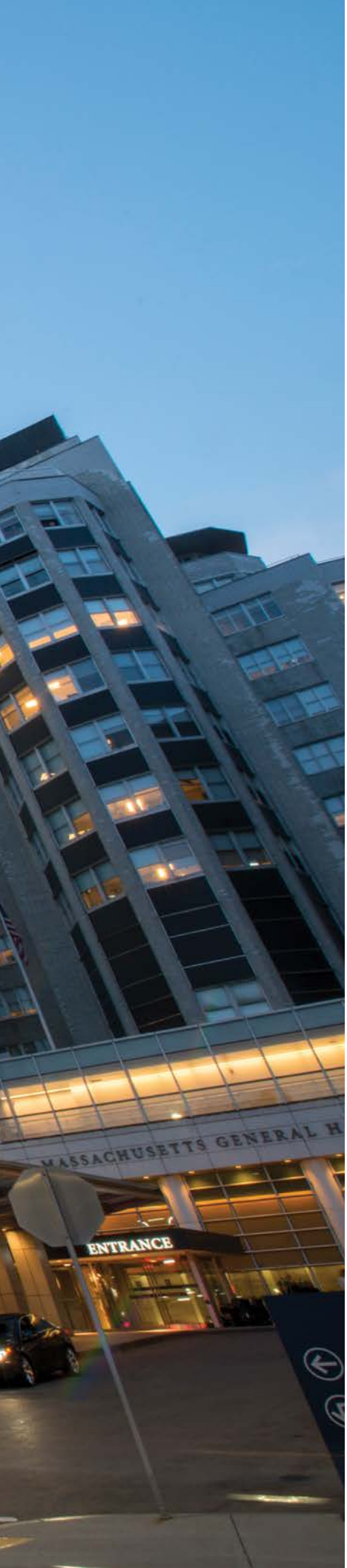
CELEBRATION *of* SCIENCE

COVID Lessons Learned: Scientific and Community Impact

72ND MEETING OF THE MGH SCIENTIFIC ADVISORY COMMITTEE

Wednesday, April 7 & Thursday, April 8, 2021


LUNDER BUILDING
EMERGENCY



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Agenda

Wednesday, April 7, 2021

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

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

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

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

Class of 2021 MGH Research Scholars
Susan A Slaugenhaupt, PhD, Scientific Director, Mass General Research Institute

Martin Prize for Fundamental Research
Large-Scale Topological Changes Restrain Malignant Progression in Colorectal Cancer
Martin Aryee, PhD, Assistant Professor, Pathology

Martin Prize for Clinical Research
Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis
Sabrina Paganoni, MD, PhD, Assistant Professor, Physical Medicine and Rehabilitation

Howard M. Goodman Fellowship
Development and Application of Therapeutic Genome Editing Technologies
Benjamin Kleinstiver, PhD, Assistant Professor, Pathology / Center for Genomic Medicine

Howard M. Goodman Fellowship
Neuro-immune Circuits Controlling the Initiation of Allergic Immunity
Caroline Sokol, MD, PhD, Assistant Professor, Medicine / Rheumatology, Allergy and Immunology

Thursday, April 8, 2021 — COVID Lessons Learned: Scientific and Community Impact

10:00 AM – 12:00 PM **COVID-19, Health Equity, and Developing the Next Generation of Population and Health Care Delivery Team Scientists**

Welcome
Peter L. Slavin, MD, President, MGH

Part I: Developing the next generation

Completing the Translational Research Arc at MGH from Discovery to Delivery Science and Health Equity
Steve Bartels MD, MS., Director, The Mongan Institute

Impact of COVID-19 on Vulnerable Research Faculty- Challenges and Opportunities
Katrina A. Armstrong, MD, Physician-in-Chief, Department of Medicine

Advancing Equity and Diversity and Growing the Pipeline of the Next Generation of Population and Health Care Delivery Scientists: the MGH COVID-Corps Research Internship Program
Long Nguyen MD, MS & Aswita Tan-McGrory, MBA, MSPH

Moderated Q & A Session
Dr. Bartels

Part II: Examples of COVID-19 Population and Health Care Delivery Team Science

Data Science: Rapid Implementation of Realtime COVID-19 Clinical Epidemiology:

- **Mobile Epidemiology of COVID-19 and the Coronavirus Pandemic Epidemiology (COPE) Consortium**
  Andrew Chan MD, MPH & David Drew PhD
- **Rapid Observational Data Collection for COVID-19 Research at Mass General Brigham**
  Ingrid Bassett, MD, MPH & Virginia Triant, MD, MPH

Data Science: Simulation Modeling of the Clinical and Economic Outcomes of COVID-19 Prevention and Treatment: From Homeless Adults in Boston to WHO Low and Middle Income Country Vaccine Distribution
Krishna Reddy, MD

Delivery Science: COVID-19, Health Disparities, and Interventions for Vulnerable Populations, a Panel Discussion
Margarita Alegría, PhD, Efren Flores, MD, Julie Levison, MD, MPH &
Ali Raja, MD, MBA, MPH

COVID-19: Global Health Equity in Pandemic Response
Louise Ivers, MD, MPH

Research on Interventions for COVID Related Stress
Luana Marques, PhD

Moderated Q and A
Dr. Bartels

12:00 – 1:00 PM **Lunch**

1:00 – 2:15 PM **COVID-19 Innovation**
Moderator: Galit Alter, PhD, Ragon Institute of MGH, MIT and Harvard

Keynote: COVID-19 From Bench to Globe
Dr. Alter

Technology
Gary Tearney, MD, PhD

Diagnostics
A. John Iafrate, MD, PhD
Keith Flaherty, MD

Immunology
Richelle Charles, MD

Vaccine Trials
Ricky Mofsen, DO

Moderated Q&A
Dr. Alter

2:15 – 2:45 PM **Executive Session (SAC members only)**

2:45 – 3:15 PM **Debrief: Research Institute Steering Committee & SAC Members (closed)**

Martin Research Prizes

2021 MARTIN RESEARCH PRIZE FOR CLINICAL AND FUNDAMENTAL RESEARCH

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

Martin Aryee, PhD
Assistant Professor,
Pathology

Large-Scale Topological Changes Restrain Malignant Progression in Colorectal Cancer

It has been known for over 100 years that tumor cells look different than normal cells under the microscope. Pathologists, for example, use the presence of misshapen nuclei as a key feature when diagnosing cancer in a patient. Despite this, the relationship between these microscopic features and the function of cancer cells have remained unknown. This study relates visible cancer cell aberrations to changes in the physical organization of DNA and shows that it surprisingly occurs in both cancer cells and some normally aging cells. The entire three-dimensional structure of the DNA in these cells is reorganized over time as they divide. About half of the genome becomes physically compacted which serves to turn off genes located in these regions. Suppressing the activity of these genes helps prevent the development of cancer by reducing the cell's ability to proliferate and metastasize. Even though cancer cells also undergo this transformation, they adapt other mechanisms to overcome the tumor suppressive effects and promote tumor growth. A key surprising finding of the study is that the well-known visible abnormalities in the nuclei of cancer cells may not be associated with cancer progression, but more likely represent a failed attempt to halt cancer development. A better understanding of this newly described tumor suppressive mechanism may open up future avenues for exploiting it to inhibit tumor progression.

Sabrina Paganoni, MD, PhD
Assistant Professor,
Physical Medicine and
Rehabilitation

Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis

The CENTAUR trial is the first trial to demonstrate positive effects of an investigational product on both functional outcomes and survival in people with ALS. The CENTAUR trial is also noteworthy as a unique collaboration between academia, foundations and industry and includes design features that are likely to have a major impact on the design of future ALS trials. The positive results of the CENTAUR trial have the potential to change clinical practice and improve the natural history of ALS. Trial results were published in the *New England Journal of Medicine*.

Howard M. Goodman Fellowship

2021 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.

Benjamin Kleinstiver, PhD
Assistant Professor of Pathology,
Center for Genomic Medicine

Development and Application of Therapeutic Genome Editing Technologies

Most human diseases are caused by faulty genetic sequences. The recent discovery that CRISPR enzymes enable researchers to perform custom DNA edits offers hope for correcting the underlying genetic defects that cause devastating disorders. However, naturally occurring CRISPR enzymes, which evolved as part of bacterial immune systems, are not optimally suited for the safe and effective treatment of patients. This is the major unmet need that my laboratory is solving. We are addressing several gaps in knowledge by pioneering the use of molecular evolution methods to overcome the natural limitations of CRISPR enzymes. By engineering highly safe, precise, and broadly effective CRISPR proteins, we have developed new editing technologies with superior characteristics that are enabling new biomedical research applications, and that hold promise to improve human therapeutics. We are applying these technologies in pre-clinical experiments to treat diseases including cancer, Huntington's disease, and other rare disorders for which there are no effective cures. The Howard Goodman Award would support our innovative and transformative research by allowing us to continue to ask and answer field-leading questions and will support our continued development of permanent genetic cures for diseases to alleviate the of suffering of patients.

Caroline Sokol, MD, PhD
Assistant Professor of Medicine,
Rheumatology, Allergy,
and Immunology

Neuro-immune circuits controlling the initiation of allergic immunity

Allergic diseases afflict 40% of the United States population, but it is unknown how allergens are sensed by the body. Allergens lead to immune activation, but paradoxically they do not directly activate immune cells. Our laboratory recently discovered that allergens are first detected by the sensory nervous system leading to itch and the release of neuropeptides that then activate innate immune cells to initiate the allergic immune response. In this proposal we seek to interrogate the immune and neuronal control of this pathway. Our *central hypothesis* is that a neuro-immune circuit exists in a feed-forward loop in which cells of the immune system prime allergen detection by sensory neurons and recurrent allergen exposure of sensory neurons boosts their activation of immune cells. Building on exciting preliminary data, our two research goals include: (1) identifying how an innate-like T cell subset, called gamma/delta T cells, in the skin controls sensory neuron activation by allergens, and (2) deciphering how sensory neurons develop a memory of prior allergen exposure, leading to enhanced itch and immune activation after subsequent exposure to the same, or different, allergens. The work proposed herein would represent a paradigm shift in our understanding and treatment of atopic diseases.

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Ex-officio

*Chair Appointment, ‡ Chiefs Council

Massachusetts General Research Institute

Executive Report

RISING TO THE CHALLENGE OF 2020—THANK YOU TO ALL MEMBERS OF THE RESEARCH INSTITUTE (RI)

[From an open letter to all members of the RI, December 10, 2020]

To say this has been a trying year for our MGH research community would be a gross understatement. We have seen our research programs completely shut down and our work and personal lives disrupted. We have endured isolation and separation from family and friends, and many of us and them have felt the impact of COVID personally. Some of us have even been drafted to perform duties far different from the jobs we were hired to do.

Yet, in this time of crisis, our research community has answered the call. Our founders' call to action—When in distress, every man becomes our neighbor—rings as true today as when those words were first written in 1810 in the letter to the Massachusetts state legislature that led to the establishment of our hospital. Hundreds of you volunteered to help our clinical colleagues handle the overload of COVID patients, many of you began COVID research programs to help us better understand and battle the disease, and all of you continued your research during the shutdown, whether remotely or in different capacities, so your vital work advancing biomedical discovery could continue to progress.

Through your diligence and tireless efforts, the Research Institute rebounded in an amazingly short time. After five months of total and then partial shutdown, onsite research activities were allowed to resume fully, and we finished the fiscal year matching our previous record of $1.013 B in research spending. And that trend is continuing, with research revenues significantly exceeding budget in the first quarter of the new fiscal year.

We have been able to successfully sustain our research programs due in large part to the strict adherence to following universal controls regarding masking and hand hygiene that you have all maintained, as well as the diligent efforts of our 200+ onsite COVID Safety Officers and our building and animal support staff.

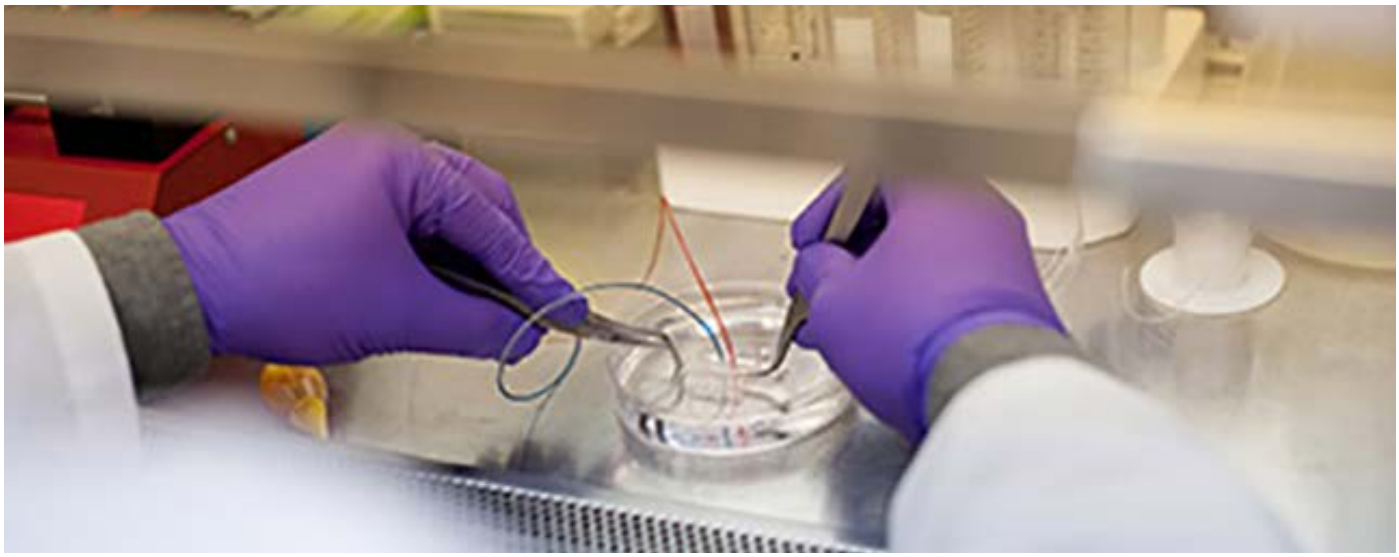
We enter into the new year with a second COVID surge spreading across the country, even as the promise of new vaccines brings hope of ending the pandemic. To ultimately succeed, we must collectively persevere, keep our guard up, and continue to rely on one another as we have done this past year.

As we reflect back on this trying year, we pause to marvel at all you have accomplished. Thank you for all you have done for the hospital, for keeping each other safe, and for sustaining our extraordinary research enterprise.

Highlights of RI accomplishments/milestones in 2020

Continuing Research While Dealing with COVID. The COVID pandemic had an immense impact on our research enterprise in 2020. We were required to shut down all lab operations for five months before partially and then fully restarting onsite research in July. Much has been done and accomplished.

- Once the shutdown was announced, we developed and published in an amazingly short period of time an MGH Coronavirus Research Guide, a document which is still in use and updated weekly.
- We assembled an army of 200+ COVID Safety Officers (CSOs) from lab managers and researchers to: (1) Evaluate all research and common spaces and make area plans for social distancing and create a safe work environment; (2) Determine occupancy for research rooms using the guidelines from hospital Infection Control; (3) Plan and implement scheduling for common-use areas/ rooms (microscope rooms, tissue culture rooms, etc.); (4) Determine and procure safety supply needs for research space; (5) Serve as an information source and primary POC for all researchers returning to onsite work with questions about COVID policies and safe practices. The CSOs continue to meet weekly and serve as our main conduit for disseminating COVID information to the onsite research community.
- PI's were required to submit work plans detailing how they would resume work while following universal controls involving masking, hand hygiene, and social distancing. Work plans were reviewed and approved by a research leadership committee. Many implemented staggered work schedules to lower personnel densities.
- Over 300 research personnel were redeployed to work in clinical and support areas of the hospital to assist caretakers in dealing with the almost overwhelming numbers of COVID patients coming here for care.
- Before coming back to conduct onsite work, researchers were required to do a one-time attestation that they have read, understand, and will follow the important policies and COVID-safety controls we have put in place. They must also attest daily that they have no COVID symptoms using a COVIDpass application developed for their smartphones. Daily attestation compliance is excellent (over 99%). Anyone who comes in and forgets to attest gets an email reminder that is also sent to their supervisor.
- Of our 4,500 onsite researchers, 3,800 have returned to work, although not everyone comes in each day. With researchers encouraged to work from home as much



as possible (writing up lab notes, researching literature, etc.), we see a daily onsite census of ca. 2,500. About 700 [15%] of our researchers have not returned to onsite locations; they continue to work fully remotely.

- COVID infections among members of the research community are tracked by Occupational Health. Prior to December, the number of research personnel testing positive for COVID numbered 23. Contract tracing confirmed that ALL of the infections were acquired OUTSIDE of the MGH workplace and, because of our strict adherence to universal controls, NO ONE working onsite was exposed as a result of contact with these COVID-positive workers. In December, an additional 27 researchers became infected but, again, all infections were community-acquired, and no one else was exposed.
- Email updates containing important COVID information were sent to the research community daily during the shutdown and initial return to onsite research. As of October, the frequency was reduced to once a week, with our publication of "Tuesday Tips" continuing as this document goes to print.
- The hospital began offering asymptomatic employee testing on the main campus in early Fall. To ensure that our off-main-campus research community was given more convenient access to this testing, Research Management used volunteers to open an additional site at the Charlestown Navy Yard.

Battling COVID—Answering the Call. As soon as the seriousness and threat of the disease became known, researchers at MGH began working to understand and combat the virus.

- Dr. Bruce Walker, Director of the Ragon Institute of MGH, MIT, and Harvard, was selected to co-direct the Massachusetts Consortium on Pathogen Readiness (MassCPR) and serves on its steering committee along with Dr. Galit Alter, Samana Cay MGH Research Scholar, and Dr. Dan Barouch, also from the Ragon Institute.
- Ragon Institute faculty also played a critical role in COVID vaccine development. Dr. Aaron Schmidt made the virus spike protein that allowed Dr. Galit Alter to develop the antibody assay that allowed Dr. Dan Barouch to test the vaccine to know if it was generating antibodies.
- A Clinical Trial Proposal Review Committee was established under the leadership of Dr. Keith Flaherty and Ms. Tatiana Koretskaia to triage proposed COVID studies at MGH and allocate patient samples equitably. As of the end of the 2020 calendar year, 331 COVID clinical trials have been reviewed and approved by the committee - 23 therapeutic, 99 non-therapeutic, and 209 data only studies.
- Many researchers across the hospital shifted their lab's focus toward COVID. In 2020, MGH received 127 COVID-related grants totaling $74.6M in COVID-related funding ($57.6M from the federal government), and our faculty have published over 1,000 articles on COVID/SARS-CoV-2.
- Recognizing the urgent need to develop capabilities to assist our clinical colleagues in dealing with the massive influx of COVID patients, MGH and BWH formed an equal partnership to create the MGB Center for COVID Innovation (MGBCCI). It was launched on March 20, 2020 with Drs. Gary Tearney from MGH and Dave Walt from BWH as co-directors, and it became fully operational

within one week. See the Research Program Updates and Initiatives section below for a more extensive description of MGBCCI and its accomplishments.

Non-COVID Accomplishments. While the COVID pandemic stalled many of our ongoing research and support programs for five months, it did not stop them. Let's look here at a summary of the other impressive non-COVID accomplishments of our research community in 2020. These include:

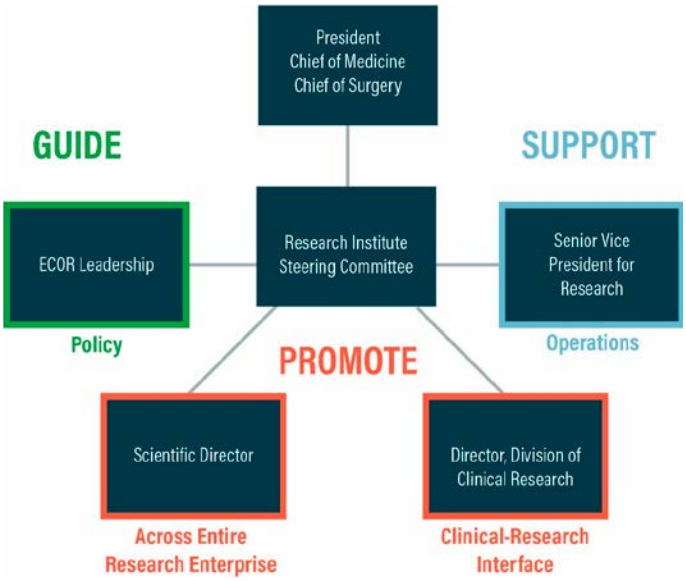
- (As stated above) Matching our previous record of $1.013 B in research spending. And the positive trend is continuing, with research revenues significantly exceeding the budget in the first quarter of the new fiscal year. In 2020, spending on NIH awards rose 10% from $500M to $551M. Grant proposal submissions increased 9% to over 4,700 in 2020, and our success rate of 26% remained 5% above the national average.
- The appointment of the 65th MGH Research Scholar (five new ones in 2020) and sixth Research Institute Endowed Chair.
- Entering into the realm of gene- and cell-based therapy with a multi-year partnership with ElevateBio, a company that has built pilot and production facilities in Waltham.
- The Clinical Trials Office achieved a number of important goals in support of MGH investigators and leadership this year. There are presently master clinical trials agreements with more than 124 industry sponsors, an additional 60 department or investigator specific master agreements, 26 master confidentiality agreements and 4 "other" masters related to emergency use, health outcomes and data research. The overall volume of executed agreements increased in FY20 by 18% from 1772 to 2083, driven in part by a high volume of COVID-related projects
- A dramatic increase in new clinical trials initiated in 2020 at the Translational and Clinical Research Centers (TCRC), reaching 52 trials at year's end. The TCRC and its staff played a vital role in the conduct and administration of many of the COVID-related trials conducted at MGH, including participation in COVID vaccine trials.
- Continued expansion of our RI external communication and marketing efforts. Bench Press, our newly renamed Research Institute Blog, won two industry awards and increased its number of views over 400%. Similar increases were seen in our Facebook, Twitter, and Instagram postings. It is likely that some or perhaps most of these increases are attributable to great interest in the innovative COVID-related work going on at the hospital.
- The addition of an eighth program (Sleep) in 2020 to our Strategic Alliance initiative, bringing the total of collaborating MGH investigators to 239 from across 22 departments and thematic centers. Also, in 2020, we executed and launched the first thematic program-driven collaboration with Amgen in the field of cardiometabolics.
- Steady growth in the MGB Biobank at MGH, with consented patient recruitment now over 120,000. It played an important role in supporting six major COVID studies in 2020.
- Expanded offerings from the Division of Clinical Research as it begins its 25th year in 2021, having given 200 live and online courses to over 6,000 participants and 470 personal consultations this past year.
- The impact of the pandemic was felt in patent filings and licensing income. MGH patents filed in FY20 dropped slightly (ca. 1500 down from 1600) as did patents issued (ca. 500 down from 600). Royalty and licensing income in FY20 was $142M. While lower than FY19 ($298M) due to a large buyout that occurred that year, the FY20 number shows good growth over the FY18 number of $95M.
- In spite of a freeze on new capital spending in 2020, our Research Space Management Group (RSMG) completed $25M of capital renovation projects to improve the use and efficiency of research space. Currently, RSMG has requests for additional lab space totaling over 139K SF, resulting from the continued growth in research funding procured over the last two years. Also, this past year, a new Division of Research Building Management was created within RSMG, with the appointment of Patricia Frederico as Director. This division oversees the building operations, runs our glasswashing and other building support cores, maintains conference room AV and other support services, and is the primary liaison with B&G and Environmental Services for facility issues.
- Continued researcher participation in the Isuggest program, with the number of suggestions to improve research services at the end of 2020 exceeding 1,500 and the number implemented exceeding 800. This past year, with the COVID lab shutdown, suggestions came in at a rate of two per week, half of our normal volume.
- Responding to the MGH Structural Equity Ten-Point Plan, a roadmap that focuses on what we as an institution can do to address structural and overt racism within and outside of the MGH, with several research-focused initiatives. See the Research Program Updates and Initiatives section below for a more extensive description of these initiatives.

- The Center for Innovation in Digital Health (CIDH) FY20 accomplishments can be summarized along several thematic areas: (1) Support of MGH and MGB Priorities; (2) Services and Activities to Accelerate Innovation; (3) Support of Research and Discovery; (4) Support of Education and Community; (5) Support of Industry Sponsored Research at MGH. Details are given in the CIDH section below.
- Research Compliance accomplished major initiatives in five areas in FY20. These include: Research Risk Assessment, Controlled Substances Database, Research Survey, Research Misconduct, and Orientation/Exit Strategy Workgroup. Details are given in the Research Compliance section below.
- Significant improvements in our animal care (CCM—Center for Comparative Medicine) and regulatory (IACUC—Institutional Animal Care and Use Committee) programs, including the creation of the Animal Research Community (ARC) Group. See the Research Program Updates and Initiatives section below for a more extensive description of animal care and regulatory program progress.
- Major programmatic and staffing changes to the Center for Faculty Development (CFD) signal a new era for the center. Director Dr. Miriam Bredella named new leaders to all five current Director-level positions in CFD and created a sixth Director-level office, the Office for Well-Being. See the Challenges and Opportunities section below for a more extensive description of the 2020 leadership and programmatic changes in CFD.

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 2021.

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.

Massachusetts General Research Institute

Executive Report

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

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

There is a total of 6 elected representatives to ECOR, two from each faculty rank. Elected representatives serve a 3-year term and represent faculty concerns and issues. To ensure a balance of continuity and renewal, terms are staggered so that two seats are up for election every year. Please see pages 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 2020 Warren Prize was scheduled to be awarded to **Dr. Mary-Claire King** for her significant contributions to the field of genetics. Unfortunately, due to COVID, Mass General Research Institute leadership made the difficult decision to *postpone* the 2020 Warren Triennial. We are planning to hold this event on a to be determined date to celebrate Dr. King.

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 174 members—54 Professors, 74 Associate Professors, and 46 Assistant Professors. Approximately 55 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) Vitality and Advocacy Committee (VAC)

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

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

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

- Obtain funding and successfully petitioned research leadership for financial support to enhance community building
- Improve transportation between campuses by:
  - Working with the city and Mass General Brigham Transportation to implement changes to the shuttle route to reduce travel time from Charlestown to the main campus
  - Update and amend parking policies across the hospital
  - Modify egress from buildings 24-7 from bridges and at the West End of 149
  - Provide bike and walking routes between campuses
- Build community and enhance interactions by:
  - Holding Town Hall meetings to allow open discussions and feedback
  - Holding a monthly Lunch Scientific Seminar Series
  - Hosting the Science as Art Event and installing a permanent art exhibit at CNY
  - Hosting the CNY Science Grand Slam with the MGRI
  - Hosting an MGH-wide Trivia Night (attended by over 400 people virtually)

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 a dinner reception
- Increase MGRI branding at CNY
- Revitalize the research community through community building and enhancing scientific interactions following COVID

Taskforce on Equity and Respect in the Research Workplace

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

Key outcomes:

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

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

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

The taskforce has been meeting regularly and presented their preliminary finding to the Research and Education subcommittee of the Board of Trustee in December 2020. At the suggestion of the Trustees, the co-chairs of the committee are currently in conversations with the Research Institute Steering Committee to establish a long-term committee.

Communication

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

Awards and Grants

ECOR manages a multi-million-dollar grant program, virtually a mini-foundation, which annually reviews over 800 applications from MGH investigators and fellows, and awards approximately 120 internal grants. 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.

ECOR Grants Program Pause

ECOR faced one of its most challenging years in FY20. Due to the financial strain on the hospital that resulted from COVID-19 and the subsequent cancellation of electives, all hospital grant programs were put on hold at the end of May 2020. Thankfully, many of our FY20 grants had been awarded by that time and are listed in the sections below. Unfortunately, we were unable to award most of the ISF and FMD Fellowship grants that were budgeted for FY20. For most of the summer, ECOR remained uncertain as to when or if the program would be reinstated.

While the internal grants program remained on hold, we continued selecting institutional nominees for limited submission funding opportunities and provided support for creating and managing the MGB Center for COVID Innovation's Funding Database.

In early September of 2020, we received the good news from hospital leadership that the ECOR grants program was reinstated. The clinical side of the hospital outperformed its expectations for financial recovery, which allowed our program to restart just in time for FY21 to begin.

COVID Pilot Grant Program

In the summer of 2020, ECOR worked with the Department of Medicine to facilitate and manage the application and selection process for the COVID Pilot Grants Program. Funding to support the program was generously provided by **MGH COVID Clinical Trials Research Fund**. The intent of these awards is to support COVID-19 related research that has **significant potential to advance the COVID-19 clinical trials effort at MGH**.

Each pilot grant award includes funding of $25,000-$50,000 inclusive of 15% indirect costs ($21,739 - $43,478 direct). In the end, nine researchers received a COVID Pilot Grant.

Tosteson & Fund for Medical Discovery Fellowship Awards

The Tosteson & Fund for Medical Discovery (FMD) Fellowship Awards are intended to support junior investigators (MD and PhD fellows/postdocs) at MGH pursuing clinical or fundamental research. The award is offered three times per year, with one cycle dedicated solely to clinical research. Each award includes a salary stipend of $50,000. Due to the pause on the grants program, only four fellows received the fellowship award in FY20.

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 FY20, six women received the Claflin Award.

Beth Costine-Bartell, PhD
Assistant Professor
Neurosurgery

Li Lan, MD, PhD
Assistant Professor
Radiation Oncology/Cancer Center

Camille Powe, MD
Assistant Professor
Medicine/Diabetes Unit

Meghan Sise, MD, MS
Assistant Professor
Medicine/Nephrology

Shannon Tessier, PhD
Instructor
Surgery

Meagan Wasfy, MD
Instructor
Medicine/Cardiology

MGH Physician-Scientist Development Award

The MGH Physician/Scientist Development Award (PSDA), which is managed by ECOR in collaboration with the Center for Diversity Inclusion (CDI), is designed for MD and/or PhD investigators at MGH to support the development of research investigators who are considered underrepresented in medicine (UIM), 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 four awards going forward, with the support of a 50% cost share between ECOR and the applicant's department. The amount of funding was also increased to $180,000 in direct costs. In FY20, four investigators received this award:

David Alagpulinsa, PhD
Research Fellow
Medicine/ Infectious Disease

Ibiayi Dagogo-Jack, MD
Instructor
Medicine/Hematology/
Oncology Unit/Cancer Center

Christian Lino Cardenas, PharmD, MSc, PhD
Instructor
Medicine/ Cardiology

Nneka Ufere, MD
Clinical Research Fellow
Medicine / Gastroenterology

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 2020, 65 Scholars have been appointed, each receiving research funding of $100,000 a year for five years.

The 2020 Class of Mass General Research Scholars:

Kate Jeffrey, PhD
John Lawrence MGH Research Scholar 2020-2025
Division of Gastroenterology,
Massachusetts General Hospital
Assistant Professor of Medicine,
Harvard Medical School

Luana Marques, PhD
Phyllis and Jerome Lyle Rappaport MGH Research Scholar 2020-2025
Department of Psychiatry,
Massachusetts General Hospital
Associate Professor of Psychiatry,
Harvard Medical School

Yakeel T. Quiroz, PhD
MGH Research Scholar 2020-2025
Departments of Psychiatry and Neurology,
Massachusetts General Hospital
Associate Professor of Psychology,
Harvard Medical School

Laurence Rahme, PhD, MSc
MGH Research Scholar 2020-2025
Center for Surgery, Innovation and Bioengineering,
Massachusetts General Hospital
Professor of Surgery,
Harvard Medical School

Mario Suvà, MD, PhD
Janet and William Ellery James MGH Research Scholar 2020-2025
Department of Pathology,
Massachusetts General Hospital
Associate Professor of Pathology,
Harvard Medical School

Other ECOR Awards

The Howard M. Goodman Fellowship honors Howard M. Goodman, PhD, founder of the MGH Department of Molecular Biology in 1982 and Chief of that Department until 2004. Dr. Goodman's guiding principle was that great science should not be encumbered by the continual need to convince the world concerning the merit of an individual scientific vision. He believed in choosing scientists of demonstrated excellence and giving them the resources to pursue their goals with vigor, a model that was resoundingly successful. Each year, a Goodman Fellow is chosen from the MGH community to honor that legacy and to support the pursuit of excellence by young scientists of uncommon passion and ability. The award is for two years at $165,000 per year. Please see page 5 for more information on the 2021 recipient.

