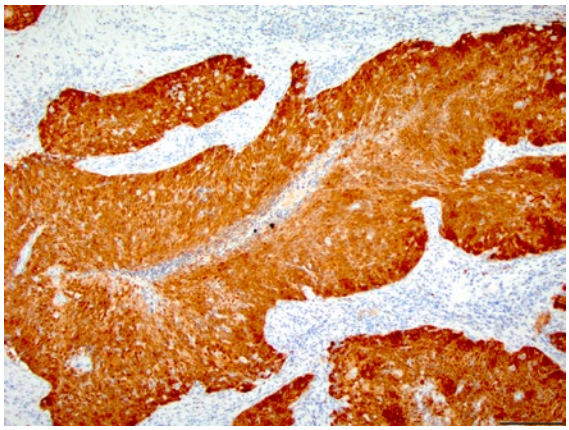
PREVENTion of Clot in Orthopaedic Trauma (PREVENT CLOT): A Randomized Pragmatic Trial Comparing the Complications and Safety of Blood Clot Prevention Medicines Used in Orthopaedic Trauma Patients
Patients who sustain trauma are well known to be at an increased risk for blood clots throughout their body, including fatal Pulmonary Embolisms. There are 6 million fractures treated each year in the United States alone and 2.3 million patients are admitted each year after trauma. Hip and femur fractures specifically are among the most common fractures and are associated with a particularly high risk of blood clots. The primary goal of the study was to compare aspirin versus low-molecular weight heparin (LMWH) (Enoxaparin) as a thromboprophylaxis in patients who sustain a fracture. We have completed enrollment following a 3.5-year enrollment period, and data regarding the outcome is currently being analyzed for publication.

PREPARE: A Pragmatic Randomized trial Evaluating Pre-operative Alcohol skin solutions in FRactured Extremities

More than one million Americans suffer an extremity fracture (broken bone in the arm, leg, or pelvis) that requires surgery each year. Approximately 5% (or 50,000) of surgical fracture patients develop a surgical site infection (SSI), which is twice the rate among most surgical patients and nearly five times the rate among patients undergoing elective orthopaedic surgeries (e.g., joint replacement). Patients who develop a SSI after their fracture fixation surgery experience a long and difficult treatment. The overarching objective of this trial is to compare the effectiveness of iodine povacrylex (0.7% free iodine) in 74% isopropyl alcohol versus 2% chlorhexidine gluconate (CHG) in 70% isopropyl alcohol for the management of extremity fractures that require surgical treatment. The primary outcome for comparison is surgical site infection (SSI), and the secondary outcome is unplanned fracture-related reoperation. We have completed enrollment and following the one-year patient follow-ups, will begin to analyze the outcomes.

Otolaryngology, Head and Neck Surgery

Department Report



Corresponding Research Advance: **Human papillomavirus-associated head and neck cancer blood test shows promise as a test to replace tissue biopsy**

P16 Immunohistochemical staining of an HPV-associated tonsil cancer from a patient enrolled in a prospective study of circulating tumor HPV DNA published in *Clinical Cancer Research*.

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. From advancements in hair cell regeneration, diagnostic tools for head and neck cancer and artificial intelligence algorithms for pediatric patients, we strive to be on the forefront of medicine in order to ensure the best possible care for our patients

Achievements:

Select 2021 Research Highlights:

Artificial intelligence algorithm provides accurate model for diagnosing ear infections

Chronic and acute otitis media, or ear infections, can result in significant consequences if misdiagnosed in children. In a study published in *Pediatrics*, researchers at Mass Eye and Ear attempted to develop a more accurate method of detecting infections in the middle ear using an artificial intelligence algorithm. Researchers who led the study, including **Matthew G. Crowson, MD; Christopher J. Hartnick, MD, MS; Gillian R. Diercks, MD, MPH; Jennifer Setlur, MD;** and **Michael S. Cohen, MD**, developed and trained an artificial intelligence algorithm to accurately predict the presence of middle-ear effusion from a photograph of the eardrum in pediatric patients. The algorithm produced a diagnosis accuracy rate of 84 percent, which was considerably higher than the human-expert, otoscopy-based diagnostic performance reported in previous studies. The high degree of accuracy provides hope for patients, families and health care systems looking for improved point-of-care diagnostic accuracy for ear infections.

Crowson MG, Hartnick CJ, Diercks GR, et al. Machine Learning for Accurate Intraoperative Pediatric Middle Ear Effusion Diagnosis. Pediatrics. Apr 2021; 147(4) e2020034546. doi: 10.1542/peds.2020-034546

Human papillomavirus-associated head and neck cancer blood test shows promise as a test to replace tissue biopsy

Head and neck cancer is a common cancer found around the world. Rates of one type of head and neck cancer known as oropharyngeal cancer have dramatically risen in recent years. This type of head and

neck cancer is driven by Human Papillomavirus (HPV), which now accounts for roughly 75 percent of all cases of oropharyngeal cancers in the United States. Unfortunately, current methods of diagnosing HPV-associated head and neck cancer are imperfect; they are often initially non-diagnostic and may need to be repeated before the final diagnosis is determined. A delay in diagnosis can potentially result in treatment delay. Researchers at Mass Eye and Ear and Mass General Hospital have developed a new blood test, or liquid biopsy, for head and neck cancer associated with HPV that has been shown to be more accurate, faster and less expensive than conventional testing methods. In a recent study published in *Clinical Cancer Research*, lead author **Daniel Faden, MD, FACS**, reported that the new blood test, or liquid biopsy, was more than 98 percent accurate and cost 38 percent less than standard methods. The study used diagnostic modeling to determine whether the biopsy could generate a diagnosis faster than conventional, invasive biopsies. From these models, the researchers determined the possibility of obtaining a diagnosis 26 days faster on average than a conventional tissue biopsy. When researchers combined the liquid biopsy with findings from routine imaging and physical exams to create a fully non-invasive diagnostic approach, diagnostic accuracy remained significantly superior to standard approaches. The study is the first time a non-invasive approach has been tested as a reliable diagnostic tool at the time of presentation for HPV-associated head and neck cancer.

Siravegna G, O'Boyle CJ, Varmeh S, et al. Cell free HPV DNA provides an accurate and rapid diagnosis of HPV-associated head and neck cancer. Clin Cancer Res. Dec 2021; DOI: 10.1158/1078-0432.CCR-21-3151

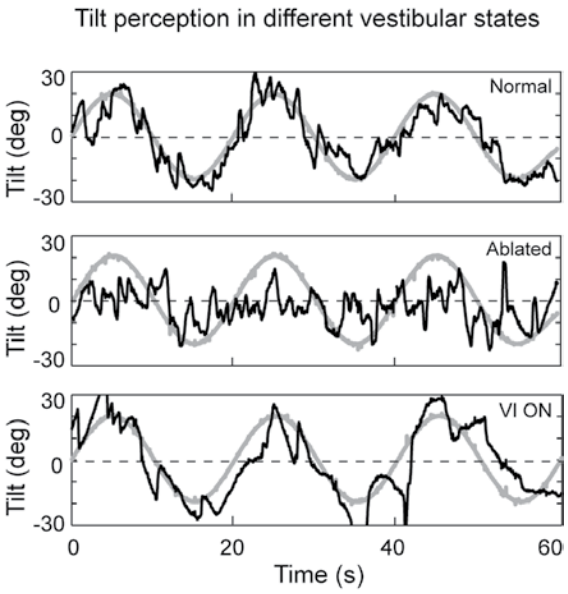
Improving spatial orientation in animals with severe vestibular damage using a vestibular implant

Patients with vestibular damage experience impaired vision, spatial perception and balance. Such symptoms are often irreversible. However, vestibular implants have the potential to improve the perception of head orientation in patients with vestibular damage. In a study published in *The Journal of Neuroscience*, a team of researchers led by **Richard F. Lewis, MD**, and **Faisal Karmali, PhD**, tested whether the normal balance signals carried in the vestibular nerve could be mimicked with a canal vestibular implant (VI) after damage to the normal vestibular organs had occurred in the inner ear. Using a subjective visual vertical task, Drs. Lewis and Karmali found that normal subjects accurately sensed the orientation of the head relative to gravity during dynamic tilts. The orientation degraded following bilateral vestibular damage and improved when the canal VI was used. Findings from the study are a promising sign for the use of canal VIs in human patients.

Karmali F, Haburcakova C, Gong W, Della Santina CC, Merfeld DM, Lewis RF. An Implanted Vestibular Prosthesis Improves Spatial Orientation in Animals with Severe Vestibular Damage. J Neurosci. 2021 Apr 28; 41(17):3879- 3888. doi: 10.1523/JNEUROSCI.2204-20.2021

Otolaryngology, Head and Neck Surgery

Department Report



Corresponding Research Advance: **Improving spatial orientation in animals with severe vestibular damage using a vestibular implant**

Perception of the earth-vertical in a non-human primate during dynamic, sinusoidal tilt about the roll (naso-occipital) axis in three vestibular states—normal (top), following ablation of both vestibular systems in the inner ear (middle), and in the ablated state when the implanted vestibular prosthesis (VI) is activated in the three semicircular canals of one ear (bottom). Illustrated are the actual tilt of the head (black traces) and the perceived tilt of the head (grey traces). Tilt perception was quantified using a subjective visual vertical (SVV) task that was derived from the SVV test commonly used in human subjects (where the aim is to align a light bar parallel to the perceived direction of gravity)

Norrie disease protein deemed essential for cochlear hair cell maturation; offers promising clues for hearing restoration

Norrie disease is an inherited disorder caused by more than 100 different mutations to the Ndp gene. The disease is rare, but causes deafness, blindness and intellectual disability in males. The disorder also holds a major clue for treating irreversible hearing loss, as discovered by a team of researchers led by **Albert Edge, PhD**. Working with research fellow Yushi Hayashi, MD, PhD, Dr. Edge and his team analyzed the downstream expression of the Ndp gene in mice and found that the gene plays a vital role in the maintenance and survival of hair cells in the cochlea, which are responsible for detecting sound. Published in *Proceedings of the National Academy of Sciences of the United States of America,* the study revealed two possible avenues for preventing deafness in mice with a mutated Ndp gene: forced activation of Ndp by secreting the gene's protein directly from cells adjacent to hair cells, or increasing the level of ß-catenin, the intracellular effector of Wnt signaling, to promote hair cell differentiation. The new discoveries may lead to promising treatment targets for this incurable disease and other forms of profound hearing loss.

Hayashi Y, Chiang H, Tian C, Indzhykulian A, Edge A. Norrie Disease Protein is Essential for Cochlear Hair Cell Maturation. Proc Natl Acad Sci U S A. Sept 2021; 118(39) e2106369118. doi: 10.1073/ pnas.2106369118

Promising method for delivering neurotrophic activity into the inner ear

For years, researchers have targeted a group of proteins called neurotrophins as a potential treatment for irreversible sensorineural hearing loss. These proteins can stimulate spiral ganglion neurons (SGNs) in the inner ear and have the potential to promote regeneration of the synapses connecting SGNs with inner hair cells (IHCs). Finding a way to deliver these proteins for extended times into the inner ear, however, has been a challenge for researchers. **David H. Jung, MD**, PhD, FACS, and his colleagues demonstrated that a small-molecule analogue of Neurotrophin-3 (NT-3) can stimulate SGNs *in vitro*. In a study published in *Frontiers in Cellular Neuroscience*, the researchers coupled this small-molecule agonist with a bisphosphonate compound designed to reversibly bind to the bone around the cochlear. The researchers showed that the paired complex was highly active in regenerating synapses between SGNs and inner-hair cells. This approach ultimately aims to use cochlear bone as a reservoir for the extended slow release of NT-3 into the inner ear. Findings from the study support the potential of bisphosphonate conjugation as another feasible strategy to deliver neurotrophic agents to SGNs.

Kempfle JS, Duro MV, Zhang A, Amador CD, Kuang R, Lu R, Kashemirov BA, Edge AS, McKenna CE and Jung DH (2021) A Novel Small Molecule Neurotrophin-3 Analogue Promotes Inner Ear Neurite Outgrowth and Synaptogenesis In vitro. Front. Cell. Neurosci. 15:666706. doi: 10.3389/ fncel.2021.666706

Additional 2021 Highlights:

Discovery of HIC1 may lead to pathway for hearing loss reversal
Over 400 million people worldwide live with sensorineural hearing loss. This type of hearing loss occurs most often when sensory hair cells, the cells responsible for hearing, degenerate as a result of aging, infections, medications or exposure to loud noises. There is no spontaneous regeneration of the missing hair cells in mammalian ears—once lost, irreversible hearing impairment ensues. **Dunia Abdul-Aziz, MD**, and **Albert Edge, PhD** used a combination of genetic tools with inner ear organoid technology to uncover a promising pathway involved in hair cell regeneration. In a study published in *Stem Cell Reports*, they reveal a new molecular player called "hypermethylated in cancer 1," or "HIC1," that hinders the regeneration of hair cells in mammals. The researchers used genetic tools to limit the expression of HIC1 in cochlear organoids and observed enhancement in the expression of ATOH1, an essential gene for hair cell development. Their approach promises to help identify and test new genes and pathways important in hair cell development and regeneration. Their findings also establish a framework by which other molecular pathways can be studied.

Abdul-Aziz, D, Hathiramani, N, Phung, L, Sykopetrites, V, Edge, A. HIC1 Represses Atoh1 Transcription and Hair Cell Differentiation in the Cochlea. Stem Cell Reports. 2021 16(4), 797–809. doi: 10.1016/j. stemcr.2021.02.022

Downregulation of molecular factors for improvement of idiopathic subglottic stenosis
Idiopathic subglottic stenosis (iSGS) is a progressive disease characterized by life-threatening airway narrowing. Although the molecular underpinnings of the disease are unknown, previous reports show that subglottic serial intralesional steroid injections (SILSIs) can improve clinical outcomes, which suggests a steroid-sensitive pathway in iSGS. In an attempt to identify steroid-sensitive profibrotic drivers, a prospective study was led by **Ramon A. Franco, Jr., MD**, to determine changes in profibrotic markers during SILSI. Seven patients newly diagnosed with iSGS were recruited for the study and had their subglottic biopsies before and after SILSI treatments evaluated for histologic and molecular markers. Findings from the study were published in *The American Journal of Pathology* and revealed that SILSI counteracted a dysregulated axis of transforming growth factor ß1, cellular communication factor 2 and matrix metalloprotease 9, all of which are involved in iSGS development.

Treviño-Villarreal JH, Reynolds JS, Langston PK, Thompson A, Mitchell JR, Franco RA. Down-Regulation of a Profibrotic Transforming Growth Factor-ß1/Cellular Communication Network Factor 2/ Matrix Metalloprotease 9 Axis by Triamcinolone Improves Idiopathic Subglottic Stenosis. Am J Pathol 2021; 191(8):1412-1430. doi: 10.1016/j. ajpath.2021.05.013

Severe sinonasal inflammation linked to changes in brain activity
A study published in *JAMA Otolaryngology–Head and Neck Surgery* reported that changes in brain activity, specifically the neural networks that modulate cognition, introspection and response to external stimuli, were reported in patients with severe sinonasal inflammation. Several meaningful advances in the understanding of the cognitive effects of severe sinonasal inflammation had been made in recent years, but never before had there been an investigation of a possible link between the condition and higher-order neural processing. Authors of the study included **Benjamin Bleier, MD, FACS**, the study's lead author, and **Kristina Simonyan, MD, PhD, Dr med**. The study reported that participants with severe sinonasal inflammation showed decreased brain connectivity within a major functional hub with a central role in modulating cognition. Twenty-two patients with severe sinonasal inflammation and 22 healthy controls were included in the analysis. Despite the brain-activity changes, however, no significant deficit was seen in the behavioral and cognitive testing of study-group participants, though it may be plausible that untreated sinusitis can lead to more clinically meaningful symptoms.

Jafari A, Xavier LDL, Bernstein J, Simonyan K, Bleier B. Association of Sinonasal Inflammation With Functional Brain Connectivity. JAMA Otolaryngol Head Neck Surg. 2021; 147(6):534-543. doi:10.1001/jamaoto.2021.0204

Sleep disorders tally $94.9 billion in health care costs each year
Approximately 30-to-40 percent of adults in the Unites States have at least one sleep disorder and the direct healthcare costs of these disorders have long been left untallied. In a study published in the Journal of *Clinical Sleep Medicine*, **Neil Bhattacharyya, MD, MA, FACS**, and **Phillip A. Huyett, MD**, examined the increased health care utilization and expenditures associated with sleep disorders using national databases. Their study found that individuals with sleep disorders had eight additional office visits, 18 additional prescriptions and $7,000 greater total costs per year when compared to similar patients without sleep disorders. Overall, the study estimated that the direct health care costs of sleep disorders in the U.S. were $94.9 billion. Furthermore, sleep disorders are woefully underdiagnosed, as highlighted by a separate study published by Drs. Huyett and Bhattacharyya in *The Laryngoscope*, and therefore so are the costs attributed to the disorders in such studies.

Huyett P, Bhattacharyya N. Incremental Health Care Utilization and Expenditures for Sleep Disorders in the United States. J Clin Sleep Med. 2021 May 4. doi: 10.5664/ jcsm.9392. Epub ahead of print.