The Martin Research Prizes are awarded annually in honor of Harvard Medical School (HMS) Dean Emeritus Joseph Martin, MD, PhD. Dr. Martin served as Dean of Harvard Medical School from July 1997 to July 2007. Each year, ECOR awards two $100,000 Martin Research Prizes to recognize outstanding research papers published by MGH investigators in Fundamental research and Clinical research. Please see page 4 for more on the 2021 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: 82% of investigators who received funding from the Interim Support Program between 2006-2019 are still working within the institution. Since the program's inception in 2006, ECOR has awarded over $60.9M of interim support funding. Our investigators have gone on to leverage these funds ten-fold, bringing in nearly $633M of federal funding to the institution. Within this program are two grant mechanisms, Formulaic Bridge Support and Deliberative Interim Support Funding, which provide similar funding under different guidelines.

- Formulaic Bridge Support (FBS) applications are accepted monthly from investigators whose R01 or R21 NIH grant received a percentile equal to or better than a 20th percentile (1-20%).
- Deliberative Interim Support Funding (ISF) applications are accepted three times a year to investigators who have a lapse or delay in their research funding from the NIH or another federal agency (i.e. National Science Foundation, Department of Defense, etc.). This grant mechanism is open to investigators whose federal grant application received a score higher than a 20th percentile (21-99%) or were not scored.

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

As mentioned above, the Interim Support Program was halted due the strain of COVID-19 on the hospital's finances. The program was reinstated in September 2020, albeit in a slightly different format. The Formulaic Bridge Support (FBS) and Deliberative Interim Support (ISF) grants were merged into one Interim Support Funding grant that will be offered several times a year. All interested applicants will be asked to apply through this call moving forward.

Awards and Honors

The summer of 2014 saw the creation of the MGH Committee on Awards and Honors. After serving for five years as chair, Dr. Samuel Thier, president of MGH from 1994-1997, stepped down and passed the baton to Dr. Jerry Rosenbaum, Psychiatrist-in-Chief Emeritus, Director, Center for Anxiety and Traumatic Stress Disorders (CATSD) and Director, Center for Neuroscience of Psychedelics. The committee ensures that there is an MGH nominee for over 40 major national and international scientific awards and prizes and provides hospital endorsements for faculty member admission to distinguished honorific societies. The committee is comprised of 18 esteemed leaders from throughout our institution who meet regularly. In 2020, the committee championed the nominations of more than 30 outstanding MGH investigators for major awards and society memberships and national and international awards.

Some of the major awards and prizes received by MGH investigators in 2020 include the following:

Academy for Radiology and Biomedical Imaging Research 2020 Distinguished Investigators

Jacob Hooker, PhD (Martinos Center)
Jyrki Ahveninen, PhD (Martinos Center)
Giorgio Bonmassar, PhD (Martinos Center)
Caterina Mainero, MD, PhD (Martinos Center)
Zdravka Medaroa, PhD (Martinos Center)
Martin Torriani, MD, MMSc (Radiology)

Aligning Science Across Parkinson's (ASAP) Collaborative Research Network Neuro-immune Interactions award
Xiqun Chen, MD (Neurology)

Alzheimer's Association International Conference (AAIC) Inge-Grundke-Iqbal Award for Alzheimer's Research
Yakeel T. Quiroz, PhD (Psychiatry)

American Academy of Arts and Sciences (AMACAD)
Katrina Armstrong, MD (Medicine)

American Academy of Dermatology (AAD) Patient Care Hero
Esther Freeman, MD, PhD (Dermatology)

American Academy of Nursing Honorary Fellow
Karen Donelan, ScD, EdM (Mongan Institute)

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

American Association for the Advancement of Science (AAAS)
Marcia Goldberg, MD (Infectious Disease)
Jeremiah Scharf, MD, PhD (Neurology, Center for Genomic Medicine)
Lee Zou, PhD (Cancer Center)

American Association for Thoracic Surgery Vice President
Yolonda Colson, MD, PhD (Surgery)

American Association for Women in Radiology Eleanor Montague Distinguished Resident Award in Radiation Oncology
Oluwadamilola Oladeru, MD, MA (Radiation Oncology)

American Cancer Society Research Professorship
Jennifer Temel, MD (Cancer Center)

American College of Cardiology Board of Governors, Chair
Malissa Wood, MD (Medicine)

American Epilepsy Society Research Training Fellowship for Clinicians
Claire Jacobs, MD, PhD (Neurology)

American Diabetes Association Junior Faculty Development Award
Jordi Merino, PhD (Diabetes Unit, Center for Genomic Medicine)

American Institute for Medical and Biological Engineering (AIMBE) College of Fellows
Dan G. Duda, DMD, PhD (Radiation Oncology)
Georges El Fakhri, PhD (Gordon Center)
Collin M. Stultz, MD, PhD (Cardiology)

American Medical Association (AMA) Moving Medicine Magazine
Fatima Cody Stanford, MD, MPH, MPA (Weight Center, Medicine/Neuroendocrine, Pediatrics/Endocrinology)

American Psychosocial Oncology Society 2020 New Investigator Award
Jamie M. Jacobs, PhD (Psychiatry)

American Psychosocial Oncology Society 2020 Ruth McCorkle Research Mentorship Award
Joseph A. Greer, PhD (Psychiatry)

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

American Society for Matrix Biology (ASMB) Founders Award
Heena Kumra, PhD (Radiation Oncology)

American Society of Addiction Medicine (ASAM) 2020 NIDA Young Investigator Travel Award
Benjamin Bearnot, MD, MPH (Medicine, Mongan Institute)

American Society of Human Genetics 2020 Early-Career Award
Benjamin Neale, PhD (Medicine)

AO Innovation Translation Center Strategic Funding Award
Nida Fatima, MD (Neurosurgery)

American Society of Clinical Oncology Clinical Cancer Advances 2020 Annual Review
Andrew Zhu, MD, PhD (Cancer Center)

American Society for Clinical Investigation
Xu Yu, MD (Ragon Institute)

American Society of Echocardiography (ASE) President
Judy Hung, MD, FASE (Cardiology)

American Society of Hematology and the European Hematology Association 2020 Translational Research Training in Hematology (TRTH) program
Konstantinos Kokkaliaris, PhD (Center for Regenerative Medicine)

American Society of Retina Specialists Honor Award
Joan W. Miller, MD (Ophthalmology)

Association of American Physicians (AAP)
Jose C. Florez, MD, PhD (Medicine)
James Meigs, MD (Medicine)
Jennifer Temel, MD (Cancer Center)

Bay Area Lyme Foundation 2020 Emerging Leader Award
Jacob Lemieux, MD, DPhil (Infectious Disease)

Bio-IT World Innovative Practices Award
MGH Center for Innovation and Bioinformatics at the Neurological Clinical Research Institute

Boston Magazine's "Best of Boston 2020: The COVID-19 Heroes Edition"
Jerome Crowley, MD, MPH (Anesthesia)

Boston Women's Workforce Council 2020 Innovative Initiatives Awards
Miriam Bredella, MD (Center for Faculty Development, Radiology)

Business Insider's list of 100 People Transforming Business in North America
Merit Cudkowicz, MD (Neurology)

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

Chan Zuckerberg Initiative (CZI) Grant
Clotilde Lagier-Tourenne, MD, PhD (Neurology)
Paul Blainey, PhD (Broad)

College on Problems of Drug Dependence Travel Award for Early Career Investigators
Alan N. Francis, PhD (Martinos Center)

Dalio Philanthropies Grant
Luana Marques, PhD (Psychiatry)

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

Epic Charitable Fund Grant
MGH Transgender Health Program

Fast Grant
Rajeev Malhotra, MD (Medicine)

Fellows of the American Association for Cancer Research (AACR) Academy Class of 2020
Rakesh K. Jain, PhD (Radiation Oncology)

Foundation for Opioid Response Efforts Grant
Alister Martin, MD, MPP (Emergency Medicine)
Shuhan He, MD (Emergency Medicine)

Greater Boston Food Bank (GBFB) Senior Health and Research Advisor
Lauren Fiechtner, MD, MPH (Pediatric Gastroenterology and Nutrition)

Hopper-Belmont Foundation Inspiration Award
William Hwang, MD, PhD (Cancer Center)

International Academy of Medical and Biological Engineering (IAMBE) Fellow
Georges El Fakhri, PhD, DABR (Gordon Center)

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

International Society of Paediatric Oncology (SIOP) 2020 Congress Young Investigator Award
Dora Correia, MD (Radiation Oncology)

John and Elizabeth Phillips Award from Phillips Exeter Academy
Emery N. Brown, MD, PhD (Anesthesia)

Leader of the Stand Up To Cancer (SU2C) Gastric Cancer Interception Research Team
Andrew T. Chan, MD, MPH (Cancer Center)

Mark Foundation for Cancer Research (MFCR) Emerging Leader Award
Mario Suvà, MD, PhD (Pathology)

Massachusetts Medical Society Lifetime Achievement Award
The late Robert Ackerman, MD (Neurology)

Massachusetts Medical Society Reducing Health Disparities Award
Maggie Samuels-Kalow, MD (Emergency Medicine)

Massachusetts Psychiatric Society 2020 Outstanding Psychiatrist Award for Advancement of the Profession
Ronald Schouten, MD, JD (Psychiatry)

Masters of the American College of Physicians (MACP)
James J. O'Connell, MD (Internal Medicine)
Kerri L. Palamara-McGrath, MD (Internal Medicine)
Nancy A. Rigotti, MD (Internal Medicine)

Medawar Prize from The Transplantation Society (TTS)
Francis L. Delmonico, MD (Surgery)

Medscape's Rising Stars List of 2020
Esther Freeman, MD, PhD (Dermatology)
Shadi Kourosh, MD, MPH (Dermatology)

Mujer Ejecutiva Magazine 30 Women Leaders in Healthcare
Marcela Del Carmen, MD (Obstetrics Gynecology & Reproductive Biology, MGPO)

National Academy of Inventors (NAI)
William Harris, MD (Orthopaedic Surgery)

National Academy of Medicine (NAM)
David Fisher, MD, PhD (Dermatology)
Yolonda Colson, MD, PhD (Surgery)
Merit Cudkowicz, MD (Neurology)

National Academy of Medicine (NAM) Healthy Longevity Catalyst Award
Alessandro Biffi, MD (Neurology)
Vidisha Mohad, PhD (Surgery)
Vineet Raghu, PhD (Radiology)

National Academy of Sciences (NAS)
Joel Habener, MD (Medicine)

National Cancer Institute Outstanding Investigator Award
Andrew T. Chan, MD, MPH (Epidemiology, Cancer Center)

National Institute for Health Care Management (NIHCM) Research Award
Zirui Song, MD, PhD (Medicine)

National Institute of Allergy and Infectious Diseases New Innovators DP2 Award
Gaurav Gaiha, MD, DPhil (Gastroenterology)

National Institutes of Health Method to Extend Research in Time (MERIT) Award
Stephanie Seminara, MD (Endocrine)

New England Crohn's and Colitis Foundation Joan Cutler Lifetime Achievement Award
Harland Winter, MD (Pediatrics)

New England Journal of Medicine (NEJM) Deputy Editor
Winfred W. Williams, MD (Nephrology)

NIH Rapid Acceleration of Diagnostics Award
MGH's Kraft Center for Community
Elsie Taveras, MD, MPH (Pediatrics)

OncLive Giants of Cancer Care Class of 2020
Keith T. Flaherty, MD (Cancer Center)

Patient-Centered Outcomes Research Institute (PCORI)
Stephen Bartels, MD, MS (Mongan Institute)
Brian Skotko, MD (Pediatrics)

Pilot Research Grant by the Osher Center for Integrative Medicine
Ryan Mace, PhD (Psychiatry)
Ana-Maria Vranceanu, PhD (Psychiatry)

Rema Lapouse Award for Achievement in Epidemiology, Mental Health and Applied Public
Health Statistics from the American Public Health Association (APHA)
Margarita Alegria, PhD (Medicine, Disparities Research Unit)

Robert Wood Johnson Foundation Clinical Scholars
Juliana Chen, MD (Psychiatry)
Justin Chen, MD, MPH (Psychiatry)

Restless Legs Syndrome (RLS) Foundation 2020 Ekbom Award
John Winkelman, MD, PhD (Psychiatry)

Science Magazine's Science Breakthrough of the Year in 2020 (runner up)
Xu Yu, MD (Ragon Institute)

Society for Clinical Ultrasound Fellowships Stellar Clinical Ultrasound Fellowship
The MGH Emergency Ultrasound Fellowship (Emergency Medicine)

Society for Neuroscience 2020 Swartz Prize for Theoretical and Computational Neuroscience
Emery N. Brown, MD, PhD (Anesthesia)

Society of Critical Care Anesthesiologists (SOCCA) Lifetime Achievement Award
Jeanine Wiener-Kronish, MD (Anesthesia)

Society of General Internal Medicine Outstanding Junior Investigator of the Year Award
Zirui Song, MD, PhD (Medicine)

Society of Neuroscience Louise Hanson Marshall Special Recognition Award
Ghazaleh Sadri-Vakili, PhD (Neurology)

2020 STAT Wunderkinds
Kirsten A. Dickins, PhD, AM, MSN, FNP-C (Munn Center for Nursing)
Altaf Saadi, MD (Neurology)

Taking Flight Award from Citizens United for Research in Epilepsy (CURE)
Chris McGraw, MD, PhD (Neurology)

Traveling Genius Award: Italians of Art, Literature, and Science…in the World
Alessio Fasano, MD (Pediatric Gastroenterology)

University of Virginia Michael O. Thorner Distinguished Lectureship in Endocrinology
Steven Grinspoon, MD (Medicine, Metabolism Unit)

University of Washington Roger H. Johnson Award
Patricia A. D'Amore, PhD, MBA (Mass. Eye and Ear)

U.S. Army Medical Research and Development Command's Telemedicine and Advanced Technology Research Center National Emergency Telecritical Care Network (NETCCN) Grants
MGH MD PnP Program

Warren Alpert Prize (shared)
Joel Habener, MD (Medicine)

Webster University Honorary Doctorate in Science
Vladimir Ivkovic, PhD (Psychiatry)

Women in Molecular Imaging Network 2020 Rising Star Award
Raiyan T. Zaman, PhD, MSEE (Gordon Center)

Young Investigator Award from the Society for Academic Emergency Medicine
Kori Sauser Zachrison, MD, MSc (Emergency Medicine)

PROMOTE

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

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

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

Our marketing efforts are focused on increasing awareness of research at Mass General, both to our own community and to audiences outside our walls. We work with the 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 Alliance 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.

Marketing and Communications
Internal communications: We continue to create and distribute our newsletter communications to help promote the remarkable work of our research community. Our most popular, Snapshot of Science, is a monthly newsletter that includes a listing of publications from high impact scientific

and medical journals in which Mass General researchers are lead authors with accompanying lay summaries. The goal of this newsletter is to promote awareness of new Mass General research studies within our community, help the Research Institute establish relationships with individual researchers, and encourage researchers to think critically about translating their science for a broad audience. We use the format of this newsletter to help us think about marketing to the external community, especially through social media. Additionally, we continued publishing monthly issues of our From the Lab Bench email newsletter, which typically features two or three articles about research at the hospital as well as news and updates from the Office of the Scientific Director.

The Research Institute Blog: Our blog, newly renamed Bench Press, is in its third year and has become a major vehicle for sharing research news and updates both within the Mass General community and to the world at large. The blog typically features 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 two awards from local and national healthcare organizations in 2020:

- Platinum Award, Best COVID-19 Communications, eHealthcare Leadership Awards
- Silver, Excellence in Writing-Blog, Nutritional Psychiatry, NESHCo Lamplighter Awards

2020 was the blog's most successful year by far, with views increasing by 440%, primarily due to COVID-19/SARS-CoV-2 research stories.

Social Media: In 2020, we posted 119 research stories on Facebook (through 12/29) and reached 330K people. Our number of followers tripled, going from 1,011 page likes to 6,133. In addition, we saw steady growth on Twitter, with over 150+ new followers each month and we added 1,802 (through December 2020) new followers over the course of the year, for a total of 6,613 followers. We also relaunched our Instagram account in 2020. Throughout the year we created 80 posts, gained 949 followers and made over 900k impressions.

Communicating Science: The Research Institute launched a series of initiatives designed to help our scientists better communicate the importance of their research to the general public. During the past year it has been harder to launch these activities due to the limitations of holding events in a COVID environment. We were able to host a virtual Science Slam in October with nine slammers and an audience of over 60. It was a great success, and we discovered that we can have an impact even virtually. We are planning more events for the new year.

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 two interns in 2020.

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.

Advancement

We work closely with our colleagues in the Development Office to inspire philanthropists and potential donors about the important role research plays in driving new discoveries in medicine. We had a successful year of fundraising, and our ability to raise unrestricted support for research continues to grow. In 2020, we selected five new MGH Research Scholars, bringing the total number of Scholars awarded unrestricted funding over the past seven years to 65. This remarkable donor-supported program has had a substantial impact on the careers of the awardees and the advancement of research at Mass General. To date, we have also named six Endowed MGH Research Institute Chairs. We continue to work towards our goal of supporting more members of our research community with MGH Research Scholar Awards and Endowed MGH Research Institute Chairs.

Our Research Institute Development team—including Drs. Slaugenhaupt, Orf, Kingston, Fisher, Fava and others in research leadership - held numerous meetings with individual donors and prospects in 2020, both in-person and virtual, including the wildly popular Lab Day hosted in October. This year, Lab Day was virtual and featured a combination of filmed laboratory tours and live talks and questions, including a panel on COVID research, which was very well received and led to some new gifts to the Mass General Research Institute.

Overall, the success of our collaboration with the Development Office can be seen in their willingness to

make research a philanthropic priority and in the growing portfolio of support for our investigators.

Strategic Alliances

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 2020.

The initiative is built on three pillars: Thematic Programs, Training and Education, and Research Community Building and Support.

Thematic Programs: Our solution-driven thematic 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 239 investigators from 22 departments and thematic centers across the institution. In total, we have organized 49 industry-focused sessions during which our investigators presented these programs to selected industry executives. In 2020, we executed and launched the first thematic program-driven collaboration with Amgen in the field of cardiometabolics. 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. To date, we have trained 31 faculty from across 15 departments and thematic research centers, engaged 66 teaching faculty (34 academia, 32 industry) and provided 1-year $150k funding to three project teams performing research and developing the corresponding go-to-market strategy.

In addition to the *Bridging Academia with Industry* educational program for faculty, Drs. Apiou and David Milan, co-host the Mass General Entrepreneurs Series which features successful innovators from Mass General and the research community at large and gives scientists at Mass General the opportunity to learn, be inspired, and benefit from their translational research expertise and experience. We have also developed the concept of a novel fellowship program in solution-driven biomedical research to foster development of the next generation of translational scientists.

Research Community Building and Support: We help build and support the Mass General research community through four main activities—building the research portfolio, developing new projects with the research community, supporting MGRI and MGB programs, and promoting the Strategic Alliances Initiative.

The research portfolio provides a common understanding of the science at Mass General, serve as a comprehensive foundation for promoting our research enterprise. In 2020, we added three outlines describing the work of seven investigators representing four departments and one thematic center. We also hosted three Portfolio Café sessions during which six investigators presented their outlines to members of the MGRI-OSD, the Mass General Development, and the Mass General Brigham Innovation teams.

We work directly with investigators to develop, advance, and promote their projects. In 2020, we helped launch four new multi-lab projects, two originating from our *Bridging Academia with Industry* educational program and three with applications in the COVID-19 pandemic.

We continue to help investigators to engage in several MGB Innovation programs such as the Novartis Global Scholars Program, Astellas GCT Golden Ticket Competition, Sanofi iAwards, and Pfizer Centers for Therapeutic Innovation. Members of our team also joined nine working groups formed as part of the MGB COVID Innovation Center and introduced one investigator and two companies working on promising COVID-19 drug candidates to the COVID Clinical Trial Steering Committee.

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 five invited talks describing the Strategic Alliances Initiative in 2020.

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 25th 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 PHS. DCR Education Center had offered 200 live and online courses with over 6,000 participants.

More recently, DCR has become the hub for all 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 is to improve the quality and quantity of clinical and fundamental research within MGH by providing educational opportunities (live and online) for investigators and study staff. The Center provides educational programs for physician scientists, PhD scientists, research nurses, project managers, coordinators and assistants. These programs are created to address the needs of the MGH research community and are responsive to the ever-changing research landscape.

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

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

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

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

Global Health Research Unit (GHRU), Jessica Haberer, MD
The Global Health Research Unit (GHRU) offers free consultations on the conduct of global health research, as well as sponsors campus-wide seminars on general principles for global health research. The GHRU research is generally cross-disciplinary and reflects several clinical fields, such as internal medicine, infectious diseases, 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 Mass General Brigham 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 Mass General Brigham 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 two cornerstone initiatives: The Mass General Brigham Biobank at MGH and the Translational Research Center (TRC).

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

The Mass General Brigham Biobank at MGH was devised to be a collaborative effort among patients, clinicians, and scientists to better understand disease, identify novel targets for therapy, and enable personalized medicine by collecting and storing fully consented blood, serum, and plasma samples, linked to electronic medical records and lifestyle and family history survey data, from patients across the institution. Through the Mass General Research Institute, resources were committed to add personnel, space, and equipment to jumpstart the consent and collection program at Mass General. With the additional resources contributed over the past five years, we have seen a dramatic increase in patient recruitment to 120,000+ consented patients—with 60,000 consented at MGH, 4,100 at McLean, 1,377 at Spaulding, and 832 at Mass Eye and Ear. Through the dedicated efforts of the team, including site-Principal Investigators Drs. Kerry Ressler (McLean), Ross Zafonte (Spaulding), Lucia Sobrin and Janey Wiggs (Mass Eye and 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 43,500 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 300 studies with specimens and data. In parallel to the genotyping work, the Biobank continues to return medically actionable genetic results for pathogenic variants within 59 genes (as recommended by the American College of Medical Genetics and Genomics) to Biobank participants. The Biobank provides genetic counseling services to return these results and assist with clinical confirmation. Over 140 medically actionable results have been returned to patients so far.

The primary focus of the MGH Biobank since March of 2020 has been to support 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 (MGH)
- 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
  - MGH Biobank Wang Registration and Phlebotomy Lab redeployed to MGH Laboratory Support Services

The secondary focus of the Biobank during 2020 was the development and approval of 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.

Goals for this coming year include continued support of Covid-19 research initiatives; re-consenting patients to the Biobank's new consent form which expands the return of research results; 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; 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 tr ials. 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 Mass General Brigham 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 2020, much of the focus of the TRC organization shifted to the execution of clinical trials, as many programs at pre-clinical stages were delayed due to COVID-19 restrictions.

Accomplishments

As with most organizations at MGH in 2020, the TRC had its priorities dramatically shifted because of COVID-19. The initial impact was a sudden, nearly complete cessation of non-COVID- 19 work that was accompanied by an equally rapid halt in industry clinical trials that could be performed in the Translational and Clinical Research Centers facility on White 12. The prospects for meaningful productivity in April and May of the year were not encouraging. Remarkably, the cessation in clinical trial work proved to be very short-lived, as investigators throughout the hospital began to seek the assistance of the TRC and TCRC staff in conducting COVID-related research. The result was a dramatic increase in new TRC studies initiated in 2020, reaching 52 trials at year's end, versus half that number in 2019. The total number of active studies in the TRC

at the end of 2020 was 60, slightly lower than at the end of 2019 (69), with the overall small decline being largely attributable to the very challenging environment industry sponsors have had in conducting any non-COVID research during the pandemic. Somewhat surprisingly, however, less than half of the TRC study visits on White 12 in 2020 (574 of the 1406 study visits conducted) were for COVID studies, as non-COVID investigators with time-sensitive therapeutic programs quickly returned to the TCRC when it re-opened to non-COVID work in the late summer of 2020. During the peak months of hospital occupancy by COVID-19 patients in 2020, and still ongoing today, the TCRC was asked to deploy its research staff to care sites outside of the TCRC facility to the inpatient units where desperately ill patients were being treated for their viral infections. 397 of the 432 study visits (92%) conducted across the MGH at sites other than White 12, referred to as scatter visits, were COVID-related. In these hundreds of scatter visits, as well as in the studies conducted on the TCRC on White 12, the TCRC staff rapidly became vital contributors to the work of scores of MGH investigators in their efforts to both understand the biology of SARS-Cov-2 and test novel treatments against the virus. One of the most important contributions of our staff to this effort was the education of the many, new, young investigators who had never before led human clinical trials until the COVID pandemic. Experienced trial staff were able to partner with these less experienced clinical investigators and enable them to perform trials with confidence, sophistication, and in accordance with good clinical trial practice standards. What much of the MGH community learned from this experience, some for the first time, was how critical a well-trained nursing and clinical coordinator workforce is to the successful conduct of appropriately designed human investigative trials, particularly when done in real-time and in the real world of inpatient medicine. This success is largely attributable to the outstanding leadership of the Nurse Director of the TCRC, Kathy Hall, MS, ANP-BC, NE-BC, who had to supervise, train, and coordinate deployment schedules for all TCRC staff involved in these studies. As 2020 progressed, it became increasingly apparent that a new generation of investigators at MGH had become acquainted with the capabilities and expertise of the TCRC staff and, as a result, the Center has seen a very significant uptick in research activity, both COVID-related and not, as 2021 begins. In short, the TRC has never been busier. One of the few positive and unanticipated consequences of COVID-19 may well be an influx of excited, passionate young physician-scientists into the clinical investigative community at MGH who now understand how they can leverage the resources of the TCRC to support their future research careers.

Half of the 30 COVID trials that the TCRC conducted in 2020 were industry supported studies with the other 15 being NIH or departmentally sponsored. Space does not permit a description of all of these trials, but a few summary comments about the kinds of work performed will indicate the breadth of the work our study staff supported in 2020. Randomized trials of multiple therapeutic agents were tested in COVID-19 patients by investigators from many units and departments, some of whom had never worked with the TCRC before; these trials included assessments of the efficacy of favipiravir (PI Boris Juelg, MD, PhD, Infectious Disease Unit), pegylated interferon lambda (Ray Chung, MD, Kevin and Polly Maroni MGH Research Scholar, GI Unit), tocilizumab (John Stone, MD, MPH, Rheumatology Unit), zanubritini (Camille Kotton, MD, Infectious Disease Unit), hydroxychloroquine (Michael Filbin, MD, Emergency Medicine Dept), and anti-Spike protein monoclonal antibodies (Arthur Kim, MD, Infectious Disease Unit; three trials with Michael Dougan, MD, PhD, Gastrointestinal Unit). Epidemiological studies investigating COVID-19 infections in differing populations were carried out by Katrina Armstrong, MD (Seroprevalence study in healthcare workers, Dept of Medicine) and Lael Yonker, MD in Pediatrics. Dr. Rick Mofsen, a new full-time member of the TRC investigative staff was selected to serve as the site PI for the Janssen (J&J) phase 3 trial of their adenovirus 26 SARS-CoV-2 prophylactic vaccine. The latter trial has been an enormous logistical undertaking involving the recruitment of scores of coordinators, nurses, co-investigators, and pharmacy staff, as well as the coordination of recruitment efforts both at MGH and Chelsea. The U.S. has recently seen just how difficult it is to roll out a vaccine to populations most in need, even when vaccine supplies are seemingly plentiful, but when the goal is not simply to vaccinate but rather study the safety and efficacy of an experimental vaccine using a randomized, double-blind, clinical trial structure, the task is an order of magnitude greater. The entire MGH research infrastructure pitched in to make this Janssen vaccine trial possible and in approximately two months, more than 300 individuals were randomized and vaccinated. It is now expected that the Janssen vaccine will become the third COVID-19 vaccine to be authorized by the FDA for emergency use in the U.S, once the efficacy and safety data from this trial are reviewed this winter. Study recruitment has concluded and the MGH will prove to be one of the major contributors of study subjects to this ~ 45,000 participant trial which has been conducted worldwide at well over 300 sites. No study at MGH this year was deemed to be of greater significance to the health of our community than this effort to speed the potential development of a prophylactic COVID-19 vaccine.

In last year's summary of the TRC, it was reported that the TRC had undertaken a new model of therapeutic development in which a TRC staff investigator would serve as the PI of a clinical trial that was conducted and managed by the TCRC staff. Dr. Mofsen's service as the PI of the Janssen vaccine trial is an exemplar of that new approach. This model enables the TCRC to assign an experienced PI to an industry trial with none of the delays that typically are occasioned by the need to recruit a non-staff investigator to a new study. Having an experienced investigator doing the work also makes all aspects of trial initiation more streamlined. A second study, led by the Director of the TRC, Mason Freeman, MD, is now underway which involves a multi-departmental effort in which the Gordon Imaging Center, the MGH Radiopharmacy, Nuclear Medicine, Surgical Services, and Neurology are all collaborating to investigate the pharmacokinetics and brain/spinal cord occupancy of a radiolabeled, novel nucleic acid therapy that is currently in development for amyotrophic lateral sclerosis. The study is complex, demanding, and technologically sophisticated and could only be done at a tertiary academic center, making it exactly the kind of study for which the TCRC was built. It is the ambition of these TRC-led projects to leverage the extensive capabilities of the MGH research community and ultimately to bring a new generation of investigators to the TCRC to utilize our services. Dr. Mofsen, a psychiatrist by training, will be conducting another study of this type beginning in the 1st quarter of 2021 that will test the safety and efficacy of an exciting novel medication for schizophrenia. In addition to the scientific interest generated by these types of studies, their requirement for extensive nursing care, overnight bed use, or dependence on utilization of the technology-rich components of our academic medical center make them substantial revenue generators for the hospital. The expectation is that this revenue can then be used to help recruit new investigative staff from multiple hospital departments who will further expand the repertoire of investigative experience the TRC can offer to the external biopharma community. It has always been a goal of the TRC to be the engine of growth for the TCRC facility and to help provide financial resources that can bolster the support that our youngest investigators frequently obtain from foundation, departmental, and early-career NIH grants that are often severely resource constrained. 2020 marked the year when these TRC-led studies began to fulfill the promise of the original vision in the MGH Research Strategic Plan of how a newly enlarged TCRC facility on White 12 could expand the translational medicine enterprise at the hospital.

Other noteworthy contributions of the TCRC staff to the MGH COVID Research effort in 2020.
Effective ~ 3/24: TCRC becomes involved with COVID 19 inpatient research at the hospital. Over time this meant:

- Our nursing director, Kathy Hall, MS, ANP-BC, NE-BC, sits on the MGH COVID Research Scientific Review Committee; from March 2020-present
- Our TRC medical director, Mason Freeman, MD assists on review of industry sponsored clinical trials on the COVID SRC; March 2020-present
- The TCRC staff worked at the MGH Respiratory Infection Clinic (RIC) to screen and enroll subjects into biobank repository studies from March 2020-July 2020
- TCRC staff began supporting all COVID research on MGH inpatients- Federal, industry sponsored clinical trials, and internal projects. March 2020-present
- TCRC staff were responsible for obtaining biospecimens via scatter visits at COVID units across the hospital. Due to PPE limitations, TCRC staff typically worked with clinical staff to obtain samples; March 2020-present
- TCRC staff assisted with procurement of Spanish speaking coordinators and clinicians to consent patients in the COVID units; March 2020-June 2020
- Staffing the Respiratory Acute Care Center (RACC) as the RIC was winding down in order to complete follow-up outpatient visits for subjects who were enrolled in studies and then discharged from MGH; March 2020-present
- Coordinators staffed clinical trials including IRB submissions, regulatory document gathering, participating in submissions sent to the Protocol Review program and subsequent trial data entry; March 2020-June 2020
- Studies were initiated through the TCRC chief code whereby TCRC staff were responsible for financial and admin oversight in addition to study activities; March 2020-present
- TCRC Staff assisting in development of rapid PCR COVID assay by internal core lab
- The TRC Director and members of the pre-clinical TRC staff have worked with Mass Eye and Ear investigator Luk Vandenberghe, PhD to create a novel adeno-associated viral vaccine against SARS-Cov-2. This project has been supported by the Bill and Melinda Gates Foundation and is currently being tested in a primate challenge study. If successful, it is slated to be in clinical trials later this year-its advantages over current authorized vaccines is the potential for single-shot efficacy with no or limited

cold-chain storage requirement. The program is also done in collaboration with Jim Wilson, MD, PhD at the University of Pennsylvania and has received substantial support from philanthropic donations, private investors and Novartis.

- The TCRC was primarily responsible for the opening and staffing of the research Respiratory Infection Clinic (RIC) and the Respiratory Acute Care Clinic (RACC) from March through present. This includes seeing COVID+ research participants for initial screening/treatment visits and their follow up visits, as well as screening and enrolling participants with possible COVID infections for enrollment in larger biorepository studies.