Huyett P, Siegel N, Bhattacharyya N. Prevalence of Sleep Disorders and Association With Mortality: Results From the NHANES. 2009-2010. Laryngoscope. 2021 Mar;131(3):686- 689. doi: 10.1002/lary.28900

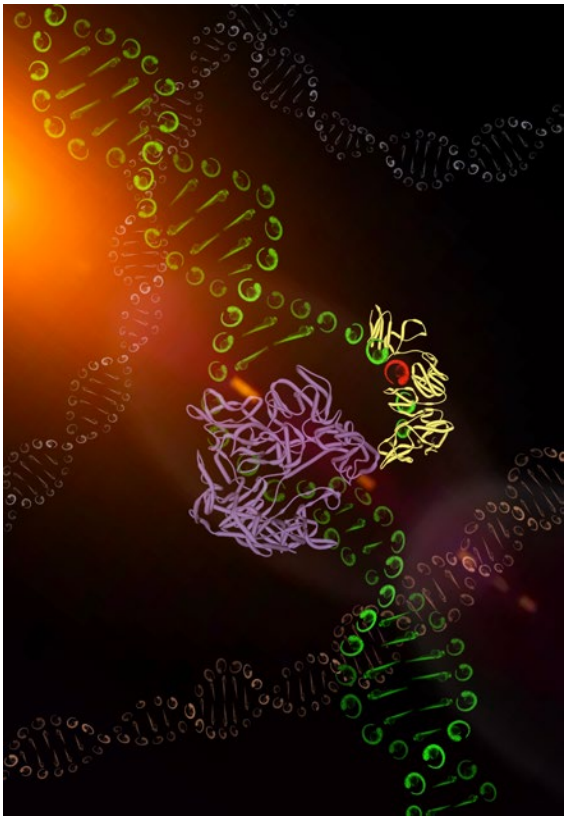
Sudden deafness reveals link to hidden hearing loss
Sudden sensorineural hearing loss (SNHL), or sudden deafness, is one of the most common emergencies seen by ENT physicians. While hearing thresholds may recover in some patients, its cause and lasting

effects remain uncertain. In a study published in *Ear and Hearing*, a team of researchers led by **Stéphane Maison, PhD, CCC-A**, examined the audiologic profiles of 166 patients at Mass Eye and Ear who had partially or fully recovered from a case of sudden SNHL. The team found that patients with hearing thresholds that completely recovered from the condition had poorer speech intelligibility performance than predicted by their audiogram. Dr. Maison and his co-authors also found evidence that recovery in hearing sensitivity depended on hearing loss configuration. The study received "Editor's Choice" honors from the publication and has led researchers to suspect hidden hearing loss as a possible explanation for the lack of clarity in speech discrimination reported by some patients following their recovery from sudden SNHL.

Okada M, Parthasarathy A, Welling DB, Liberman MC, Maison S. Idiopathic Sudden Sensorineural Hearing Loss: Speech Intelligibility Deficits Following Threshold Recovery. Ear and Hearing. July/August 2021; 42:782-792. doi: 10.1097/AUD.0000000000000987

Pathology

Department Report



Schematic rendering of the CRISPR prime editor 2 (PE2) protein interacting with DNA represented using photos of zebrafish embryos. PE2 consists of a Cas9 nickase (shown in purple) and a reverse transcriptase (shown in yellow). In this depiction, a single nucleotide (depicted by a red fluorescent zebrafish embryo) is the target of editing. Image courtesy of Weiting Zhang and Joanna Yeh *(Petri et al., Nature Biotechnology, in press).*

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 and activity of MGH Pathology and is complemented by productive clinical research activities. As a result, MGH Pathology provides an exciting stage for basic and translational research.

MGH Pathology Research has grown considerably over the past two decades, building an exceptional and well-funded group of basic science and translational investigators with particular strengths and expertise in cancer biology, animal modeling, bioinformatics, genomics, and epigenetics as well as with single-cell and genome editing technologies. 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 through our Center for Integrated Diagnostics. We believe that these efforts will help to ensure that MGH Pathology faculty remain at the forefronts of their fields, enabling them to continue advancing our understanding and diagnosis of human diseases.

Achievements:

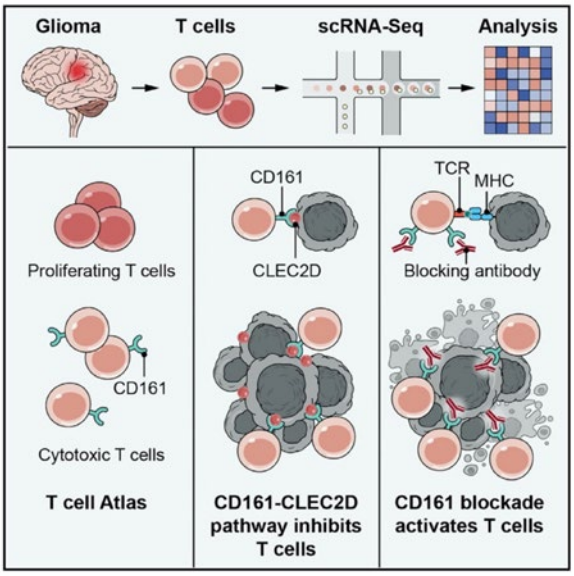
CRISPR prime editing with ribonucleoprotein complexes in zebrafish and primary human cells
Petri K, Zhang W, Ma J, Schmidts A, Lee H, Horng JE, Kim DY, Kurt IC, Clement K, Hsu JY, ***Pinello L****, Maus MV,* ***Joung JK*****, Yeh JJ*. Nat Biotechnol., in press.*

CRISPR prime editors (PEs) can induce essentially any small genetic alteration in a range of cell types and organisms. PEs have been delivered previously using DNA or RNA vectors but the large size of the PE2 protein required for editing presents challenges for use of viral vectors or messenger RNA. Delivery using RNPs offers the potential for fewer off-target effects and avoids genomic integration of vector DNA. Here we show that PEs delivered as ribonucleoprotein (RNP) complexes can efficiently induce somatic and germline transmissible mutations in zebrafish. Our analysis of prime editing outcomes in zebrafish also revealed unintended insertions, deletions and prime editing guide RNA scaffold incorporations. We also show that PE

RNPs can introduce desired edits with high efficiencies in both transformed HEK293T and primary human T cells. In sum, our findings should facilitate the use of PEs in a wide variety of experimental systems and therapeutic applications.

Inhibitory CD161 receptor identified in glioma-infiltrating T cells by single-cell analysis.
Mathewson ND, Ashenberg O, Tirosh I, Gritsch S, Perez EM, Marx S, Jerby-Arnon L, Chanoch-Myers R, Hara T, Richman AR, Ito Y, Pyrdol J, Friedrich M, Schumann K, Poitras MJ, Gokhale PC, Gonzalez Castro LN, Shore ME, Hebert CM, Shaw B, Cahill HL, Drummond M, Zhang W, Olawoyin O, Wakimoto H, Rozenblatt-Rosen O, Brastianos PK, Liu XS, Jones PS, Cahill DP, ***Frosch MP****, Louis DN, Freeman GJ, Ligon KL, Marson A, Chiocca EA, Reardon DA, Regev A,* ***Suvà ML****, Wucherpfennig KW*. Cell. 2021;184(5):1281-1298.e26. PMID: 33592174*

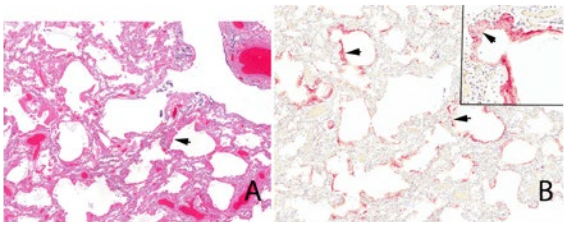
T cells are critical effectors of cancer immunotherapies, but little is known about their gene expression programs in brain tumors. In our study, we leveraged single-cell RNA sequencing (scRNA-seq) to chart the gene expression and clonal landscape of tumor-infiltrating T cells across 31 patients with glioblastoma and IDH-mutant glioma. We identify potential effectors of anti-tumor immunity in subsets of T cells that co-express cytotoxic programs and several natural killer (NK) cell genes. Analysis of clonally expanded tumor-infiltrating T cells further identifies the NK gene KLRB1 (encoding CD161) as a candidate inhibitory receptor. CLEC2D, the ligand for CD161, is a surface molecule expressed by myeloid cells and malignant cells, suggesting a ligand-receptor pathway for immunotherapy. Accordingly, genetic inactivation of KLRB1 or antibody-mediated CD161 blockade enhances T cell-mediated killing of glioma cells in vitro and their anti-tumor function *in vivo*. KLRB1 and its associated transcriptional program are also expressed by substantial T cell populations in other human cancers. Our work provides an atlas of T cells in gliomas and highlights CD161 and other NK cell receptors as immunotherapy targets.



Single-cell analysis charts expression, clonal landscape of glioma-infiltrating T cells. T cells with a cytotoxicity program express multiple NK cell receptors. The NK cell receptor CD161 interacts with its ligand CLEC2D expressed by cancer cells and myeloid cells. This interaction inhibits killing of glioma cells by T cells. CD161 blockade (by CRISPR knockout or by a blocking antibody) activates cytotoxic T cells and enhances tumor cell killing *(Mathewson et al., Cell 2021).*

Temporal and spatial heterogeneity of host response to SARS-CoV-2 pulmonary infection.
Desai N, Neyaz A, Szabolcs A, Shih AR, ***Chen JH****, Thapar V, Nieman LT, Solovyov A, Mehta A, Lieb DJ, Kulkarni AS, Jaicks C, Xu KH, Raabe MJ, Pinto CJ, Juric D, Chebib I,* ***Colvin RB****, Kim AY, Monroe R, Warren SE, Danaher P, Reeves JW, Gong J, Rueckert EH, Greenbaum BD, Hacohen N, Lagana SM,* ***Rivera MN****, Sholl LM,* ***Stone JR****, Ting DT,* ***Deshpande V****. Nat Commun. 2020;11(1):6319. PMID: 33298930*

The temporal and spatial relationship of SARS-CoV-2 pulmonary infection and severity of disease is not fully understood. Here, we showed analysis of autopsy specimens from 24 patients who succumbed to SARS-CoV-2 infection using RNA in situ hybridization (RNA-ISH), immunohistochemistry, and digital spatial transcriptomics



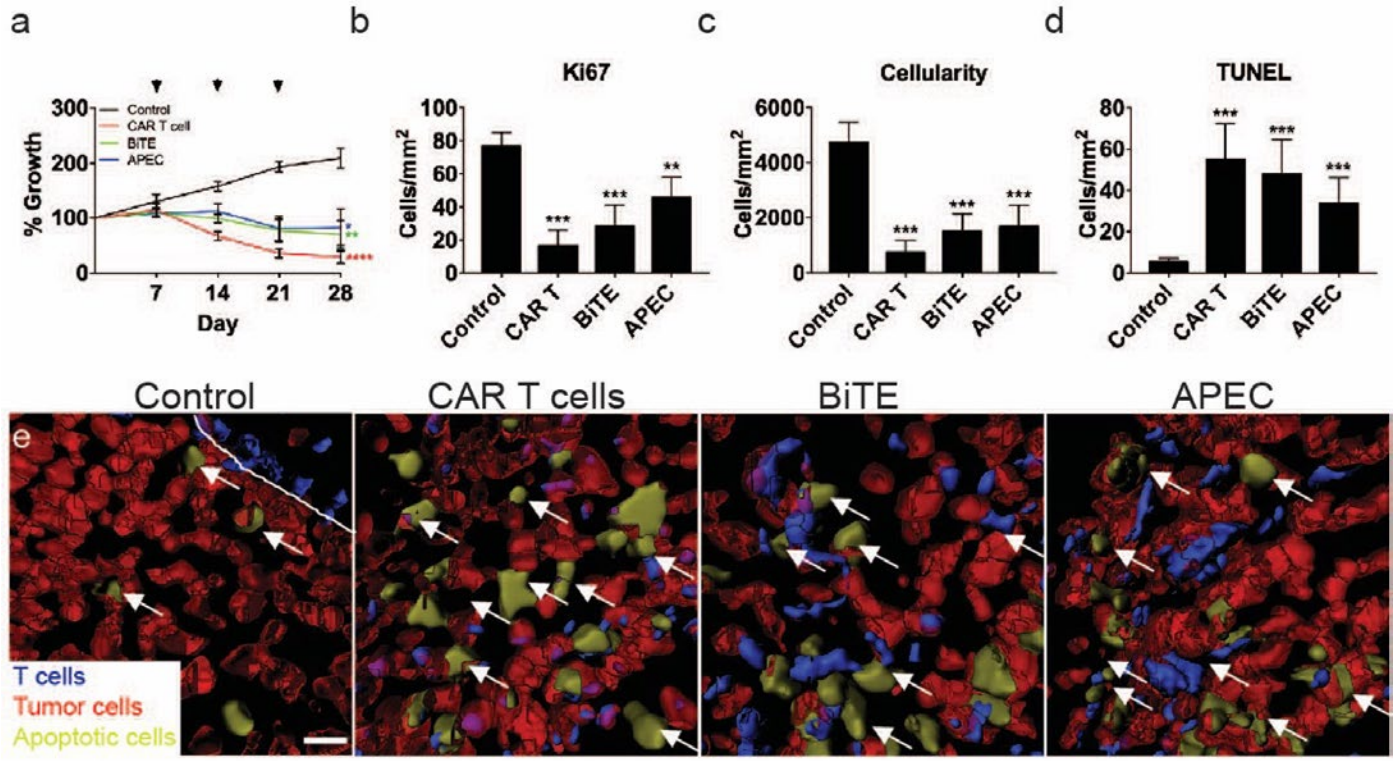
Autopsy lung specimen from a patient with SARS-CoV-2 infection hematoxylin and eosin stain showing diffuse alveolar damage with hyaline membranes (arrow) (Panel A). An RNA in-situ hybridization stain for SARS-CoV-2 shows abundant viral RNA (arrow) within hyaline membranes (Panel B and Panel B inset). Most of the virus (red) in SARS-CoV-2 pneumonia is detected within hyaline membranes presumably representing cytopathic destruction of normal lung cells. Virus is also seen in pneumocytes and immune cells (not shown). The presence of the virus was confirmed on sequential slides by quantitative reverse transcriptase polymerase chain reaction using SARS-CoV-2 probes specific for the nucleocapsid (N) gene and by Total RNA-seq. *(Desai et al.,Nature Communications 2020).*

to characterize inter-patient and intra-patient heterogeneity of pulmonary virus infection. There was a spectrum of high and low virus cases associated with duration of disease. High viral cases had high activation of interferon pathway genes and a predominant M1-like macrophage infiltrate. Low viral cases were more heterogeneous likely reflecting inherent patient differences in the evolution of host response, but there was consistent indication of pulmonary epithelial cell recovery based on napsin A immunohistochemistry and RNA expression of surfactant and mucin genes. Using the NanoString GeoMx digital spatial profiling platform, we found significant intra-pulmonary spatial heterogeneity of interferon response genes with the presence of SARS-CoV-2 virus.

Single-cell imaging of T cell immunotherapy responses *in vivo*.

Yan C, Yang Q, Zhang S, Millar DG, Alpert EJ, Do D, Veloso A, Brunson DC, Drapkin BJ, Stanzione M, Scarfò I, Moore JC, Iyer S, Qin Q, Wei Y, McCarthy KM, Rawls JF, Dyson NJ, Cobbold M, Maus MV, ***Langenau DM****. J Exp Med. 2021;218(10):e20210314. PMID: 34415995*

T cell immunotherapies have revolutionized treatment for a subset of cancers. Yet, a major hurdle has been the lack of facile and predicative preclinical animal models that permit dynamic visualization of T cell immune responses at single-cell resolution *in vivo*. We have developed an optically clear immunocompromised zebrafish that can robustly engraft human T lymphocytes and cancer cells. These animals are especially suitable for preclinical modelling of T cell adoptive therapies, including chimeric antigen receptor T cells, bispecific T cell engagers (BiTEs), and antibody peptide epitope conjugates (APECs) at single-cell resolution. Our work uncovered important differences in the kinetics of T cell infiltration, tumor cell engagement, and killing between these immunotherapies and established early endpoint analysis to predict therapy responses. We also established EGFR-targeted immunotherapies as a powerful approach to kill rhabdomyosarcoma muscle cancers, providing strong preclinical rationale for assessing a wider array of T cell immunotherapies in this disease.



EGFR-specific T cell immunotherapies for the treatment of RMS. a-d, rag2?/?, il2rga-/- animals were engrafted with human EGFP+ RMS cells and then co-administered weekly with i) control EGFR antibody along with human CD8+ T cells, ii) EGFR CAR T cells, iii) EGFR/CD3 BiTE with CD8+ T cells, or iv) EGFR APEC with CMV-specific T cells. Relative growth assessed by whole animal imaging with dosing noted by arrows (a). Quantification of proliferation by Ki67 IHC (b), cellularity based on H&E staining (c), and cell apoptosis by TUNEL (d) at 28 dpt. (b-d). e-i, 3D modelling of T cell immunotherapy responses in live animals engrafted with mCherry+/ZipGFP-Casp3+ human RMS cells into the periocular muscle imaged at 11dpt. Control treated T cells (left, e) and T cell immunotherapy (right panels, e). Arrows denote representative examples of apoptotic tumor cells. **p<0.01, ***p<0.001, ****p<0.0001, Student's t-test. Scale bar equals 10 μm (e). Error bars ± STD (a-d, f-i). *(Yan et al., Journal of Experimental Medicine 2021).*

Pediatrics

Department Report

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 Mass General Hospital for Children (MGHfc) recognizes the challenges and opportunities for child health research dictated by the changing social, economic and health care policy landscape in the US, including the shift toward Precision Medicine. Across the Department, our research integrates multidisciplinary clinical and scientific expertise with local, regional, national and international collaborations.

With the appreciation that biological events beginning during gestation and continuing into childhood can strongly influence disease onset during childhood and beyond, we 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. Finally, we have established a Pediatric Biobank that has collected biospecimens from more than 500 children exposed or affected by SARS-CoV2 infection, including its complication of Multiorgan Inflammatory Syndrome (MIS-C). Over the past year the research faculty has continued to pursue all of their major research efforts, and in addition we have maintained a very active portfolio of COVID-19-related research We are currently focused on the following specific research missions:

Allergy & Immunology

The research mission for Pediatric Allergy & Immunology is to partner with our patients to advance new therapeutic, preventative and educational interventions for the millions of children affecting by the spectrum of allergic disease including both IgE- and non IgE-mediated forms of food allergy and asthma. A major research focus within the Division is on the mechanisms of immune-mediated food hypersensitivities including IgE-mediated food allergy, chronic gastrointestinal inflammatory diseases related to food allergy such as eosinophilic esophagitis and allergic proctocolitis. To advance this

research effort, The Food Allergy Center at Massachusetts General Hospital (FAC@MGH) was established in 2010 as a multi-disciplinary research and clinical care virtual center with the recruitment of 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 leads our program on Prevention, Education and Advocacy. This program is one of the largest in the country targeting high risk infants by collaborating with primary care pediatricians in the MGH/Partners network to lower the barriers of access in order to expand the early childhood diet to include common allergens—the most effective means of allergy prevention currently proven—and to develop a national model for doing this in other settings. Because of Dr. Pistiner's efforts, effective December 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. Dr. Pistiner 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.

Pediatrics

Department Report

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 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 better characterizing Multisystem Inflammatory Syndrome in Children due to SARS CoV-2 infection and to the use of inhaled nitric oxide therapy to treat 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 techniques coupled with investigations of circulating hormones important in appetite regulation, and carbohydrate, fat and bone metabolism. Other areas of interest include investigations of novel technologies related to diabetes care, and the impact of administration of the growth hormone releasing hormone analog, tesamorelin, on carbohydrate and fat metabolism. We will continue to foster an environment of inquiry and investigation among our faculty and fellows, work on optimizing funding opportunities to maintain a strong research base within the division. This includes intra- and extra-mural collaborations with other laboratories actively engaged in these areas to create a rich and interactive reinforcing environment that will lead to changes in medical care paradigms for children with endocrine disorders.

Gastroenterology, Hepatology & Nutrition

Mucosal Immunology and Biology Research Center
Our mission is to expand clinical, basic and translational research in pediatric gastroenterology and nutrition to provide better outcomes for pediatric patients. Using a multidisciplinary approach, our major basic research mission is to characterize the role of the enteric mucosa and its mucosal barrier function at the interface between microbial luminal stimuli and lymphoid effector responses. We focus on the enterocyte and its involvement in microbial “crosstalk,” lymphoid-nerve-epithelial interactions and inappropriate developmental responses secondary to epigenetic pressure by the gut microbiota during the first 1000 days of life. We also look at host-pathogen interactions during infection as well as how the enterocyte functions both as a barrier to antigen trafficking and as a site for the beneficial effects of probiotics in chronic inflammation. Finally, we are interested in the gut-brain axis, particularly as concerns small intestinal and blood brain barriers in the contest of neuroinflammatory diseases. Our researchers examine strategies used by gut microbiota to affect the host and how these interactions lead to both local and systemic chronic inflammation and autoimmunity in the Mucosal Immunology and Biology Research Center (MIBRC). The MIBRC also took the lead in supporting many of its investigators to work on COVID-19-related research, which included establishing a large biobank collecting samples (including urine, nasal swabs, saliva, urine, stools) from nearly 1,700 children with COVID-19 or Multisystem Inflammatory Syndrome in Children (MIS-C), newborns born to mothers with COVID-19 or mRNA vaccination, children receiving the COVID-19 vaccine, and pediatric controls. 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.

Pediatrics

Department Report

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 life course 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:

- 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.
- Providing comprehensive, high quality care to children with special health care needs, including autism spectrum disorder through collaborations such as the Autism Care Network, an 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.
- 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 MGH*f*C 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, each of which has a research component, 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 with the largest experience with these patients of any site in the world and regularly have international referrals seeking our expertise. Active clinical trials are also underway with lysosomal storage diseases and mitochondrial diseases. The MGH Genetics Division has been at the forefront of applying clinical whole exomic sequencing for diagnosis and new gene discovery in selected patients and participates in the NIH sponsored Undiagnosed Diseases Network. Our services impact every field of pediatric and adult medicine. We have active engagement throughout the hospital in advisory and teaching capacities assisting other providers and committees in the implementation of genetics in medicine.

Global Health
Founded in 2010, the Division of Global Health at Mass General 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 subspecialists, we have developed multi-disciplinary programs and clinics for children with brain tumors, long-term survivors of childhood cancer, stroke, and hemophilia. In addition to our cooperative group and industry sponsored therapeutic clinical trials, we have important companion imaging and biomarker studies. In collaboration with our neuropsychology colleagues, we have been investigating quality of

life and neurocognitive sequelae in children who have been receiving different methods of radiation therapy (Protons and Photons). We are active members and co-investigators in an international clinical research group known as the Children's Oncology Group, as well as members of a Neuroblastoma and Brain Tumor Research Consortium. These are the leading groups investigating novel therapies for children with all types of cancer and include Phase 1, 2, and 3 clinical trials. 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. In the lab of David Sweetser, MD, PhD there is focus on the interaction of the bone marrow microenvironment and leukemic stem cells. The tumor microenvironment is has become important of investigation in cancer pathogenesis. In addition, we have exciting research projects with our colleagues in radiation oncology, molecular pathology, and pediatric radiology. Examples of these collaborations include Miguel Rivera, MD's research in the Department of Pathology using epigenome editing tools to examine the genetic drivers in Ewing sarcoma and medulloblastoma and Shannon Stott, PhD's research in the MGH Cancer Center isolating exosomes and circulating tumor cells ("liquid biopsy") from the peripheral blood of patients with brain tumors and sarcomas for diagnosis and a noninvasive method to monitor response to therapy.

Infectious Disease

The Pediatric Infectious Disease Unit has been active in both basic science and in translational/clinical research. Jason Harris, MD, MPH's externally funded cholera research efforts encompass investigation of the immune response to Vibrio cholerae infection with an emphasis on vaccine response and development, and exploration of the molecular epidemiology and ecology of V. cholerae. He has also initiated a series of studies relating to the serologic response to SARS-CoV 2 infection. Shaw Warren, MD's pivotal discovery over the past several years of the differential genomic responses between humans and mice to sepsis and inflammation has led to the establishment of a large multicenter project to investigate mechanisms responsible for species-specific sensitivity to inflammation and to develop novel therapies to treat human sepsis. 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). Virginia Pierce, MD is engaged in the development of novel molecular diagnostic tools for the clinical microbiology laboratory.

Lurie Center for Autism

At the Lurie Center for Autism, the primary focus is to partner with individuals and families to incorporate groundbreaking research into the practice of clinical medicine. The integration of clinical care and clinical research through the initiation of clinical treatment trials continues to be a focus. Chris McDougle, MD, Director of the Lurie Center, partners with biotechnology and pharmaceutical companies to

enable access to the latest therapeutic innovations for autism patients and Ann Neumeyer, MD, medical director, leads a major node of the Autism Treatment Network of Autism Speaks. For example, the Center (Chris Keary, MD and Robyn Thom, MD) is leading clinical studies for the treatment of irritability and anxiety in neurodevelopmental disorders. Beyond the many clinical trials, the Lurie Center is developing technology-based strategies to enhance behavioral and cognitive therapies. For example, along with researchers at the Lincoln and Media Labs of MIT, Lisa Nowinski, PhD and Chris McDougle, MD have initiated a study of vocal, facial and movement biomarkers of autism that will ultimately help in a feedback loop to improve communication and language development for minimally verbal patients. The Center is also engaged in research to subtype and understand the etiologies of ASD. For example, the new scientific director at the Lurie Center, Jacob Hooker, PhD and Nicole Zurcher Wimmer, PhD (Martinos Center) are developing methods to classify an "inflammatory subtype" of autism and to determine if this subtype may explain the 4:1 difference in ASD in males versus females. Importantly, the clinical research at Lurie is tightly coupled to preclinical research so that findings can be explored in detail at the mechanistic level. This coupling of basic and clinical work also makes findings translatable to patient interventional trials more quickly. For example, Evan Bordt, PhD the newest faculty member to join the Lurie Center has developed a mouse model that may explain the neuroimaging findings from Dr. Zurcher Wimmer and that points mechanistically to early life inflammation altering mitochondrial function in adulthood. The Center also has a strong translational program aimed at understanding the microbiome in ASD (Marcy Kingsbury, PhD and Yamini Howe, MD), its relationships to symptoms and mechanisms that may underly features of ASD. The research program is poised to grow tremendously over the next few years and will continue focusing on how to improve ASD patient care. A key focus of the growth strategy will be to expand and leverage the scientific connectivity to other departments at MGH and in the greater Boston area.

Neonatology and Newborn Medicine

The research effort in the Neonatology and Newborn Medicine Unit is multifaceted and ranges from developmental lung biology 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 or 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.

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 therefore 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. In addition to our previous contributions, we recently identified a novel duplication within the *GNAS* locus that leads to loss-of-methylation at one of the differentially methylated regions within *GNAS*, thus explaining the PTH-resistant hypocalcemia in this patient. We furthermore showed that female carriers of *STX16-GNAS* mutations, i.e. mutations that are responsible for autosomal dominant pseudohypoparathyroidism type Ib (PHP1B), preferentially pass the genetic defect to their children, which has considerable implications for genetic counseling and genetic testing. Lastly, we showed through the analysis of numerous patients with PHP1B due to a *STX16* deletion that PTH-resistance does not develop before the age of two years. Furthermore, screening the children of affected and unaffected female carriers of *STX16* deletion, indicates who needs 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.

We also explored the efficacy of a PTH inverse agonist (PTH-IA) to partially rescue the skeletal defects in mice expressing a constitutively active mutant PTH receptor that causes Jansen's metaphyseal chondrodysplasia. These findings are the basis for developing, through the NIH-TRND program, PTH-IA for the treatment of this very rare disease. The production of GMP-grade PTH-IA (240 grams) has now been completed. A written response to the FDA's review of our preIND application was submitted this past summer and since no major concerns were raised, the proposed toxicology studies will now be conducted in a single animal species, namely in juvenile rats. Earlier dose-finding toxicology studies had revealed no

obvious systemic side effects. Once the long-term studies in rats are completed and no concerns are raised, the first clinical trials in adult patients affected by Jansen's disease will be started towards the end of 2022 or early 2023.

We are furthermore involved in the search for novel factors involved in the regulation of FGF23, a major phosphate-regulating hormone. In addition, we performed extensive studies to characterize *in vivo* an inhibitor of the sodium-dependent phosphate co-transporter NPT2a that regulates renal phosphate excretion. In our animal studies, we were able to show that the inhibitor promotes phosphate excretion even in mice lacking FGF23 or GALNT3, thus lowering serum phosphate levels. This suggests that a small molecule could be used in the treatment of patients affected by tumoral calcinosis and possible chronic kidney disease (CKD). In fact, the NPT2a inhibitor increases phosphate excretion in models of acute and chronic kidney disease, and could thus be beneficial in preventing hyperphosphatemia, vascular calcifications, and elevations in FGF23 levels in CKD patients.

Pediatric Palliative Care

In 2019, we embarked on a pilot of a novel model of care for children with serious illness. We have combined the medical home model of the Coordinated Care Clinic with the predominantly inpatient palliative care service to provide more comprehensive and seamless care to a small population of children whose care represents the most expensive and intensive. These patients are characterized by frequent or prolonged admissions to hospital and repeated transitions from home to hospital to outpatient and community services.

Pulmonary

The research focus of the Pulmonary Division has remained broad and continues to have a significant COVID-19 focus. The first area of research, led by Lael Yonker, MD is directed towards defining the immunological basis of MIS-C and COVID inflammation. Dr. Yonker 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, led by Dr. Kinane and Florian Eichler, MD, focuses on gene therapy in Canavan's disease. They are using AAV to deliver the ASPA gene to affected neurons. The fourth area of research, led by Dr. Kinane, 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 its cases in Pediatric Pulmonology.

Rheumatology

Investigators in the Pediatric Rheumatology Program lead and participate in clinical research that include observational research studies and randomized clinical trials, as well as investigator-initiated outcomes and adverse event studies, across a wide range of childhood-onset rheumatic diseases. As part of such research

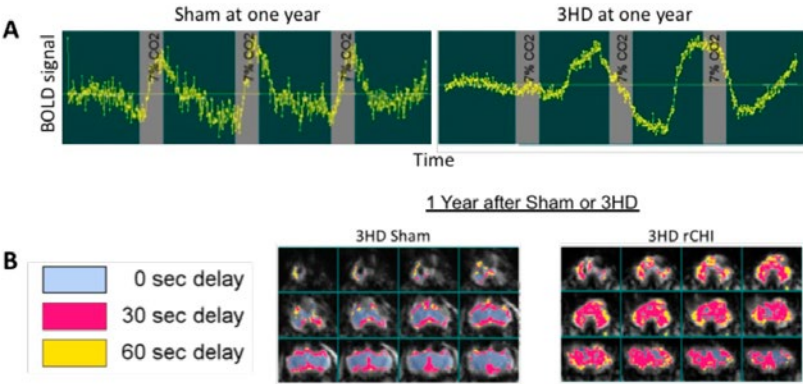
efforts, our faculty members are continuing enrollment of patients as a member site of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, which is a long-term, multi-site prospective observational study focused on safety and disease outcomes that combines FDA Phase IV post-marketing surveillance with outcomes research.

Other research in our program focuses on creating and improving guidelines for the safety monitoring of children receiving rituximab and strategies for preventing immunosuppression-related infections among high-risk patients with pediatric-onset rheumatologic diseases. Deborah Rothman, MD, PhD, completed a grant from CARRA to study the association between rituximab and infection risk, with results now published in the peer-reviewed journal Rheumatology. Marc Natter, MD has published a number of other submissions to peer-reviewed journals recently, including 12 and 24-month outcomes reports from the PCORI-funded CARRA Registry STOP-JIA clinical trial—the largest pragmatic treatment trial of patients with polyarticular JIA to date—and a review article regarding usage of the EHR for enhancing care in pediatric rheumatology. Holly Rothermel, MD has recently published peer-reviewed manuscripts regarding MRI assessment of JIA-associated TMJ arthritis and recent case report in *NEJM*.

Achievements:

Critical Care Medicine

Michael Whalen, MD: We have now published our 7-year study in the journal Cell Death and Disease in which we showed that RIPK1, MLKL, and RIPK3 are induced in brain after controlled cortical impact in mice but that RIPK3 is the most impactful driver of motor and cognitive outcome in part by regulating HMGB1 release and IL-1 beta activation. We also show that RIPK3 links to neurodegeneration processes at 2 months after injury. The data are significant because drivers of functional outcome and neurodegeneration are incompletely defined and need to be understood in order to develop therapies to improve functional outcome after severe TBI, and to prevent mechanisms of neurodegeneration. We also obtained new RO1 funding to study the role of RIPK3 as a driver of neurodegeneration after TBI.



(A) Representative fMRI/BOLD traces after three 7% CO_2 inhalation challenges in sham and 3HD mice (mice with three closed head injuries spaced one day apart) examined at one year after injuries. Note the delays in response to CO_2 challenge in the 3HD mouse. (B) Representative fMRI/BOLD response maps in sham and 3HD mice at one year after injuries. Red and yellow pixels represent brain regions with greater than 30s delay in fMRI/BOLD response to the CO_2 challenge. Note widespread delays in fMRI/BOLD response in the 3HD brain.

Wu et al., 2021. Genetic inhibition of RIPK3 ameliorates functional outcome in controlled cortical impact independent of necroptosis. Cell Death and Disease 2021, 12:1064. doi: 10.1038/s41419-021-04333-z. PMID: 34753914

Gastroenterology, Hepatology & Nutrition

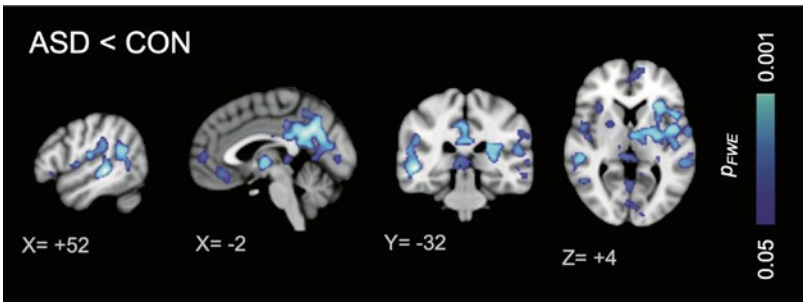
Mucosal Immunology and Biology Research Center
Dr. Lael Yonker, pediatric pulmonologist and principal investigator in the MIBRC, established and led the MGH Pediatric COVID-19 Biorepository, collecting biospecimens from nearly 1,700 children with COVID-19 or Multisystem Inflammatory Syndrome in Children (MIS-C), newborns born to mothers with COVID-19 or mRNA vaccination, children receiving the COVID-19 vaccine, and pediatric controls. Together with other MIBRC investigators, including Dr. Evan Bordt and Alessio Fasano, MD. 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. She has also shown that treatment of MIS-C with larazotide, a zonulin antagonist, appears to be an effective treatment for MIS-C, and 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 24 manuscripts in high impact journals including *Cell, Nature Medicine, Journal of Clinical Investigation, 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 Magazine, 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.

General Academic Pediatrics

HIV
The HIV Prevention Trials Network (HPTN) 083 demonstrated superiority of long-acting injectable cabotegravir (CAB-LA) compared to oral tenofovir disoproxil fumarate/emtricitabine (F/TDF) for HIV pre-exposure prophylaxis (PrEP). CAB-LA cost is expected to be higher than that of generic F/TDF and branded F/TAF. In light of this finding, Anne Neilan, MD, MPH and colleagues completed an analysis to evaluate the clinical benefit of CAB-LA and the cost at which it would be cost-effective in the United States. The preliminary results demonstrated that compared with F/TDF and F/TAF, CAB-LA increases life expectancy by 37,000 QALYs. In order to be cost-effective, the maximum price premium of CAB-LA over F/TDF (F/TAF) would be $800/year ($1,700/year). This analysis shows that despite

the superiority of long-acting injectable PrEP, the presence of highly effective alternatives limits the additional markup that payers should be willing to pay for CAB-LA. The preliminary results were presented as an oral abstract at the 2021 Conference on Retroviruses and Opportunistic Infections (CROI); a manuscript draft is under review at Annals of Internal Medicine. The abstract was cited in the UNAIDS Global AIDS update 2021 (page 81) https://www.unaids.org/sites/default/files/media_asset/2021-global-aids-update_en.pdf and was featured in an article on www.aidsmap.com. Abstract materials were also shared with the World Health Organization.

Lurie Center for Autism



Statistical difference in neuroimmune function, measured by [11C]PBR28 SUVR60–90 between ASD and CON groups. Bilateral insular cortex, putamen, precuneus/posterior cingulate cortex, orbitofrontal cortex, lateral occipital cortex, superior temporal gyrus, angular gyrus, supramarginal gyrus, and the left postcentral gyrus showed lower relative TSPO expression in ASD compared with CON. There was no brain region, which showed higher relative TSPO expression in ASD compared with CON.