Adaptations Planned

2021 appears to be the first year in which the new model of TRC-staff led trials will be fully implemented for the entire calendar year. The success of these trials will depend on how well study subject recruitment proceeds and how flawlessly the trials can be executed. Recruitment of study subjects is a prerequisite for completion of any trial and is the key determinant of financial success of the enterprise. It also remains an incredibly difficult challenge at ours and other academic medical centers. We continue to explore novel tools to improve study recruitment, including the use of third-party social media platforms and other emerging technologies that give investigators better access to potential trial subjects. We also continue to push the limits of what is technologically feasible while sometimes encountering long-standing barriers in our institutional administrative processes that serve as obstacles to technological adaptation. When we encounter those, we push hard for change, while doing our best not to disrupt the collegiality of our community. This is the single biggest issue we must solve for the TRC to achieve the promise of the vision outlined in the MGH Strategic Research Plan that led to its creation. We believe that the 2020 accomplishments outlined in this report have significantly raised the profile of the TCRC in the MGH and MGB community and we hope to have created the foundation upon which an outstanding translational research center can be built at our hospital.

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.)

The MGH Research Institute (MGRI) reached a very impressive milestone of $1 billion in research activity in FY 20 for the second consecutive year. An amazing accomplishment considering we spent half the fiscal year in a pandemic that severely curtailed our on-site research activities. This is a real testament to not only the talent within the MGRI, but their durability and grit during this extremely difficult period.

Research revenues finished the year at $1,013B ($773M direct costs and $240M indirect), which is the same as FY19. Our awarded dollars from the National Institutes of Health (NIH) in FY20 increased from $500M to $551M (10.2% increase). In FY20, MGH ranked #12 (down from #11 in FY19) in NIH funding for all institutions, and we continue 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) remained steady compared to the previous FY at 1.7%.

Overall, MGH submitted an all-time record of 4,737 research proposals to all sponsors in FY20, an impressive increase of 8.8% from the prior fiscal year. This breaks a string of three consecutive years of decreases of proposal submissions. Remarkable considering the disruption of the pandemic, and that many of the investigators and staff responsible for preparing the applications have been working remotely since March. DHHS success rates for MGH proposals is an impressive 26%, 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 from $433M in FY19 to $442M in FY20. Federal Subcontract (predominately NIH) expenditures were $102M in FY20, decreasing from $105M in the previous year. Although our expenditures for Federal Subcontracts decreased slightly from the prior fiscal year, our collaborations with NIH funded investigators at other academic institutions continue to remain strong.

Research expenditures for all our other non-NIH sponsor types in FY20 totaled $469M which was a slight 1.5%

decrease from FY19. The All Other Sponsor category was the only non-NIH sponsor category that increased (6.6%) compared to the previous year. Non-Profit (-6.3%), Foundations (-22.7%) and Other Federal (-7.7%) categories saw decreases from FY19. Industry/Corporate remained the same compared to the previous FY. Our research activity type is split evenly between clinical (clinical trials and other clinical research) and basic/fundamental research at 47% each of the total research portfolio. Training activities make up the remaining 6%.

In aggregate, research activity (direct + indirect dollars) continues to comprise slightly under one quarter (22%) of the total MGH annual operating budget and is distributed across more than 40 departments and centers.

Our financial outlook for FY21 is strong. Early indications (first quarter FY21) show overall research expenditures running ahead of budget and are expected to exceed FY20. Coupled with the significant increase in grant proposals we saw in FY20, we anticipate that FY21 will be another record setting year 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) and the Research Space Advisory Committee (RSAC). RSMG manages all aspects of research space including space requests and allocations, proper space utilization, and renovations, which can range from minor site reconfigurations to major building/floor construction projects. Partnering with RSAC and MGH leadership, RSMG assists in developing space strategies, providing recommendations to fulfill space requests, optimizing space use, and supporting the overall Institutional research space objectives.

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

MGH currently owns or leases approximately 1.31M net assignable square feet (nasf) of space, essentially no net increase from last year. Research sites now exist in forty-three buildings across seven campuses in five cities. The percent allocations amongst the campuses are also similar to last year with 42% in the Charlestown Navy Yard campus, 21% on the Main Campus, 22% in Charles River Park, 7% on the Boston Campus, and the remainder in various metro Boston and Cambridge locations.

This year the Indirect Cost (IDC) density (defined as the recovered indirect costs per square foot) increased from an average of $181 per square foot in Fiscal Year 2019 to $185 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, $316. Major research groups contributing to the high IDC density have research sites at, Building 75, 100 Cambridge St., 165 Cambridge St., 175 Cambridge St., Bartlett, 101 Merrimac St., 125 Nashua St.

Fulfilling outstanding space requests remains one of RSMG's most difficult challenges, particularly when there are few, if any, opportunities to add new space to our current inventory; thus, the only option available is to renovate existing space to make it more efficient. RSMG works with RSAC and the research community to better understand the true space requirements and promote space adjacencies amongst collaborative groups. Outstanding space requests from departments with valid funded grants averaged 88,871 nasf over the past five years. In September of this year space requests increased to 65,525 nasf for wet space and 58,650 nasf for dry space, a total of 124,175 nasf. Never static, the current space request total in December 2020 is approximately 139,175 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 2020, twenty-five renovation projects, whose costs totaled approximately $25M, were completed. These projects included the I3/IBC Research Program on B149-10, CTS/CCM Large Animal Facility on B149-09, the recruitment renovations on Simches-04, and Dry Research expansion at 1 Bowdoin Square-01. Due to the unexpected

effects of the pandemic, on-going Capital projects were on hold for the remainder of 2020.

RSMG continues to work with the Mass General Brigham Research Applications and Analytics team to update and improve the functionality of the Research Space Management System and the Microstrategy Reporting module. In Fiscal Year 2020, enhancements were made to the yearly certification of space, agreements, and people in Insight and was certified by the Departments electronically. New to Fiscal Year 2020, asset tracking and certification were added to the Insight Space model. Access to asset inventory allows Departments to track what equipment is available in their Department and what is necessary to maintain for compliance purposes.

RSMG is responsible for updating all floorplans for research space, contributing research space data for the Medicare Cost Report, and providing accurate densities to Senior Leadership. As part of the ongoing award process, RSMG, in conjunction with Research Management, documents site locations for all research grants, helping to ensure the correct IDC rate is applied. This year RSMG, in collaboration with BWH, McLean, Spaulding, and MEEI, collaborate regularly to ensure all Academic Medical Centers are following the same policy and protocols to be consistent across Mass General Brigham. In addition to Departmental reporting, RSMG is in the process of designating sites as Wet or Dry and reporting out on those attributes.

In 2020 a new division of RSMG, Research Building Management was created, with the appointment of Patricia Frederico as Director. This division oversees the building operations and is the primary contact for facility issues. Additionally, this division manages the Research Glass Washing Core which services over 75 Departments. The Core remained open during the shutdown, providing essential support for COVID-related research. Other oversight includes management of the developer rooms, the Electronic bulletin boards for the facilities, copy machine shared usage, and the AV for all conference rooms under the Research purview. Monthly surveillance rounds are organized and conducted with other key support departments. Providing support through-out the pandemic, necessary supplies, a mask distribution program, and an asymptomatic employee clinic was instituted to ensure safe conditions for those staff who were onsite. Goals for 2021 include conference room upgrades with the incorporation of collaborative applications such as Zoom and Teams.

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

On any given day, approximately 105,000 mice, rats, guinea pigs, rabbits, sheep, pigs, non-human primates, and amphibians plus more than 35,000 zebrafish are housed and used within 95,000 square feet dedicated for such purposes on all three MGRI campuses. In addition, the MGRI operates two off-site facilities including a BL-2/BL-3 rodent facility that supports the Ragon Institute in Cambridge, MA, and a rodent facility at 65 Landsdowne Street. In addition, several off-site contractual agreements are in place for long-term housing of USDA-regulated animal species. Currently we have contracts with Biomere (Worcester, MA), Accuro Farms, Inc. (Southbridge, MA) and Tufts University's Cummings College of Veterinary Medicine (Grafton, MA). This expands our overall census capacity by an additional 40-50 housing units and offers relief to our heavily-utilized in-house large animal 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 Main Campus, 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 six ACLAM-boarded veterinarians (plus one vacancy) and a leadership team of 25 mid- and director-level managers, who provide these services throughout the MGRI. CCM currently has two veterinary residents in the Laboratory Animal Medicine and Management (LAMM) residency program with an equal focus on clinical medicine and program management in the country. This residency is recognized by the American College of Laboratory Animal Medicine (ACLAM) as well as MGH's Graduate Medical Education (GME) Program.

Special efforts in 2020:

As can be imagined, 2020 was a unique experience in the face of the pandemic. CCM staff maintained between 80-100+% of the pre-pandemic census throughout the year, particularly from March through June when most of the

research was shutdown. The CCM Emergency Response Plan was implemented until the actual circumstances faced extended beyond any emergency planning. Weekly to Bi-weekly guidance documents were published, in collaboration with the IACUC, on a specific MGRI webpage specifically for animal researchers to ensure everyone was informed of expectations related to animal and personnel safety. It's noteworthy that during the close to 300 days from initial shutdown to the end of 2020, all of the CCM staff worked tirelessly and competently to ensure the well-being and conservation the over 100,000 animals in-house. As researchers started to return to the laboratories in the summer, CCM's procedures and expectations, especially involving PPE, were key contributors to the fact that no COVID-19 viral transmission occurred in the workplace even as individuals worked less than six feet apart in many cases.

CCM served as a stakeholder in the design and planning of the new Ragon Institute facility regarding the new rodent facility being planned.

In addition, partnerships grew with off-site rodent breeding services by CCM Operations, producing mice for the Ragon's researchers as well as the Cancer Center researchers. Improvements in health quality, operations efficiency and total production costs were realized. Veterinary collaborations also increased significantly, especially in large animal anesthesia administration and monitoring as well as in new animal model development and/or refinement.

Actively participated in several PHS-wide animal program initiatives including 1) legislative advocacy by PHS Govt Relations for monitoring legislative initiative associated with the adoption of laboratory animals and regulatory burden reduction, 2) establishment of an animal program consortium of all MGB program leaders to look for harmonization opportunities and 3) pandemic response planning. Harmonization rose in importance over the past year as more collaborations between local academic institutions increased.

Lastly, in response to a call for more diversity, equity and inclusion in the biomedical and scientific industry, CCM initiated a "Be Better" program in June 2020 with the goals of 1) understanding where CCM policies, processes and expectations have a negative bias on our staff members of color; 2) assessing our culture to ensure that diversity and inclusion are embraced and 3) ensuring that there is demonstrated evidence of our anti-racist culture. This 6-month initiative included leadership team development sessions on racial injustice, implicit bias and systemic racism. A "Be Better" Task Force including both leadership team members and non-leadership team members was established to advise the Director, senior leaders and mid-level leaders' decision and direction as well as championing through individual actions, their support of this initiative. At the end of 2020, CCM collaborated with MGB Talent Management, to survey the staff to measure our "current state" when it comes to ensuring that all members of CCM staff realize our Mission Statement of feeling fulfilled, respected and safe in the workplace.

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 scientist, non-scientist and veterinary members, as well as representatives from IACUC administration and the public. The IACUC Chair is Dr. Warren Zapol, Reginald Jenney Professor of Anesthesia and (HMS) Chief Emeritus, Department of Anesthesiology and Critical Care Medicine (MGH). Dr. Zapol is supported by Dr. James Allan, Assistant Professor of Surgery and Associate Vice Chair-IACUC and Mark Randolph, M.A.Sc., Director, Plastic Surgery Research Laboratory, and Assistant Vice Chair-IACUC. The IACUC professional staff office supporting the IACUC is led by Anne Clancy, PhD.

MGH is registered with the U.S. Department of Agriculture Animal and Plant Health Inspection Service (USDA APHIS), holds an Assurance with the NIH Office of Laboratory Animal Welfare (OLAW) and is licensed with the Massachusetts Department of Public Health and City of Cambridge. The hospital has been accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALACi) since July 30, 1993. While the AAALACi site visit, planned for 2020, was postponed this year due to the COVID-19 pandemic, USDA and the Cambridge Commissioner conducted their annual inspection of our program, albeit a bit differently, with a focus on safe, socially-distanced inspection protocols and remote document review. Both agencies commended the institution and the program on its management and oversight of the animal research program during the pandemic.

A primary role of the IACUC is the review and approval of IACUC applications. Currently, there are approximately 950 active protocols being performed by 400 Principal Investigators. Approximately 2,800 transactions were processed by the MGH IACUC in the past year, comprised of new protocols, triennial reviews and study amendments. Complete metrics data for the MGH IACUC are available on the Mass General Brigham Research Navigator website, Research-Analytics-Reporting.

Massachusetts General Research Institute

Executive Report

After a year of experience with the new Animals Module in Insight 4.0, some of the year was spent refining the program and incorporating necessary changes to improve the user experience. One of the most significant efforts was to populate the FAQs/Instructions for the twenty-eight forms that make up the IACUC protocol form set. The instructions include references to relevant policies and guidelines and should serve as a helpful resource to research teams as they complete their IACUC protocols. The office pivoted from focusing on the electronic review system to concentrating on the IACUC committee membership. It is important the IACUC includes members from all major departments and research centers throughout the MGH Research Institute. This ensures the committee has the expertise to review the research protocols submitted and that there are enough members to process the high volume of studies submitted in a timely manner, while maintaining regulatory expectations for review. In collaboration with Dr. Harry Orf and Department Chiefs, new members were recruited from the under-represented research departments at the institute. Seven new scientist members, and two new community representatives, were identified and added to the committee roster. A new member orientation and training was created. All members participated in a half-day training that established regulatory and institutional standards and requirements for IACUC members. The training will be kept current and implemented for new members to promote uniformity between all members conducting reviews. While members cannot be compensated, each member was provided an iPad for conducting their IACUC work and as a thank-you for their service.

A highlight this year was the release of the new IACUC Web site. The site was built on the same platform as the Research Intranet and the content was developed with the research community in mind. It is populated with IACUC policies and guidelines to provide important regulatory information, but also includes information on protocol review procedures and timelines, helpful templates, tools and checklists for semiannual inspections, record cards and other items, and language and other material for grant submissions and collaborations. The COVID-19 pandemic took a center role this year and the IACUC collaborated closely with the Attending Veterinarian, Dr. Matthews Jarrell, to implement and oversee the response plan for the animal care and use program. A page on the IACUC Web site was dedicated to the COVID-19 response that served as a central resource for communications between IACUC/CCM and the research community. All IACUC-approved guidance documents and important resource information continues to be available on this Web page.

Significantly, the Director Office of Animal Welfare Assurance, the Attending Veterinarian/Director CCM, and the Institutional Official created the Animal Research Community (ARC) Group this year. The ARC Group serves as the educational outreach arm of the animal care and use program. ARC was implemented to bridge the gap in understanding between the program leadership and the community regarding the expectations and standards for successfully conducting animal research at MGH. Each IACUC Protocol Principal Investigator was asked to identify a representative for their animal research group. The representatives were asked to participate in a monthly meeting by videoconference and share information presented at the meeting to their teams. Topics included an overview of regulatory standards, facility access requirements, protocol review expectations and considerations for successful implementation of approved protocols. Examples of noncompliance were shared at each meeting in an effort to help laboratories avoid similar situations. Our USDA Veterinary Medical Officer presented at the inaugural meeting and applauded the program for implementing ARC. There was excellent attendance and participation at these meetings, and we look forward to seeing the ARC representatives at the 2021 meeting series.

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

In FY20, the Research Institute continued to support IS needs of project teams across MGH and MGB. Misha Pivovarov was named as the Director of Research IT Solitons role. He started meeting with various 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 cutting edge and dynamic technical needs of the research community.

Much of the work in research IS during FY20 was related to COVID-19 projects. The Research Institute supported departmental IS teams that worked very hard to enable remote work by providing hardware and software support. Zoom and Jabber were implemented across the enterprise. Online systems were developed and implemented in support of shutdown and lab reopening that helped COVID Safety Officers and departmental mangers achieve >95% compliance with policies.

In FY20, under the individual working groups, progress was made in several areas.

- **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, developing PI Workplans for lab reopening, monitoring COVIDPass compliance; (b) built a database of people with information loaded from multiple MGB systems; (c) built new consult system to support applications for COVID-19 clinical projects.
- **Applications for Research Administration:** (a) developed and deployed web-based management system for controlled substance licenses; (b) continued enhancement of the HR online evaluations and started to roll out across all MGB institutions (c) developed MGH Help and Safety App for mobile phones
- **Work on Applications for Research Training and Education:** (a) worked with DCR on selection and implementation of a new learning management system for research; (b) implemented accurate roster composition based on various criteria to use for communication and course assignment.
- **Infrastructure Improvements:** (a) continues to work with MGB IS to enhance infrastructure platforms such as OpenShift, other computing and storage options for researchers (b) accelerated adoption of cloud computing by developing pilot

Research Compliance—Kelé Piper, Director, Research Compliance

In FY19, we changed the model of Research Compliance to 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:

- "…transformed from the bodies that had almost exclusively controlled the services to bodies that assumed more partnership roles, explaining the regulations and actively helping investigators follow them."
- "I am writing to express my sincere thanks and gratitude for your support and guidance over the past few weeks as we negotiated the… (text omitted). I feel so fortunate to be at an institution that provides its investigators with thoughtful, expert advice and that considers the potential impact of each research project when making high-level contractual decisions."
- "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 FY20. A few examples below:

- **Research Risk Assessment:** Research Compliance developed and conducted a comprehensive review of MGH research risk to establish a baseline risk for resource allocation. The outcome from this work has put into place a platform to continuously assess risk and develop risk-based work plans to address those issues that pose the greatest risk to the organization.
- **Controlled Substances Database:** FY19, we created a new infrastructure for how we register, document, and dispose of controlled substances. In FY20, we took that process and created a database. For the first time, MGH now has a process to track registrations to make sure they are current and accurate. We are also able to track the locations and types of substances stored within the facility. Recently, a DEA agent commented they wished they could clone our process so that everyone could use as we literally check off all the boxes. We are currently looking to be able to expand this process to make it a MGB resource.
- **Research Survey:** The research survey has been a work in progress for several years. However, in the last year we have been able to verify all of the training, update training modules, move them to one platform, get feeds for training completion data, and refine the communication. We also added the survey to the orientation process which significantly improved compliance. For example, since adding the IATA training module to the survey, we have seen an increase year over year in individuals taking the training. We are also working to make this a MGB resource.

- **Research Misconduct:** The number of cases this year tripled from the previous year. There is a growing trend through anonymous sources for individuals to make allegations of misconduct; mostly in relation to figures in published papers. However, we are also seeing trends in federal agencies making reports. In FY20, we saw 34 allegations of research misconduct. We have made significant improvements in our process of sequestration and HMS made significant improvements in their process improving the timeframes; however, this still requires a significant FTE commitment. These improvements were shared as a MGB resource.
- **Orientation/Exit Strategy Workgroup:** In response to recent federal investigations resulting from sample and data seizures at Logan Airport, we looked at ways to improve communication of key information with the research community. In FY20, a new orientation checklist was developed and will be implemented in FY21. Additionally, work began on an exit strategy to address all of the areas that require closure prior to an individual leaving the institution and the information, agreements, and processes that need to be followed. We are looking to an electronic solution utilizing current infrastructure. We have invited representatives from the other hospitals to make this a MGB initiative.

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

In FY20, 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, promotion and advocacy. This year, Ms. Sara Silacci assumed the role of Senior Managing Director while retaining oversight of Strategic Alliances, and David Louis, MD, MGH Chief of Pathology, continued to serve as the Executive Sponsor for CIDH. With Co-Chairs, David Ting, MD, Chief Digital Health Officer for MGH and Shawn Murphy, MD, PhD, Chief Research Information Officer at Mass General Brigham (MGB), CIDH expanded its support capabilities by enlarging its faculty and project staff numbers, and assuming administrative oversight of MGB Connected Health Innovation (Joseph Kvedar, MD) and the MGH Medical Device Plug'N'Play lab (Julian Goldman, MD). Simultaneously, CIDH encouraged MGH innovators to connect with MGB enterprise-workstreams, in order to ensure MGH research and innovation interests are visible and appropriately supported by the system.

As with most MGH support units, the CIDH pivoted in FY20 to support system and local efforts to address the COVID-19 pandemic. CIDH staff were seconded to MGH IS, MGH Telehealth, and MGB Center for COVID Innovation teams where they led or assisted in deploying video intercom systems, evaluating remote patient monitoring solutions, producing COVID-related dashboards, and contributing to health equities work. As of the time writing this report, much of this work continues.

In FY20, CIDH accomplishments may be summarized along several thematic areas:

Support of MGH and MGB Priorities. CIDH prioritized activities that aligned with the mission of MGH and the system priorities of Mass General Brigham, including increased collaboration with BWH iHub, continuing to work with the Enterprise Data and Digital Health (EDDH) Digital Health Innovation (DHI) and MGB Innovation teams, and co-chairing several MGB Center for COVID Innovation workstreams, while assisting local MGH responses to COVID.

Services and Activities to Accelerate Innovation. (1) Provided guidance and support to 1,382 MGH innovators across 88 MGH departments, divisions and innovation groups. (2) Worked with 9 CIDH senior faculty to develop two CIDH-led programs to guide, champion and advocate for responsible digital health experimentation and innovation: CIDH Executive Committee for Innovation and Technology (ExCITe), MGB Innovation Digital Education Academy (IDEA). (3) Promoted MGH digital health innovation activities and publications by developing several web and social media channels, resulting in accelerating key hires for sponsored research studies via the CIDH LinkedIn page (the page is second only to MGH itself for most followers of any MGH LinkedIn page); and CIDH was named #1 in Digital Transformation programs by Becker's Healthcare.

Support of Research and Discovery. (1) Engaged with startup accelerators to gain exposure to early-stage digital health startups who address MGH challenge areas. (2) Worked with Dr. Goldman and his lab to formalize a MGB research CORE and State of Massachusetts-designated "Sandbox," providing an environment for cybersecurity and interoperability innovation. (3) Organized small pilots to test usability and feasibility; supported research protocol development; collaborated on clinical trial design and data analysis. (4) Created a comprehensive digital health research training manual and curriculum for research teams.

Support of Education and Community. (1) Prepared to launch the Biomedical Informatics Initiative provides a vehicle for academic and scientific growth for faculty, informatics training, and education. (2) Worked with clinical

departments on targeted recruitment/retention efforts and helps facilitate a new academic appointment. (3) Secured support to launch the Community Health Innovation Learning Lab "CHILL" which supports underserved communities by convening MGH faculty to participate in collaborative research and the accelerated development of commercial products to manage at-risk populations. (4) Committed to be dedicated advisor to Wolomi (via MassChallenge), the only digital community that offers support to women of color to improve maternal health outcomes.

Support of Industry Sponsored Research at MGH. (1) Secured $33M in externally sponsored and contracted revenue since launch (October 2018); Includes $14M cash received through FY20. (2) Co-created the MVP for a comprehensive virtual monitoring solution, CoronaCare, with Strategic Alliance partners CarePassport, Discovery Genomics, and BioIntellisense. (3) Led an evaluation of the technical and financial requirements to "scale" and commercialize ePAL (pain management app) to educate, empower, and improve pain management for cancer patients.

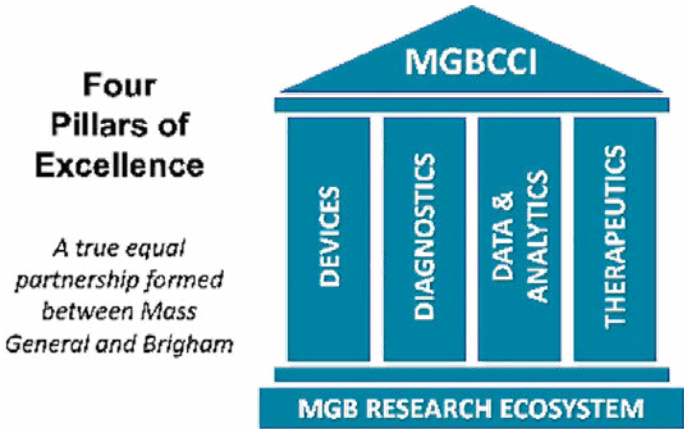
Research Institute Training and Education Committee—Andrew A. Nierenberg, MD, Chair

The Research Institute Training and Education Committee (RITE) has focused on consolidating research compliance and voluntary trainings across MGB. The goal is to maintain MGH specific training and education for researchers when necessary and moving to common MGB training when appropriate. We will also identify MGB-wide compliance issues to develop education solutions to prevent future problems.

Research Program Updates and Initiatives—Harry W. Orf, PhD

Initiative—MGB Center for COVID Innovation (MGBCCI)
[Condensed from MGBCCI summary slide by Gary Tearney, MD and David Walt, MD]

Recognizing the urgent need to develop capabilities to assist our clinical colleagues in dealing with the massive influx of COVID patients, MGH and BWH formed an equal partnership to create the MGBCCI. It was launched on March 20, 2020 with Drs. Gary Tearney from MGH and Dave Walt from BWH as co-directors, and it became fully operational within one week. Its mission: To rapidly investigate and clinically deploy new devices, diagnostics, data & analytics, and therapeutics developed by



Four Pillars of Excellence where COVID-19 solutions were developed and implemented throughout the crisis.

Figure 2 Jackson Walnut Park School (Newton, MA) students donate face shields that were utilized at MGH after MGBCCI testing.

researchers and clinicians in the MGB ecosystem, aimed at combating the COVID-19 crisis.

The Center rapidly engaged 125 full-time employees repurposed from the MGB research pool. They formed 23 working groups led by MGB/Harvard/Wyss researchers and had participation in these groups from over 2,000 researchers across the system. As of the end of 2020, MGBCCI had held ten virtual town halls and has produced a dozen publications disseminating progress to local, national, and international communities.

Highlights include:

- Generated > 10 new devices implemented clinically in MGB hospitals
- Conducted studies that brought Battelle N95 reprocessing unit to MGB/MA, resolving N95 shortage crisis
- Became the statewide experts on respirators and emergency use ventilators, served as consultant to governor
- Developed/implemented patient isolation booths - improved testing throughput by 300%, reduced testing PPE use by 95%, and saved more than $1M
- Established laboratory to test and validate new serology, antigen, and nucleic acid diagnostics assays and testing platforms
- Developed interactive website for selecting testing platforms
- Created implementation projects for testing new diagnostics platforms in community, healthcare, and global settings
- Created COVID Data-Mart - patient data repository for developing clinical trial support tools
- Curated a web-based, MGB comprehensive research funding database

Initiative—The Animal Research Community (ARC) Group
Significant improvements in our animal care (CCM—Center for Comparative Medicine) and regulatory (IACUC—Institutional Animal Care and Use Committee) programs. In spite of the challenges to colony management presented by COVID and the lab shutdown, critical animals and vital programs were maintained, improvements to the electronic animal protocol modules in Insight were made, and a new IACUC website was developed. Also, the Director Office of Animal Welfare Assurance, the Attending Veterinarian/Director CCM, and the Institutional Official created the Animal Research Community (ARC) Group this year. ARC serves as the educational outreach arm of the animal care and use program and was implemented to bridge the gap in understanding between the program leadership and the community regarding the expectations and standards for successfully conducting animal research at MGH. Each IACUC Protocol Principal Investigator has a representative on ARC who participates in monthly meetings by videoconference and then shares information presented at the meeting with their lab members who work with animals.

Initiatives—Diversity and Equity Programs in Research
Responded to the MGH Structural Equity Ten-Point Plan, a roadmap that focuses on what we as an institution can do to address structural and overt racism within and outside of the MGH, with several research-focused initiatives. The Taskforce on Equity and Respect in the Research Workplace is using the results of its extensive survey to study gender- and race-based inequities in research salaries and resource allocation. Our Center for Comparative Medicine (CCM), with a large number of URM employees in its 130+ member staff, initiated a “Be Better” program in June 2020 with the goals of 1) understanding where CCM policies, processes and expectations have a negative bias on our staff members of color; 2) assessing our culture to ensure that diversity and inclusion are embraced; and 3) ensuring that there is demonstrated evidence of our anti-racist culture. This six-month initiative included leadership team development sessions on racial injustice, implicit bias and systemic racism.

Update—Isuggest Surpasses 1,500 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 2020, Isuggest received over 100 new suggestions, bringing its total to over 1,500. Of these, over half (811) have been implemented. Since its renewed launch in 2016, Isuggest has been receiving 3-5 new suggestions a week, indicating that the program has effectively reached a steady state where it is known and used routinely across the research enterprise. This past year, with the COVID lab shutdown, the weekly suggestion average fell to two per week. 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 suggestor is shown at the beginning of every research meeting (ECOR, Research Council, RADG, etc.).

While many of the working groups within the Isuggest structure are functioning well and addressing their suggestions in a timely manner, some were lagging in their responses. To address this issue, new metrics were developed in 2018 to show both working group leaders and the Isuggest administrative management group which working groups are not operating effectively. Use of these metrics throughout FY20 has resulted in increased attention being paid to previously neglected suggestions.

Update—Research Safety Committee Completes Its Eighth Year

Meeting #32 of the Research Safety Committee (RSC) took place in December, marking the end of eight 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) Important COVID safety education/updates on clustering, contact tracing, asymptomatic testing, PPE distribution, etc.; 2) Additions of two new regular agenda items—hospital monthly safety reports review and the Good, Bad, and Ugly examples of lab practices; 3) Development of a comprehensive risk assessment survey and use of results to set compliance goals; 4) Major review and rewrite of the policy regarding the transport of biological materials; 5) Update of departmental chemical hygiene plan template.

Goals for 2021 include: 1) Roll out of a controlled substance database that allows us to track permit holders and proactively notify them about renewals and training; 2) Dissemination of the "Help and Safety" app across the entire hospital; 3) Get full compliance with the new, mandatory employee research training survey, having it completed by all employees during orientation; 4) Led by our Research Compliance Officer, develop a comprehensive offboarding process for all research personnel leaving the hospital.

Update—MGH Onsite Indirect Cost Rate Holds Steady

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

The federal negotiators were not able to site visit MGH in FY19 or FY20, but their review of our submitted documentation resulted in them agreeing to hold our onsite and offsite fixed rates for 2020 and 2021 at 68% and 34%, respectively. We also received approval to hold these numbers as provisional rates for 2022, subject to their next site visit, scheduled for next year. Overall, we were pleased that the 2021 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, and Ross Zafonte, DO Senior Vice President Medical Affairs Research and Education at Spaulding—as well as Mass Eye and Ear and the Institute for Healthcare Professions, to create a collaborative and compliant research culture that directly supports the research community and provides key infrastructures to enable advances in basic and clinical research. At MGH, the Mass General Brigham CAO works closely with the MGHRI and its scientific director, Sue Slaugenhaupt, PhD and ECOR leadership.

Massachusetts General Research Institute

Executive Report

The office of the Mass General Brigham CAO directly oversees several departments that support a $1.8 Billion research enterprise ($1 Billion MGH research) including the IRB, 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 Management, 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 four areas: (1) the Institutional Review Boards (IRBs); (2) the Human Research Office supporting the IRB operations; (3) the Quality Improvement Program (QI) and (4) the Human Embryonic Stem Cell Research Oversight Committee (ESCRO).

The HRA provides oversight of all research involving humans conducted by 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, 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 subjects research.

IRBs: Research that is not exempt from the regulations must be initially approved by an IRB before any subject is recruited or enrolled. During the life of the protocol, the IRBs are then responsible for continuing review, review of any change to the protocol (amendments), adverse events, unanticipated problems, and non-compliance 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.

Human Research Office (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 determination under the federal regulations for research that is exempt from IRB review and research that falls outside of the definition of human subjects research. The HRO also provides education and support to the research community, maintains policies and procedures, and documentation required by the federal regulations.

HRA IRB and HRO Activity
10/1/19 - 9/30/20 (FY19)

Activity	Full	Expedited	Administrative
Initial protocol review	347	3,021	
Continuing review	837	5,707	
Administrative Annual Check-In			1,431
Staff amendments	0	0	17,823
Non- staff amendments	164	8,089	
Other Events (e.g., adverse events	75	1,405	
Cede Reviews			239
Total transactions	**1,423**	**18,222**	**19,493**

QI Program: The QI Program provides resources for investigators as well as the IRB with the primary goal of supporting research that is compliant with ethical standards and regulatory requirements. The QI program works one-on-one and generally face-to-face with Investigators and study teams to conduct for-cause and not-for-cause on-site audits of study files; supports sites through external audits (e.g., FDA inspection); provides specific training for holders of investigational drug and device applications from the FDA; supports study teams with educational activities

including study specific consultations, provides Regulatory Binder consultations, and presents at numerous department and institution educational sessions. In addition, the QI Program administrates the ClincalTrials.gov program required for compliance with federal law.