Mechanisms of neuroimmune and mitochondrial dysfunction have been repeatedly implicated in autism spectrum disorder (ASD). In 2021, the Lurie Center published circuit-level insights of neuroimmune dysfunction in patients with ASD. ASD is behaviorally defined by the presence of deficits in social communication, and the presence of repetitive behaviors and restricted interests. ASD, which affects 1 in 59 children, is characterized by phenotypic and genetic heterogeneity, and likely has several etiologies. Among candidate mechanisms for the underlying neuropathology are neuroimmune mechanisms as well as mitochondrial dysfunction, which have been repeatedly associated with ASD. Based on the collective evidence, we investigated neuroimmune and mitochondrial dysfunction-related mechanisms *in vivo* in adults with ASD using cutting-edge magnetic resonance (MR) and positron emission tomography (PET) imaging. This included probing the translocator protein (18 kDa) (TSPO), a mitochondrial protein expressed on microglia and astrocytes, that has been implicated in several physiological processes, including immune modulation and mitochondrial homeostasis. TSPO has been suggested as potential endophenotype and therapeutic target for psychiatric disorders and can be imaged *in vivo* using positron emission tomography imaging (PET). By comparing TSPO in 15 young adult males with ASD with 18 age- and sex-matched controls, we showed that individuals with ASD exhibited lower regional TSPO expression in several brain regions, including the bilateral insular cortex, bilateral precuneus/posterior cingulate cortex, and bilateral temporal, angular, and supramarginal gyri, which have previously been implicated in autism in functional MR imaging studies.

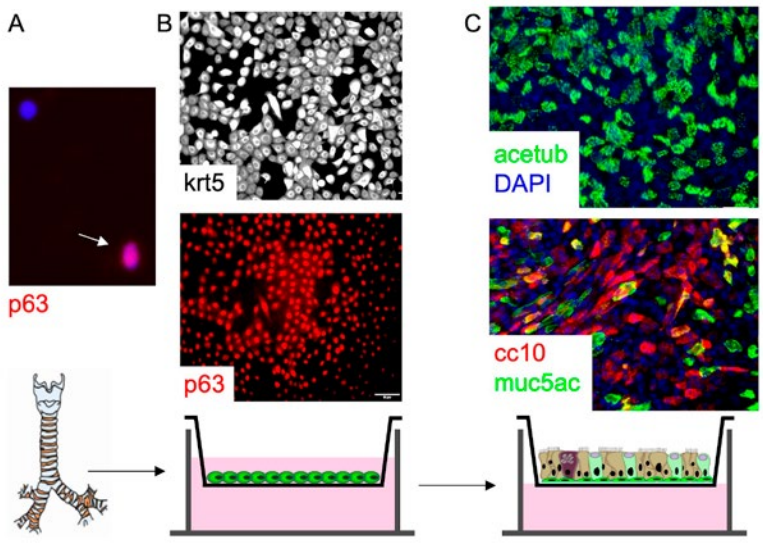
Zürcher et al., [11C]PBR28 MR-PET imaging reveals lower regional brain expression of translocator protein (TSPO) in young adult males with autism spectrum disorder. Mol Psychiatry. 2021 May;26(5):1659-1669

Neonatology and Newborn Medicine

Bronchopulmonary dysplasia remains one of the most common complications of prematurity, despite significant improvements in perinatal care. Functional modeling of human lung development and disease, like BPD, is limited by our ability to access the lung and to maintain relevant progenitor cell populations in culture. We supplemented Rho/SMAD signaling inhibition with mTOR inhibition to generate epithelial basal cell-like cell lines from tracheal aspirates of neonates.

Single-cell RNA-sequencing confirmed the presence of epithelial cells in tracheal aspirates obtained from intubated neonates. Using Rho/SMAD/mTOR triple signaling inhibition, neonatal tracheal aspirate-derived (nTAD) basal cell-like cells can be expanded long term and retain the ability to differentiate into pseudostratified airway epithelium. Our data demonstrate that neonatal tracheal aspirate-derived epithelial cells can provide a novel ex vivo human cellular model to study neonatal lung development and disease.

Airway epithelial basal cell-like cell lines were derived from human neonatal tracheal aspirates. mTOR inhibition significantly extends in vitro proliferation of neonatal tracheal aspirate-derived basal cell-like cells (nTAD BCCs). nTAD BCCs can be differentiated into functional airway epithelium. nTAD BCCs provide a novel model to investigate perinatal lung development and diseases.



(A) Tracheal aspirates contain P63+ cells (white arrow). (B) Expanded basal cells from tracheal aspirates. (C) Air-liquid interface differentiation results in ciliated (AceTub) and secretory cells: club (CC10) and goblet (Muc5ac).

Rho/SMAD/mTOR triple inhibition enables long-term expansion of human neonatal tracheal aspirate-derived airway basal cell-like cells. ***Lu J****, Zhu X, Shui JE, Xiong L, Gierahn T, Zhang C, Wood M, Hally S, Love JC, Li H, Crawford BC, Mou H,* ***Lerou PH****. Pediatr Res. 2021 Feb;89(3):502-509. doi: 10.1038/s41390-020-0925-3. Epub 2020 May 4. PMID: 32365352*

Psychiatry

Department Report

MAURIZIO FAVA, MD, CHIEF

Overview:

Psychiatric disorders are the leading cause of disability worldwide. The MGH Department of Psychiatry is dedicated to alleviating the suffering and burden of mental illness through its four-fold mission 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 600 psychiatrists, psychologists 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 27 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 100 adult and child/adolescent psychiatry residents, psychology interns and clinical fellows to be leaders in their areas of specialization. Further, dozens or more 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 the Mass General 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 FY21, Department faculty received $86 million in research funding, increasing support by almost 23% over FY20, and continuing its record of successful funding despite a challenging environment. Further, our researchers published over 1220 original articles in 2021, 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.

- In addition, two of our faculty collaborators quickly stood up a much-heralded web-based guide to mental health resources for health care professionals and the public, alike.
- Several of our clinicians are critical members of the MGB COVID-19 Survivors Clinic.
- The Covid States Project (covidstates.org) is a multi-university consortium surveying ~20k US adults in all 50 states approximately every 4-6 weeks since spring 2020. The NSF-sponsored survey continues to offer insight regarding covid-related behaviors and attitudes. It has led to discoveries regarding neuropsychiatric sequelae of COVID-19 (*JAMA Network* 2021a and b), sex-specificity of resilience (*Depression and Anxiety* 2021), and most recently the relationship between depressed mood and vaccine-related misinformation (*JAMA Network* 2022).
- Finally, in evaluating initiatives focused on frontline clinicians and workers, our clinical researchers found that peer support, virtual groups, and asynchronous resiliency interventions, focused on pandemic stressors, could be protective for the emotional well-being of frontline clinicians and workers.

Psychiatry

Department Report

Key Recruitments

- **Aderonke Pederson, MD:** Dr. Pederson completed her undergraduate degree at the University of Chicago and medical school at Northwestern University's Feinberg School of Medicine, where she also completed her residency in psychiatry. Her research interest centers around the content and characteristics that contribute to mental health stigma frameworks among Black adults and determining the psychosocial factors that lead to low engagement in mental health services and act as barriers to participation in care among this population.
- **Benjamin Wade, PhD:** Dr. Wade completed his undergraduate degree at the University of California, Los Angeles and his PhD in Bioengineering at the University of California, Berkeley. He has worked in large multicenter projects such as the human connectome project aiming to understand the mechanisms of action of antidepressant therapies including Electroconvulsive therapy and ketamine. He will be conducting research in our division of Neuropsychiatry on machine learning applications using large neuroimaging datasets, aiming to identify severity and response biomarkers in neuropsychiatry, with a focus on mood disorders.

Important New Research Initiative-CHOIR

The Center for Health Outcomes and Interdisciplinary Research (CHOIR) under the leadership of Ana-Maria Vranceanu, PhD, was launched in late 2021. CHOIR's mission is to conduct interdisciplinary research to promote health, well-being, and equity across the lifespan. CHOIR aims to be a home for trainees and investigators who are interested in working together to develop innovative solutions at the intersection of psychology and medicine and strives to embody the values of community, collaboration, innovation, and inclusion. CHOIR has grown out of the Integrated Brain Health Clinical and Research Program, and its associated clinical psychology internship track, to accommodate the expansion of its research platform from brain health to overall health and wellbeing. As such, CHOIR develops, tests, and implements technology-enhanced mind-body and lifestyle toolkits to promote health and well-being for persons with acute and chronic illness and their family caregivers, in both hospital and community settings.

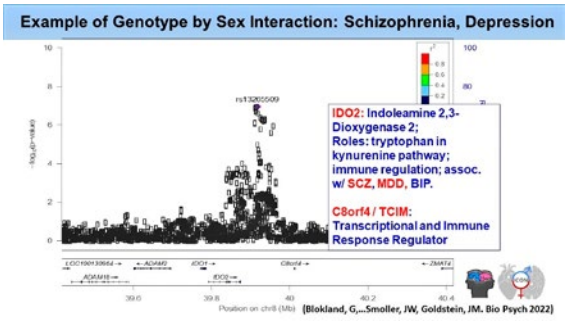
Initiation of Two Important "Think-Tanks"

- The Resilience, Prevention and Wellbeing Think Tank was established in 2021 with the mission of coalescing the many individual departmental programs in this space and integrating the strengths of each to improve resilience and wellbeing knowledge and prevention services. To date, we have benefited from the dedication of 15 regular members and 20 other faculty who have taken part and have been developing four projects—including the creation of a compendium of our programs and services that will provide both inward and outward facing information and the submission of a HRSA grant on resilience building in a community health network.

- A department-wide Digital Health Think Tank was launched in the fall of 2019 and now has over 80 members. It is a forum to share knowledge among multidisciplinary stakeholders (e.g., researchers, technology developers, healthcare providers) to support the use of digital tools to improve mental health outcomes. Think tank meetings occur quarterly and members share resources via a list-serv. The meetings focus on navigating the research process at MGH and providing guidance on interactions with industry, obtaining grants, and managing potential conflict of interest. The Digital Health Think tank has also had many invited speakers from industry and academia and has offered educational panels with faculty members and department leaders.

Achievements:

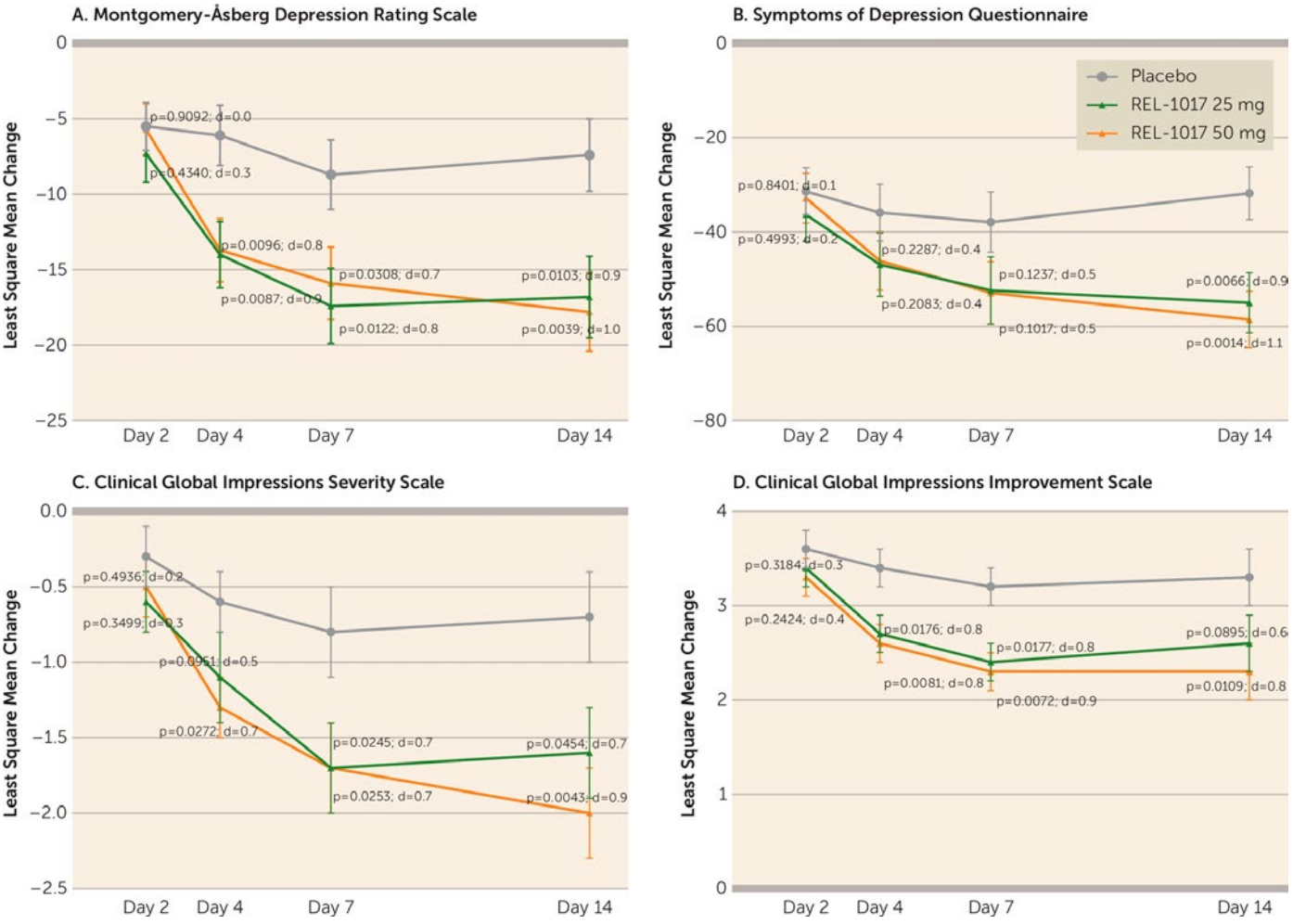
Blokland et al, 2021. Sex Differences Cross-Disorder Analysis Group of the Psychiatric Genomics Consortium.
It is well known there are sex differences in the risk and prevalence of mood and psychotic disorders. Large-scale genetic studies have demonstrated that these psychiatric disorders are, in part, heritable and often have overlapping genetic underpinnings. But to what extent do genetic contributions differ by sex? This large collaborative study, led by Professor Jill Goldstein, PhD and others in the MGH Department of Psychiatry, combined genome-wide and clinical data for 86,000 cases with major depression (MDD), bipolar disorder (BIP), and schizophrenia (SCZ) and 110,000 healthy controls to test for sex differences (i.e., sex by genotype interaction effects) in the shared and non-shared genetic architecture across these disorders. Although there was substantial genetic overlap among the disorders, SNP-based heritability estimates were significantly different between the sexes for SCZ and MDD, but not for BIP. Genotype-by-sex interaction analyses identified specific loci and genes with sex-dependent effects within and across disorders. Further analyses showed that significant sex-dependent effects were enriched for genes related to neuronal development and immune and vascular functions across and within SCZ, BIP, and MDD at the variant, gene, and pathway levels. This study represents the largest ever genome-wide genotype-by-sex examination of risk for these disorders and identified potential targets for sex-dependent or sex-specific therapeutic interventions.



Blokland GAM, Grove J, Chen CY, … Sex Differences Cross-Disorder Analysis Group of the Psychiatric Genomics Consortium; iPSYCH, Hougaard DM, Nordentoft M, Mors O, Mortensen PB, Werge T, Als TD, Børglum AD, Petryshen TL, Smoller JW, Goldstein JM. Sex-Dependent Shared and Nonshared Genetic Architecture Across Mood and Psychotic Disorders. Biol Psychiatry. 2022 Jan 1;91(1):102-117. doi: 10.1016/j.biopsych.2021.02.972. Epub 2021 Mar 23. PMID: 34099189; PMCID: PMC8458480.

Fava et al, 2021: REL-1017 (Esmethadone) as Adjunctive Treatment in Patients With Major Depressive Disorder: A Phase 2a Randomized Double-Blind Trial

We wanted to examine in a phase 2 study the effects of REL-1017 (esmethadone), a novel N-methyl-D-aspartate receptor (NMDAR) channel blocker, in patients with major depressive disorder who failed to benefit from one to three standard antidepressant treatments in their current major depressive episode. We carried out a 7-day phase 2 multicenter randomized double-blind placebo-controlled trial, comprising three arms in order to assess the safety, tolerability, pharmacokinetics, and efficacy of two dosages of REL-1017 (25 mg or 50 mg orally once a day). Patients were randomly assigned



Efficacy endpoints in patients receiving placebo (N=22), REL-1017 25 mg/day (N=19), or REL-1017 50 mg/day (N=21)[a]

[a]Panels A–D show the change from baseline in the least square mean from day 2 through day 14, compared with placebo, in the full analysis set population for the Montgomery-Åsberg Depression Rating Scale, the Symptoms of Depression Questionnaire, the Clinical Global Impressions severity scale, and the Clinical Global Impressions improvement scale, respectively. Error bars indicate standard error of the mean. The p values and Cohen's d values indicate drug treatment compared with placebo.
https://ajp.psychiatryonline.org/doi/10.1176/appi.ajp.2021.21020197?url_ver=Z39.88-2003&rfr_id=ori%3Arid%3Acrossref.org&rfr_dat=cr_pub++0pubmed&

in a 1:1:1 ratio to placebo (N=22), REL-1017 25 mg/day (N=19), or REL-1017 50 mg/day (N=21). Safety scales included the 4-item Positive Symptom Rating Scale for psychotomimetic symptoms, the Clinician-Administered Dissociative States Scale for dissociative symptoms, the Clinical Opiate Withdrawal Scale for withdrawal signs and symptoms, and the Columbia-Suicide Severity Rating Scale for suicidality. The primary efficacy endpoint was the Montgomery-Åsberg Depression Scale (MADRS) score. All 62 randomly assigned patients were included in the full analysis set population analysis. Patients experienced mild or moderate transient adverse events and no evidence of dissociative or psychotomimetic effects, opioid effects, or withdrawal signs and symptoms. The improvement in MADRS score shown on day 4 in both of the REL-1017 dosage groups was sustained through day 7 (last dose) and day 14 (7 days after the last dose), with effect sizes from 0.7 to 1.0. This trial showed favorable safety, tolerability, and pharmacokinetic profiles and suggests that REL-1017 may have rapid and sustained antidepressant effects compared with placebo in patients with inadequate responses to antidepressant treatments. A phase 3 program is now in progress, with the goal of providing confirmation of these results in larger and longer trials.