HRA QI Program Activity 10/1/2019-9/30/2020 (FY20)	
Type of Activity	**Number**
On-site reviews	99
Consultations	242
Presentations/education	50

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 and electronic resources for clinical trials management. These service areas are designed to provide clinical researchers with resources to engage in local, national and international clinical trials initiated by both industry and our investigators. Through participation in these trials, MGH is able to provide its patients with the most innovative and state of the art treatments for a variety of disease states and contribute to medical knowledge in support of the Hospital's scientific mission.

The Clinical Trials Office achieved a number of important goals in support of MGH investigators and leadership this year. There are presently master clinical trials agreements with more than 124 industry sponsors, an additional 60 department or investigator specific master agreements, 26 master confidentiality agreements and four "other" masters related to emergency use, health outcomes and data research. These master agreements allow for efficient start-up of new clinical trials. Overall, volume of executed agreements increased significantly between FY19 and 20 (Table) by 18% overall from 1,772 to 2,083 in part driven by a high volume of COVID-related projects. Amendments, support agreements and confidentiality disclosure agreements increased significantly while new clinical trials agreements held steady and subcontracts decreased.

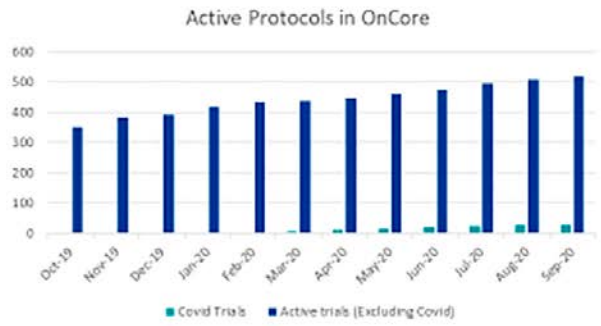
CTO Executed Agreements Volume (all-MGB)					
Agreement Type	FY20	% Change FY20-19	FY19	% Change FY19-18	FY18
Clinical Trial Agreements	364	-1%	366	-1%	370
Amendments	579	28%	451	17%	387
Support & Other* Agreements	308	29%	239	14%	210
Confidentiality Disclosure Agreements	731	22%	598	3%	581
Subcontracts	101	-14%	118	57%	75
Total	**2083**	18%	**1772**	9%	**1623**

Significant advances in FY 20 have been achieved in the area of electronic clinical trial support services. OnCore CTMS optimization and utilization continued to grow throughout the fiscal year. The CTO CTMS team migrated OnCore CTMS from on-prem database and servers to our vendor hosted infrastructure, resulting in a reduced MGB IS support workload. The increased efficiency overall agility for the OnCore CTMS technical teams to enhance and optimize the application with a streamlined upgrading process. Monthly reports of clinical trials activity are presented to MGH and MGB leadership highlighting the ability to manage trials in real-time.

The clinical trials office continued to optimize the integration between OnCore and MGB PeopleSoft that was implemented in FY19. Working closely with the research management, the CTO has been working on clinical trial revenue cycle refinements.

The MGB research community's adoption of Advarra (formerly Forte) Payments, a streamlined, real-time subject payment system continued to grow significantly. Advarra Payments in the FY20 Q4 had a significant increase in payments made to study subjects due to the many COVID

FY20 OnCore CTMS



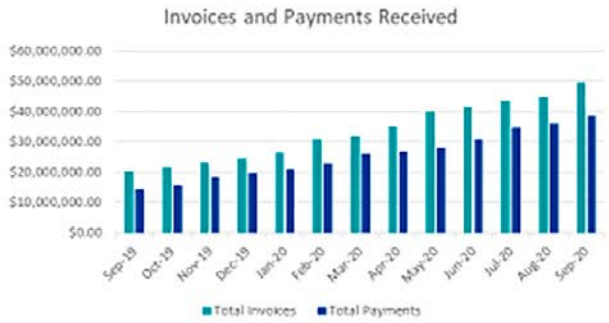
1169 Invoices Created

692 Payments recorded

225 Protocols Open to Accrual

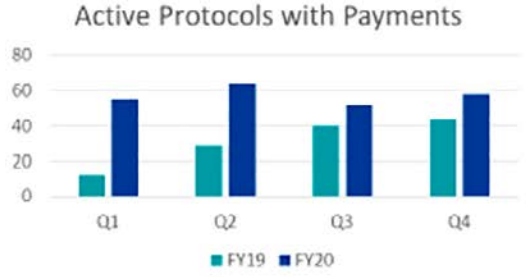
610 Active Users

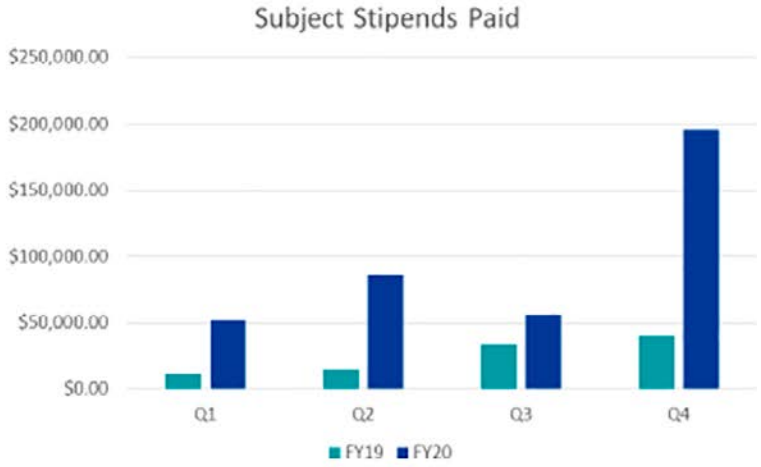
302 Users Trained



FY20 Advarra Patient Payments

Formerly Forte Payments





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 Forte Payments.

The OnCore CTMS Central Billing Office Pilot successfully closed in September 2020. The findings have been presented in several leadership forums. Based on the success of the pilot, the CTO continues to present metrics and funding models to expand services offered to the study teams in FY21.

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—Mary Mitchell, Chief Research Compliance Officer

Mary Mitchell leads the Mass General Brigham Research Compliance Office (RCO) which was established in 2007 to provide 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 RCO 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 and 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.

Covid-19 Compliance Program: From the onset of the Commonwealth's and Federal government's Covid-19 restrictions in March 2020, the Mass General Brigham Research Compliance program worked with the hospitals and relevant Mass General Brigham Research Management offices to ensure that Principal Investigators (PI) and Research Administrators managed their grants in accordance with the flexibilities granted by the Federal government. This included offering multiple Mass General Brigham Town Halls on NIH requirements for basic science and clinical research, publishing guidance documents, and participating in hospital-based educational activities. Where appropriate, research policies were formally revised to reflect new Covid-19 requirements to provide the hospitals and investigators with a basis for their actions and documentation if requested by sponsors. The human research, biosafety and animal research compliance committees greatly expanded their activities in order to address new Covid-19 studies and related activities so that studies could proceed expeditiously.

International Research Collaborations and "Foreign Interference": International collaborations and responding to federal concerns about "foreign interference" continued as a top compliance priority for a second year. The Mass General Brigham Foreign Collaboration Working Group (WG), a system-wide group of legal, compliance, and research administrators, continued its work during 2019-20. 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.
- Development of policy, guidance, and education for transporting/sharing biological materials for research with external researchers.
- Expansion of the Mass General Brigham Export Control Program to encompass not only research projects but also non-research international advisory activities in screening and related activities.
- Development of data sharing and transport agreements and guidance to enable departing foreign postdoctoral fellows to complete publications and continue collaborations with Mass General Brigham investigators in compliance with Mass General Brigham data security requirements.

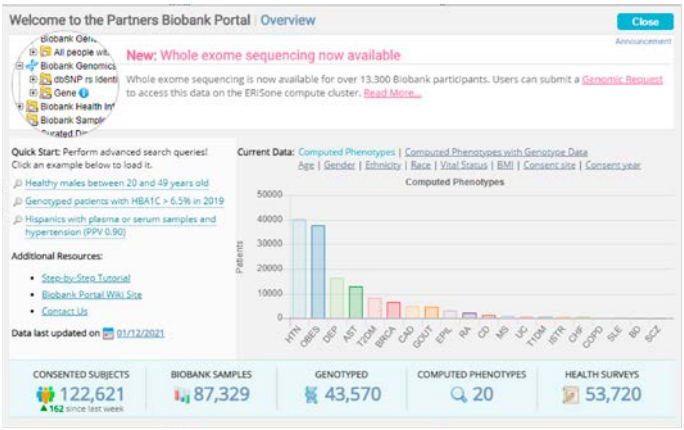
Training and Education: A key component of the RCO's role in supporting the research hospitals is the maintenance of a training and education program for investigators, postdoctoral fellows, and research administrators. RCO educational activities in 2020 consisted of:

- 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.

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 upon Mass General Brigham-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 1800 scientists in a year, obtaining over 5,500 sets of EHR data in 2020. Calculated over four years the total agreement amounts attached to projects obtaining sets of data from the RPDR were $2.27 Billion, and when surveyed the annual per year consumption critically dependent on RPDR data was $244 Million. 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 **Mass General Brigham Big Data Commons** enables the 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 Mass General Brigham 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 122,000 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 2.2 million imaging studies to over 800 research projects. In 2020, the MGB Data Enclave was built and offered to researchers through 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 2020, almost 82,000 people have identified themselves to over 1,200 studies using this system. At patient registration, patients can opt into being contacted for studies that researchers determine may be a good fit for the patient; consented patients can be messaged directly using outreach tools built into Epic. For patients that have not opted in to be contacted directly by researchers, a workflow to contact patients through their providers is provided by the RPDR.

The RISC **Health Innovation Platform (HIP)** allows the efficient development and deployment of secure, Epic-linked apps into our clinical environment. Using HIP, sophisticated clinical decision support (CDS) apps can be built leveraging RISC capabilities for machine learning and providing high quality data. These apps can then be used to alter clinical workflows and/or improve decision making as well as allowing unique clinical data elements collected through the apps to flow back into research. This has been implemented through Digital Care Transformation to help manage lipids and hypertension in over 1200 patients as part of the EDDH program.

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

RISC's Research Applications' data capture services are enabled through a suite of secure HIPAA-compliant data collection and survey tools such as Research Electronic Data Capture (REDCap), 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. In 2020, 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. Our REDCap supports over 23,000 research projects. In 2020, REDCap eConsent with 21 CFR Part 11 compliance was launched in August to support the need for social distancing while still recruiting for research projects. There are 610 REDCap eConsent projects and over 570 COVID Related REDCap Projects to date.

Mass General Brigham Personalized Medicine (PPM)—Scott Weiss, 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 four 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. The Biobank includes samples and data from across Mass General Brigham hospitals and community sites and enables individual investigators at MGH and across the Mass General Brigham to access this resource for research with appropriate IRB approval. It leverages a common electronic health record which spans Mass General Brigham. As of December 2020, 120,000+ participants consented and 88,000+ samples have been collected. In addition, the Biobank has supported over $340M in research activities through the distribution of Biobank samples and data as well as through the sample management services, such as DNA Extraction services, cell lines, and discarded samples distribution.

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

- Access to DNA, serum, plasma, and PBMCS (for COVID-19 patients only). In 2020, in particular, the Biobank collaborated with studies at MGH and BWH to recruit COVID-19 patients and collect, process, and distribute their 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., self-reported surveys).
- Sample management services.
- GWAS data, exome sequence data, and imputed genomic data.
- Support inventory, storage and distribution of COVID-19 vaccines for Mass General Brigham hospitals and non-Mass General Brigham affiliated physicians.
- Support CCOVID-19 serologic studies across Mass General Brigham hospitals in the shape of 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 program, All of Us, which aims to consent over 90,000 participants in New England (as part of the larger goal of 1M+ participants) via a $53M grant at MGH that includes BWH and Boston Medical Center.
- Participation in a NIH-funded research network, eMERGE IV, that aims to develop polygenic risk scores for 15 medical conditions and disseminate those risk scores in clinical practice at eight academic medical centers and assess the impact of this genetic information on health care quality and cost. The grant is for $6.7M over five years plus $1.3M in two supplements.

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:

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

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

- Supporting NIH-funded genomic medicine programs requiring cutting edge clinical genetic and genomic testing
- Supporting Biobank Return of Research Result (RoR)

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 Biobank, LMM and BGC
- Develop functionality required to maintain near real-time programmatic access to patient genetic data for the LMM and Biobank
- Offer custom analysis for NGS data to Mass General Brigham Investigators thru the BGC, such as: Genome/Exome/Panel variant calling and filtration
- Support data processing, analysis, and storage of Genotyping results for Biobank participants' samples
- Assist in the development of the Health Innovation Platform (HIP) and associated apps to improve clinical workflows

- Support eMERGE development of processes for return new types of clinical genetic results

Mass General Brigham Innovation—Chris Coburn, Chief Innovation Officer

Mass General Brigham Innovation monetizes the unique assets of MGH and its Harvard faculty. Its business development responsibilities include company creation, license transactions, securing research collaborations, technology development funding and managing intellectual property including patent prosecution. Mass General Brigham Innovation is the largest academic organization of its kind with 140 staff that includes 7 MDs, 30 PhDs, 26 MBA/MAs, and 20 JDs. These totals include the favorable impact of a pathology royalty buyout.

More than 329 companies have been established based in whole or in part on the work of Mass General Brigham investigators with 2/3 of those tied to MGH. Mass General Brigham has $171 million in capital under management. The Fund has invested in 44 companies, realized 14 successful exits, and produced top quartile venture returns. It is currently raising a $250 million Fund III under its new name Mass General Brigham Ventures that includes strategic investment from Astellas Pharma, Eli Lilly, Fosun Pharma, ShangPharma, and Simcere Pharmaceutical Group. Its net internal rate of return equates to top quartile performance in the venture industry and is largely unrivaled in the academic realm. A translational innovation fund to drive MGH developed technologies into clinically useful applications and an artificial intelligence and digital innovation fund has been initiated.

A system-wide Gene and Cell Therapy strategy is under development and implementation. The World Medical Innovation Forum will be held virtually May 19-21, 2021 and will focus on gene and cell therapy as part of the strategy. More than 12,000 registrants from around the globe representing more than 600 organizations registered last year with a large number being MGH faculty and trainees who will experience first-hand how commercial innovation priorities are set.

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

MGB Research 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.

Within the grant's continuum, Research Management staff strive to deliver the highest level of service to the MGH research community throughout each segment of the grant. The Pre-Award team reviews and supports the submission of proposals to sponsors. Next, the Post Award staff supports the execution of agreements and subcontracts then the management and oversight of the award for the duration of the grant. Research Finance monitors the financial activity and supports the billing, reimbursement, and financial reporting for the project. There are also groups who support the oversight of research cores as well as a training team. Finally, the Research Support Services (RSS) team supports PIs and Departments who may be short staffed, dealing with a leave of absence, or just needs

MGH Outcomes	FY15	FY16	FY17	FY18	FY19	FY20
Licensing Activity	127	130	133	198	197	**145**
Material Transfer Agreements	987	1067	1360	1374	1,537	**1,256**
New Disclosures	318	365	311	366	355	**384**
Patents Filed (US)	228	910	1091	1643	1,593	**1,483**
Patents Filed (Int'l)	399					
Patents Issued (US)	89	126	136	150	165	**149**
Patents Issued (Int'l)*	120	311	421	317	464	**335**
Royalty and Licensing Income	$80M	$77M	$87.7M	$94.6M	$298.0M	**$142.9M**

* 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.

an extra pair of hands during a peak proposal deadline. RSS staff are proficient in all phases of the grant and their services have been enthusiastically embraced by many departments and PIs at MGH.

FY20 was a challenging, transformational, stressful, yet very successful year for research. Throughout the year, Research Management experienced unprecedented volume increases. Proposal volumes increased 8% with 787 COVID submissions, contracting volume soared, driven by a 40% increase in unfunded agreements such as Data Use Agreements, and increases were seen across other operational areas. This unparalleled volume required Research Management to think innovatively, work collaboratively with colleagues and implement process changes to meet the challenges and demand encountered in FY20. Despite disruptions due to COVID, including lab shutdowns and Research staff redeployment, MGH maintained $1.013B of research activity. Additionally, many were challenged with safety protocols, increased federal scrutiny, hiring restrictions and remote work all adding to a year to remember.

Research Management united with colleagues from Innovation to collaboratively worked together to address the contracting increase. Pre and Post Award staff were also reassigned to help the contracting volume. Jointly, Research Management and Clinical Trial (CTO) offices focused on enhancing the impact of the OnCore Clinical Trial Management System for the clinical research community. Research Management assisted with data analysis, reporting and cash application improvements for CTO funds.

To support the success of the MGH research community, Research Management continues to make improvements to systems and the support infrastructure for the MGH investigators. With the growing volume and complexity of the Research Portfolio and the overall pressure to contain costs, Research Management continues to improve the systems and reporting tools available to departments. A new Other Support page was added to Insight to comply with new Federal regulations from Foreign Interference. “Deliverable” functionality was enhanced across areas in Insight and bi-weekly updates continue to increase functionality for the Research Community. Robotic Process Automation (RPA) was deployed with four new BOTs replacing manual work.

A formal training curriculum for Hospital Grants Administrators, Research Staff, and Investigators continues to be a focus for Research Management. All Research Management “in person” trainings have been transitioned to on-line trainings both self-paced and facilitated sessions. A mandatory training curriculum, including job aides for grants administrators across MGH is complete and will be implemented in FY21. This training initiative will both level set expectations for a professional grants administrator and help drive improved understanding of challenging and often changing regulations and sponsor requirements.

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 relationship 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:

- 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 Mass General Brigham and Harvard Medical School conflict of interest policies.

- The **Outside Activities** section reviews the outside activities (personal consulting arrangements and the like) of physicians and staff to ensure they are consistent with MGB policy and is responsible for obtaining COA and PICC review of outside activities of senior institutional officials.
- The **Educational Grants** section oversees the receipt of industry funding in support of 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.
- 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.

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, FY20 continued the work to implement policy and education with the newest members of the MGB system, Mass Eye and Ear and Schepens Eye Institute.

Significant accomplishments in each of the OII sections during FY20 included the following:

1. **Research Activities—**in addition to handling, as part of the normal workflow, the processing of over 17,000 financial interest disclosures needed for compliance with MGB regulations and HMS and Mass General Brigham COI policies:
   - Streamlined the COI review process for research sponsored by entities that are not subject to the Public Health Service COI regulations, reducing administrative work for investigators.
   - Continued to advance system improvements for the COI review process of research grants by working with Research Applications and Analytics to design and implement new functionality in the Insight Disclosures Module, including automated handling of the disclosure of certain types of interests, in order to increase efficiency.
   - Conducted extensive process to increase timely reporting of financial interests by investigators, including individualized educational outreach, in order to increase institutional and individual investigator compliance with regulatory requirements.
2. **Outside Activities—**In addition to handling, as part of normal workflow, over 2,300 consulting and related agreements:
   - Participated in multi-departmental process, along with MGB Innovation, Clinical Trials Office, Research Management, and Supply Chain to provide more clear guidance to investigator community on proper processing of different kinds of agreements.
   - Refined and submitted for implementation system requirements for new functionality in Insight for the review and processing of outside activities in order to more effectively service the Mass General Brigham community. Once completed, the system will involve a platform that integrates with the Mass General Brigham CTO, Innovation and Research Management offices; increases efficiency in the review and processing of agreement; and streamlines the overall tracking and metrics associated with outside activities.
   - Worked in conjunction with Public Affairs to review and manage various social medial engagements by faculty members with outside entities, including podcasts, webinars, and use of various social media platforms.
   - Continued streamlining processes for handling consulting and other outside activity agreements, in part by developing alternative approaches to the review of certain outside activities, reducing administrative work for investigators.
   - Maintained approach of constantly revisiting policies leading to revisions in several Mass General Brigham policies, including the Guidelines for the review of Industry-Physician Appointments in consultation with the Committee on Outside Activities and senior clinical and research leadership; and Guidelines for Addressing Supervisory Conflicts of Interest.
3. **Education Grants, Research Gifts, and Procurement Section—**in addition to handling, as part of the normal workflow, over 168 educational grants bringing in about $4M in funding:
   - Reconfigured section, formerly Educational Grants, to Educational Grants, Research Gifts, and Procurement, to reflect the expanded responsibilities of the section.

- Continued a Process Improvement initiative related to industry support of MGB educational programs, focusing on clarifications and revisions to numerous policy and process standards, including:
  - Multifunder Rule Guidelines;
  - Guidelines for Promotional Opportunities;
  - Budget Guidelines for Mass General Brigham Educational Activities; and
  - Guidance for programs evolving to a virtual format.
- Continued process improvement and continued the review and approval of industry gifts for research, coordinating with the hospital Development Offices, Mass General Brigham Innovation, Mass General Brigham Clinical Trials Office, and the Office of the General Counsel. During the year, OII finalized 37 industry gifts for research, totaling over $7M.
- Reviewed over 90 purchasing and other transactions for conflicts of interest, and improved OII's process for handling these transactions.

4. **Systems and Education—**in addition to handling, as part of the normal workflow, the distribution and completion of annual disclosure forms to over 15,000 Mass General Brigham staff:
   - Working with Research Applications & Analytics, continued to refine and enhance the functionality of the Insight Disclosures Module. This past year, enhancements included simplifying disclosure requirements for certain new research proposals; creating new functionality for validating and handling disclosure data; adding auto-scripts that reduced the time required for conducting certain low risk financial interest reviews.
   - Facilitated the Conflicts of Interest in Research online training course for over 1400 faculty.
   - Collaborated with Research Compliance, Research Management, and Research Applications to collect additional information through the Insight Disclosure Module to address on-going NIH and other Federal agencies' concerns relating to foreign interference with US research and protection of US intellectual property.
   - Continued emphasis on integrating OII systems and workflow with that of other MGB offices in order to assist end-users in a more seamless navigation of MGB offices, policies and processes.

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

As the previous sections of this report document, significant progress has been made in 2020 despite the extraordinary challenges encountered during the COVID pandemic. As we continue to battle the pandemic into 2021, 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.

Leadership Changes. 2020 saw numerous leadership changes across the MGH research community.

Executive Committee on Research (ECOR). Every three years, the leadership of ECOR changes, and this change will take place at the conclusion of the 2021 SAC meeting. The current Past Chair, Dr. David Louis, will vacate that position and step off the Research Institute Steering Committee. Dr. David Fisher, current ECOR Chair, will move to the Past Chair seat, and Dr. Merit Cudkowicz, current Vice Chair, will become ECOR Chair. And Dr. Maurizio Fava, MGH Chief of Psychiatry, has been chosen by Drs. Slavin and Ferris to become the next ECOR Vice Chair.

Division of Clinical Research (DCR). Given Dr. Fava's upcoming ECOR responsibilities coupled with his duties as Chief of Psychiatry, Executive Director of the MGH Clinical Trials Network and Institute, and Associate Dean for Clinical and Translational Research at Harvard Medical School, he will step down as director of the MGH Division of Clinical Research. We have initiated a search for a new director and have distributed the position description to our research community. Dr. Cudkowicz is chairing that search effort, and we hope to name a new Director sometime this Summer.

Center for Faculty Development (CFD). Following the appointment last year of Dr. Miriam Bredella from Radiology as the new CFD Director, all of the director leadership positions within CFD transitioned in 2020. Dr. Marcia Goldberg, Professor of Medicine and Microbiology and Immunobiology, left her position as Director of the Postdoctoral Division within CFD to become the new Director of the Office for Research Careers. Dr. Bakhos Tannous, Associate Professor of Neurology, was selected to replace Dr. Goldberg as the Postdoctoral Division Director. Dr. Mary Bouxsein, Professor of Orthopedic Surgery, was named as the new Director of the Graduate Student Division. Dr. Cristina Ferrone, an Associate Professor of Surgery, became the Director of the Office for Clinical Careers, and Dr. Louisa Sylvia, an Associate Professor of Psychiatry, was selected as the new Director of the Office for Women's Careers. Finally, Dr. Bredella

created a new Office for Well-Being within CFD in 2020 and named Dr. Darshan Mehta, Assistant Professor of Medicine and Medical Director of the MGH Benson-Henry Institute for Mind Body Medicine, as its inaugural Director.

Center for Genomic Medicine (CGM). In June of 2019, Dr. Sekar Kathiresan left MGH and his position as Director of CGM, our largest thematic center, to lead a new biotechnology company. Dr. Susan Slaugenhaupt, Elizabeth G. Riley and Dan E. Smith Jr. MGH Research Scholar, Scientific Director of the Mass General Research Institute and longtime member of CGM, served as interim CGM Director until September 1, 2020, when Dr. Michael Talkowski, Desmond and Ann Heathwood MGH Research Scholar, was selected after a national search as the new CGM Director. Dr. Talkowski is well-known for his many contributions across the fields of human genetics and genomics. He is a CGM faculty member, Associate Professor of Neurology with cross-appointments in Psychiatry and Pathology, and the Desmond and Ann Heathwood MGH Research Scholar. Within the CGM, he is affiliated with the Molecular Neurogenetics and Psychiatric and Neurodevelopmental Genetics Units, as well as the MGH Analytical and Translational Genetics Unit, and directs the MGH Genomics and Technology Core. He is also core faculty in the department of Neurology Collaborative Center for X-linked Dystonia Parkinsonism, and an Institute Member of the Broad Institute of MIT and Harvard. We congratulate Dr. Talkowski and thank Dr. Slaugenhaupt for her leadership serving as interim director over the course of the search process. [excerpted from CGM Director announcement, August 7, 2020]

Jumping into Gene- and Cell-Based Therapy (GCT). In 2019, MGH entered into a multi-year partnership with ElevateBio, a company that has built in Waltham a gene- and cell-based therapy pilot and production facility. MGH has an equity stake in the company and a large number of guaranteed patient slots allocated to us for use in CAR T (Chimeric Antigen Receptor T-cell) and other gene- and cell-based therapies. We also have a board seat in BaseCamp, the manufacturing group within ElevateBio.

With the facility now coming online, MGH has brought together a committee to triage requests for facility use and an operations group to interface with ElevateBio staff and provide overall project management. The six-member triage committee has as its members Drs. Harry Orf (Executive Sponsor), Keith Flaherty (Chair), Jay Rajagopal (Vice Chair), Marcela Maus (Cancer Center rep), James Berry (Neurology rep), and Jim Markmann (Surgery rep). Tatiana Koretskaia, the Administrative Director for our Division of Clinical Research, will serve as our Project Manager and primary liaison to the ElevateBio team. Work has already begun with projects developed in Dr. Maus' lab using next generation genetically-modified CAR T cells as immunotherapy in patients with cancer.

A Second COVID Surge? New Challenges. Unlike the first COVID surge, when NIH allowed researchers supported by grants to continue to be paid during the lab shutdown, NIH has stated that no one may be paid from a grant going forward unless they are actively working on the grant that supports them. Accordingly, a state or federal shutdown to research operations could devastate our research enterprise. A shutdown could threaten entire research programs and the careers of junior PIs. A shutdown would also result in additional major revenue losses to our animal care program and research cores, threatening the loss of essential services. Since we have demonstrated that we can work safely in a COVID environment, we must lobby strongly to allow research to continue as the second surge (January 2021) approaches.

Mandatory Electronic Lab Notebooks. With a continued increase in the number of research misconduct cases related to the inability to produce original experimental data, MGH (and all of MGB) mandated use of approved electronic lab notebooks (ELN's). An enterprise-wide license for Lab Archives was procured and made available at no cost to all researchers and, as of the end of 2020, all research labs are using Lab Archives or an alternate system vetted and approved by MGB IS Security. As difficult as it has been to get everyone using ELN's, the preservation of original research data and, with it, the protection of the PI's and researchers who generated it from those who would manipulate or falsify research data has been well worth the effort.

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.

We began counting gifts received towards the Campaign total on 1 October 2019, at the beginning of FY18. During the current "silent phase" (prior to public announcement) of the campaign, we have exceeded the ambitious annual goals and are optimistic this trend will continue. To date, with the public phase of the campaign starting later this year, we have now raised over half of our $3B working goal for the campaign.

Massachusetts General Research Institute

Executive Report

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 focus on these objectives in 2021.

Research Space—Continuing Needs and Lessons Learned from the Pandemic

The pandemic has 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. 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 initiative is being directed by the MGB CAO office with full cooperation from the MGH RSMG group.

Despite these dry space consolidation opportunities, the demand for wet research space remains high. The current space request total as of December 2020 is 140,000 SF (75,000 wet, 65,000 dry), reflecting new Institutional and Departmental initiatives. Additionally, 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.

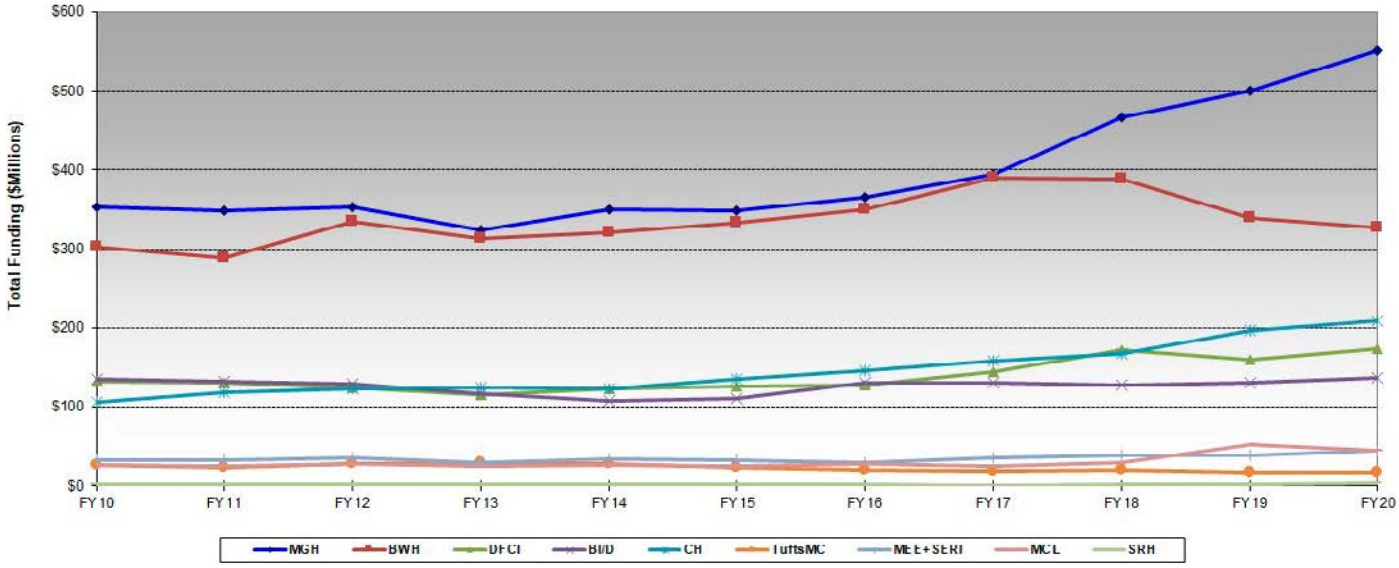
While space metrics put in place last year by RSMG will assist us in consolidating areas of underutilized current space, it alone will not come close to meeting the wet space demand. Options that were explored in 2020 included: (1) relocating components of the Wellman Center, the Center for Engineering in Medicine, and the Center for Systems Biology (all components with significant engineering assets) to the new Harvard Allston Engineering Building slated to come online Summer of 2021, and (2) talking with the Shriners Hospital about the possibility of relocating some of our pediatric research programs to their lab space. At the time of the writing of this report (early 2021), both possibilities still exist but neither negotiation has moved forward and other options are being explored.

The second consecutive $1 billion research revenue landmark reached in 2020 during the unprecedented 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.