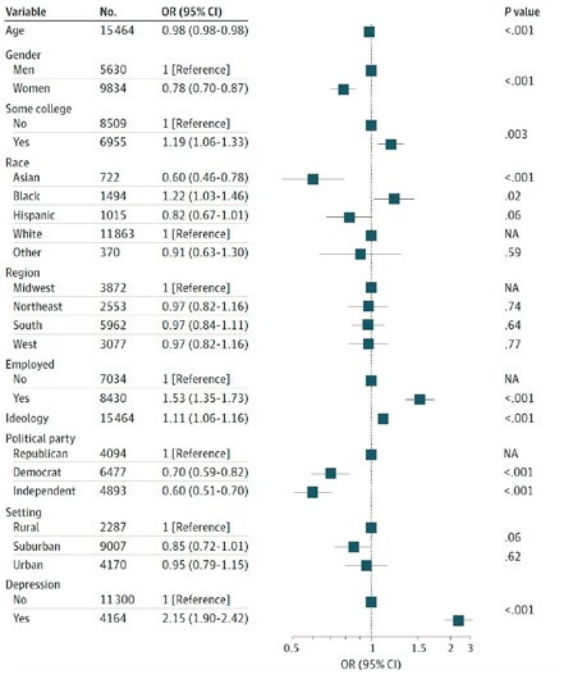
Fava M, Stahl S, Pani L, De Martin S, Pappagallo M, Guidetti C, Alimonti A, Bettini E, Mangano RM, Wessel T, de Somer M, Caron J, Vitolo OV, Gilbert A, Mehta H, Kearney M, Mattarei A, Gentilucci M, Folli F, Traversa S, Inturrisi CE, Manfredi PL. REL-1017 (Esmethadone) as Adjunctive Treatment in Patients With Major Depressive Disorder: A Phase 2a Randomized Double-Blind Trial. Am J Psychiatry. 2021 Dec 22:appiajp202121020197. doi: 10.1176/appi.ajp.2021.21020197. Online ahead of print.

Perlis R, et al, 2022. Association of Major Depressive Symptoms With Endorsement of COVID-19 Vaccine Misinformation Among US Adults.

The COVID States Project (covidstates.org) is a multi-university consortium surveying ~20k US adults in all 50 states approximately every 4-6 weeks since spring 2020. The NSF-sponsored survey—co-led by Roy Perlis, MD—continues to offer insight regarding covid-related behaviors and attitudes. It has led to discoveries regarding neuropsychiatric sequelae of covid (JAMA Network 2021a and b), sex-specificity of resilience (Depression and Anxiety 2021), and most recently the relationship between depressed mood and vaccine-related misinformation (JAMA Network 2022).

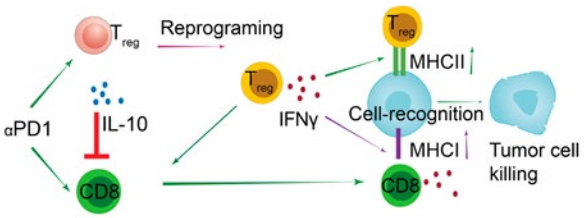
Perlis Roy H, Ognyanova Katherine, Santillana Mauricio, Lin Jennifer, Druckman James, Lazer David, Green Jon, Simonson Matthew, Baum Matthew A, Della Volpe John. Association of Major Depressive Symptoms With Endorsement of COVID-19 Vaccine Misinformation Among US Adults. JAMA network open. 2022;5(1):e2145697. doi: 10.1001/jamanetworkopen.2021.45697

Figure 1. Regression Model for Endorsing at Least 1 Misinformation Item in Initial Survey Wave



Radiation Oncology

Department Report



Schematic representation of the identified mechanism: converted Treg cells and re-activated CD8 T cells post αPD1 + αGITR treatment cooperate in activity, produce IFNγ that induces MHC upregulation on tumor cells allowing for recognition and brain tumor cell killing. From: *Amoozgar et al., Nature Communications 2021.*

ANTHONY ZIETMAN, MD, CHIEF

Research Overview:

The Mass General Department of Radiation Oncology had approximately **$20.5M** in research expenditures in Fiscal Year 2021. Nearly **28%** 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 **303** publications in 2021. Additionally, in 2021, the Department of Radiation Oncology maintained **33** active clinical trials, and **331** clinical trial accruals.

Presently, the main areas of research focus within the department include clinical trials, proton research, pediatric research, physics research, translational research, and laboratory-based basic research. The department boasts an extensive physics research program including efforts in bio-mathematical modeling, outcome modeling, Monte Carlo simulations, and optimization of intensity-modulated photon and proton therapy. Mass General Radiation Oncology also has an active tumor and radiation biology program with major interests in tumor microenvironment, DNA repair, and precision radiation medicine. The Edwin L. Steele Labs aim to reveal how different components of the abnormal tumor microenvironment fuel tumor progression and confer treatment resistance; develop innovative strategies to overcome this resistance by “normalizing” the microenvironment; and then translate these strategies from bench to bedside. It is anticipated that research conducted in the Department of Radiation Oncology will lead to improved approaches to radiation therapy in cancer treatment and will help further understanding of mechanisms of radiation-induced toxicities, leading to development of novel targets for cancer therapy as well as new preventative approaches.

Department General Achievements:

The National Cancer Institute (NCI) of the National Institutes of Health awarded a **P01 Program Project Grant** in the amount of $13.97M jointly to Massachusetts General Hospital and the MD Anderson Cancer Center (MDACC) for five years beginning September 1, 2021. This P01 program project, led by **Theodore Hong, MD** at MGH and Radhe Mohan, PhD at MDACC, is a multidisciplinary multi-institution research study entitled “Integrating patient-specific clinical and biological factors towards individualizing utilization of proton and photon radiation therapy.” Upon receiving news of the grant award, Dr. Hong said, “This research will fundamentally alter our understanding of the clinical impact of protons and photons and will lead to a paradigm shift in the application of radiation therapy as a cancer treatment modality.”

Anthony Zietman, MD recently announced the launch of the **Departmental Program for Radiation Biology & Research**. The main mission of this new program is to broadly support radiation

biology research and education by serving as a platform for research collaborations, idea exchanges, and resource sharing, with the overarching goal of promoting team science across the main disciplines of radiation oncology: clinical, biology, and physics. **Henning Willers, MD** oversees the program as Director, with **Li Lan, PhD** and **Clemens Grassberger, PhD** serving as Associate Directors. Multiple research initiatives are being developed under this new program such as the Interdepartmental Peer Review Initiative. The purpose of this initiative is to leverage the collective expertise and experience of current and former PIs in Radiation Oncology to improve NIH grant applicants for investigators of all levels. The program also aims to enhance interactions with our biophysics investigators and the MGH Center for Cancer Research (CCR).

The Department of Radiation Oncology inaugurated its **Grand Rounds lecture series**, overseen by the department's Clinical Trials Steering Committee, in March 2021 with a talk by Professor Jenny L Donovan, PhD of the University of Bristol entitled "Solving hidden challenges to randomized clinical trial recruitment." In 2021 the department hosted six Grand Rounds speakers (two each in the areas of clinical, biology and physics). These Grand Rounds talks have drawn attendees from MGH Radiation Oncology, BWH Radiation Oncology and the MGH Cancer Center.

The ninth **MGH Radiation Oncology Research Retreat** took place virtually on Thursday, September 23, 2021. Entitled "Clinical Research and Trials," the retreat celebrated the accomplishments of MGH Radiation Oncology investigators while exploring the department's visions for future research themes. In his opening remarks, Interim Chief, **Anthony Zietman, MD**, emphasized the department's legacy of visionary research endeavors, dating from the earliest days of Founding Chief, Dr. Herman Suit's, "Science Festivity Days," noting that our "culture is to innovate." Our keynote speaker was Jeff Meyerhardt, MD, MPH, Associate Director for Clinical Research at Dana-Farber/Harvard Cancer Center, who spoke on "Navigating Opportunities for Clinical Research at Dana-Farber/Harvard Cancer Center and the National Clinical Trials Network." In his engaging and accessible talk, he explained how to bring an idea for a clinical trial to fruition. Over 100 attendees joined the retreat, which also featured brief "Rad Onc Showcase" talks as well as sessions on "Networking with industry," "Nuts and Bolts of Conducting Research in MGH Radiation Oncology," and "The future of clinical trials and innovation in our department."

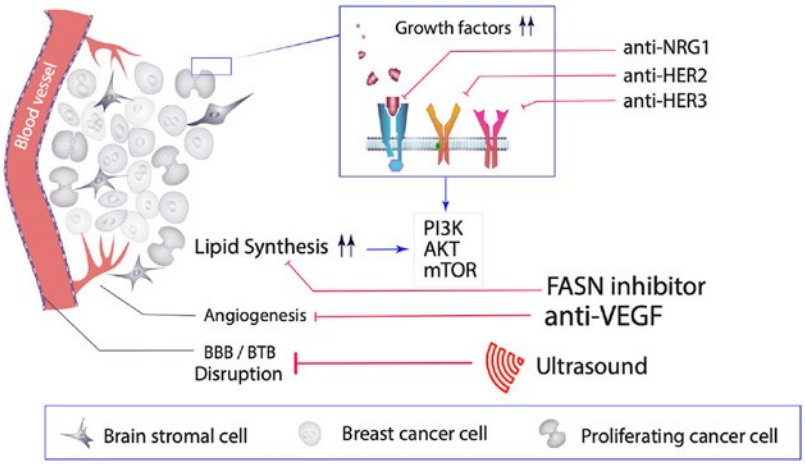
Clinical Research and Radiation Biology Research Achievements:

Jason Efstathiou, MD led the first ever initiated contemporary phase III RCT of protons vs photons in any disease site that completed full accrual of **400 patients in 24 months** for the PARTIQoL trial: Prostate Advanced Radiation Technologies Investigating Quality of Life. A Phase III Randomized Clinical Trial of Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer.

Radiation Oncology

Department Report

Brain metastases are refractory to therapies that control systemic disease in patients with human epidermal growth factor receptor 2 (HER2+) breast cancer, and the brain microenvironment contributes to this therapy resistance. Nutrient availability can vary across tissues, so metabolic adaptations required for brain metastatic breast cancer growth may introduce liabilities that can be exploited for therapy. We found that fatty acid synthesis is elevated in breast tumors growing in brain and that this phenotype is an adaptation to decreased lipid availability in brain relative to other tissues. This results in a site-specific dependency on fatty acid synthesis for breast tumors growing in the brain, thus representing targetable metabolic dependencies. From *Ferraro et al. Nat Cancer, DOI: 10.1038/s43018-021-00183-y.*



Alice Ho, MD was elected as a representative to The Executive Committee on Research (ECOR) of MGH.

William Hwang, MD, PhD was awarded a 2021 MGH American Cancer Society Institutional Research Grant for his proposal "Cell state plasticity in pancreatic cancer tumorigenesis and therapeutic resistance elucidated by concurrent single-nucleus chromatin accessibility and gene expression."

William Hwang, MD, PhD was chosen as one of the NextGen Star speakers at the 2022 AACR Annual Meeting. NextGen Star supports the career growth and development of investigators.

William Hwang, MD, PhD received a Neuroendocrine Tumor Research Foundation Pilot Project Award. This award is given to investigators with the skills and knowledge to study neuroendocrine cancers in impactful ways.

The Lan Lab, headed by **Li Lan, MD, PhD**, led multiple investigations into using RNA-regulated repair (RR) as a Biomarker and a Therapeutic Target. With the ultimate goal of improving breast cancer therapy, the lab found that RNA transcripts are modified in a DNA damage-induced manner, generating a 'DNA damage code' to attract DNA repair proteins. Moreover, the Lan Lab is also actively searching for new ways to generate "synthetic lethality" in cancer cells and recently discovered a surprising link between DNA replication and anti-tumor immunity in cancer cells.

David Miyamoto, MD, PhD received a Radiation Oncology Institute (ROI) Biomarkers for Radiation Oncology Research Award for his research on Liquid Biopsy-Guided Trimodality Therapy for Muscle-Invasive Bladder Cancer.

Research by **Andrzej Niemierko, PhD, Sophia Kamran, MD**, and **Henning Willers, MD** that examineddemographic data for nearly 6,000 enrollees of 93 precision oncology clinical trials was the subject of a November 14, 2021 *Washington Post* article titled "White and Asian American patients overrepresented in cancer trials."

Shervin Tabrizi, MD and **Sophia Kamran, MD** each received a Young Investigator Award from the 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.

The work of **Alphonse Taghian, MD** and his colleagues was featured in an April 29, 2021 *New York Times* article regarding COVID-19 vaccines and lymphedema. The article, "Do I Have to Get the Covid Vaccine in My Arm?", describes the Mass General Lymphedema Research Program's investigations into how many current and former breast cancer patients report swollen lymph nodes following the vaccine, as well as the timing and duration of this side effect.

New Grants:
The National Cancer Institute has awarded the P01 Program Project Grant 1P01CA261669-01 jointly to Massachusetts General Hospital and MD Anderson Cancer Center for five years (09/21/2021 to 08/31/2026). This P01 grant entitled "Integrating patient-specific clinical and biological factors towards individualizing utilization of proton and photon radiation therapy" is led by **Theodore Hong, MD** at MGH.

Physics Achievements:

As part of ongoing efforts to increase awareness around diversity, equity, and inclusion (DEI), the Physics Division hosted in-person and virtual screenings of "Picture a Scientist," followed by a panel discussion on Monday, November 15th. The film examines the experiences of women and underrepresented minorities in science fields and the types of discrimination they face daily. The five panel members were **Leah Gordon, DNP, Rachel Jimenez, MD, Aimee McNamara, PhD, Thomas Bortfeld, PhD**, and **Marc Bussière, MSc**, with moderators **Jan Schuemann, PhD** and J**en Pursley, PhD**.

On May 10, 2021, the Harvard Medical Physics Residency Program welcomed Carri Glide-Hurst, PhD, DABR, FAAPM, for the annual **Kent J. Riley Memorial Lecture**, in honor of Kent Riley who was a physics resident in the Harvard Medical Physics Residency Program from 2011 until he passed away from multiple myeloma in June 2014. Dr. Glide-Hurst, Director of Medical Physics and Associate Professor with Tenure at the University of Wisconsin Department of Human Oncology and a nationally recognized expert in MR-guided radiotherapy, delivered a lecture entitled "Personalizing Cancer Treatment with MR-guided Radiation Therapy."

Thomas Bortfeld, PhD was elected to the **German National Academy of Sciences**. Previous members of this academy include Johann Wolfgang von Goethe and Albert Einstein.

Thomas Bortfeld, PhD was named an honorary member of European Society of Radiation Oncology (ESTRO).

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Clemens Grassberger, PhD was awarded the 2021 American Association of Physicists in Medicine John S. Laughlin Young Scientist Award. This award recognizes outstanding scientific achievement in medical physics for early-career members of the AAPM. Only one award is granted per year.

Jennifer Pursley, PhD was named Vice-Chair of the American Physical Society (APS) Topical Group on Medical Physics (GMED). The Topical Group is dedicated to the advancement and diffusion of knowledge of physics in various areas of medicine. This includes, but is not limited to, the physics of imaging, therapy, and modeling, with applications in oncology, neurology, cardiology, as well other diseases and normal physiological states.

Jennifer Pursley, PhD was named Editor of the American Association of Physicists in Medicine (AAPM) Newsletter. The newsletter, which is published bi-monthly on the AAPM's website, provides information on activities of the AAPM and topics of interest to its membership. Dr Pursley's three-year term began January 1, 2021.

Jan Schuemann, PhD was named VP-elect for the Radiation Research Society (RRS). The RRS works to advance radiation research in all disciplines of science and medicine, foster collaboration, disseminate knowledge, and promote equity, diversity and inclusion in radiation research.

Greg Sharp, PhD was recognized as a 2021 American Association of Physicists in Medicine (AAPM) Fellow.

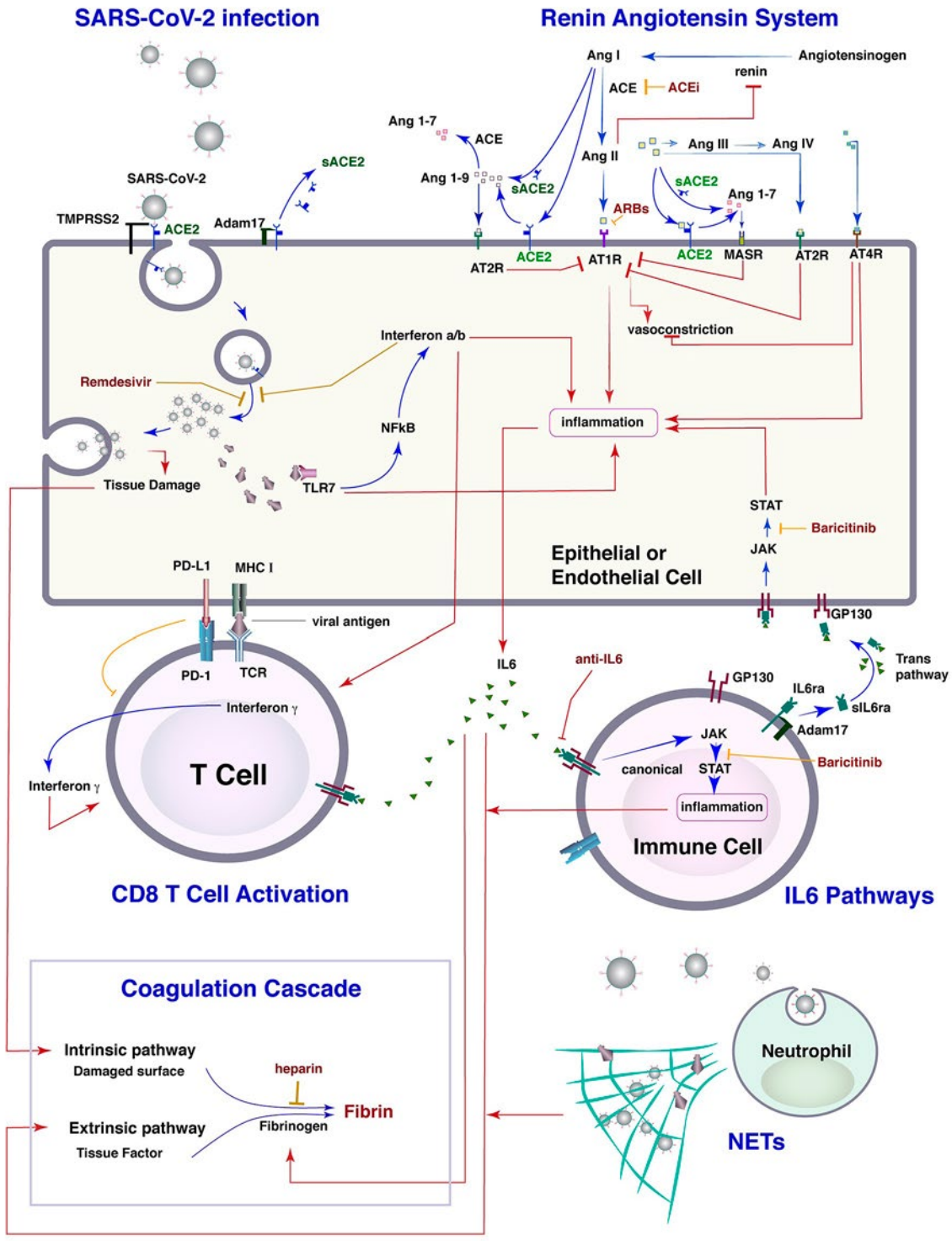
Shu (Stella) Xing, PhD was selected as an AAPM (American Association of Physicists in Medicine) Science Council Associate Mentorship Program Fellow. The fellowship provides a cash award to cover expenses related to attending the next two AAPM annual meetings and the opportunity to work with a senior member of the AAPM Science Council.