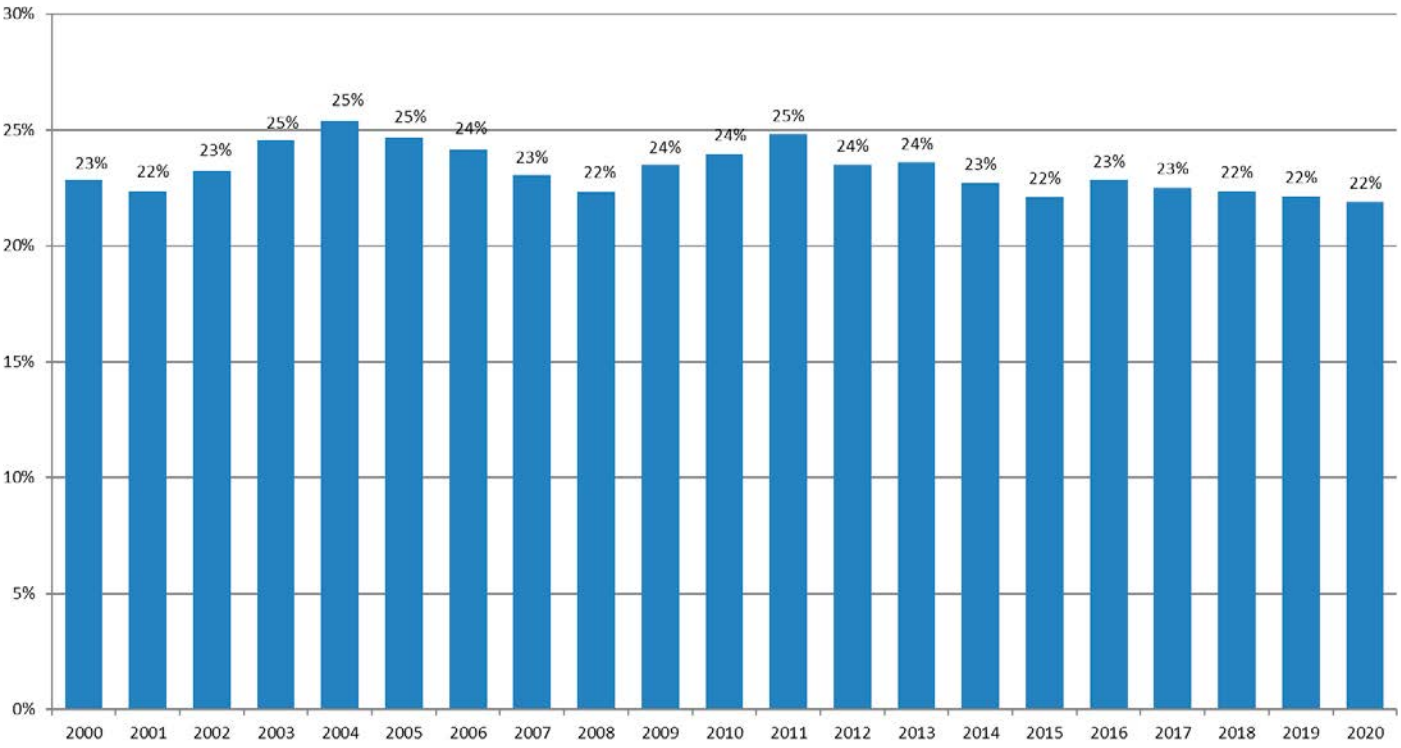
Respectfully submitted,

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

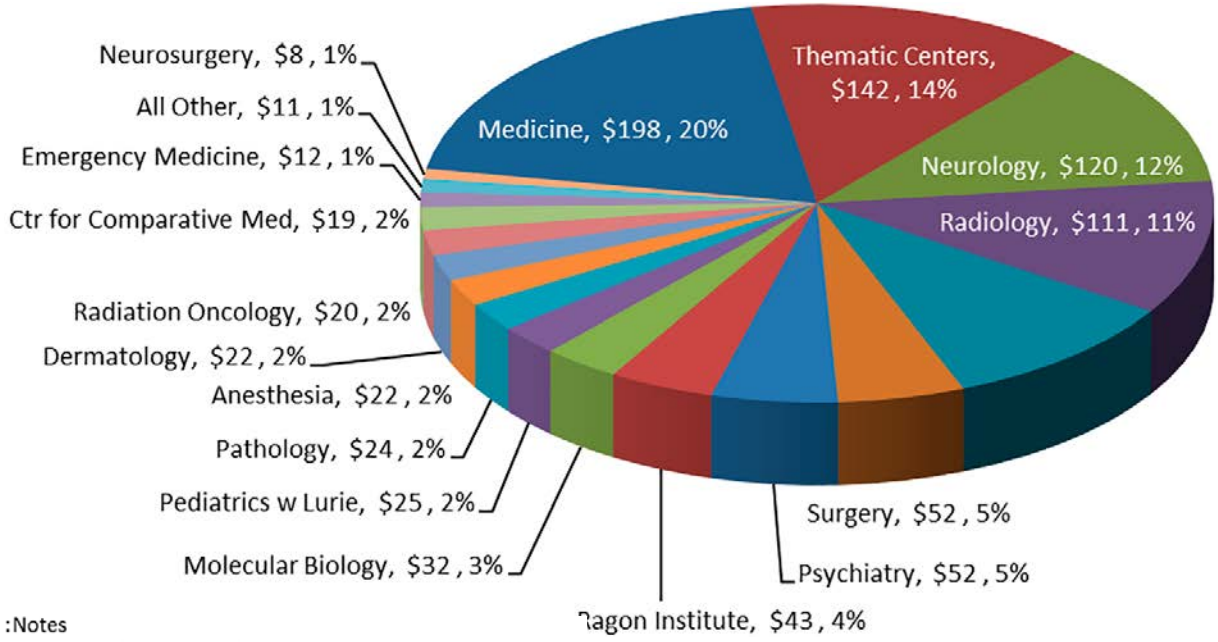
FY2010 – FY2020 Top Local Independent Hospitals NIH Extramural Funding



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

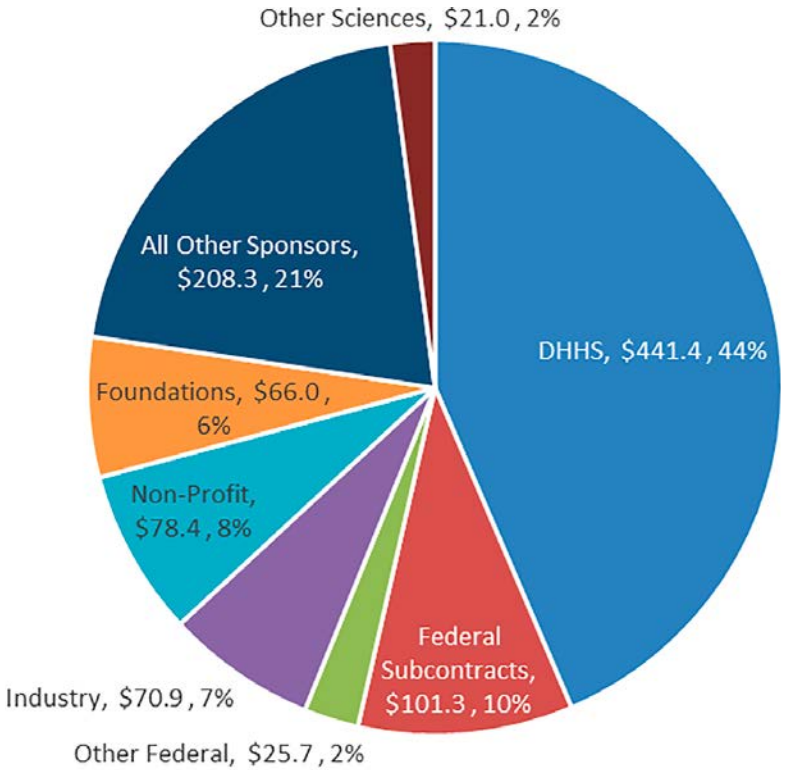


FY2020 MGH Research Expenditures by Department (Direct and Indirect Expenditures $1,013 M) (In millions)

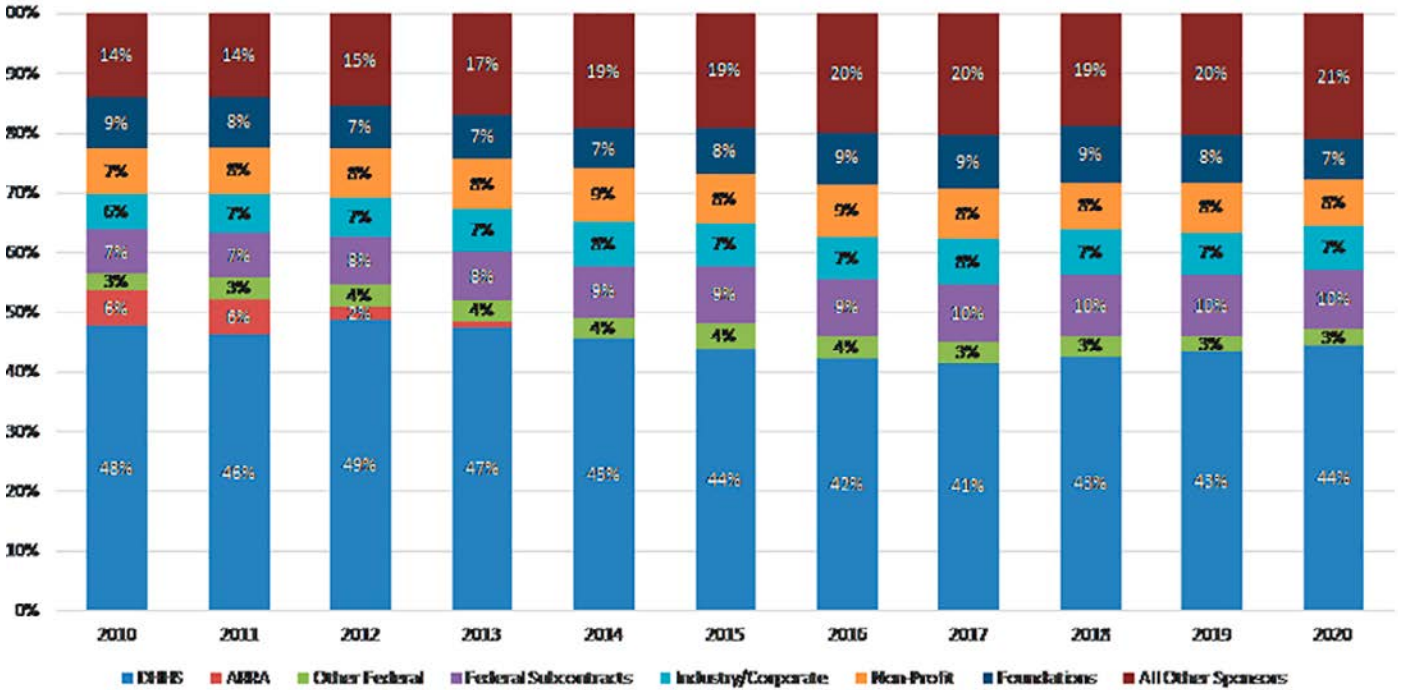


:Notes
Based on Full Year FY20 data
Expenditures include ARRA funding and Other Science -1
.Surgery includes Pediatric Surgery, Oral Surgery and Urology -2
Other includes Administrative Departments -3

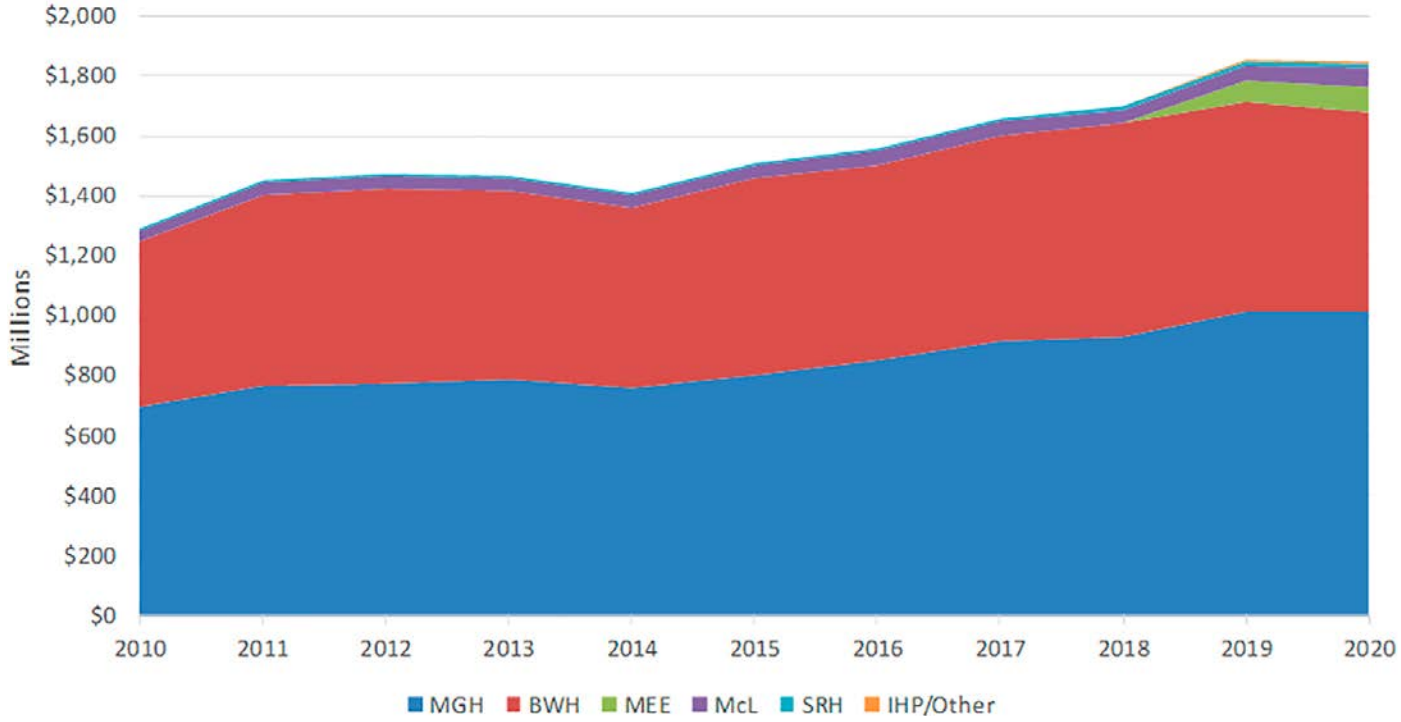
FY20 MGH Total Research Revenue by Sponsor = $1,013 M (in millions)



MGH Research Revenue Sponsor Mix



Mass General Brigham Research Activity



Massachusetts General Research Institute

Executive Report

MASSACHUSETTS GENERAL HOSPITAL Science Activity by Sponsor			
	Fiscal Year 10/01/19-09/30/20		
Type of Activity	**Direct**	**Indirect**	**Total**
Federal & State	336,848,202	139,915,081	476,763,283
Non-Federal	437,191,839	98,950,647	536,142,486
Total Expenses FY 19	774,040,041	238,865,728	1,012,905,768
Analysis of:			
Federal Activity by Sponsor			
NIH	311,916,050	130,345,521	442,261,571
DOD	12,314,105	6,889,271	19,203,376
DARPA	2,502,872	1,118,647	3,621,519
NASA	316,038	171,470	487,508
NSF	391,373	195,860	587,233
Other Federal	1,342,950	452,363	1,795,314
Total Other Federal Activity	16,867,338	8,827,610	25,694,949
Subtotal Federal	328,783,389	139,173,131	467,956,520
State	8,064,813	741,950	8,806,763
Total State Activity	8,064,813	741,950	8,806,763
Total Federal and State	336,848,202	139,915,081	476,763,283
Non-Federal Activity by Sponsor			
Industry	53,611,349	21,752,493	75,363,843
Foundations	60,013,028	6,490,473	66,503,501
Subcontracts/Other Nonprofit	126,801,991	45,486,408	172,288,399
MGH Endowment & Gifts	195,755,343	25,221,273	220,976,616
Total Non-Federal Activity	436,181,711	98,950,647	535,132,358
Total Expenses	773,029,913	238,865,728	1,011,895,641
Harvard Medical School	1,010,127	-	1,010,127
Grand Total	**774,040,041**	**238,865,728**	**1,012,905,768**

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 and scientists 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
- Cross-cultural education of staff and physicians to enhance the quality of care of patients and employee engagement
- Advancing the science of diversity and inclusion by measuring outcomes of our programs and interventions

Strategic 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:

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

Notable Achievements For The 2020 Year

1. **New reporting structure.**
   CDI reports directly to the new Sr. VP for Equity and Community Health and is under the umbrella of the Office for Equity and Community Health established in 2019. CDI leadership is working closely with this executive leader in addressing disparities, diversifying researchers, research participants and the research agenda; and other clinical, education, and community health hospital-wide priorities.
2. **Establishment of the MGH Structural Equity Plan and expansion of CDI.**
   In 2020, MGH established the 10-point Structural Equity Plan to help advance equity across MGH under the umbrella of the Office for Equity and Community Health. As part of this plan, the scope of CDI is in the process of 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 patient care services staff.
3. **Led workforce workstream of the COVID Equity and Community Health response team.**
   CDI's role pivoted when COVID hit our country and the MGH community in March 2020. In order to care for the increasing number of non-English speaking COVID patients being admitted to MGH, CDI leadership created a multilingual registry identifying other languages spoken by our clinical and research staff for redeployment to areas of clinical need (employee attestations, post-acute care sites, virtual visits, etc). The research workforce was available to assist as MGH research enterprise had to shut down temporarily. In addition, CDI collaborated with the Sr. VP for Equity to create the novel Gonzalez Spanish Language Care Group (GSLCG), where 51 native Spanish speaking providers, including several research MDs who had been clinically trained, helped provide round the clock culturally and linguistically competent care to Limited English Proficient COVID patients. They assisted with Emergency Room admissions, as well as critical patient discharges, family conversations, and research informed consents in the inpatient units and ICUs. The GSLCG team also provided education and public service announcements for our Spanish speaking community of employees and patients/families on COVID masking and social distancing protocols, as well as vaccination hesitancy.
4. **Awarded 4 Physician/Scientist Development Awards.**
   The Physician/Scientist Development Award (PSDA) was established to enhance research faculty retention and career advancement. In 2019, ECOR approved funding 4 PSDAs, doubling the number of awards and increasing the amount of funding for each award to $180,000 cost-sharing with the recipient's department for 2020. Typically saddled with huge debt and a challenging national funding landscape, more 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. During COVID, although internal institutional research grants were put on hold, the PSDA was the only grant awarded to four recipients. See

more details under the Professional Workforce Diversity section below.

5. **Provided virtual experience or Summer Research Trainee Program students.**
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. Due to the COVID pandemic, the 2020 summer program was redesigned to provide weekly mentoring career sessions to 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. In 2021, the program will resume with a virtual research experience.
6. **Implementation of a resident stipend pilot program.**
The high cost of living in Boston has consistently been identified as a barrier by many residency applicants—especially UIMs—who could have come to train here. To address this issue, the CDI worked closely with various strategic partners including Mass General Brigham Graduate Medical Education, Human Resources, and the BWH Physicians Organization and Center for Diversity and Inclusion to create a pilot program based on national criteria for economic need last year. We now have a few exciting outcomes. 65% of the stipend recipients in the first-year pilot program are UIM. As part of the second year roll out, we incorporated more expansive criteria for all Mass General Brigham residents within their first 3 years of training. Go to https://www.partners.org/Graduate-Medical-Education/Residents-Clinical-Fellows/Prospective-Trainees/Match-Resident-Stipend-Pilot.aspx to learn more about this stipend pilot.
7. **Record match of UIM residents to MGH training programs.**
CDI helped recruit record numbers of UIMs in residency spots: In 2020, 18% (n=41) of the residents who matched in 20 MGH/integrated residency programs were UIM, with several programs exceeding on third. This is well above the percentage of UIM national medical graduates. CDI worked closely with all MGH affiliated residency programs in their recruiting efforts. CDI hosted 12 applicant receptions during the interview season to provide an opportunity for applicants to meet the CDI community of UIM residents, fellows and faculty in a more relaxed setting and receive a perspective on training at MGH and living in the Boston area. CDI also participated in, and sponsored trainees to attend, national recruitment fairs (virtual during COVID) to meet students and potential applicants throughout the year (e.g., SNMA, LMSA, HMS residency showcase).
8. **Champions in race discussions and advocacy.**
Both in our community and across the hospital, CDI and the RFC led important and difficult discussions about race. The CDI was a signature sponsor for several anti-racism events at the MGH in 2020, including topics addressing xenophobia, white privilege, and racism in healthcare in our communities. We also participated in a hospital-wide kneel-in in solidarity in the aftermath of the murder of George Floyd and other African Americans across the country. These education sessions and advocacy efforts help us create an environment of inclusion, equity and belonging at Mass General.

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. During this past year, CDI served over 450 UIM students, trainees and faculty, and provided cross-cultural education and unconscious bias training to approximately 2,500 physicians, scientists and interdisciplinary teams.

Professional Workforce Diversity

We recognize that decisions of faculty recruitment occur at the departmental level, and that the focus must be deliberate if we expect to achieve results. CDI is working 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 2021; 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 five faculty development awards in 2020. Since 2004, CDI has awarded 62 faculty development awards totaling over $7 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 new 10 Point Structural Equity plan. This includes an initiative to review all hospital policies through an equity lens, and identifying external policies and providing advocacy to impact equity in our communities.

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

In February 2020, Dr. Miriam A. Bredella became the Director of the CFD, taking over the role held by Dr. Anne Klibanksi for nine years, and Dr. Ted Stern, who served as Interim Director. Dr. Bredella is Professor of Radiology and Vice Chair for Faculty Affairs in the Department of Radiology. She is 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. She was joined by Maire Leyne, MS, MBA, as Executive Director. Maire has worked in research at Mass General for the past 25 years. In the last eight years, Maire has worked as the Director for the Executive Committee on Research (ECOR) within the Mass General Research Institute (MGRI); her role was expanded to include the Center for Faculty Development in March of 2020.

In 2020, the CFD and its offices saw continued success in the integrated approach to providing services and resources to our faculty and trainees. A new Office for Well-Being was implemented to improve well-being of our faculty and trainees across the career span. The center also designed a new CFD website with many resources on promotion, mentoring, and well-being. Additionally, a new position was created, Senior Program Manager, and filled by Dr. Anne Levy, to assist with ongoing and new initiatives to ensure implementation of best practices in providing faculty support in the areas of teaching and learning; mentoring; research; promotions and leadership development. Due to the COVID-19 pandemic, all programs were offered virtually via Zoom. This change allowed a much larger group of people to participate in the Center's offerings. The CFD also expanded its online and virtual presence through recorded webinars and by creating a podcast channel for our programs.

Over the past 12 months the CFD created several new 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, postdoctoral fellows and graduate students.
- The 'Anne Klibanski Visiting Scholars Awards' to support women faculty in the COVID pandemic by providing an opportunity for selected Scholars to serve as "virtual" Visiting Professors and give presentations at a national or international institution, organized by the CFD. This initiative has been selected as a 2020 Innovative Initiatives Awards winner from the Boston Women's Workforce Council.
- MGB Community Helps and MGB Community Connects: During the height of the COVID-19 pandemic, the CFD created Mass General Brigham Community Help, which provided ways for employees who live in the same neighborhood to support each other by running errands (grocery/pharmacy runs), pet care, transportation, or help around the house. With school closing and childcare challenges, the CFD created Mass General Brigham (MGB) Community Connects for employees who live in the same neighborhood to connect for childcare, nanny sharing, formation of education pods, family activities, and transportation and carpooling. These initiatives have been adopted MGB-wide.
- The introduction of the TEDxMGH platform to share inspirational stories from the MGH community, and how people have handled challenges—through innovation, resilience, vulnerability, and connection. Some talks have been viewed over 1500 times.
- MentorMGB—A New Mentoring and Research Collaboration Website available for faculty, postdocs, graduate students and others across MGH, BWH and MGB-affiliated hospitals to encourage cross-specialty mentorship and research collaboration.
- Introduction of Mentoring Round Tables for MGH departmental mentor leaders to exchange ideas and spearhead innovation in mentoring across all departments and Peer Mentoring Groups for Senior and Mid-Career Women Faculty.

Center for Faculty Development (CFD)

Programmatic Report

Strategic Priorities for the Coming Year

- 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 currently being worked on are:
  - Anne Klibanski Visiting Scholar Monthly Lecture Series
  - Maurizio Fava Well-Being Lecture Series
  - Stress-Resiliency Series
  - Writing Workshops
  - Speed Mentoring sessions
  - Marcela Del Carmen Lecture Series for the Advancement of Women
- Recognize and further celebrate outstanding mentorship by continuing to sponsor the annual John T. Potts, Jr., MD, Faculty Mentoring Award and creating new mentoring awards for other groups.
- Offer individual consultations to help faculty, research fellows and graduate students with advice and guidance.
- Create an 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.
- 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, Graduate Student Division (GSD)—Mary Bouxsein, PhD, Director, Postdoctoral Division (PDD)—Bakhos A. Tannous, PhD, Director

In 2020, the CFD announced new Directors for the Office of Research Careers, Graduate Student Division, and Postdoctoral Division. Dr. Marcia Goldberg, Professor of Medicine and of Microbiology, who was the Director of the Postdoctoral Division, started her new position as the Director for the Office of Research Careers. Dr. Bakhos Tannous, Associate Professor of Neurology, was named to lead the Postdoctoral Division and Mary Bouxsein, Professor of Orthopedic Surgery at HMS, is spearheading the Graduate Student Division.

ORC, GSD and PDD Achievements

- Started a 9-month long Leadership Development Program for Researchers (24 Faculty members, 17 fellows, and 2 graduate students) that prepares investigators for challenges inherent in establishing and maintaining a successful research program.
- Presented the 2020 GSD Mentoring Award to recognize a PI for his outstanding contribution in helping graduate students to advance their skills and provide academic support. The 2020 GSD mentoring Award recipient was Dr. Hakho Lee, PhD, the Hostetter MGH Research Scholar 2017-2022, Associate Professor in Radiology at HMS, and the Director of the Biomedical Engineering Program at the Center for Systems Biology (CSB), Massachusetts General Hospital (MGH)
- Created two Mentoring Programs:
  - Peer Mentoring Program: This formal program provides mentees focused professional and personal development, while mentors gain valuable mentoring and leadership experience.
  - Peer to Peer Program: A revamped version of the previous Buddy System that connects experienced graduate students with those that recently joined the organization and need an introduction to life at MGH and Boston.
- Created a Slack Group for Graduate Student to facilitate convenient transfer of information and to stimulate conversations, networking, and communication among graduate students during the pandemic.
- Built two onboarding checklists for postdocs and graduates that will assist them in acclimating and navigating them to MGH and also familiarize themselves with the resources available to them.
- Modified the Annual Career Planning Form to promote the requirement for a secondary mentor.
- Created a Postdoctoral Fellowship Certificate that postdocs can utilize as confirmation of their postdoctoral training at MGH.
- Collected sample grant applications for junior researchers to utilize as a resource when submitting their first grants.

Center for Faculty Development (CFD)

Programmatic Report

- Launched an internal job database platform that principal investigators and postdocs can utilize to post and seek employment opportunities.
- Processed roughly 56 extension requests for post docs using a newly designed and automated process on Redcap.
- Provided English for Speakers of Other Language (ESOL) classes specifically designed for researchers. A 12-week semester of ESOL served 80-90 students, divided into four class levels based on their English skill.
- Continued to advise and collaborate with the MGPA, which offers research fellows leadership opportunities and the chance to develop careers through programming and networking events.
- Continued to offer seminars and workshops targeted specifically to graduate students and postdoctoral fellows (e.g., overview of careers in the life sciences industry; identifying funding opportunities, tips for writing fellowship applications).

Strategic Priorities—ORC

- Continue to facilitate collaborations between the ORC, 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.
- 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.

Strategic Priorities—GSD

- Enhance communication with graduate students and PIs through more prevalent digital platforms and website resources besides the conventional emailing.
- Collaborate with other offices within the CFD to build strong support for the research community at MGH.
- Host programs and events in areas and topics that graduate students highlighted as areas of improvement to them.
- Support scholarly activities of PhD graduate students who are currently doing research at MGH by offering an Uber Program that graduate students can utilize to travel between classes and their research labs.
- Collaborate with Postdoctoral Division and Mass General Postdoc Association to host combined mentoring programs, events, and networking opportunities that that increase collaboration and communication among graduate students and postdocs.
- Foster and promote the peer-to-peer mentoring programs.
- Identify opportunities for MGH faculty to participate in graduate student training at local institutions.
- Provide examples of successful fellowship applications, providing writing workshops for graduate funding opportunities.

Strategic Priorities—PDD

- Establish an online appointment platform for postdoctoral fellows, which 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 creating 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 getting a better understanding of various career paths available to them.

- Build relationships with alumni to help foster a community and accessible resource for our current postdoctoral research fellows.
- Continue to enhance and streamline communication through more convenient and prevalent digital platforms in addition to emailing.
- 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.
- Create a Postdoctoral Division Mentoring Award for PIs that have exhibited excellence in fostering the careers of postdoctoral fellows.

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

After 10 years as Director of the Office of Women's Careers, in September of 2020, Dr. Nancy Rigotti stepped down from her in the CFD. Over the past decade, as the number of women faculty and trainees at MGH rose dramatically, Dr. Rigotti effectively advocated for their career advancement, worked to promote gender equity, and provided advice and guidance to countless faculty members and trainees. We are very grateful and thank Nancy for her dedication and service to the Center.

In the fall of 2020, we welcomed Dr. Louisa G. Sylvia as the new 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 female 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 2020.
- Implemented a new lecture series "Parenting and your Career" to support families during the COVID-19 pandemic.
- The new Director met with all department Chiefs as well as female leaders within each department (i.e., over 30 meetings planned, 17 completed).
- Began to establish a new OWC Advisory Committee to oversee and advise the OWC strategic mission and priorities.
- Identified and vetted a financial course specific to female faculty and trainees.
- Supported the growing community of Claflin Distinguished Scholars with a panel discussion for prospective applicants and the Claflin Consultation Initiative (CCI) to provide individual coaching to applicants by alumnae, and the annual Claflin Luncheon to welcome the newest Scholars.

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 female leaders to take advantage of outside resources such as the Executive Leadership in Academic Medicine (ELAM) program, and advocating for parental leave, lactation, and childcare initiatives.
- Increase engagement with, and awareness of, the OWC across MGH.
- Improve recognition of female faculty and encourage their support and mentoring across MGH.
- Improve networking and peer support for female faculty and trainees.
- Improve mentoring and sponsorship for women across MGH.
- Create scholarship opportunities for female 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.

Center for Faculty Development (CFD)

Programmatic Report

- 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 with Dept Chairs and leadership annually.
- Provide updates on key initiatives and outcomes quarterly.

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

After completing a 10-year term as the inaugural Director of the Office for Clinical Careers, Dr. Stern stepped down from his role in the Center in the fall of 2020. In the OCC, Dr. Stern met with roughly 1000 members of our faculty in one-on-one meetings for career advice, mentorship, and development of strategies for academic promotion. We are very grateful and thank Ted for his dedication and service to the Center.

In the fall of 2020, we welcomed Dr. Cristina Ferrone as the new Director of the Office for Clinical Careers. 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
- The new Director met with all department Chiefs.
- Advised faculty and trainees from different departments regarding career advice, CV/cover letter critique, mentorship, and promotion.
- Collaborated with the CFD to hold Crafting Your CV Narrative and Promoting Academic Advancement to help "demystify" the HMS promotions' process.
- Will be participating in departmental outreach by speaking at departmental meetings to present on the CFD, facilitate career advancement via seminars, and discuss how we are hoping to improve Annual Career Conference.

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

In March 2020, the CFD created a new Office for Well-Being and appointed Dr. Darshan H. Mehta as its Interim Director. Dr. Mehta is 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.

Achievements

- Introduced 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. Talks have been planned for the remainder of 2021.
- Introduced a well-being curriculum for NIH training grants. Based upon the work at BHI-MGH, this curriculum has been incorporated into two T32 grant renewal applications, which are presently under review. If successful, this can be a model for future NIH training grant submissions.
- Led a weekly meditation series for the MGH community. The OWB, in collaboration with the MGPO Frigoletto committee, began a weekly guided meditation series led by the director, Dr. Darshan Mehta.

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.
- Meet with appointed well-being champions within department at MGH, and develop a comprehensive report of the well-being activities happening across the system.
- Develop a comprehensive, easy-to-navigate website that can promote resources and guide faculty to their respective departmental/divisional well-being champions.
- Establish the Maurizio Fava Well-Being Grand Round series. This quarterly series will feature experts in well-being, with the intent of featuring one external speaker, and three internal ones. The series will focus on sharing of best practices and research in well-being in academic health centers.
- 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

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.

This year, the CCIB is happy to welcome Christopher Smillie as its newest faculty member. Dr. Smillie joins us from the Broad Institute of MIT and Harvard, where he used single-cell genomics to study the cellular architecture of the human gut and the enteric nervous system in health and disease. We look forward to helping Dr. Smillie advance his research program, and anticipate many productive collaborations within MGH and the larger Boston research community.

Over the past year, as research continued in areas of focus that include understanding the origins of life, mechanisms of cellular pathway dysregulation in disease, and how the microbiome modulates host susceptibility to disease, CCIB investigators also actively led and participated in research activities in response to the rapidly evolving COVID-19 pandemic. Among these are studies geared toward understanding the molecular mechanisms of SARS-CoV-2/host interactions and the development of COVID-19 diagnostics, vaccines and therapeutics. The studies we highlight below showcase the breadth of research interests and expertise in our Center.

Achievements:

The emergence of the RNA World following the prebiotic synthesis of activated nucleotides requires both RNA replication and ribozyme assembly. In a series of studies published over the past year *(Zhou, et al., RNA, 27(1), pp. 1–11; Zhou, et al., J Am Chem Soc, 142(37), pp. 15961–15965; Zhou, et al., Angew Chem, 59(36), pp. 15682–15687),* the Szostak lab proposed that the genomes of primitive protocells consisted of sets of short oligonucleotides beginning and ending at all possible positions on both strands of a virtual circular sequence. This model resolves several problems with RNA copying and serves as a framework for the study of nonenzymatic RNA replication. The Szostak lab also demonstrated the assembly of an RNA ligase ribozyme by the splinted, non-enzymatic ligation of short oligonucleotides of only

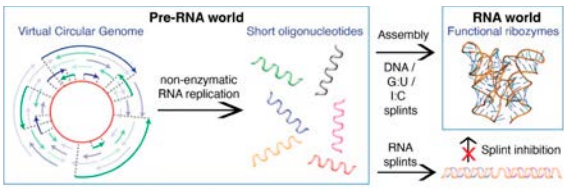


Figure 1. A model for RNA replication and ribozyme assembly in the RNA World.

8-12 nucleotides in length. Ribozyme assembly was efficient, but the splints used to direct ligation inhibited ribozyme activity. This inhibition could be relieved, however, by replacing guanosine with inosine, thus weakening splint binding without losing specificity. These observations strengthen the case for inosine as a prebiotically plausible progenitor of guanosine.

Endoplasmic reticulum (ER) stress in cells causes inflammation and exacerbates tissue pathology across a broad range of human diseases. Cells respond to ER stress by triggering the unfolded protein response (UPR), which results in either restoration of ER homeostasis (adaptive UPR) or programmed cell death (terminal UPR). Investigators in the Xavier lab and their colleagues used single-cell RNA sequencing and genome-scale CRISPR screening to identify transcriptional states associated with the adaptive and terminal UPRs in the mouse intestinal epithelium. The researchers report *(You et al., Science, 371(6524))* that QRICH1, a previously uncharacterized protein, is a transcriptional regulator that dictates cell fate under ER stress through control of a transcriptional program that modulates translation and secretory networks. Moreover, QRICH1 activity is tightly regulated by the PERK-eIF2α axis. Analysis of biopsies of patients with liver or colon disease revealed an increased QRICH1 transcriptional signature, supporting its broader role in managing cellular stress across a range of human disease.

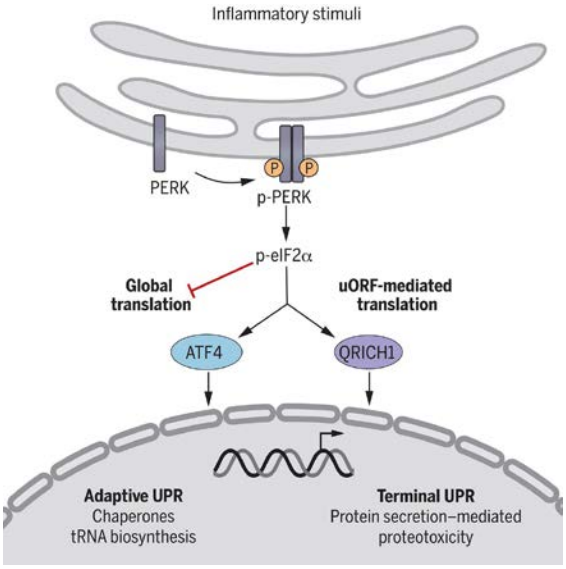


Figure 2. QRICH1 is a key effector of the PERK-eIF2α axis acting to modulate proteostasis and dictate entry into the adaptive versus terminal UPR.

Accumulating evidence suggests that early life microbial exposures, including those arising *in utero,* can determine disease risk throughout life. The Jain lab, in collaboration with Brian Seed and colleagues, found that early gut microbes regulate the development of specialized immune cells in the thymus that play a critical role in mucosal tolerance *(Ennamorati et al., PNAS, 117(5), pp. 2570–2578)*. Their studies focused on a subset of immune cells, PLZF+ innate lymphoid effectors (ILEs), that typically function at the gut mucosal barrier interface and provide immune protection at mucosal sites. Development of PLZF+ ILEs is impaired in microbiota-perturbed infant mice which contributes to their increased susceptibility to colitis in adulthood. In this model, host protective immune responses can be restored either by monocolonization of these neonatal mice with *Bacteroides fragilis,* a human commensal, or by the transfer of PLZF+ cells from mice that developed with normal microbiota. These findings have significant implications for the design of therapeutic strategies to treat inflammatory disorders such as inflammatory bowel disease (IBD).

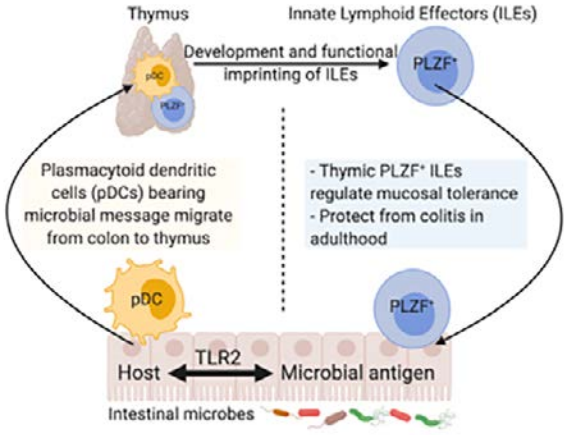


Figure 3. Early life entero-thymic communication: complex interplay between the host immune cells and intestinal microbes in early life influences the development and functional imprinting of ILEs in the thymus. This has consequences on disease susceptibility in later life.

Working within the Human Cell Atlas Lung Biological Network, CCIB investigators joined an international effort led by researchers at the Wellcome Sanger Institute to identify potential entry points for SARS-CoV-2 into the body. Using single-cell RNA sequencing data from many tissues and organs, the researchers found that two cell types in the nose—goblet cells and ciliated cells—express high levels of ACE2 and another key entry protein, TMPRSS2, as

do cells in the eye and intestines. The study, published in the April 23 issue of *Nature Medicine (Sungnak et al., Nat Med, 26(5), pp. 681–687)* is complemented by a user friendly interface at https://www.covid19cellatlas.org/ that allows comprehensive and open visualization of the data. Locally, Biogen leaders contacted partners in the biomedical community, including Deb Hung, to consider ways in which Biogen employees who contracted and recovered from COVID-19 could contribute to ongoing investigations. Thus, a consortium composed of Biogen, the Broad Institute of MIT and Harvard, and Mass General Brigham came together to build and share a COVID-19 biobank. This large collection of de-identified data and samples is being used to identify and characterize neutralizing antibodies against SARS-CoV2. These antibodies are central to efforts to design prophylactic (vaccines) or therapeutic (convalescent plasma) strategies for COVID-19.

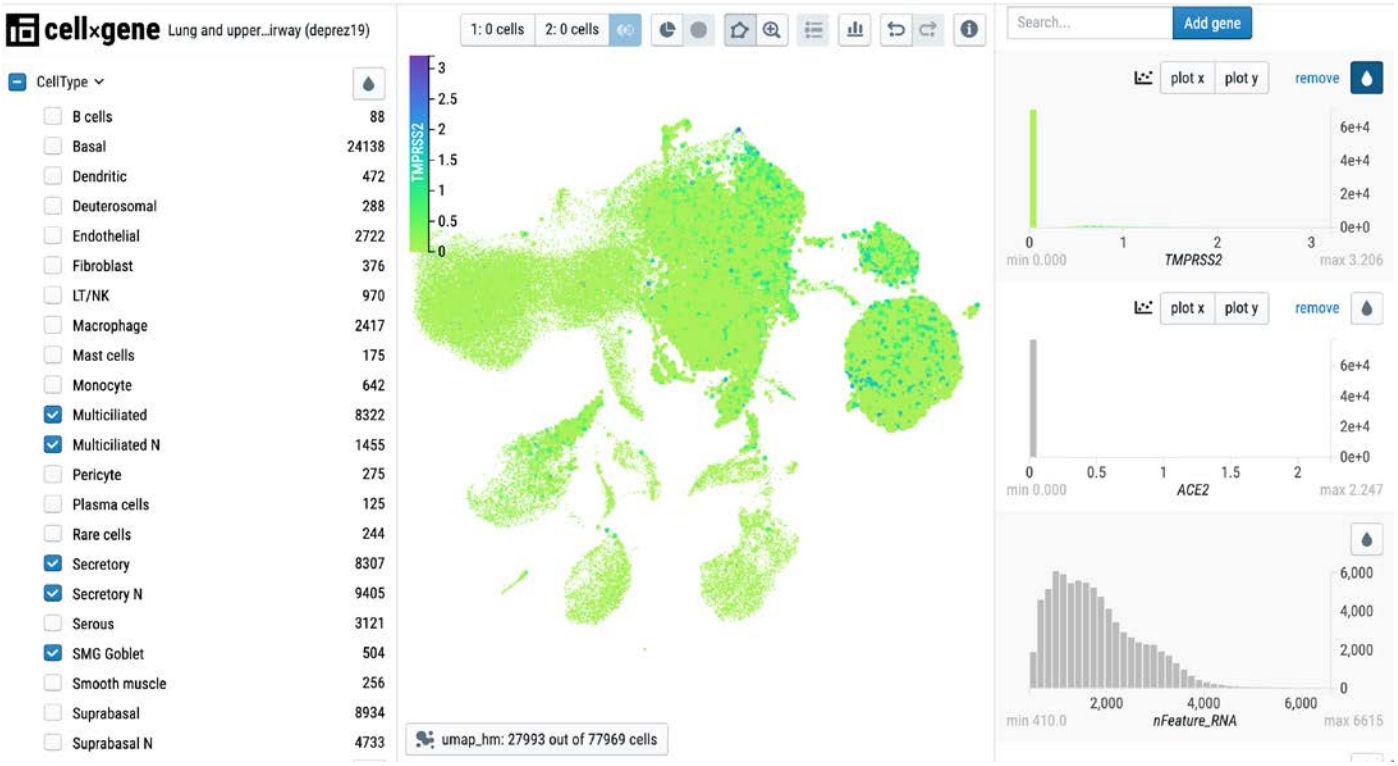


Figure 4. Expression of TMPRSS2 in cell subsets of the lung and upper airway.


RICHARD B. SIMCHES RESEARCH CENTER

Center for Genomic Medicine

Thematic Center Report

The Cas9 enzyme (red, artist's impression) snips DNA (orange). Improved versions of Cas9 promise to expand the usefulness of the CRISPR–Cas9 genome-editing technique. Credit: Alamy.

MICHAEL TALKOWSKI, PHD, DIRECTOR

Overview:

The MGH Center for Genomic Medicine (CGM) represents one of the largest and most vibrant hubs of genomic medicine research in the world. 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 by comparing human genomes and phenotypes to identify genetic variation that contributes to differences between individuals and across populations, then progresses to characterizing the mechanisms by which underlying DNA differences lead to disease, and is completed when the knowledge gained delivers benefit back to individuals in the form of diagnosis and treatment.

In 2020, MGH completed an international search and **Dr. Michael Talkowski was named the Director of the CGM**. Dr. Talkowski is an Associate Professor of Neurology at MGH and Harvard Medical School, and an Institute Member of the Broad Institute. Dr. Talkowski is the third CGM Director since the inception of the thematic Center, succeeding Dr. Sekar Kathiresan and Dr. James Gusella in this role.

Achievements:

The CGM is a large and diverse thematic center comprised of 46 faculty engaged in virtually all facets of genomic medicine research. Our programs cut across **seven MGH departments**, including Medicine, Neurology, Psychiatry, Pathology, Pediatrics, Molecular Biology, and Anesthesiology. The CGM is a community of over 400 scientists at all career stages and encompasses four mission driven MGH 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). In 2020, despite the pandemic and near complete shutdown of facilities for several months, the CGM still submitted **177 grant proposals** and saw a **2.2% increase** in research funding to **$51M**. The CGM publication record was prolific in 2020, including **469 published articles** and **136 preprints** to assure new, unpublished discoveries are immediately accessible. In addition, **seven faculty** were among the Clarivate Analytics' Web of Science 2020 list of Highly Cited Researchers.

The CGM faculty led numerous international genomics initiatives in 2020. Among these, 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 the early stage of the pandemic, an initiative formed by a team of investigators from the CGM and MGH Departments of Medicine and Neurology obtained blood samples from affected cases at MGH, extracted DNA in the CGM Genomics and Technology Core, and performed whole-genome sequencing (WGS) at the Broad Institute. This effort has expanded into a **WGS working group in the HGI**. In

the initial phase, **10,000 genomes** will soon be completed; 5,000 individuals with severe COVID-19 infection and 5,000 individuals with asymptomatic or mild COVID-19 infection collected with the support of other hospitals in the Boston area, Cleveland Clinic, and SUNY Downstate Medical Center. The long-term goal is to create and share **100,000 sequenced genomes** that may provide critical new insights into the host genetic influences on COVID-19 infection.

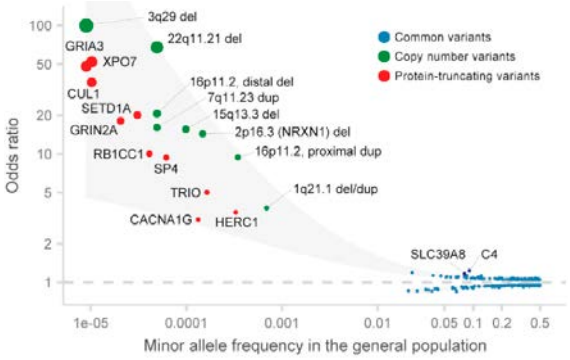
A significant new training initiative in the CGM that was spearheaded Drs. Kathiresan and Smoller was the pursuit of an NHGRI Ruth L. Kirschstein National Research Service Award (NRSA) Institutional Research Training Grant (T32) program: **"Partners Training Program in Precision and Genomic Medicine"**. 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 has now opened its third annual call for new trainees in Precision and Genomic Medicine.

Scientific Discoveries:

Despite the need to re-envision how we pursue genomics research and team science, CGM scientists continued to produce amazing breakthroughs. Just a few highlights are provided below.

Unprecedented flexibility in genome editing. The Kleinstiver lab provided a significant advance in gnome editing in *Walton et al., Science: Unconstrained Genome Targeting with near-PAMless Engineered CRISPR-Cas9 Variants.* While CRISPR-Cas9 enzymes can be reprogrammed to target different sites by altering their guide RNA, Cas9 proteins must also recognize a short sequence called a protospacer adjacent motif, or 'PAM' (NGG for prototypical Cas9). Here, a multi-faceted protein engineering approach sought to relax the PAM requirement of Cas9 and converged on two new Cas9 proteins, SpG and SpRY, that can target almost all PAMs. These enzymes enable genome targeting that is unconstrained by limitations due to PAM requirements, and will catalyze a wide range of previously intractable genome editing applications. This technology will provide remarkable flexibility for precise genome editing.

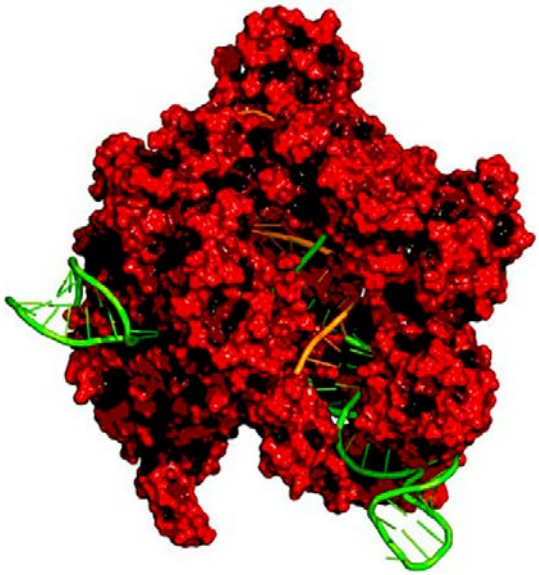
A massive human genetic reference resource—the Genome Aggregation Database (gnomAD). A team of investigators, led by trainees and staff scientists from the labs of ATGU and CGM faculty Drs. Daniel MacArthur, Michael Talkowski, Benjamin Neale, and Mark Daly have created the largest maps of human genetic variation ever constructed and openly distributed these data to the community through the gnomAD browser. The gnomAD resource includes sequencing data from over 140,000 individuals to explore variation across global populations. The insights this team derived from these data have profoundly impacted human disease research, clinical diagnostic interpretation, and efforts to develop targeted therapeutics. The team published their analyses in a package of seven papers in *Nature* (4 papers), *Nature Communications* (2), and *Nature Medicine* (1).



In May 2020, *Nature* journals published a package of seven manuscripts based on the gnomAD dataset, including four papers in *Nature*.

Center for Genomic Medicine

Thematic Center Report



Genetic diversity across global populations represented in gnomAD.

The flagship paper by *Karczewski et al., Nature: The mutational constraint spectrum quantified from variation in 141,456 humans,* discovered over 241M variants that were openly released several years prior to publication in a clear commitment to open access science. This resource has provided foundational insights for the biomedical community, as evidenced by more than 1,200 citations since release of the package. In companion studies, *Collins, Brand et al., Nature: A structural variation reference for medical and population genetics,* developed computational and analytic approaches to build a resource of 433,371 structural variants (SVs) in gnomAD, including 13 subclasses of complex SVs. These analyses revealed that evolutionary constraint against LoF variation underlies a subset of genes that are dosage sensitive in the human genome. A study from *Cummings et al., Nature: Transcript expression-aware annotation improves rare variant interpretation,* developed a transcript expression-based annotation framework to integrate results from transcriptome sequencing into clinical variant interpretation. A final study by *Minikel et al., Nature: Evaluating drug targets through human loss-of-function genetic variation* probed how the gnomAD might offer the opportunity to use naturally occurring human DNA variations to predict the effects of new drugs against targets or pathways. The study provides a guide to interpret human LoF variants to bolster success rates in drug development.

Therapeutic development in tauopathies. In a paper from the lab of Dr. Stephen Haggarty, Stuart and Suzanne Steele MGH Research Scholar, *Silva et al., Nat Communications: Prolonged Tau Clearance and Rescue of Stress Vulnerability by Transient Pharmacological Activation of Autophagy in Tauopathy Patient-Derived Neurons,* explored autophagy as a mechanism to reduce tau abnormal accumulation in human neurons. A small-molecule screen identified mTOR inhibitor compounds more potent than rapamycin that robustly downregulate phosphorylated and insoluble tau, consequently reducing tau-mediated neuronal stress vulnerability. This new insight into the pharmacodynamics of mTOR inhibitors in regulation of neuronal autophagy may contribute to development of therapies for tauopathies.

Therapeutic targets for preventing onset of Huntington's disease. In a pair of papers from the Huntington's disease (HD) research team, including JongMin Lee, Ihn Sik Seong, Vanessa Wheeler, Marcy MacDonald and James Gusella, presented a follow-up to their recent groundbreaking genetic modifier studies in *HD. Kim et al., Am J Hum Genet: Genetic and Functional Analyses Point to FAN1 as the Source of Multiple Huntington Disease Modifier Effects* showed that the source of a locus on chromosome 15 associated age at onset of HD is the DNA crosslink repair gene *FAN1*. The study revealed that missense mutations in *FAN1* that hinder its DNA-binding functions act to hasten HD onset whereas variants associated with increased *FAN1* expression in the cerebral cortex link to delayed onset. In *Loupe et al., Hum Mol Genet: Promotion of somatic CAG repeat expansion by Fan1 knock-out in Huntington's disease knock-in mice is blocked by Mlh1*

knock-out, this team showed in precise genetic mouse models that *FAN1* activity influences HD onset by virtue of its effects on somatic expansion of the expanded CAG segment and that the effect can itself be modified by the mismatch repair gene *MLH1,* which his another HD modifier locus. These studies, along with unpublished work, point strongly to a set of DNA maintenance processes as prime targets for therapeutic development to delay of prevent onset of HD by inhibiting somatic CAG expansion.

Coming Soon: Preprints from the CGM

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

Gene therapy finds benefits in severe neurological disorder. In the Grishchuk lab, DeRosa et al. *(bioRxiv)* find that brain-targeted AAV-mediated gene transfer can be a disease altering therapeutic strategy for patients with MLIV, an orphan disease leading to debilitating psychomotor deficits and vision loss.

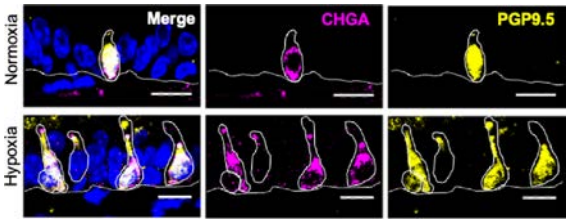
Deep learning suggests novel therapeutic targets for existing compounds. In this preprint from the Slaugenhaupt lab, Gao, Morini et al. *(bioRxiv)* show that novel machine learning approaches can predict response to pharmacological modulation, strongly supporting the use of in silico approaches to expand the therapeutic potential of drugs that modulate splicing.

Exome sequencing powers gene discovery in schizophrenia. In a preprint from the Neale and Daly labs, Singh et al. *(medRxiv)* 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 (ASD), and severe neurodevelopmental disorders (DD/ID), supporting a neurodevelopmental etiology for schizophrenia.

Variant discovery in schizophrenia

Center for Regenerative Medicine

Thematic Center Report



Sensing and protecting the lung from hypoxic injury: Stem cells sense hypoxia and differentiate into protective neuroendocrine cells that mitigate hypoxia-induced damage. Neuroendocrine cells are identified by canonical markers PGP9.5 and Chromogranin A (CHGR). (Shivaraju and Rajagopal)

DAVID SCADDEN, MD, DIRECTOR

Overview:

The Center for Regenerative Medicine focuses on stem biology to guide development of novel therapeutics. It is comprised of a collaborative team of scientists and clinicians with diverse areas of expertise and a shared mission.

Achievements:

Rajagopal Lab

Shivaraju M, Chitta UK, Grange RMH, Jain IH, Capen D, Liao L, Xu J, Ichinose F, Zapol WM, Mootha VK, Rajagopal J. Airway stem cells sense hypoxia and differentiate into protective solitary neuroendocrine cells. Science. 2021 Jan 1;371(6524):52-57. doi: 10.1126/science. aba0629. PMID: 33384370

The lung experiences constantly changing oxygen concentrations and must recognize and respond to a low-oxygen environment. The lab of Dr. Jayaraj Rajagopal, Kevin and Polly Maroni MGH Research Scholar, found that airway stem cells directly sense hypoxia and respond by differentiating into protective neuroendocrine (NE) cells that secrete a peptide that mitigates tissue damage. This work suggests that the observed NE cell hyperplasia that accompanies lung diseases such as asthma, cystic fibrosis, and chronic obstructive pulmonary disease represents a compensatory physiologic response. More broadly, it raises the possibility that stem cells throughout the body may sense hypoxia and differentiate into organ-specific NE cells.

Galloway Lab

Chen JW, Niu X, King MJ, Noedl MT, Tabin CJ, Galloway JL. (2020) The mevalonate pathway is a critical regulator of tendon cell specification. Development Jun 24;147(12): dev185389 PMC7328158

Using a screen-based approach and genetic and chemical functional studies in the zebrafish, the Galloway identified the mevalonate pathway to regulate cranial tendon specification. We found that inhibition of the mevalonate pathway expanded cranial tendon progenitors. The increase in tendon progenitor numbers was not due to increased progenitor proliferation, but rather the recruitment of *sox10*$^{+}$/*sox9a*$^{+}$ cranial neural crest/skeletal progenitors to tendon fates. This effect was rescued by the addition of geranylgeranyl pyrophosphate to mevalonate pathway-inhibited embryos and reproduced by inhibition of Rac GTPases. Together, these data indicate that this specific isoprenoid branch of the mevalonate pathway through Rac GTPases acts by limiting the number of tendon progenitors formed during cranial skeletal development. Therefore, our chemical screen was successful in identifying a new pathway regulating tendon cell specification.

Dou Lab

Vizioli MG, Liu T, Miller KN, Robertson NA, Gilroy K, Lagnado AB, Perez-Garcia A, Kiourtis C, Dasgupta N, Lei X, Kruger PJ, Nixon C, Clark W, Jurk D, Bird TG, Passos JF, Berger SL, Dou Z, Adams PD* (co-corresponding authors). Mitochondria-to-nucleus retrograde signaling drives formation of cytoplasmic chromatin and inflammation in senescence. Genes Dev. 2020 Mar 1;34(5-6):428-445.*

Cellular senescence contributes to aging and aging-related diseases. It is characterized by stable cell cycle arrest and the senescence-associated secretory phenotype (SASP). We recently discovered that cytoplasmic chromatin fragments (CCFs), extruded from the nucleus of senescent cells, trigger the SASP through activation of the innate immunity cytosolic DNA sensing cGAS-STING pathway. However, the upstream signaling events that instigate CCF formation remain unknown. The Dou lab showed that dysfunctional mitochondria, linked to down-regulation of nuclear-encoded mitochondrial oxidative phosphorylation genes, trigger a ROS-JNK retrograde signaling pathway that drives CCF formation and hence the SASP. JNK links to 53BP1, a nuclear protein that negatively regulates DNA double-strand break (DSB) end resection and CCF formation. Importantly, we show that low-dose HDAC inhibitors restore expression of most nuclear-encoded mitochondrial oxidative phosphorylation genes, improve mitochondrial function, and suppress CCFs and the SASP in senescent cells. In mouse models, HDAC inhibitors also suppress oxidative stress, CCF, inflammation, and tissue damage caused by senescence-inducing irradiation and/or acetaminophen-induced mitochondria dysfunction. Overall, our findings outline an extended mitochondria-to-nucleus retrograde signaling pathway that initiates formation of CCF during senescence and is a potential target for drug-based interventions to inhibit the proaging SASP.

Sahay Lab

Besnard A, Miller SM, Sahay A. Distinct Dorsal and Ventral Hippocampal CA3 Outputs Govern Contextual Fear Discrimination. Cell Rep. 2020 Feb 18;30(7):2360-2373.e5. doi: 10.1016/j.celrep.2020.01.055.PMID: 32075769

Using terminal-specific optogenetic silencing, the Sahay lab identified opposing roles for dorsal CA3-CA1 (dCA3-dCA1) and dorsal CA3-dorsolateral septum (dCA3-DLS) projections in fear responses. Ventral CA3-DLS (vCA3-DLS) projections suppress fear responses in both certain and ambiguous contexts, whereas ventral CA3-CA1 (vCA3-vCA1) projections promote fear responses in both these contexts. These studies point to circuits involved in psychiatric disorders such as PTSD that are characterized by maladaptive expression of fear to innocuous cues in the environment.

Scadden Lab

van Gastel N, Stegen S, Eelen G, Schoors S, Carlier A, Daniëls VW, Baryawno N, Przybylski D, Depypere M, Stiers PJ, Lambrechts D, Van Looveren R, Torrekens S, Sharda A, Agostinis P, Lambrechts D, Maes F, Swinnen JV, Geris L, Van Oosterwyck H, Thienpont B, Carmeliet P, Scadden DT, Carmeliet G. Lipid availability determines fate of skeletal progenitor cells via SOX9. Nature. 2020 Mar;579(7797):111-117. doi: 10.1038/s41586-020-2050-1. Epub 2020 Feb 26.PMID: 32103177

The avascular nature of cartilage makes it a unique tissue, but whether and how the absence of nutrient supply regulates chondrogenesis remains unknown. Here, we show that obstruction of vascular invasion during bone healing favors chondrogenic over osteogenic differentiation of skeletal progenitor cells. Unexpectedly, this process is driven by a decreased availability of extracellular lipids. When lipids are scarce, skeletal progenitors activate FoxO transcription factors, which bind to the *Sox9* promoter and increase its expression. Besides initiating chondrogenesis, SOX9 acts as a regulator of cellular metabolism by suppressing fatty acid oxidation, and thus adapts the cells to an avascular life. Our results define lipid scarcity as an important determinant of chondrogenic commitment, reveal a role for FoxOs during lipid starvation, and identify SOX9 as a critical metabolic mediator. These data highlight the importance of the nutritional microenvironment in the specification of skeletal stem cell fate.

Center for Systems Biology

Thematic Center Report

RALPH WEISSLEDER, MD, PHD, DIRECTOR

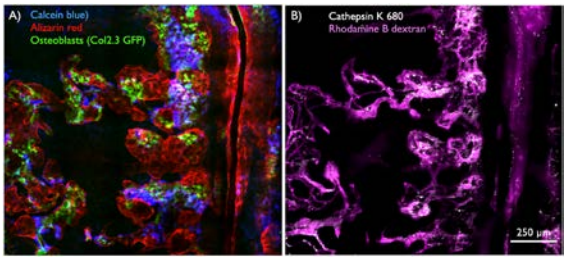
Overview:

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, Bernstein, Castro, Higgins, Lee, Lin, Im, Miller, Nahrendorf, Naxerova, Pittet, Swirski and Weissleder), Core Platforms (Imaging, Chemistry, Biocomputing) and several thematic research programs. The CSB is located within the Simches and CNY Research buildings. There are currently 193 full time employees, including 35 faculty.

Achievements:

All metastases are not created equal

Metastases can form in locoregional lymph nodes–a form of progression that portends a worse prognosis but can still be curable–or they can develop in distant organs. Treatments for the latter case are typically considered palliative. It is unknown whether lymph node and distant metastases are only distinguished by their different prognostic implications, or whether the biology underlying their formation is also distinct. The Naxerova lab at CSB and collaborators at Stanford now show that lymph node and distant metastases develop through different evolutionary mechanisms. Reconstructing the evolutionary histories of dozens of colorectal cancers, the team showed that lymph node metastases are a genetically highly diverse group. Their pronounced heterogeneity indicates that they can be seeded by many different primary tumor sub-lineages. In contrast, distant metastases are homogeneous. They typically resemble each other and have a recent common ancestor, suggesting that fewer primary tumor subclones possess the ability to form lesions in distant organs. These results show that the selective pressures shaping metastasis development in different anatomical sites differ substantially.



Live-animal imaging of bone remodeling activity (Lin lab)

Intravital microscopy visualizes osteoblasts (Col2.3 GFP), osteoclasts (CatK), vasculature (dextran), and bone fronts (labeled by calcein blue and alizarin red) in the bone marrow of live mice. This imaging helped dissect bone marrow niche heterogeneity and its association with hematopoietic stem cell behaviors. *Christodoulou C, Spencer JA, Yeh SA, Turcotte R, Kokkaliaris KD, Panero R, Ramos A, Guo G, Seyedhassantehrani N, Esipova TV, Vinogradov SA, Rudzinskas S, Zhang Y, Perkins AS, Orkin SH, Calogero RA, Schroeder T, Lin CP, Camargo FD. Live-animal imaging of native haematopoietic stem and progenitor cells. Nature. 2020;578(7794):278-283.*

Reiter JG, Hung WT, Lee IH, Nagpal S, Giunta P, Degner S, Liu G, Wassenaar ECE, Jeck WR, Taylor MS, Farahani AA, Marble HD, Knott S, Kranenburg O, Lennerz JK, Naxerova K. Lymph node metastases develop through a wider evolutionary bottleneck than distant metastases. Nat Genet. 2020;52(7):692-700 - PMID: 32451459 - PMCID: PMC7343611

New breakthrough for ultrafast bed-side cancer diagnosis

Rapid, automated, and point-of-care cellular diagnosis of cancer remains difficult in resource-limited settings due to lack of specialists and medical infrastructure. In a recent paper published in Science Translational Medicine, the biomedical engineering team at the CSB has developed an automated image cytometry system (CytoPAN) that allows rapid breast cancer diagnosis and receptor subtyping in 1 hour using as few as 50 cells obtained by fine needle aspiration (FNA). The combination of FNA and CytoPAN offers an alternative strategy for faster, minimally invasive cancer diagnosis in both developed and developing countries. Coupled with recently developed cycling technologies for FNA, this will also enable rapid molecular and cellular profiling of serial tumor samples in clinical trials.