Two new patents were granted under **Thomas Bortfeld, PhD** and team:

- Papp D, Unkelbach J, Bortfeld T, Bal M. Volumetric Modulated Arc Therapy (VMAT) with Non-Coplanar Trajectories. U.S. patent 10549115, **and**
- Bortfeld T, Flanz J, Lu H-M, Yan S. System and method for gantry-less particle therapy. U.S. patent 10880983.

An article by **Eikelder** et al. was highlighted in the 2021 ESTRO spring newsletter: https://www.estro.org/About/Newsroom/Newsletter/Physics/Optimal-treatment-plan-adaptation-using-mid-treatm

Thomas Bortfeld, PhD received a fellowship from the Center for Advanced Studies at the Ludwig Maximilians University in Munich.



Modeling COVID-19 infection. The mathematical model incorporates SARS -CoV2 infection of epithelial and endothelial cells, the RAS, T cell activation and immune checkpoints, the known IL6 pathways, neutrophils, and macrophages, as well as the formation of NETs, and the coagulation cascade. The model also includes systemic circulation of virus and microthrombi. From: *Voutouri et al., Proc Natl Acad Sci U S A 2021.*

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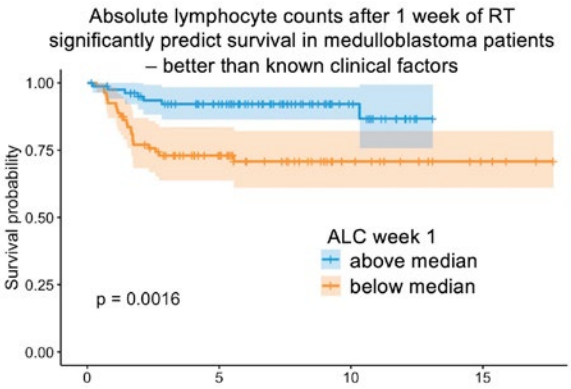


Circulating Lymphocyte Counts Early During Radiation Therapy Are Associated With Recurrence in Pediatric Medulloblastoma. Grassberger et al. Int J Radiat Oncol Biol Phys. 2021 Jul 15;110(4):1044-1052. doi: 10.1016/j.ijrobp.2021.01.035. Epub 2021 Feb 5. PMID: 33556478

New Grants:

Harald Paganetti, PhD, received a new grant from the **NIH/NIBIB (R01 EB031102)**

Jan Schuemann, PhD, received a new grant from the **NIH/NCI (R21 CA252562)**

Alejandro Bertolet Reina, PhD, received a new grant from the **NIH/NCI (K99 CA267560)**.

Tumor Biology (Edwin Steele Laboratories Achievements):

Rakesh Jain, PhD, and **Dai Fukumura, MD, PhD** were named Highly Cited Researchers, for the 8th and 3rd 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). In 2021, fewer than 6,700, or about 0.1% of the world's researchers in 21 research fields and across multiple fields, earned this distinction.

Rakesh Jain, PhD (ranked 29th), Lance Munn, PhD (42,639th), Dai Fukumura, MD, PhD (52,264th) and **Dan Duda, DMD, PhD (67,408th)** are among the top 2 percent of scientists (186,177) in the world based on a composite score [c-score] of citations, co-authorships, and collaborations *[Baas, Jeroen; Boyack, Kevin; Ioannidis, John P.A. (2021), "August 2021 data-update for "Updated science-wide author databases of standardized citation indicators"", Mendeley Data, V3, doi: 10.17632/btchxktzyw.3]*

Rakesh Jain, PhD (ranked 99th) among the most highly cited researchers (h-index >100). [https://www.webometrics.info/en/hlargerthan100]

Rakesh Jain, PhD became a "five-star fellow," having been recognized as a Fellow by five prestigious national academies: the National Academy of Inventors, the American Academy of Arts and Sciences, the National Academy of Engineering, the National Academy of Medicine, and the National Academy of Sciences.

Dan Duda, DMD, PhD was honored with the election to the rank of Fellow of the American Association for the Advancement of Science (AAAS) Fellow and will be inducted at the Annual AAAS Meeting in Philadelphia in February 2022. AAAS Fellows are a distinguished cadre of scientists, engineers and innovators who have been recognized for their achievements across disciplines.

Tim Padera, PhD was named a member of the Class of 2021 MGH Research Scholars. The MGH Research Scholars program began in 2011 to provide forward-thinking researchers with the unrestricted funding they need to take their work into new and uncharted territories.

Heena Kumra, PhD, Postdoctoral Fellow, received the American Society for Matrix Biology Founder's Award.

The following are new findings from the Steele Labs:
Rakesh Jain, PhD, and **Lance Munn, PhD** of the Steele Labs worked with Triantafyllos

Stylianopoulos, PhD, and Valantis Voutouri, PhD, of the University of Cyprus. Other authors included **Melin Khandekar, MD**, and **Mohammad Nikmaneshi** of the Department of Radiation Oncology, as well as a multidisciplinary team from MGB and the University of Cyprus. The mathematical model developed by the team, published in the *Proceedings of the National Academy of Sciences*, investigated the use of computer simulations to improve our understanding of COVID-19 risks and treatments. This team has now extended this model to include vaccines to predict the frequency of boosters needed to contain COVID-variants.

Rakesh Jain, PhD, and Matthew Vander Heiden, MD, PhD, Director of the MIT/Koch Institute, in collaboration with a team of MGH and MIT researchers, discovered fatty-acid metabolism as a new target to treat breast cancer brain metastases that are refractory to targeted therapies. This study was published in *Nature Cancer* and was accompanied by a commentary.

Rakesh Jain, PhD, and Hye-Jung Kim, PhD of DFCI, in collaboration with a team MGH, DFCI and MIT researchers, discovered a new strategy to improve immunotherapy of glioblastoma—where all randomized clinical trials of immune-checkpoint blockers have failed to date. This study was published in *Nature Communications*.

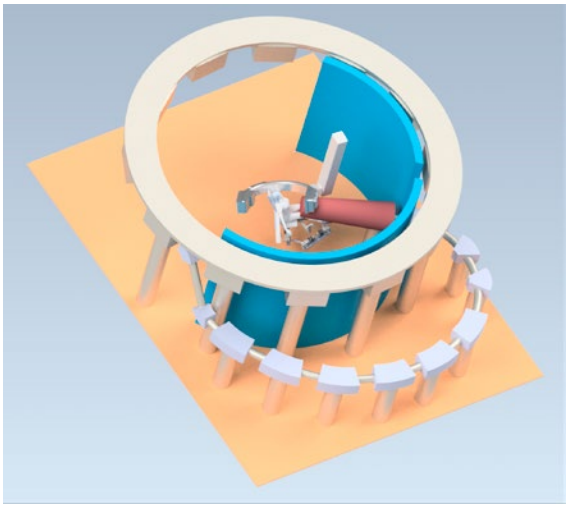
Dan Duda, DMD, PhD, and **Rakesh Jain, PhD**, in collaboration with a team of researchers, discovered a promising approach to inhibiting a less frequent but highly treatment-refractory liver cancer. This study was published in *Gut*.

Dai Fukumura, MD, PhD and **Rakesh Jain, PhD**, in collaboration with a team of researchers discovered a new approach to improve immunotherapy of type of colorectal cancer that are refractory to immune-checkpoint blockers. This study was published in the *Proceedings of the National Academy of Sciences*.

Dai Fukumura, MD, PhD and **Rakesh Jain, PhD**, in collaboration with a team of researchers discovered a new mechanism of how physical exercise slows tumor growth and how it can improve the outcome immune-therapy and decrease metastasis. This study was published in *Cancer Immunology Research* and featured on the journal cover.

Tim Padera, PhD, and colleagues uncovered a critical mechanism that lymph node metastasis use to prevent lymphocyte infiltration into the lesions and suppress anti-cancer immune responses. This study was published in *Nature Biomedical Engineering*.

Lei Xu, MD, PhD, and colleagues uncovered a novel strategy to prevent tumor-induced hearing loss and to enhance radiation treatment efficacy in Neurofibromatosis type II vestibular schwannomas. This study was supported by the Department of Defense Neurofibromatosis Research Mechanisms and published in *Science Translational Medicine.*



Thomas Bortfeld, Matthew Fernandez deViana, Susu Yan: "The societal impact of ion beam therapy", Zeitschrift für Medizinische Physik, Volume 31, Issue 2, May 2021, Pages 102-104.

New Grants:
Rakesh Jain, PhD, received two new grants from the NCI (**R01CA259253 and U01CA261842**)

Dan Duda, DMD, PhD, received new grants from the NCI (**R01CA260872, R01CA260857, R01CA247441, R03CA256764**) and the DoD (**W81XWH-21-1-0738**).

Dai Fukumura, MD, PhD, received a new grant from the NIH/NINDS (**R01NS118929**).

Lance Munn, PhD, received three new grants from NIH (**U01CA261842, R01CA247441 and R21EB031982**)

Lei Xu, MD, PhD, received a new grant from the American Cancer Society.

New Fellowships:
Satoru Morita, MD, PhD, Postdoctoral Fellow, received the JSPS Fellowship, Japan

Mohammad Ravazi, PhD, Research Fellow in the Steele Labs, received an NCI F32 Postdoctoral Fellowship Award.

Nilesh Talele, PhD, Postdoctoral Fellow was named a Cancer Research Institute Merck Fellow.

Hajime Taniguchi, MD, PhD, Postdoctoral Fellow, received a Fellowship from the NextSurgery Foundation Fellowship, Japan

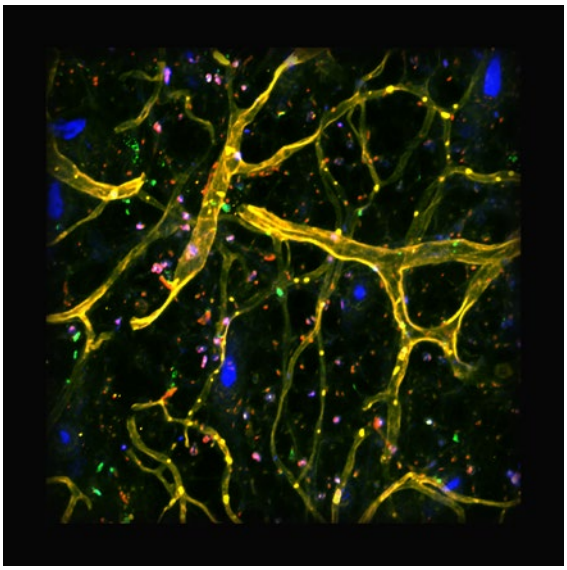
Valantis Voutouri, PhD, Postdoctoral Fellow, received a Marie Curie Fellowship from the European Research Council

Xinyue Dong, PhD, Postdoctoral Fellow, received the Fund for Medical Discovery (FMD) Research Fellowship Award, MGH ECOR

Name: Nicole DaSilva RT(R)(N)(CT)(ARRT), CNMT, Radiology, Gordon Center for Medical Imaging PET Core
Category: Humans of MGRI
Title: Never Bored

Radiology

Department Report



The Mass General Research Institute (MGRI) Image Awards were created to celebrate research at Mass General and to share with the world the cutting-edge science done in the hospital. The 2021 Image Awards saw a host of excellent submissions from Radiology researchers, including the above: "Golden Fabric in the Skin" by Satoshi Kashiwagi, MD, PhD, of the Gordon Center for Medical Imaging.

Dr. Kashiwagi says of this image: "Our regular life is supported not by special but ordinary things like ambient light. Our body can respond to light with a coordinated work of our own cells. This image revealed such a secret life of our own cells."

JAMES A. 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 and total research activity of $140M for the 2021 fiscal year—a nearly 8% increase over the year before. 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.

Because the department's research portfolio is so broad, we focus here on achievements in a few select areas: the ongoing COVID-19 pandemic, breast imaging and neuroimaging. Research in another area—artificial intelligence—is woven throughout the studies we describe. These achievements are representative of the important work done across the department in the past year.

Achievements:

Nearly two years after its onset, **COVID-19** remains an active area of investigation in the Mass General Department of Radiology. For example, researchers have explored the potential of artificial intelligence in predicting negative outcomes in patients with COVID-19, information that could prove critical in managing the patients. In a study described in *Scientific Reports* [1], a team of investigators in the Webster Center for Quality and Safety in the Department of Radiology and the Mass General & BWH Center for Clinical Data Science showed that assessment of chest X-rays with AI could predict recovery and/or the need for mechanical ventilation. Similarly, in a paper published in *Medical Image Analysis* [2], a team based in the 3D Imaging Research lab showed that unsupervised deep learning based on computed tomography (CT) images offered significantly better prognosis in patients with COVID-19 than established laboratory tests and existing image-based visual and quantitative survival predictors.

Researchers also looked beyond critical care to potential societal impacts of COVID-19. As the pandemic continued, investigators at the Martinos Center for Biomedical Imaging who had been using functional MRI to examine the relationship between "personal space" requirements and social dysfunction in patients with schizophrenia (as described in *Neuroimage: Clinical* [3], for example), started looking into possible detrimental effects of social distancing. They have already observed increases in subjects' personal space requirements since the onset of the pandemic. Whether the increases endure after the pandemic subsides is an important question, particularly because of the relationship between personal space requirements and social functioning.

Other concerns arose as COVID-19 vaccines became available. Swelling of lymph nodes in the armpit area is a normal response to COVID-19 vaccinations, for example, but when they are seen

on mammograms, they can be mistaken for nodes that are swollen because of cancer. To avoid confusion by patients and their providers, and to avoid delays in either vaccinations or recommended mammograms for the duration of the pandemic, investigators in the Breast Imaging Research Center (BIRC) reported guidance for what to do when a mammogram reveals swollen lymph nodes in women recently vaccinated for COVID-19. They described the approach in the *American Journal of Roentgenology* [4].

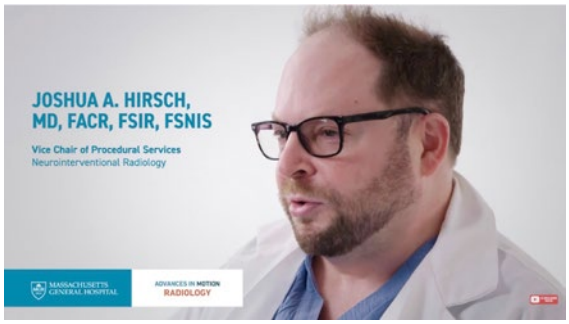
The past year has also seen other achievements in **breast imaging**: not least, in the surveillance of patients with breast cancer. With increasing concerns about overtreatment, active surveillance programs have been introduced to monitor disease and help patients avoid unnecessary surgery and radiation. To support these efforts, BIRC researchers developed an artificial intelligence tool to identify women with low-risk disease who are appropriate candidates for the programs. Similarly, in a paper published in *Radiology* [5], researchers demonstrated that digital breast tomosynthesis (DBT) is superior to mammography for routine surveillance of breast cancer survivors who have not undergone a bilateral mastectomy.

Artificial intelligence has benefited other areas as well. In a study reported in *Science Translational Medicine* [6], BIRC researchers collaborated with researchers at MIT to develop a new AI model to predict a woman's future risk of breast cancer based on her mammogram alone. Validation trials in patient populations in Europe and Asia showed that the system was significantly more accurate than prior methods in predicting cancer risk and identifying high-risk groups.

On the technology development front, researchers at the Martinos Center for Biomedical Imaging demonstrated that magnetic particle imaging (MPI), an emerging imaging technology similar to magnetic resonance imaging but with much higher sensitivity, may allow intraoperative breast tumor margin assessment. Currently, up to 66 percent of women who undergo lumpectomy require a second surgery because positive margins are found postoperatively. As described in *Scientific Reports* [7], repeated use of MPI during breast-conserving surgery could better achieve complete tumor removal and thus reduce the need for follow-up surgeries.

Neuroimaging studies, especially studies advancing our understandings of and helping improve management of neurodegenerative disease, also continued apace in the past year. In a study reported in *Nature* [8], for example, using imaging, researchers in the Center for Systems Biology and colleagues identified a signaling molecule that can help modify inflammation and the immune system to protect against Alzheimer's disease. The findings could have important clinical implications for the management of Alzheimer's. In another study, reported in *Science Translational Medicine* [9], researchers in the Gordon Center for Medical Imaging developed an automated imaging method that can identify and track the development of tau deposits in a patient's brain; tau is one of two key abnormal protein deposits that accumulate in the brain during the

Hyperfine, a company co-founded by the Martinos Center's Matthew Rosen, PhD, has introduced a portable MRI scanner based on technology developed in Dr. Rosen's lab. Shown here are Dr. Rosen (left) and collaborator Taylor Kimberly, MD, PhD, chief of the Division of Neurocritical Care at Mass General, with a Hyperfine scanner now in use at the hospital.