Min J, Chin LK*, Oh J, Landeros C, Vinegoni C, Lee J, Lee SJ, Park JY, Liu AQ, Castro CM, Lee H, Im H, Weissleder R. CytoPAN—Portable cellular analyses for rapid point-of-care cancer diagnosis. Sci Transl Med. 2020;12:eaaz9746 - PMID: 32759277*

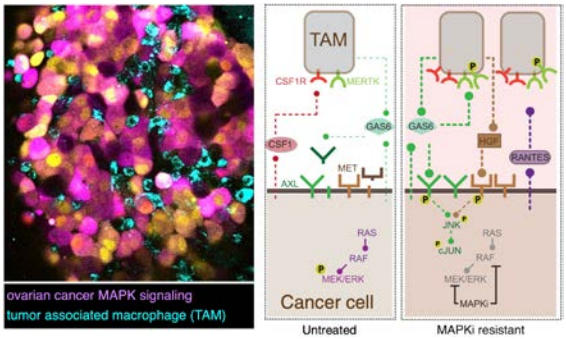
Routine blood test may predict COVID-19 hospital death risk

Coronavirus disease 2019 (COVID-19) is an acute respiratory illness with a high rate of hospitalization and mortality. Biomarkers are urgently needed for patient risk stratification. In a recent paper in JAMA Network Open, a team of investigators at CSB has reported that a standard test assessesing variations in red blood cell volume (RDW) can identify hospitalized patients with COVID-19 at the time of admission who have a 2.7x increased risk of mortality. Patients who had RDW values above the normal range when they were admitted to the hospital had a mortality rate of 31 percent compared with 11 percent in patients with normal RDW values. An increasing RDW during hospitalization was also associated with increased mortality.

Foy BH, Carlson JCT, Reinertsen E, Padros I Valls R, Pallares Lopez R, Palanques-Tost E, Mow C, Westover MB, Aguirre AD, Higgins JM. Association of Red Blood Cell Distribution Width With Mortality Risk in Hospitalized Adults With SARS-CoV-2 Infection. JAMA Netw Open. 2020;3(9):e2022058 - PMID: 32965501

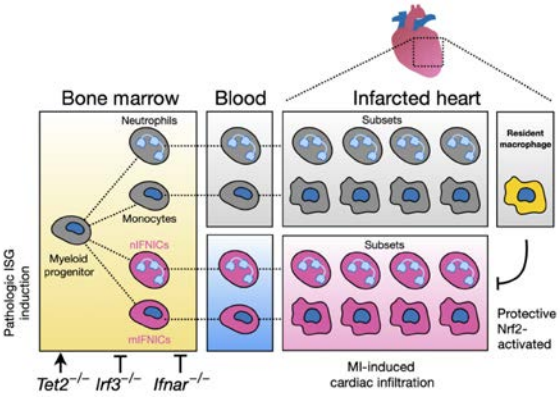
The biology of bacterial-host interface in staph endocarditis

Acute bacterial endocarditis is a rapid, difficult to manage, and frequently lethal disease. Potent antibiotics often cannot efficiently kill *Staphylococcus aureus* that may colonize the heart's valves in this disease. *S. aureus* relies on virulence factors to evade therapeutics



Targeted kinase inhibitors (Miller lab)

Intravital microscopy visualizes osteoblasts (Col2.3 GFP), osteoclasts (CatK), vasculature (dextran), and bone fronts (labeled by calcein blue and alizarin red) in the bone marrow of live mice. This imaging helped dissect bone marrow niche heterogeneity and its association with hematopoietic stem cell behaviors. *Christodoulou C, Spencer JA, Yeh SA, Turcotte R, Kokkaliaris KD, Panero R, Ramos A, Guo G, Seyedhassantehrani N, Esipova TV, Vinogradov SA, Rudzinskas S, Zhang Y, Perkins AS, Orkin SH, Calogero RA, Schroeder T, Lin CP, Camargo FD. Live-animal imaging of native haematopoietic stem and progenitor cells. Nature. 2020;578(7794):278-283.*



Myocardial infarction induces a type I interferon (IFN) response in myeloid cells (Aguirre and Weissleder labs)

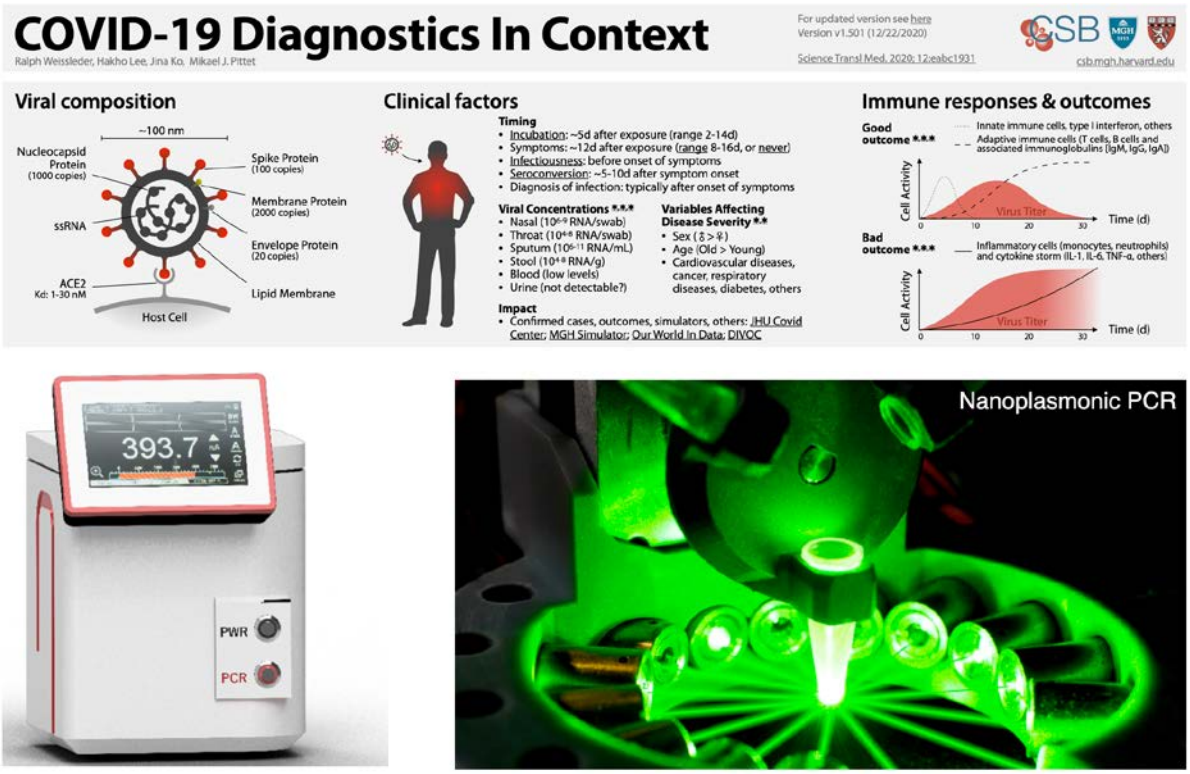
A study from Kevin King MD, PhD, a CSB alumnus and faculty now at UCSD, with collaboration from CSB faculty Aaron Aguirre MD, PhD, and Ralph Weissleder MD, PhD, showed that a subset of pre-neutrophils and pre-monocytes are IFN-stimulated (pink) during hematopoiesis resulting in the concerted expression of a multitude of interferon-stimulated genes (ISG's) dependent on Ifnar and Irf3. ISG expression increases with myeloid maturation and is restrained by Tet2. After MI, ISG+ myeloid cells infiltrate the infarcted myocardium and specialize into several time-dependent transcriptional programs with a differentiation potential equivalent to their ISG– counterparts (gray) with the exception of Nrf2 activation. In response to myocardial ischemia, a Nrf2-dependent program in cardiac macrophages negatively regulates ISG expression. *Calcagno DM, Ng RP, Toomu A, Zhang C, Huang K, Aguirre AD, Weissleder R, Daniels LB, Fu Z, King KR. Type I interferon responses to ischemic injury begin in the bone marrow of mice and humans and depend on Tet2, Nrf2, and Irf3. Sci Immunol. 2020;5(51):eaaz1974*

and the host's immune response, usurping the host's clotting system by activating circulating prothrombin with staphylocoagulase and von Willebrand factor-binding protein. An insoluble fibrin barrier then forms around the bacterial colony, shielding the pathogen from immune cell clearance. Targeting virulence factors may provide previously unidentified avenues to better diagnose and treat endocarditis. To tap into this unused therapeutic opportunity, a collaborative team led by the lab of Dr. Matthias Nahrendorf, Weissman Family MGH Research Scholar, at CSB, and CSB alumnus Peter Panizzi, PhD, who is now faculty at Auburn University, codeveloped therapeutics and multimodal molecular imaging to probe the host-pathogen interface. The team introduced and validated a family of small-molecule optical and positron emission tomography (PET) reporters targeting active thrombin in the fibrin-rich environment of bacterial colonies. The imaging agents, based on the clinical thrombin inhibitor dabigatran, are bound to heart valve vegetations in mice. Using optical imaging, the team monitored therapy with antibodies neutralizing staphylocoagulase and von Willebrand factor-binding protein in mice with *S. aureus* endocarditis. This treatment deactivated bacterial defenses against innate immune cells, decreased *in vivo* imaging signal, and improved survival. Aortic or tricuspid *S. aureus* endocarditis in piglets was also imaged with clinical PET/magnetic resonance imaging. These data map a route toward adjuvant immunotherapy for endocarditis and provide tools to monitor this drug class for infectious diseases.

Panizzi P, Krohn-Grimberghe M, Keliher E, Ye YX, Grune J, Frodermann V, Sun Y, Muse CG, Bushey K, Iwamoto Y, van Leent MMT, Meerwaldt A, Toner YC, Munitz J, Maier A, Soultanidis G, Calcagno C, Pérez-Medina C, Carlucci G, Riddell KP, Barney S, Horne G, Anderson B, Maddur-Appajaiah A, Verhamme IM, Bock PE, Wojtkiewicz GR, Courties G, Swirski FK, Church WR, Walz PH, Tillson DM, Mulder WJM, Nahrendorf M. Multimodal imaging of bacterial-host interface in mice and piglets with Staphylococcus aureus endocarditis. Sci Transl Med. 2020;12(568):ePub - PMID: 33148623

For a complete list of 2020 publications, please see here:

https://csb.mgh.harvard.edu/publications?year=2020



CSB responses to COVID-19 diagnostic challenges (Lee lab)
Comprehensive review on different COVID-19 tests, comparing their intended uses, working principles, and clinical performances was published in *Sci Transl Med, 2020; 12:eabc1931* and is continually updated (https://csb.mgh.harvard.edu/covid). The bottom shows a novel principle of a nanoplasmonic PCR system designed for onsite COVID-19 detection. The system enables an ultrafast RT-PCR reaction complete in 17 minutes. *Nat Biomed Eng 2020; 4:1159.*

A smartphone-based point-of-care detector for volatile organic compounds (Im lab)
A paper strip with 75 independent sensing arrays can detect 35 different volatile complexes. By applying a machine-learning algorithm, the device was able to detect and identify toxic compounds at the point-of-detection. Kim et al. Kaleidoscopic fluorescent arrays for machine-learning-based point-of-care chemical sensing. *Sensors and Actuators B: Chemical. 2020;329:129248.*

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. Fulfilling our mission sometimes leads us beyond photomedicine. Major research themes include: advanced live microscopy, point-of-care optical diagnostics, light-activated treatments for cancer and infection, wound repair and healing, trauma interventions, photobiomodulation (light-stimulated metabolic changes), melanoma genetics, bio-inspired optical technologies and dozens of problem-driven projects.

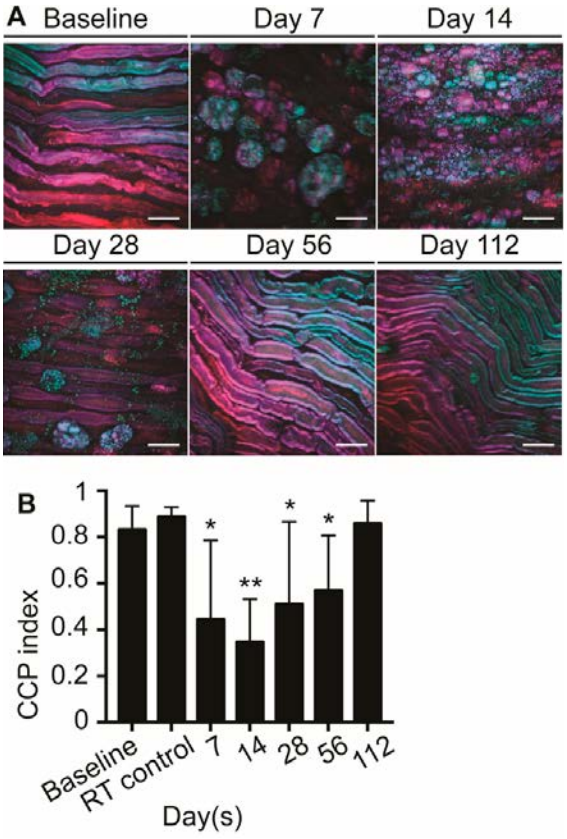
Strategic priorities

- *Leadership and excellent faculty.* We are the world's largest research center in a rapidly expanding field, with over 250 personnel. This year, our research revenues were $40M. Our core strength is the intellectual diversity of excellent faculty who aim for real impact.
- *Innovation.* WCP is the birthplace of many inventions and discoveries now in widespread use, and we are a leading source of MGH royalty income. This year there were dozens of new invention disclosures, new US and international patents, and 3 new startup companies were formed from Wellman IP licensed by MGH.
- *COVID response and World Health.* Prof. Gary Tearney, MD, PhD, Mike and Sue Hazard Family MGH Research Scholar, cofounded the MGB COVID Innovation Center; Wellman scientists and staff volunteered during the pandemic; a practical UVC device for decontamination of PPE was designed and built, pending FDA approval. We are pursuing collaborative research on problems from every continent including Antarctica, with emphasis on effective prevention of respiratory diseases, environmental change, trauma, malnutrition, child health, infection and cancer in developing countries.
- *Education.* Our regular seminar and lecture series and several CME courses have resumed in virtual format. An NSF-supported Biomedical Optics summer school for undergraduates, cancelled in 2020, is set to resume. Wellman Center sponsors three endowed research fellowships in biomedical optics (Bullock, Deutsch, Hillenkamp).

- *Return value to MGH.* Wellman is non-departmental, and collaborates broadly at MGH. Our faculty lead or serve on many MGH committees. We welcome, solicit and support collaborative research at all stages.

Achievements:

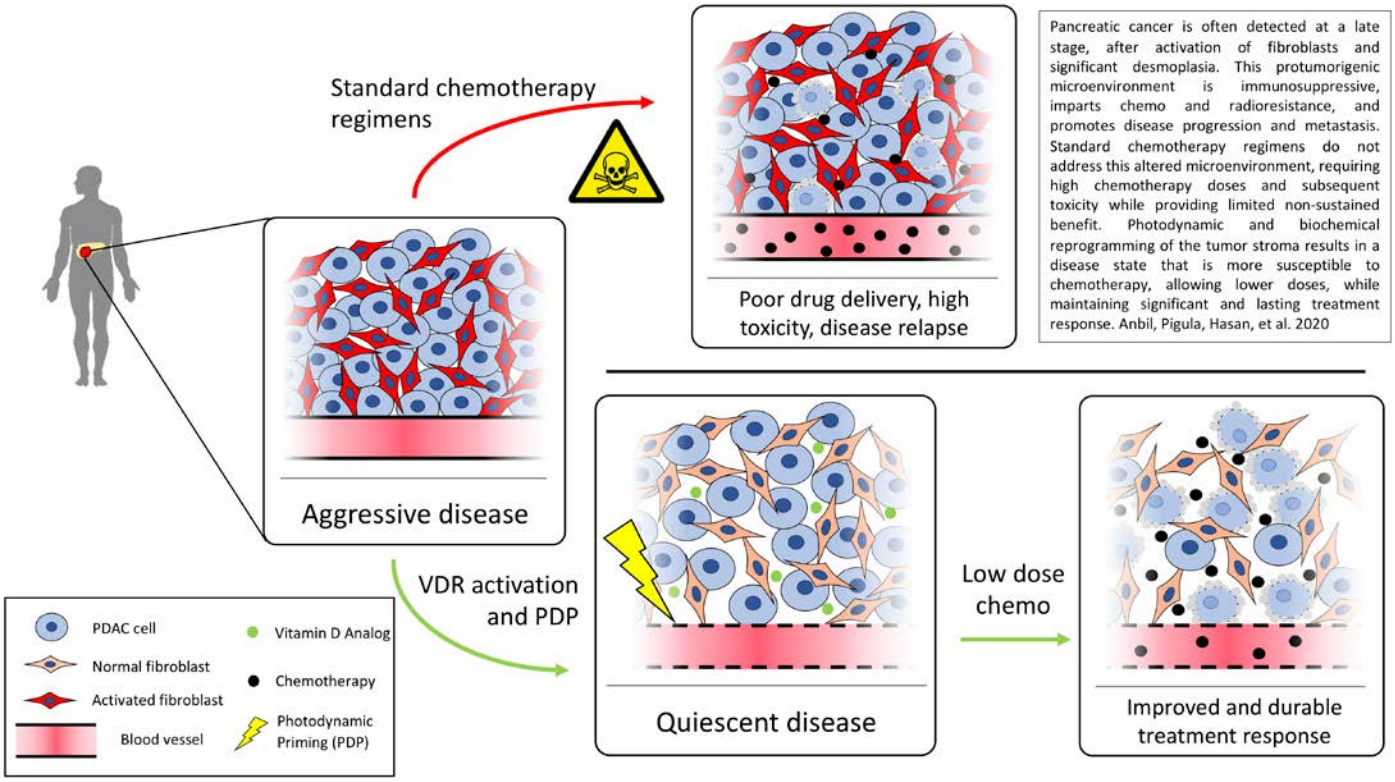
- **Keloids are driven by hypoxia.** Hensin Tsao's laboratory discovered that hypoxia is a key driver for keloids, the painful scar tumors common in African-Americans after injury. Genome-wide expression revealed that fibroblasts from keloids constitutively over-express HIF1a, a potent transcription factor induced by hypoxia, and that this overdrives collagen production leading to the massive deposition of connective tissue. Inhibiting HIF1a is a new strategy for prevention and treatment of keloids. *Kang Y, Roh MR, Rajadurai S, Rajadurai A, Kumar R, Njauw CN, Zheng Z, Tsao H. Hypoxia and HIF-1α Regulate Collagen Production in Keloids. J Invest Dermatol. 2020 Nov;140(11):2157-2165. doi: 10.1016/j.jid.2020.01.036.*
- **Blue light plus a natural phytochemical (carvacrol) selectively and rapidly treats antibiotic-resistant bacterial wound infections.** Bacteria contain high levels of porphyrin that can be activated by light. When carvacrol is added, downstream photo-oxidative products rapidly inactivate bacteria, regardless of their sensitivity to antibiotic drugs. Resistance to this new treatment did not occur after 20 cycles of repeated application. *Lu M, Wang S, Wang T, Hu S, … Wu MX. "Bacteria-specific phototoxic reactions triggered by blue light and phytochemical carvacrol." Science Translational Medicine 06 Jan 2021:Vol. 13, Issue 575, eaba3571. DOI:10.1126/scitranslmed.aba3571*
- **Prolonged pain control is possible by local injection of ice slurry, which causes a reversible nerve block lasting more than a month.** Injectable ice slurries were invented here to cause selective interactions with lipids such as adipose tissue, and myelin. This year Lilit Garibyan and colleagues showed that a single injection (similar to giving local anesthesia) causes prolonged nerve block in a rat model of chronic pain. A startup company has licensed the technology for human studies and medical use. *Garibyan L, Moradi Tuchayi S, Wang Y, Khodorova A, Stemmer-Rachamimov A, Purschke M, Osseiran S, Evans CL, Mao J, Strichartz G, Anderson RR. Neural Selective Cryoneurolysis with Ice Slurry Injection in a Rat Model. Anesthesiology. 2020 Jul;133(1):185-194. doi: 10.1097/ALN.0000000000003124.*
- **Photodynamic therapy is highly synergistic with chemotherapy for pancreatic cancer.** Tayyaba Hasan and colleagues found that combining two FDA approved treatments allows low-dose chemotherapy to be effective and well tolerated. Photodynamic therapy using an approved iv drug and red light activated vitamin D receptors of desmoplastic cancer fibroblasts, allowing greater local uptake of irinotectan, an approved chemotherapy drug for pancreatic cancer. *Anbil S, Pigula M, Huang HC, Mallidi S, Broekgaarden M, Baglo Y, De Silva P, Simeone DM, Mino-Kenudson*



A single injection of ice slurry causes a nerve block that lasts for about two months, with significant pain reduction as shown in the bar chart. Temporary, selective loss of myelin sheath and axon structure occurs as shown, followed by full recovery.

Wellman Center for Photomedicine

Thematic Center Report



Pictorial strategy for synergy between photodynamic therapy (PDT, using systemic drug and local light exposure) and chemotherapy for treatment of pancreatic cancer. Desmoplastic tumor fibroblasts are targeted by PDT, causing much greater, tumor-specific local uptake of chemotherapy agents.

M, Maytin EV, Rizvi I, Hasan T. Vitamin D Receptor Activation and Photodynamic Priming Enables Durable Low-dose Chemotherapy. Mol Cancer Ther. 2020 Jun;19(6):1308-1319. doi: 10.1158/1535-7163.MCT-19-0791. Epub 2020 Mar 27.

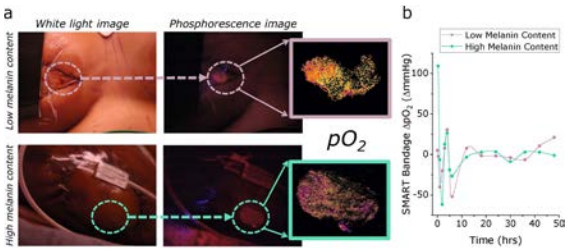
- **Optical blood-coagulation sensing is a rapid and accurate predictor of coagulopathy.** Spontaneous or iatrogenic coagulopathy is a common medical problem, strongly correlated with morbidity and mortality. Seemantini Nadkarni's lab invented a device using optical speckle modulation analysis, that was tested on blood samples from MGH ICU patients, and compared directly against classical thromboelastography. The optical measurement was rapid, used less blood, and predicted bleeding risk with significantly higher diagnostic specificity. The technology has been licensed to a startup company for development. *Tripathi MM, Tshikudi DM, Hajjarian Z, Hack DC, Van Cott EM, Nadkarni SK. Comprehensive Blood Coagulation Profiling in Patients Using iCoagLab: Comparison Against Thromboelastography. Thromb Haemost. 2020 Jul;120(7):1116-1127. doi: 10.1055/s-0040-1712956. Epub 2020 Jun 22. PMID: 32572866.*
- **Heterogeneous bone marrow stem cells that occupy unique niches, respond and divide differently to stimuli, can now be visualized *in vivo*.** Charles Lin's laboratory, a shared resource for the Wellman and Systems Biology centers at MGH, has added tremendously to our understanding of bone marrow stem cells that

play key roles in transplantation, immunity, and cancer. This year, the most quiescent long-term stem cells were selectively labelled using a new genetic approach. Advanced *in vivo* microscopy was then used to characterize their niche localization, pO2, proliferation, migration and differentiation in response to stimuli. *Christodoulou C, Spencer JA, Yeh SA, et al. Live-animal imaging of native haematopoietic stem and progenitor cells. Nature. 2020;578(7794):278-283. doi:10.1038/s41586-020-1971-z*

- **Tissue oxygenation can be seen and monitored using a paintable, oxygen-sensing "bandage".** Ischemia and hypoxia are common causes for morbidity, tissue loss, ulceration, poor surgical outcomes, and death. Conor Evans lab synthesized a very bright phosphorescent oxygen reporter, and incorporated that into a paint applied directly to human skin. Tissue oxygenation can then be visualized and monitored. A first-in-mankind study was reported using this after breast reconstruction surgery. *Marks H, Bucknor A, Roussakis E, Nowell N, Kamali P, Cascales JP, Kazei D, Lin SJ, Evans CL. A paintable phosphorescent bandage for postoperative tissue oxygen assessment in DIEP flap reconstruction. Sci Adv. 2020 Dec 18;6(51):eabd1061. doi: 10.1126/sciadv.abd1061. PMID: 33355131.*

- **The highest resolution yet was achieved for micro-optical coherence tomography (mOCT), and used to visualize nerves in cornea.** OCT is a fast, non-invasive, *in vivo* imaging modality developed at Wellman Center for cardiovascular, GI, airway, neurological, eye and other applications. Dr. Gary Tearney's lab invented mOCT and reported this year the ability to directly visualize superficial corneal nerves using mOCT; the nerves are affected by diabetes and neuropathies. *Wartak A, Schenk MS, Bühler V, Kassumeh SA, Birngruber R, Tearney GJ. Micro-optical coherence tomography for high-resolution morphologic imaging of cellular and nerval corneal micro-structures. Biomed Opt Express. 2020 Sep 28;11(10):5920-5933. doi: 10.1364/BOE.402971. PMID: 33149996; PMCID: PMC7587290.*

- **Intimal hyperplasia of arteriovenous grafts, the major cause for failure of coronary artery bypass grafts, is significantly reduced by photochemical "passivation" at the time of grafting.** Veins grafted to arteries for cardiac, peripheral vascular, and renal diseases often fail because of intimal hyperplasia induced by exposure of the vein to arterial blood pressure. Robert Redmond and colleagues have shown that one brief treatment with topically-applied rose Bengal and green light, can stabilize vein grafts in a large animal model. The technology will be licensed and developed for human use. *Goldstein RL, McCormack MC, Mallidi S, Runyan G, Randolph MA, Austen WG Jr, Redmond RW. Photochemical Tissue Passivation of Arteriovenous Grafts Prevents Long-Term Development of Intimal Hyperplasia in a Swine Model. J Surg Res. 2020 Sep;253:280-287. doi: 10.1016/j.jss.2020.03.006. Epub 2020 May 8. PMID: 32402853.*



Tissue oxygenation in a patient's wound after surgical breast reconstruction is displayed by a paint-on, oxygen-sensing phosphorescent "bandage" invented and developed in Conor Evans' lab, tested in the first-in-mankind clinical trial.

Anesthesia, Critical Care and Pain Medicine

Department Report

SEUN JOHNSON-AKEJU, MD, CHIEF

Overview:

Research activities at the Department of Anesthesia, Critical Care and Pain Medicine (DACCPM) are an integral aspect of the 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, and new drug and medical device development, and clinical research.
    i. DACCPM has over 175 research staff including M.D. and/or Ph.D. investigators, postdoctoral fellows, graduate students, administrative and supporting staff.
    ii. Laboratories and clinical research units are located in the main MGH campus and the MGH-East research facility at the Charlestown Navy Yard.
    iii. Despite the unprecedented challenges of the COVID-19 pandemic in 2020, research activities at DACCPM continue to grow and are currently supported by over 90 grants, including 52 NIH grants as of FY 2020. During 2020, the number of grant applications was increased by nearly 30%, and total grant awards from NIH were increased by 10% as compared to those of 2019.
    iv. In 2020, the DACCPM faculty published 381 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.

Achievements:

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, as well as a large group of top-notch non-clinician Ph.D. investigators, in our department. The following are several representative achievements in 2020.

1. **COVID-19 research:** During challenging times of the COVID-19 pandemic, investigators in our department (Sylvia Ranjeva, Bijan Safaee Fakhr, Caio Morais, Stefano Gianni, Raffaele Di Fenza, Riccardo Pinciroli, Hatus Wanderley, Fumito Ichinose, Robert Kacmarek, Warren Zapol, Lorenzo Berra) initiated a number of COVID-19-related clinical studies focusing on clinical phenotyping of and potential therapeutic breakthroughs for COVID-19 cases. There were two goals of this research initiative: to characterize COVID-19 disease and to test new therapies to improve outcomes in COVID-19 patients.

   i. During the first pandemic wave, we identified two distinct phenotypes with substantial differences in biochemical profiles and short-term mortality risk, despite minimal differences

Anesthesia, Critical Care and Pain Medicine

Department Report

Department of Anesthesia podcast, hosted by Dr. David Hao.

Yumiko Ishizawa,MD, MPH, PhD—recipient of Anne Kilbanski Visiting Scholar Awards.

in respiratory dynamics. Our results suggested that clinical variation in COVID-19-associated ARDS depends largely on extrapulmonary manifestations, and that vascular dysregulation is an important phenotypic axis.

ii. Respiratory therapeutic options for the acute symptomatic treatment of non-intubated patients with COVID-19 are limited. Nitric Oxide (NO) gas, a selective pulmonary vasodilator, can relieve patients from respiratory symptoms due to COVID-19 and act as a virucidal agent against SARS-CoV-2. At MGH, we tested, in a randomized clinical trial that enrolled 66 patients, the effectiveness and safety of spontaneously breathing 160 ppm NO by mask twice daily for 30 minutes to reduce respiratory disease progression. Nitric oxide inhalation was associated with an acute reduction of respiratory symptoms with an improvement in the respiratory rate and peripheral oxygen saturation. Furthermore, the use of inhaled NO was associated with the absence of hospital readmission compared to the 20% of COVID-19 patients who received standard care and required hospital readmission. No adverse events were recorded with the use of high concentration NO breathing.

iii. As there are no hospital systems to deliver high concentration NO, we designed and built a novel NO delivery system for spontaneously breathing subjects by a snug-fitting mask. Using this system, we can now administer an inhaled NO concentration up to 250 parts-per-million with an oxygen inspired fraction between 0.21 and 0.5. The system that we designed allows for the administration of NO outside the ICU setting without a mechanical ventilator and has potential applications on the front lines, in an emergency room or in low-resource clinical settings.

iv. At MGH, we organized a multidisciplinary team with anesthesiologists, respiratory therapists, and maternal fetal medicine doctors to deliver NO gas treatment to COVID-19 pregnant patients, often excluded from clinical trials for other treatments. We were able to treat 13 patients with severe and critical forms of COVID-19 with improvement in respiratory symptoms, were discharged home in good conditions, delivered healthy children and no adverse events to NO breathing were recorded.

v. Prone position in mechanically ventilated patients with acute respiratory failure (ARDS) showed to improve survival. However, it is unclear whether ventilator management should be re-evaluated when patient is placed prone and the effects of prone position on lung heterogeneity. We evaluated patients monitored with electrical impedance tomography and esophageal manometry on supine and prone positions. We observed that regional and global respiratory mechanics varies during prone and lung behavioral changes cannot be predicted, suggesting that ventilation needs to be re-assessed every time when patient position is changed to avoid ventilator induced lung injury.

vi. Anesthesia machines have been used as alternatives to traditional ICU mechanical ventilators. However, the outcomes for patients with COVID-19 respiratory failure cared for with anesthesia machines is currently unknow. We designed a retrospective study of patients admitted with a confirmed COVID-19. Seventeen patients were included in the Anesthesia Machines group, whereas 72 were in the ICU Ventilator group. Disease severity and intensity of treatment were comparable between the two groups. The 60-day mortality was significantly higher in the Anesthesia Machines group as compared to the ICU-Ventilator group (12/17 vs. 27/72, 70.6% vs. 37.5%, respectively, p=0.016). Allocation to the Anesthesia Machines group was associated with a significantly increased risk of death after adjusting for covariates (HR 4.05, 95% CI: 1.75-9.33, p= 0.001). Our results support the hypothesis that care associated with the use of anesthesia machines is inadequate to provide long-term critical care to patients with COVID-19. Added safety risks must be considered if no other option is available to treat severely ill patients during the ongoing pandemic.

2. **Honors and Awards:** In 2020, numerous faculty members in our department received honors and awards for contributions to their respective research fields. Several are highlighted as follows.

   i. **David Hao, MD** is the creator and host of a podcast with attendings and residents titled “Depth of Anesthesia” that critically explores our clinical practices. The podcast is available through the Podcast application (iPhones) and on iTunes as well as Spotify. https://podcasts.apple.com/us/podcast/depth-of-anesthesia/id1461664155

   ii. **Yumiko Ishizawa, MD, MPH, PhD** was selected to receive an Anne Klibanski Visiting Scholar Award by the Mass General Hospital, Center for Faculty Development. The award will provide an opportunity to serve as “virtual” Visiting Professor and give a lecture at a national or international institution, organized by the Center for Faculty Development.

   iii. DACCPM social scientist and simulationist **Jenny Rudolph, PhD** has used her expertise on team communication and social networks to help develop just-in-time training and knowledge dissemination for airway management in the COVID-19 Pandemic. Teaming up with Albert Chan, a Hong Kong based anesthesiologist at Prince of Wales hospital, they developed a video review and simulation program to prepare OR teams at Prince of Wales for infection control and PPE during intubations. Chan then translated this work into an infographic shared thousands of times on social media. Their work appears in Anesthesia and British Medical Journal-Simulation Technology and Learning.

   iv. **Emery Brown, MD, PhD,** is the 2020 recipient of the Society for Neuroscience’s Swartz Prize for Theoretical and Computational Neuroscience. This award honors an individual whose work has produced a significant contribution to theoretical models or computational methods in neuroscience or made a particularly noteworthy recent advance to the field.