Research in the department also included important work in interventional radiology. In a video shared on Mass General's Advances in Motion news platform, Joshua Hirsch, MD, described a series of studies demonstrating the benefits of the image-guided procedure vertebral augmentation in treating patients with spine compression fractures.

development of Alzheimer's disease. This work could lead to earlier diagnosis of Alzheimer's.

Other studies have probed the mechanisms of pain. For instance, researchers at the Martinos Center for Biomedical Imaging have uncovered a relationship between widespread pain across patients' body and catastrophizing thoughts about their pain. Better understandings of how these processes interact could lead to new therapies for patients with chronic pain. They described the study in *Arthritis & Rheumatology* [10]. In other work at the Martinos Center, researchers showed that multimodal imaging with positron emission tomography (PET) and magnetic resonance imaging (MRI) could reproducibly discriminate between individuals with and without chronic low back pain. Their observations, reported in *Brain* [11], support investigation of neuroinflammation as a therapeutic target for chronic pain.

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Ragon Institute of MGH, MIT & Harvard

Department Report

BRUCE D. WALKER, MD, DIRECTOR
FACUNDO BATISTA, PHD, ASSOCIATE DIRECTOR

The mission of the Ragon Institute 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. Being embedded in the most robust biomedical research ecosystem in the world, we have shown over our first 12 years of existence that this model works. Our initial goal of making an effective global HIV vaccine is still underway and, despite a recent failure to protect in a Phase 3 trial in Africa, we have used the same platform to generate an effective COVID vaccine in collaboration with Johnson and Johnson. Moreover, we are developing other promising additional platforms for HIV, both to elicit B cells and T cells. In addition to extensive work on COVID, we have expanded to focus on additional pathogens (e.g., tuberculosis, influenza, Zika, malaria) as well as new areas of immunological research (e.g., microbiome, cancer, artificial intelligence). Notably, several of the Ragon's investigators were named to Clarivate Analytics' Highly Cited Researchers list for 2021.

Achievements:

Among the important accomplishments in 2021 are the following:

1. Artificial Intelligence, Machine Learning and the Immune System

Through a $2M gift from Mark and Lisa Schwartz, and MIT leadership from Dr. Regina Barzilay, we have established a new Ragon/MIT initiative to apply Artificial Intelligence (AI) and Machine Learning (ML) to understanding the human immune system.

Human immune responses are dynamic, multi-scale processes driven by numerous interacting components. This initiative is based on the hypothesis that a deep functional understanding of these multi-dimensional processes, whether effective or dysregulated, can only be achieved by subjecting data collected from well pedigreed cohorts and their avatars to iterative integrations of machine learning, mechanistic modeling, experiments with animal models, and validation in human model systems. By pursuing this approach, we will achieve a working knowledge of human immunity, enabling us to harness the immune system to prevent and cure disease.

To support this initiative, we are in the process of releasing a request for proposals for collaborative projects involving both Ragon and MIT faculty, with the goal of funding a PhD or postdoctoral fellow to be imbedded at the Ragon Institute. Also planned are an internal workshop among Ragon and MIT investigators and a major symposium for later in the spring of 2022.

Artist's rendition of the new Ragon Institute at 600 Main Street in Kendall Square

2. COVID-19 Response

With the advent of the COVID pandemic, Ragon Institute investigators pivoted their efforts, applying our strategy of cross-disciplinary, collaborative science to help catalyze a Massachusetts-wide effort through helping to create the Massachusetts Consortium on Pathogen Readiness (MassCPR). Funded in part through a $5M donation from Mark and Lisa Schwartz, this effort consists of over 500 investigators from Harvard, MIT, Tufts, BU and UMasss, as well as all of the academic teaching hospitals in Massachusetts, the Broad Institute, the Wyss Institute, the Ragon Institute, Moderna and the MA Department of Health. Under this umbrella, the Ragon BSL3 has been made available to MassCPR investigators, as well as our protein production facilities, and we have also led efforts in sample acquisition and distribution.

Ragon Investigators provide important MassCPR Executive Committee Leadership, and our own efforts have provided key insights into COVID pathogenesis and prevention. In addition to development of the Johnson and Johnson Ad26 COVID vaccine by Ragon member **Dan Barouch, MD, PhD**, (*Cell* 2021, *Science* 2021), key additional contributions in 2021 include, among many others, demonstration of immunogenicity of Ad26.COV2.S vaccine against SARS-CoV-2 variants in humans (*Nature* 2021), correlates of protection against SARS-CoV-2 in rhesus macaques (*Nature* 2021), differential kinetics of immune responses elicited by Covid-19 vaccines (*NEJM* 2021), demonstration that COVID-19-neutralizing antibodies predict disease severity and survival (*Cell* 2021), distinct early serological signatures track with SARS-CoV-2 survival (*Immunity* 2020), quick COVID-19 healers sustain anti-SARS-CoV-2 antibody production (*Cell* 2021), compromised SARS-CoV-2-specific placental antibody transfer (*Cell*

Ragon Institute of MGH, MIT & Harvard

Department Report

(May 2021) The FRESH clinical research team celebrate the launch of the first clinical trial to be conducted at the Ragon's FRESH site. The NIH funded trial is testing a live biotherapeutic product, ***LACTIN-V***, on its ability to decrease genital tract inflammation associated with increased HIV acquisition in young women at extraordinarily high-risk of HIV infection.

2021), compromised humoral functional evolution tracks with SARS-CoV-2 mortality (*Cell* 2021), impaired local intrinsic immunity to SARS-CoV-2 infection in severe COVID-19 (*Cell* 2021), network guided design of a potential T cell COVID immunogen targeting responses to mutationally constrained amino acids (*Cell* 2021), and application machine learning algorithms originally developed for human natural language to predict viral evolution (*Science* 2021).

3. Infrastructure and support

In the past year, we have expanded to an additional floor in our existing building at 400 Technology Square in Cambridge, allowing us to recruit five additional junior faculty. These assistant professors are on a tenure track through their affiliation with MIT, each covered by an individual $6M endowment provided by an additional $30M donation from Terry and Susan Ragon. This has not only expanded the scope of research at the institute but has also increased faculty diversity. In addition, we have launched The Ragon Early Independence Fellows Program, which provides a unique career development pathway for exceptional basic scientists and clinician-scientists who have recently completed graduate training. One physician-scientist and one PhD scientist have been recruited as the inaugural fellows, again expanding the scope of research and also diversity of the Ragon Institute.

In addition to the new space in our current building, in 2021 we acquired land, completed the design and broke ground for our new building at 600 Main Street, across from our current location (figure). The 225,000 square foot building is slated for completion in Q1 of 2024.

4. Expansion of global initiatives

One of the unique features of the Ragon Institute is a longstanding collaboration in South Africa, where we have helped to build two interconnected state-of-the-art research institutes, the Africa Health Research (AHRI) and the Doris Duke Medical Research Institute (DDMRI). There we have also established a program called FRESH (Females Rising through Education and Health) that is both a pathway out of poverty and HIV prevention program for young women at high risk of HIV infection, as well as a platform for studying hyperacute HIV infection. FRESH is located within a shopping mall in a former township in KwaZulu Natal, to avoid stigma that would be associated with a medical care facility and was relocated to expanded facilities at a newer shopping mall in 2021. The expanded facilities include a pharmacy, allowing the team led by Ragon member Krista Dong, MD and Ragon Associate Member Thumbi Ndung'u, PhD, to initiate interventional clinical trials. The first to launch is an interventional trial called the Lactin-V Study which seeks to alter the vaginal microbiome to prevent HIV infection, based on previous Ragon studies showing that the nature of the vaginal microbiome impacts acquisition risk (*Immunity* 2015, *Immunity* 2017).

Name: Ankita Banerjee, MSc, Department of Surgery
PI: Laurence Rahme, PhD
Category: A Closer Look
Title: Scientific Hues in a Jar

Surgery

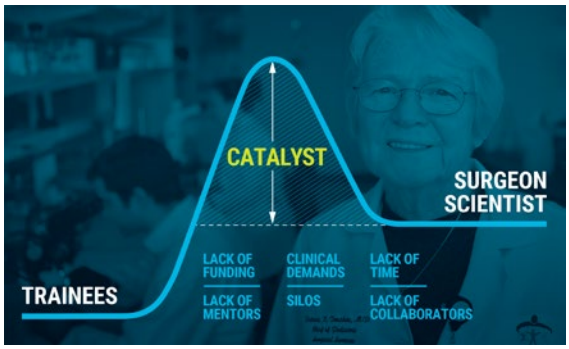
Department Report

KEITH D. LILLEMOE, MD, SURGEON-IN-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.

Spotlight on Research



Patricia K. Donahoe, MD, Surgeon-Scientist Research Program

Patricia K. Donahoe, MD, Surgeon-Scientist Research Program
The future of surgical innovation depends on the curiosity and dedication of the surgeon-scientists and those who collaborate with them, who can take the challenges their patients face today and turn them into the therapies of tomorrow. We are enormously grateful for the vision and friendship of Wei-Wu He, PhD, and the Huiying Memorial Foundation for providing a generous gift honoring Dr. Patricia K. Donahoe for her exemplary career and her immense contributions to science and patient care.

This gift enables the creation of the Patricia K. Donahoe, MD, Surgeon-Scientist Research Program, with the mission to nurture the careers of Mass General's surgical residents and faculty to pursue innovative research and launch the best ideas with the goal of making a meaningful difference for our patients.

The Patricia K. Donahoe, MD, Surgeon-Scientist Research Program will achieve its mission of developing the next generation of leaders with three award mechanisms: The Incubator Award, Resident Catalyst Award, and the Faculty Catalyst Award.

The inaugural award recipients are:

Catalyst Awards

Principal Investigator	Division/Center	Award
David Pepin, PhD	Pediatric Surgery Research Laboratories	Mid-Career Catalyst Award
Uma Sachdeva, MD, PhD	Division of Thoracic Surgery	Early Career Catalyst Award
Richard Guyer, MD, PhD	Pediatric Surgery Research Laboratories	Resident Catalyst Award

Incubator Awards

Principal Investigator	Division/Center	Co-Investigator(s)
Eric C. Liao, MD, PhD	Division of Plastic and Reconstructive Surgery	Allan Goldstein, MD
Alessandro Alessandrini, PhD	Center for Transplantation Sciences	Sareh Parangi, MD Nabeel El-Bardessy, PhD
Korkut Uygun, PhD	Center for Engineering in Medicine & Surgery	Kimberly Ann Krautkramer, MD, PhD Raul Mostoslavsky, MD, PhD

New $47.5M research center for genomic mechanisms of disease
Based at the Broad Institute of MIT and Harvard in Cambridge, MA, and supported by a $47.5 million grant from Novo Nordisk Foundation, the Center will develop tools and publish datasets that will be shared freely with the research community. A key activity of the Center is to launch and facilitate close collaborations between the Broad Institute and researchers at Danish universities investigating the genetic basis of common complex disease, with an initial focus on type 2 diabetes and obesity.

This new center will be directed by **Kasper Lage, PhD**, an MGH faculty member and Associate Professor of Surgery at Harvard Medical School, who is both a native of Denmark as well as a long-time member of the Broad Institute community. Kasper currently serves as the Director of Bioinformatics in the Department of Surgery.

It is the hope that this collaborative initiative will give the next generation of Danish scientists an opportunity to benefit from the Broad's unique technology platforms, as well as their expertise in genomic technologies in data science, and potentially create a stronger connection between scientists in Denmark, the Broad Institute, Harvard Medical School, and the MGH Department of Surgery.

Kasper Lage, PhD, MGH faculty member and Associate Professor of Surgery at Harvard Medical School

Centers of Excellence

The Department of Surgery has four specialized centers of excellence in research and the Surgical Artificial Intelligence and Innovation Laboratory—all of which are designed to enhance the research environment, foster collaboration, and leverage expertise and resources to expand the productivity and output in areas of interest.

Center for Transplantation Sciences (CTS)
The CTS at Massachusetts General Hospital is a multidisciplinary research center working at the interface between basic science and clinical applications in transplantation immunology and related fields. It was established in 2015 by merging the Transplantation Unit Surgery Research Laboratory and the Transplantation Biology Research Center, with **Joren C. Madsen, MD, DPhil**, and **James F. Markmann MD, PhD**, serving as co-directors, with newly recruited, **Richard N. Pierson III, MD**, serving as scientific director. The position of scientific advisor is held by **David H. Sachs, MD**.

The mission of the Center for Transplantation Sciences (CTS) at Massachusetts General Hospital is to improve the number and the lives of recipients with organ, tissue and cell transplants by:

- Better understanding the mechanisms underlying the immune response
- Developing novel means of inducing immune tolerance
- Finding creative ways of increasing the supply of donor organs

Center for Engineering in Medicine & Surgery (CEMS)
The CEMS engages in basic sciences, clinical medicine and engineering to solve every day biomedical challenges for patients. Our team of clinically-inspired engineers, physicians and biologists, among others, use creative scientific approaches to improve health care delivery and further the use of personalized medicine, minimally invasive therapies, and new technologies for today's and tomorrow's diagnostics and treatments.

The Center's position within the MGH clinical and research environments enables not only the traditional academic triad of sciences, technology, and clinical medicine, but its position also enables a fourth dimension—innovation. Serving as co-directors are **Mehmet Toner, PhD**, and **Martin Yarmush, MD, PhD**.

Center for Organ Engineering
In the Center for Organ Engineering, **Harald Ott, MD**, is currently integrating stem cell biology, developmental biology, tissue engineering and transplantation science to develop novel solutions for end organ failure. The Center is linked to the Harvard Stem Cell Institute, MIT, Harvard Medical School, the New England Organ Bank and various clinical departments of MGH. The research has a high potential clinical impact and may help develop new forms of treatment for diseases such as heart failure, end stage lung disease, renal failure and diabetes. Their research projects are highly innovative and give us the unique opportunity to maintain a clear translational focus in a multidisciplinary team.

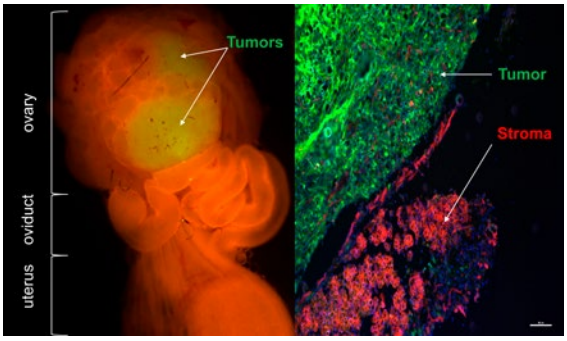
Codman Center for Clinical Effectiveness in Surgery
The Codman Center's mission is to deliver the safest, highest value patient care through innovative research and education. Local, regional and national initiatives analyze and promote the clinical effectiveness of surgical care. The Codman Center collaborates with Mass General Brigham hospitals and other hospitals throughout the state to promote quality improvement in Massachusetts. Nationally, the center's leaders are the architects of quality and safety metrics used in hospitals across the country with **Matthew Hutter, MD**, serving as the medical director, **David Shahian, MD**, serving as the associate director, and **David Chang, PhD**, as the director of healthcare research and policy development

Achievements:

Genetically defined syngeneic mouse models of ovarian cancer as tools for the discovery of combination immunotherapy
Currently available immunotherapies, which have dramatically improved outcomes for many cancer patients, have not yet been successful in ovarian cancer. To address this gap, **David Pepin, PhD**, and his team developed clinically relevant syngeneic mouse models that recapitulate molecular subtypes of this disease, which can be used to study immunotherapies in ovarian cancer.

In one panel, we engineered murine Fallopian tube epithelial cells using CRISPR-CAS9 to phenocopy homologous recombination-deficient tumors through the combined loss of p53, Brca1, Pten, Nf1 and overexpression of Myc and mutant p53R172H. In a second panel, modeling homologous recombination-proficient tumors, we constructed genotypes bearing combinations of loss of p53, and overexpression of Ccne1, Akt2, mutant p53R172H, and mutant KrasG12V. When implanted into syngeneic immunocompetent C57BL/6 hosts, these engineered murine Fallopian tube epithelial cells form tumors recapitulating human disease, including genotype-driven differences in response to treatment.

Using these models, we compared the efficacy of combination immunotherapies based on the genetic makeup of the tumors. In one such subtype, CCNE1-amplified tumors, which comprises about 20% of high grade serous ovarian cancers, a combination immunotherapy including anti-CTLA4, and anti-PD-L1 antibodies produced complete responses in mice. Strikingly, we observed strong inter-clonal differences in this response despite identical genotypes, which lead us to identify epigenetic differences in follistatin as a potent driver of resistance. Overexpression of follistatin in cancer cells was sufficient to induce resistance to the combination immunotherapy, while knockout could restore complete response in otherwise resistant clones. Thus, follistatin represents a novel therapeutic target to sensitize ovarian cancers to immune checkpoint inhibitors.



Left: A CCNE-1overexpressing ovarian tumor (GFP) invading the ovary of a syngeneic tdTomato reporter mouse.

Right: Interface between cancer cells (GFP) and stromal cells (tdTomato) within an omental metastasis of the same tumor.

Generation of an objective measure of thrombotic risk via viscoelastic assays to predict graft thrombosis after revascularization

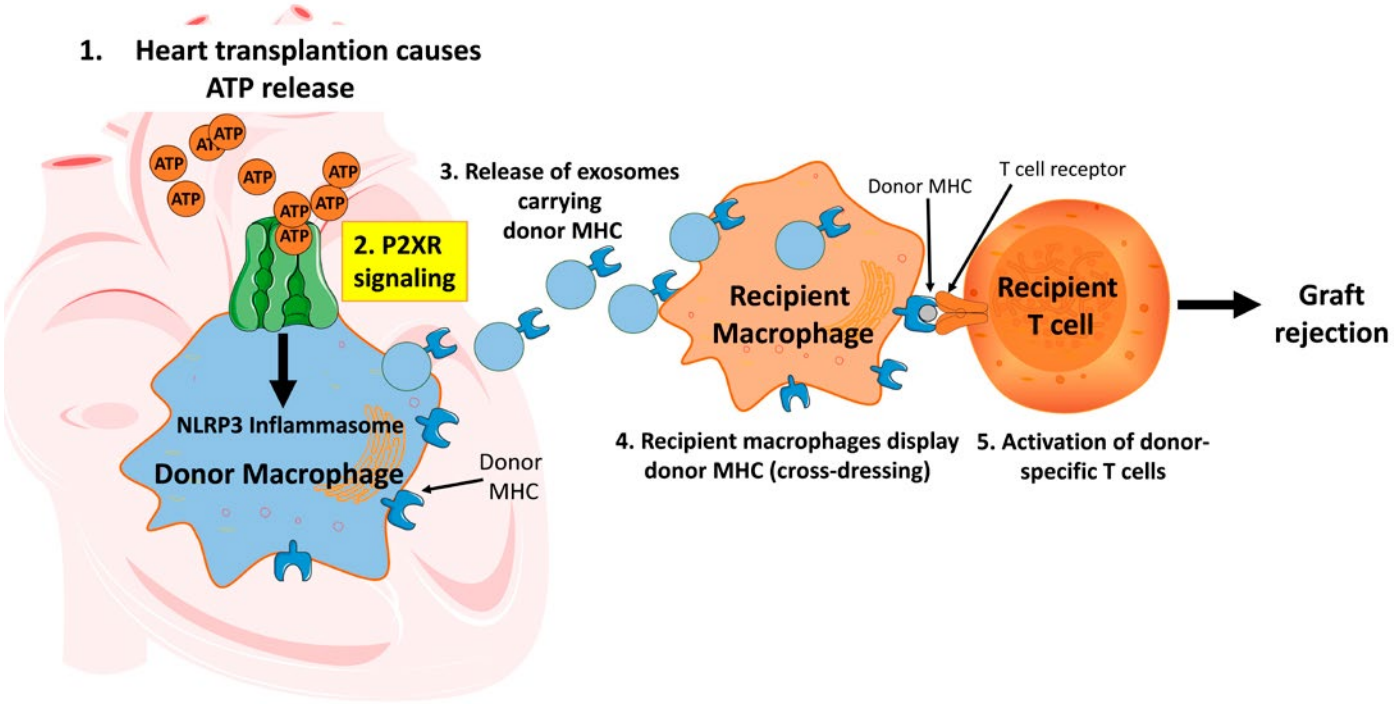
There are myriad factors that contribute to a patient's thrombotic risk; some factors are transient (i.e. inflammation, trauma, surgery) and interplay with baseline genetics, co-morbidities and extrinsic factors such as smoking—making patient's coagulation profile fluctuate longitudinally. There is currently no objective measure to determine an individual's coagulative state at a given point in time and no actionable test that allows antiplatelet and anticoagulation to be targeted appropriately in a personalized fashion. **Anahita Dua, MD, MS, MBA, FACS**, and her team focuses on identification of objective measures to guide thromboprophylaxis. Her team has conducted a large, prospective observational study to identify cut-points within viscoelastic testing that can predict an individual patient's thrombotic risk.

The TEG team found that patients in the thrombotic group had significantly higher platelet aggregation and lower platelet inhibition as compared to the nonevent group ($p<0.01$). Platelet aggregation and inhibition were confirmed as independent predictors of thrombotic events via logistic regression analysis ($p<0.05$). The TEG team was able to identify an optimal cut-point of >70.8% platelet aggregation [area under the curve (AUC)=0.792, 95% CI 0.66-0.93] and <29.2% platelet inhibition [AUC=0.782, 95% CI 0.64-0.92] to identify those at high risk of thrombosis with 84.6% sensitivity –this is a novel, objective measure of thrombotic risk. Based on the optimal cut-points of >70.8% platelet aggregation and <29.2% platelet inhibition, the recommendation is a step-up approach with antiplatelet therapy to achieve optimal platelet activity and decrease the risk of thrombosis. This data is being submitted to the NIH to ultimately fund a randomized control trial using TEG guidance as the interventional arm to guide thromboprophylaxis.

P2X7 receptor signaling initiates acute inflammation leading to transplant rejection

It is now firmly established that innate immunity triggered immediately after organ transplantation is essential to subsequent activation of donor-specific recipient T cells leading to immune rejection. However, the mechanisms by which innate immunity controls T cell responses after transplantation are still elusive. A better understanding of the relationships between innate and adaptive immunity is not only important for the design of new therapies in transplantation but also to harness inflammatory processes occurring after any surgical procedure.

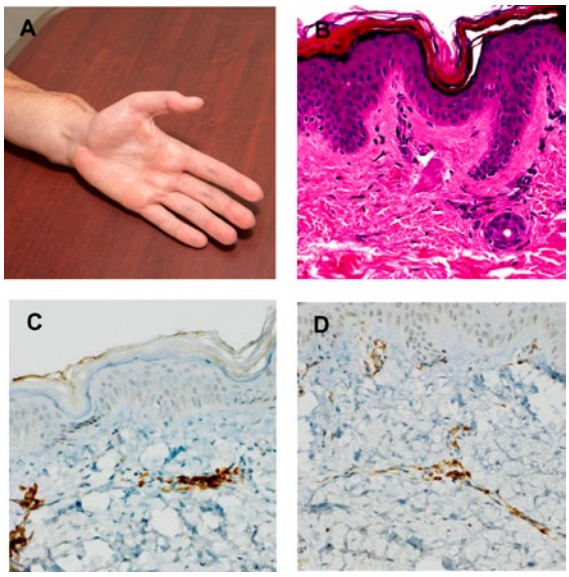
Transplantation surgery is associated with tissue injury leading to instantaneous extracellular release of ATP by intragraft cells. These ATP molecules bind to purinergic receptors called P2XRs that are expressed on macrophages. P2XR signaling leads to macrophage activation and triggers an inflammatory cascade associated with the recruitment and activation of recipient myeloid and lymphoid cells.



In 2016, **Gilles Benichou, PhD**, and his team at MGH documented for the first time that nanovesicles called exosomes are released by donor cells after skin and organ transplantation. We showed that these donor exosomes contribute to alloimmunity by transferring donor MHC molecules on recipient antigen presenting cells (APCs). This process, called MHC cross-dressing, initiates activation of donor specific T cells in the recipient's lymphoid organs and presumably in the graft. There is now plenty of evidence showing that this phenomenon plays a key role in allograft rejection.

In 2021, we investigated the role of ATP-mediated P2XR signaling in donor exosome release and MHC cross-dressing *in vitro* and in skin- and heart-grafted mice. We showed that inhibition of P2XR signaling using an agent called A-438079 abolished exosome release by activated macrophages *in vitro*. Most importantly, treatment of skin- and heart- transplanted mice with A-438079 prevented donor MHC cross-dressing and led to long-term survival of these transplants.

This study shows for the first time the role of P2X7R signaling in exosome release by macrophages and subsequent cell-cell transfer of MHC molecules. This reveals a new aspect of the relationships between innate and adaptive immunity in transplantation. Furthermore, our study set the path for the design of P2XR-based therapies designed to prevent deleterious acute inflammatory reactions associated with transplantation and other surgical procedures.



Recipient T cells identified in skin of transplanted human hand without evidence of rejection. (A) Clinical photograph of transplant hand at 1 year. (B) H&E stained section of protocol biopsy obtained at 1 year – no signs of rejection are observed. Immunohistochemical staining for (C) CD4+ and (D) CD8+ at the same time point demonstrate low numbers of these cells, consistent with the absence of acute rejection.

Cutaneous leukocyte lineages in tolerant large animal and immunosuppressed clinical vascularized composite allograft recipients

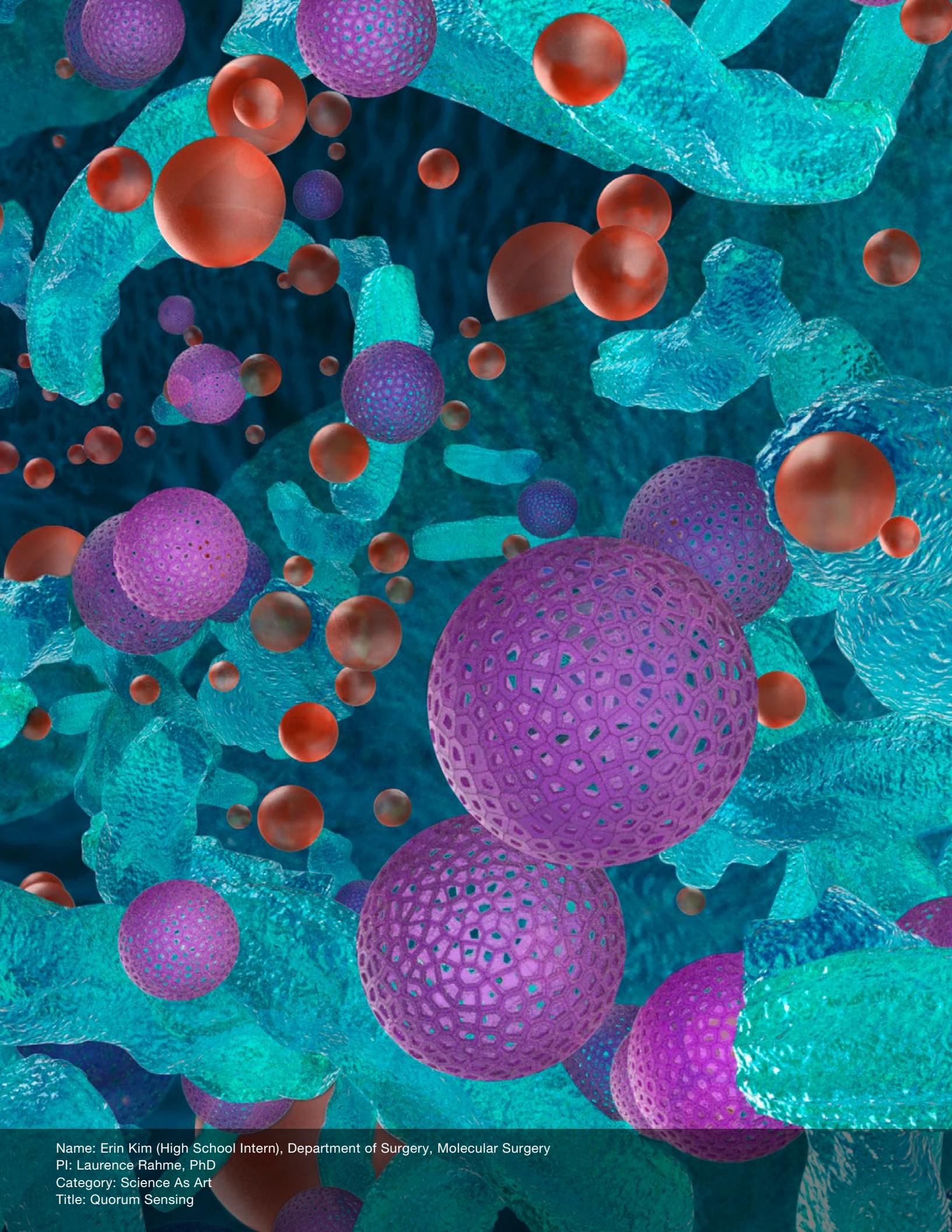
Vascularized Composite Allografts (VCAs) include the transplantation of hands and faces to restore fully functional anatomic units in patients with limb amputations or severe facial tissue loss. Like heart and kidney transplants, however, immune rejection of the allotransplanted hand or face by the host patient is frequently observed and can lead to failure of the grafts and subsequent removal and potentially more disfigurement. The skin in VCAs has been found to be one of the most immunogenic tissue in the allografts and is often the nidus of the initial rejection episodes.

In a study published this year, **Curt Cetrulo, MD**, and his team characterized the skin immune system in VCAs. We demonstrated infiltration of recipient leukocytes, regardless of rejection status, and we showed the co-existence of these cells with donor leukocytes in the absence of rejection in tolerant mixed hematopoietic chimeras. Here we characterize the dermal T cell and epidermal Langerhans cell components of the skin immune system in our porcine model of VCA tolerance, and the kinetics of cutaneous chimerism in both of these populations in VCAs transplanted to tolerant and non-tolerant recipients, as well as in host skin. Furthermore, in biopsies from the first patient to receive a hand transplant in our program, we demonstrate the presence of recipient T cells in the skin of the transplanted limb in the absence of clinical or histological evidence of rejection. Characterization of the components of the skin immune system reveal potential cell population targets for therapeutic intervention for maintenance and/or tolerance induction in clinical VCA.

Pig-to-baboon lung xenotransplantation: Extended survival with targeted genetic modifications and pharmacologic treatments

Richard Pierson, MD, and his team published a landmark manuscript in the American Journal of Transplantation, reporting progress made over the last decade in a pig-to-baboon lung xenotransplant model. Using mechanistically targeted genetic modifications and drug treatments, initial life-supporting lung function was frequently achieved, and recipient survival was extended from hours to days and, in two instances, for over a week.

Separately they reported that ‘humanizing’ pig von Willebrands factor significantly improves the biocompatibility of pig lungs and livers in several models. In principle, the combination of approaches they have studied together chart a ‘way forward’ to clinical lung xenotransplantation. Given the wind in the sails of xenotransplantation generally, fueled by significant progress at MGH and elsewhere toward clinical kidney xenotransplantation, they hope to attract financial support through grants, partnerships, or philanthropy for creating pigs genetically optimized for lung xenotransplantation. Dr. Pierson is “optimistic that, with these animals, we can successfully ‘cross the lung xeno barrier’, and translate this work into a clinical therapeutic”.



Name: Erin Kim (High School Intern), Department of Surgery, Molecular Surgery
PI: Laurence Rahme, PhD
Category: Science As Art
Title: Quorum Sensing

Urology

Department Report

MICHAEL L. BLUTE, SR., MD, CHIEF

Introduction:

The research program in the Department of Urology at the MGH involves a wide breath of funded and unfunded endeavors investigating a range of topics across the field 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 now an additional 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 Biomedial Imaging and Eli Van Allen, MD, PhD of Medical Oncology at DFHCC.

In addition to active labs within the department, our busy clinical surgeons also actively collaborate with translational and basic science researchers at MGH and around the Harvard-MIT community. Douglas Dahl, MD actively recruits patients and contributes intellectually to his collaborative work, including single-cell RNA sequencing of fresh prostate and kidney cancers for evaluation of immune reaction to primary tumors and circulating tumor cell analysis of high-grade prostate cancers and correlation with genomic evaluation of the primary tumor. Brian Eisner, MD continues his collaborative basic science and clinical outcomes work in nephrolithiasis with researchers at MIT and others nationally. Michelle Kim, MD, PhD continues

to develop her Health Services Research endeavors with recent publications as listed below.

Department Research Strategy for the Future:

As we move forward, we aim to continue to build our research infrastructure to allow our faculty to more effectively pursue meaningful research that will improve patient care. We are currently working with Development to raise funds that will help us support our vision for The MGH Urologic Research Institute. This will include three subdivisions, including the Urologic Clinical Outcomes Research Division, the Basic Science and Translational Research Division and the Urologic Clinical Trials Division. Philanthropic and Departmental support will help our busy surgeon-scientists protect the time needed to accomplish research goals while the development of a research support infrastructure will allow us to improve research efficiency and productivity.

Notable Research Awards in 2021:

In 2021, Dr. Keyan Salari was 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.

Publications in 2021:

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A 25-year perspective on evaluation and understanding of biomarkers in urologic cancers. Feldman AS, Lokeshwar V, Lin DW. Urol Oncol. 2021 Sep;39(9):602-617. doi: 10.1016/j.urolonc.2021.06.010. Epub 2021 Jul 24. PMID: 34315659

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. Urol Oncol. 2021 Aug 28:S1078-1439(21)00366-5. doi: 10.1016/j.urolonc.2021.08.007. Online ahead of print. PMID: 34465541

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To stage or not to stage: determining the true clinical significance of the biopsy tract through perinephric fat in assessing renal cell carcinoma. Valencia-Guerrero A, Oliva E, Wu CL, Wu S, Rice-Stitt T, Sadow PM, Dahl DM, Feldman AS, Arellano RS, Cornejo KM. Histopathology. 2021 Jun;78(7):951-962. doi: 10.1111/his.14309. Epub 2021 Apr 19. PMID: 33236381

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Surgical challenges and considerations in Tri-modal therapy for muscle invasive bladder cancer. Feldman AS, Kulkarni GS, Bivalacqua TJ, Black PC, Delacroix S, Lerner SP, Kamat AM, Kassouf W. Urol Oncol. 2021 Feb 25:S1078-1439(21)00012-0. doi: 10.1016/j.urolonc.2021.01.013. PMID: 33642229

Biologically informed deep neural network for prostate cancer discovery. Elmarakeby HA, Hwang J, Arafeh R, Crowdis J, Gang S, Liu D, AlDubayan SH, Salari K, Kregel S, Richter C, Arnoff TE, Park J, Hahn WC, Van Allen EM. Nature. 2021 Oct;598(7880):348-352. doi: 10.1038/s41586-021-03922-4. Epub 2021 Sep 22. PMID: 34552244

Incorporating PSMA-Targeting Theranostics Into Personalized Prostate Cancer Treatment: a Multidisciplinary Perspective. Ng TSC, Gao X, Salari K, Zlatev DV, Heidari P, Kamran SC. Front Oncol. 2021 Jul 28;11:722277. doi: 10.3389/fonc.2021.722277. eCollection 2021. PMID: 34395293

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DM. Urology. 2021 Sep;155:26-32. doi: 10.1016/j.urology.2021.04.040. Epub 2021 May 25. PMID: 34048827

Genome-wide profiling of BK polyomavirus integration in bladder cancer of kidney transplant recipients reveals mechanisms of the integration at the nucleotide level. Jin Y, Zhou Y, Deng W, Wang Y, Lee RJ, Liu Y, Elias N, Hu Y, Luo MH, Liu R, Guan B, Geng J, Xu J, Ma J, Zhou J, Liu N, Blute ML, Colvin RB, Wu CL, Miao Y. Oncogene. 2021 Jan;40(1):46-54. doi: 10.1038/s41388-020-01502-w. Epub 2020 Oct 13. PMID: 33051598

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