DACCPM social scientist and simulationist Jenny Rudolph, PhD

Emery Brown, MD, PhD—2020 recipient of the Society for Neuroscience’s Swartz Prize for Theoretical and Computational Neuroscience

Cancer Center

Department Report

DANIEL A. HABER, MD, PHD, DIRECTOR

Overview:

The **mission** of the Massachusetts General Hospital Cancer Center (MGH Cancer Center) is to deepen our understanding of cancer and to rapidly translate our discoveries into exceptional, personalized care for all cancer patients. Our researchers conduct fundamental basic and translational 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, 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 2020 include major discoveries and observations from investigators within the multi-departmental Center for Cancer Research (CCR) and the Division of Hematology Oncology (Department of Medicine), both of which are administered through the Cancer Center. **Dr. David Ryan** is Clinical Director of the Cancer Center and Chief of Hematology/Oncology; **Dr. Lee Zou, Jim and Ann Orr MGH Research Scholar,** and **Dr. Raul Mostoslavsky, Kristine and Bob Higgins MGH Research Scholar,** are the co-Scientific Directors; and **Dr. Keith Flaherty** is Director of Clinical Research.

Total annual research expenditures for CCR and Hematology/Oncology in FY20 were $100 million (including industry clinical trials contracts). In 2020, the MGH Cancer Center enrolled 2855 patients on all cancer clinical trials (975 patients on therapeutic/interventional trials, 44% (425) of which were early Phase 1/II trials of first-in-human drugs).

Achievements:

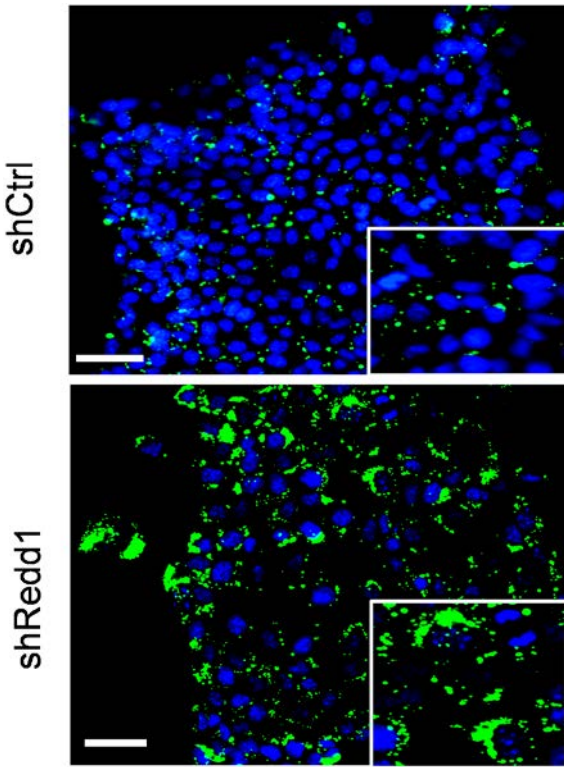
COVID-19 efforts: In addition to featuring some of our notable achievements, this year we are also recognizing and celebrating all of our staff members who exemplify the unsung heroes of the COVID-19 pandemic. Our dedicated staff members have shown incredible commitment to our traditions of scientific excellence, collaboration, collegiality and kindness during this challenging and difficult time. Physicians, nurses and other caregivers were redeployed to care for patients with COVID-19 during the Spring pandemic, and laboratory personnel monitored ventilator alarms in ICUs, helped with diagnostic testing, and gave out masks to patients and visitors. **Dr. Keith Flaherty** was recruited to oversee and coordinate COVID-19-related clinical trials throughout MGH, and staff from our Cancer

Center Clinical Protocol Office helped manage multiple COVID-19 therapeutic trials. We acknowledge **Dr. John Iafrate** (Pathology) and colleagues who oversaw COVID-19 diagnostic testing at MGH, studies of neutralizing antibody efficacy *(Wilfredo et al, Cell 2020 PMID 33412089),* and who personally led deployment of the tests in underserved Boston communities; **Dr. Nir Hacohen, MGH Research Scholar,** who led and collaborated with multiple blood-based studies of immune subsets and cytokine expression during early steps of infection *(Shrock et al., Science 2020, PMID 32994364; Filbin et al., bioRxiv 2020, PMID 33173871; Weinbarten-Gabbay, bioRxiv 2020, PMID 33024965; Chen et al, bioRxiv 2020, PMID 33140055; Reyes et al., bioRxiv 2020, PMID 32908980; Fava et al., JCI Insight 2020, PMID 32396533);* **Drs. David Ting, Dejan Juric** and **Migeul Rivera, Thomas F. and Diana L. Ryan MGH Research Scholar,** who along with Dr. Vikram Deshpande (Pathology), conducted rapid autopsy studies, discovering dramatic differences in viral load at the time of death, using *in situ* hybridization *(Desai et al., Nat Commun 2020, PMID 33298930);* and many other cancer investigators who contributed their expertise and skills to combat the pandemic; **Dr. Matthew Frigault** collaborated with Dr. Jim Stone (Rheumatology) in a seminal *NEJM* publication describing the lack of efficacy of the IL6 inhibitor Tocilizumab in suppressing COVID-19 inflammatory symptoms *(Stone et al., NEJM 2020, PMID 33085857).* Finally, we thank **Mr. Robert Herman** and the staff of the Cancer Clinical Protocol Office for successfully prioritizing key cancer clinical trials during the Spring pandemic, and then rebuilding and managing our clinical research engine, as we continue to operate in a highly challenging environment.

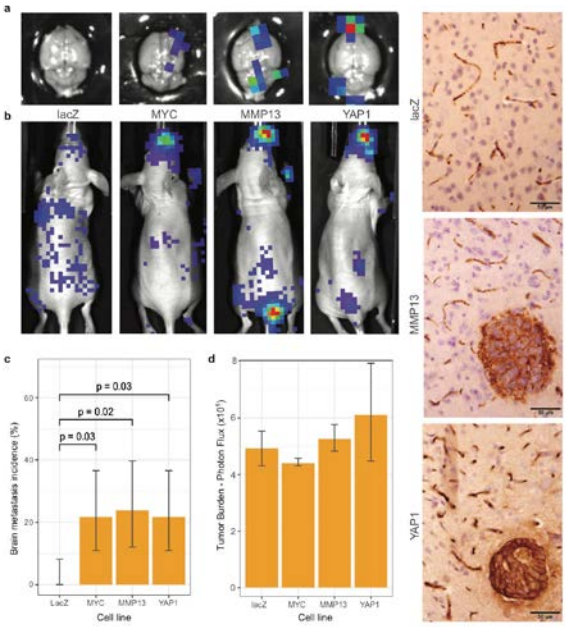
Highlighted research accomplishments for the Cancer Center during 2020 are grouped into three thematic areas:

Molecular Genetics

Computational biologists **Dr. Esther Rheinbay** and **Gad Getz** led an international consortium focused on the annotation of non-coding drivers of tumorigenesis across the genome *(Rheinbay et al., Nature 2020, PMID 32025015)* and their integration into whole genome analyses across large cancer datasets *(ICGC/TCGA, Nature 2020, PMID 32025007)*. Extending the concept of cancer drivers to 3D topological nuclear organization of genes in cancer cells, **Drs. Brad Bernstein** and **Martin Aryee** (Pathology) described the role of large hypomethylated domains within cancer cells in modulating both localization and expression of key cancer genes *(Johnstone et al., Cell 2020, PMID 32841603).* Taking on genetic lesions that underlie selective metastasis to the brain, **Dr. Priscilla Brastianos** and her colleagues identified amplification of MYC, YAP1 and MMP13 as potential drivers of brain metastasis in lung cancer *(Shih et al. Nat Genet. 2020, PMID 32203465).* Metabolic alterations in cancer have also been highlighted by **Dr. Leif Ellisen, Weissman Family MGH Research Scholar,** and his laboratory, who discovered that loss of the stress-induced metabolic regulator REDD1 reprograms lipid metabolism and drives progression of *RAS* mutant cancers. *(Qiao S, et*



This figure shows dramatic lipid uptake and storage (green dots) induced by loss of the metabolic regulator REDD1 (lower panel) in primary pancreatic epithelial cells. White boxes show magnified images.



Functional validation of brain-metastatic drivers in a patient-derived xenograft model.
a, Representative *ex vivo* and **b,** *in vivo* bioluminescence images 12 days after intracardiac injections with LN-001 tumor cells. **c,** Incidence of brain metastasis and **d,** overall tumor burden 12 days after intracardiac injections of LN-001 tumor cells overexpressing lacZ (n = 27), MYC (n = 28), MMP13 (n = 26), or YAP1 (n = 28). Error bars denote 80% confidence intervals. Data were aggregated over 3 independent experiments, and significance was assessed by the Fisher's exact test. **e,** Representative images of mouse brain sections stained for human keratin, showing presence of brain metastases 12 days after intracardiac injections of LN-001 tumor cells.

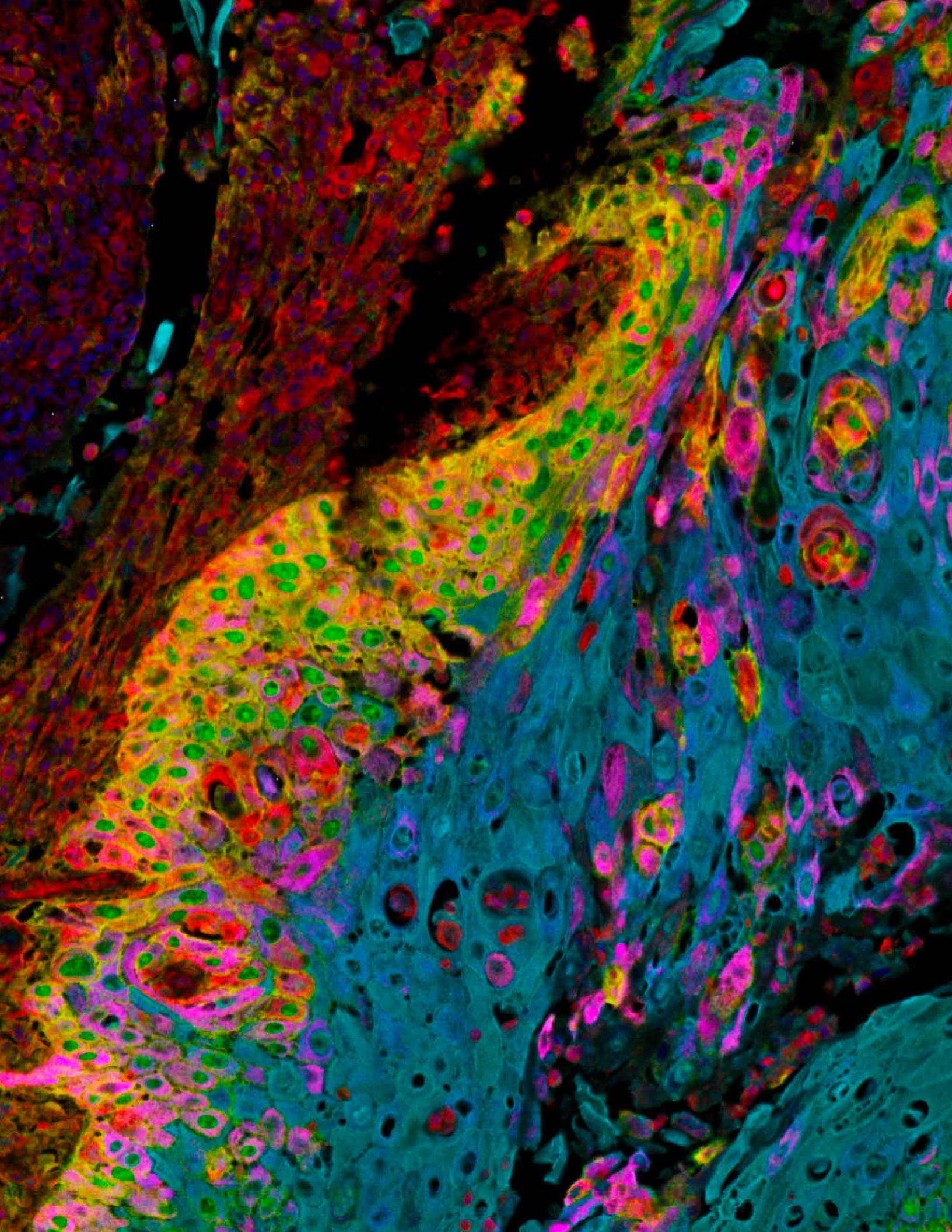
al. Genes Dev. 2020; PMID 32273287). **Drs. Shyamala Maheswaran** and **Daniel Habertogether** with their colleagues used *ex vivo* cultures of Circulating Tumor Cells (CTCs) to identify the roles of ribosome protein upregulation in mediating metastatic propensity *(Ebright RY et al. Science, 2020 PMID 32029688),* and of lipogenesis regulators and the iron carrier Transferrin in suppressing ferroptosis *(Hong et al., Cancer Discovery, 2020, PMID 33203734).*

Targeted Cancer Therapeutics

Our clinical investigators have reported important new applications of molecularly targeted compounds in cancer. **Dr. Rebecca Heist** led the pivotal study demonstrating the exceptional efficacy of the MET inhibitor Capmatinib in patients with non-small cell lung cancer harboring a MET exon 14 skipping mutation *(Wolf et al. NEJM, 2020, PMID: 32877583)*, and **Dr. Lori Wirth** led the first-in-human clinical trial of Selpercatinib in patients with *RET*-mutant thyroid and lung cancers *(Wirth et al. NEJM, 2020, PMID 32846061)*. Both studies led to FDA Breakthrough designation for these novel agents and indications. Leading analysis of a phase 3 trial, **Dr. Matthew Smith** and colleagues reported that the anti-androgen Darolutamide improves survival in men with nonmetastatic, castration-resistant prostate cancer *(Fizazi et al. NEJM, 2020 PMID 32905676).* In the field of cellular cancer immunotherapy, **Dr. Jeremy Abramson** led a study of the CD19-directed CAR-T cell product Lisocabtagene maraleucel in patients with relapsed or refractory large B-cell lymphoma, demonstrating a high objective response rate, with a low incidence of cytokine release syndrome and neurotoxicity *(Abramson et al. Lancet, 2020, PMID 32888407).*

Palliative Care and Outcomes

In a landmark study in the field of palliative care and cancer outcomes, **Dr. Areej El-Jawahri** and **Dr. Jennifer Temel, Hostetter MGH Research Scholar,** conducted a randomized clinical trial of patients with Acute Myeloid Leukemia (AML), demonstrating that early integration of palliative and oncological care leads to substantial improvements in measures of quality of life (QOL) and end of life (EOL) care *(Jawahri A et al. JAMA Oncol, 2020, PMID 33331857).* Building on their previous seminal work in lung cancer, this trial establishes a new standard of care paradigm for patients with leukemia receiving intensive chemotherapy.



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

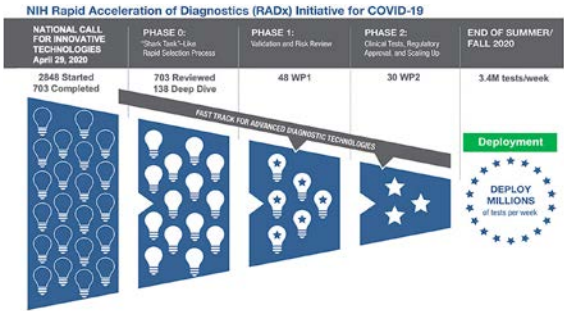
CIMIT leadership and its funded investigators conducted a Clinical Impact Study to assess the outcomes of supported projects and learn how to improve innovation in healthcare. The first study was conducted in 2012 (CIS; http://cimit.org/web/cimit/clinical-impact) and was updated in 2014. Based on the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

In 2020, CIMIT leveraged its processes to provide extramural support one of the largest-ever NIH programs–RADx Tech–as described further below.

The Consortia for Improving Medicine with Innovation & Technology

Achievements:

Rapid Acceleration of Diagnostics (RADx Tech)
On April 24, 2020, Congress appropriated $1.5 billion for SARS-CoV-2 testing to the U.S. National Institutes of Health (NIH). Within 5 days after the legislation was signed into law, the NIH launched RADx Tech with CIMIT as the Coordinating Center to support the development, commercialization, production scale-up, and deployment of accurate, rapid antigen and molecular tests across the United States. The goal was to expand capacity so that by December 2020, approximately 2% of the U.S. population (6 million persons) could be tested per day, with more tests ready for rapid deployment in proportion to national demand. During its first six months, the RADx Tech program evaluated over 700 applications and moved 22 projects into large-scale manufacturing and approximately 4 million tests per week entering the marketplace within the first eight months of RADx Tech.



CIMIT is the Coordinating Center for NIBIB's RADx Tech to develop SARS-CoV-2 Testing.

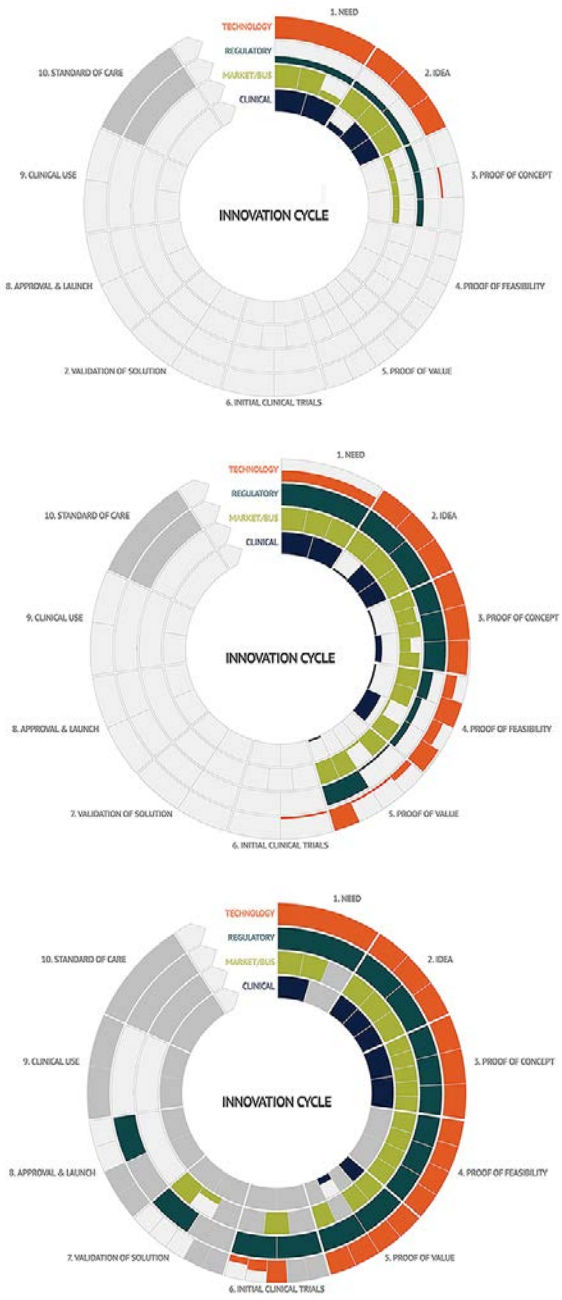
Point-of-Care Translational Research Network
The Point-of-Care Technologies Research Network (POCTRN) was created by NIH to drive the development of appropriate point-of-care diagnostic technologies though collaborative efforts that simultaneously merge scientific and technological capabilities with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

In 2020, CIMIT has continued as a Coordinating Center for Year 3 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.

CIMIT's CRAASH Course
In 2020, CIMIT continued to hold healthcare commercialization boot camps, including in Europe. With funding from the National Science Foundation, CIMIT customized the traditional I-Corps program to focus on healthcare. The 10-week program facilitates the acceleration of healthcare innovations from the academic lab through commercialization. It is taught by industry veterans and is based on decades of experience from the Coulter Foundation, MIT, Yale, and CIMIT. The program formalizes development of a tested business model through the process of validating business hypotheses. Emphasis is placed on understanding economic buyers and their problems to be solved. Teams from around the country collect evidence to support the assumptions around the entire business (not just the science) through interviews and market testing. Each week teams present and defend findings to a panel of experts, attend lectures, and complete readings. Teams develop a

The Consortia for Improving Medicine with Innovation & Technology

Department Report

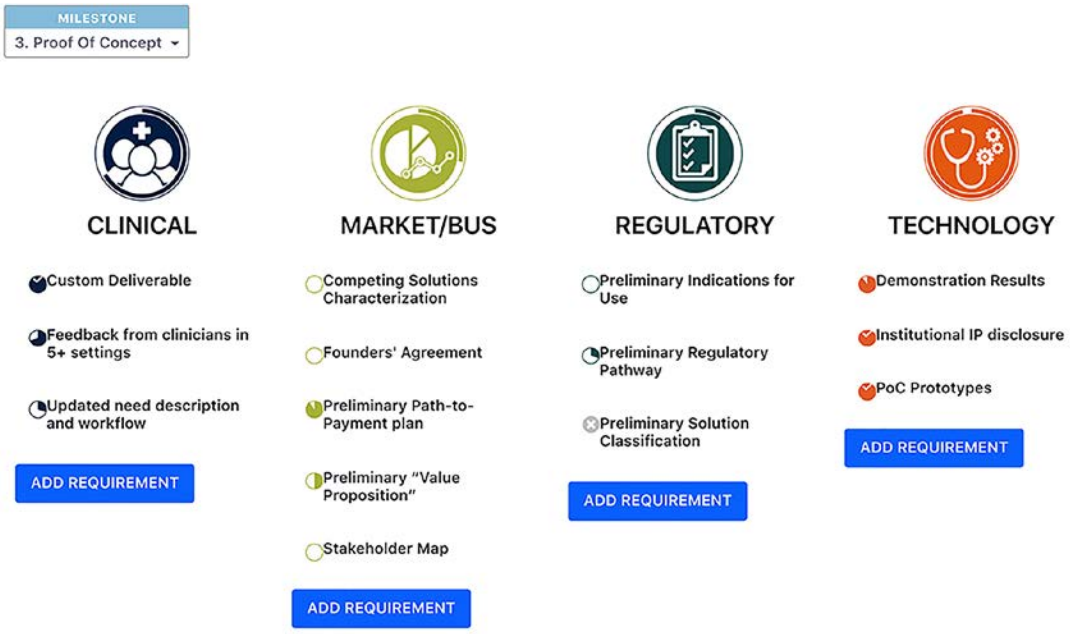


GAITS builds on the CIMIT Healthcare Innovation Cycle as a foundation to support teams and portfolio managers so they can learn and use best practices with four interrelated functions: guidance, innovation record, visualization, and analysis.

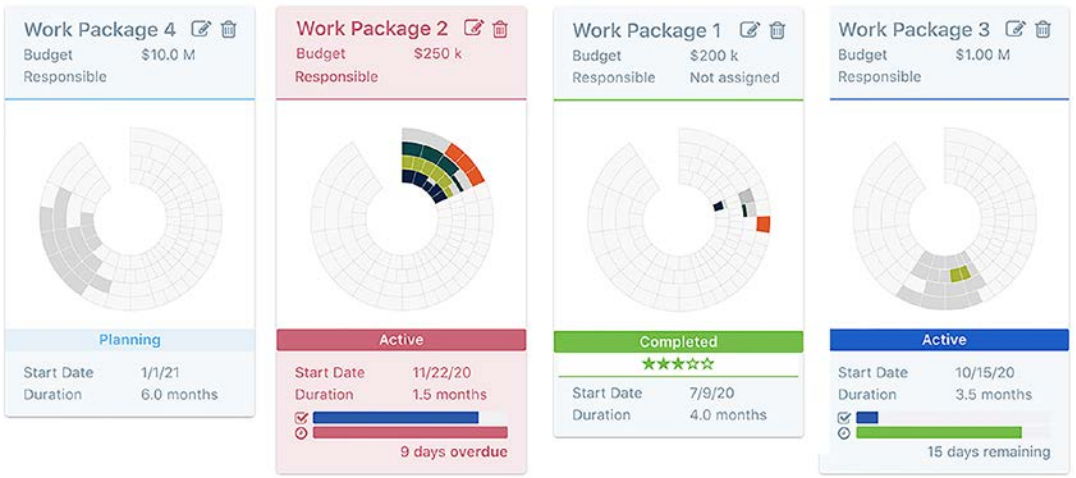
commercialization roadmap based on data from actual customers and other stakeholders. Teams also receive 1:1 mentoring from successful healthcare entrepreneurs and group coaching from commercialization experts and investors.

CIMIT's GAITS

Based on lessons learned since its first Clinical Impact Study in 2010, CIMIT created the CIMIT Innovation Guidance and Impact Tracking System (GAITS) in 2017 and further developed its functionality in 2020. GAITS parallels the Department of Defense's well-established Technology Readiness Levels (TRLs) and establishes a sequence of 10 healthcare specific milestones. GAITS helps innovators navigate the complex journey of innovation in healthcare and adds significant guidance to teams by defining core set of deliverables at each milestone in four domains critical to success in healthcare innovation: Clinical, Market/Business, Regulatory/Approvals, and Technology. In addition, GAITS curated resources (descriptions, videos, templates, examples, etc.) are provided to help teams complete the deliverables. It also enables funders/institutions to provide teams with a secure site to track their progress and measure their impact. CIMIT has organized a consortium of leading healthcare innovation organizations across the globe to use GAITS and to build on CIMIT's experience of facilitating teams by providing an online tool that supports teams and portfolio managers to ¬increase the likelihood of innovations reaching patient care. The consortium will provide a robust database to study the innovation process in healthcare to establish and share best practices.



Status of each Deliverable along the Four Domains: Clinical, Market/ Business, Regulatory and Technology.



Plan and Track Milestones, Define Time line and Track Budgets.

Dermatology

Department Report

DAVID E. FISHER, MD, PHD, CHIEF

Overview:

The Dermatology Department at MGH is a historically important contributor to the modern field of skin biology and cutaneous medicine. Its distinguished faculty dates back to the 1800's and included many innovators for whom clinical conditions are named and through whom the modern field of dermatology was derived. One notable feature and source of particularly pride for MGH Dermatology faculty was its hiring of the first female physician at MGH, Dr. Loretta Cummings, a Dermatologist working at MGH in the early 1900s who subsequently left a portion of her estate to the MGH Dermatology Department. The proceeds of that fund are currently utilized to fund an annual research award pertaining to a female-related dermatologic study. The greatest challenge to MGH Dermatology during 2020 was the COVID epidemic which caused near-complete shutdowns of all non-urgent clinic operations as well as laboratory research activities. Moreover, Dermatology Faculty contributed in redeployment efforts of multiple types across MGH, in order to assist in the wave of patients that has so deeply stressed our medical community. Dermatology Department trainees (particularly Residents) also actively contributed to COVID patient care, especially in the inpatient units, as part of the hospital re-deployment activities. In addition, certain faculty carried out COVID-related research activities, with Dr. Esther Freeman becoming a national and international leader in cutaneous manifestations of COVID—and director of an international registry of COVID skin manifestations (see below). Other department members, such as research personnel who were unable to carry out laboratory research during the surge peak, generously volunteered in various roles including ICU ventilator monitoring roles.

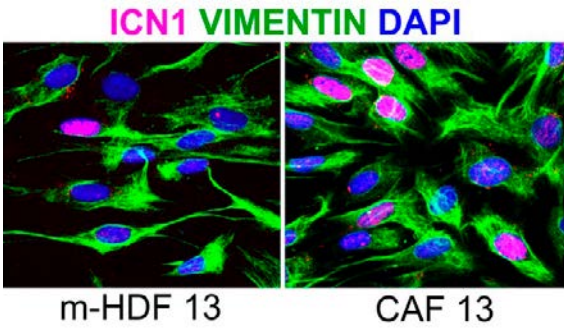
The department's core missions are to deliver excellent clinical care, research, education, and community outreach. The department is also deeply committed to close collaborations with colleagues across nearly all departments at MGH, as well as numerous colleagues at other academic institutions. The Department has a global dermatology interest with faculty representation on WHO dermatologic leadership (Dr. Esther Freeman). And the care of the homeless remains a high priority for which the department commits resources in a program spearheaded by Dr. Jennifer Tan. On an annual basis MGH Dermatology delivers care in approximately 90,000 patient visits. Care is provided at MGH main campus as well as multiple community care centers and MGH-Northshore in Danvers. In collaboration with MGH Pathology, an outreach community-based Dermatopathology Lab has become one of the busiest of its type across New England. In addition to providing general medical dermatologic care, the department also provides specialty clinics in topics including Pediatric Dermatology, High-Risk Non-melanoma Skin Cancer, Pigmented Lesions/Melanoma, Dermatologic & Mohs Surgery, Hair-loss, Urgent-care, Rheumatologic

Dermatology, Laser and Cosmetic Unit, and Inpatient-Consultation Services. The Pigmented Lesions/Melanoma Clinic was the first of its kind in the US, and celebrated its 50 year anniversary recently. Aside from the Clinical Service, the MGH Dermatology Department contains multiple research-oriented programs. These include the Clinical Trials Unit (CURTIS: Clinical Unit for Research Trials In Skin) and the Cutaneous Biology Research Center (CBRC). CURTIS typically runs 10-20 ongoing clinical trials, with a combination of Industry Sponsored and Investigator Initiated investigations. The Cutaneous Biology Research Center was founded in 1990 and currently houses 14 Principal Investigators who collectively represent a highly distinguished center for skin research. During 2020, the CBRC recruited a new outstanding Principal Investigator, Jian Shu PhD, who had recently trained at the Broad Institute and the Whitehead Institute (MIT). The Center has attracted substantive federal grant support as well as Industry funding that includes a longstanding a deep collaborative relationship with Shiseido Cosmetics. A highlight of this relationship was a recent celebration of the 30th anniversary of the CBRC-Shiseido program which provided one of the largest Industry-Academic collaborations in modern history. CBRC faculty direct research laboratories which study topics including melanoma, non-melanoma skin cancers, hair, cryobiology, itch, stem cells, inflammatory pathways, drug discovery, UV radiation, pigmentation, epigenetics, cancer immunotherapy, laser biology, targeted therapy, metabolomics, RNA biology in skin, and developmental/differentiation pathway control. Close collaborations exist with MGH Cancer Center (in which several CBRC faculty hold joint appointments) as well as collaborations with MGH Dermatopathology and numerous additional departments. Additional research faculty whose academic home is in Dermatology include many researchers in the Wellman Center for Photomedicine, an MGH Thematic Center that has made seminal contributions to the current practice of dermatology largely through the development of devices used in the diagnostic or therapeutic aspects of medicine (including dermatology).

During 2020 faculty members from the Department of Dermatology published 276 scholarly articles and gave 215 speaking engagements. During this period $21.2M in research support was spent, which included funds from NIH, Dept of Defense, numerous Foundations, Industry partners, royalties, and philanthropy. The Department also holds the leadership role in a Harvard-wide NCI-sponsored multi-million dollar Program Project Grant on Melanoma, which is highly collaborative with investigators across Harvard Medical School. The Department also hosts numerous visiting trainees including specific initiatives to enhance diversity representation in the field of Dermatology and skin research. Finally, MGH Dermatology particularly prides itself on its close interactions and collaborations with most departments across the hospital—in clinical care initiatives, research projects, medical education, and community outreach.

Dermatology

Department Report



Nuclear NOTCH1 (also called ICN1) is present in higher proportions of Cancer Associated Fibroblasts (CAFs) from a squamous cell carcinoma, than from normal skin (m-HDF). Image taken from *Nature Comm. doi: 10.1038/s41467-020-18919-2.*

Achievements:

Freeman EE, McMahon DE, Fitzgerald ME, Lipoff JB, Rosenbach M, Kovarik C, Desai S, Harp J, Takeshita J, French LE, Lim H, Thiers BH, Hruza GJ, Fox LP. The spectrum of COVID-19-associated dermatologic manifestations: an international registry of 716 patients from 31 countries. J. Amer. Acad. Dermatol. July 2 2020 S0190-9622(20)32126-5.

In the era of COVID surges throughout the world, skin manifestations became prominent and were rapidly and thoroughly assessed in this study spearheaded by Dr. Esther Freeman.

Guhan SM, Nathan NR, Raef H, Cavanaugh-Hussey M, Tan JK. "COVID-19 and healthcare disparities: innovative ways to meet the dermatologic needs of patients experiencing homelessness." Published online J Amer Acad Dermatol 2020 Oct 23. doi: 10.1016/j.jaad.2020.10.042

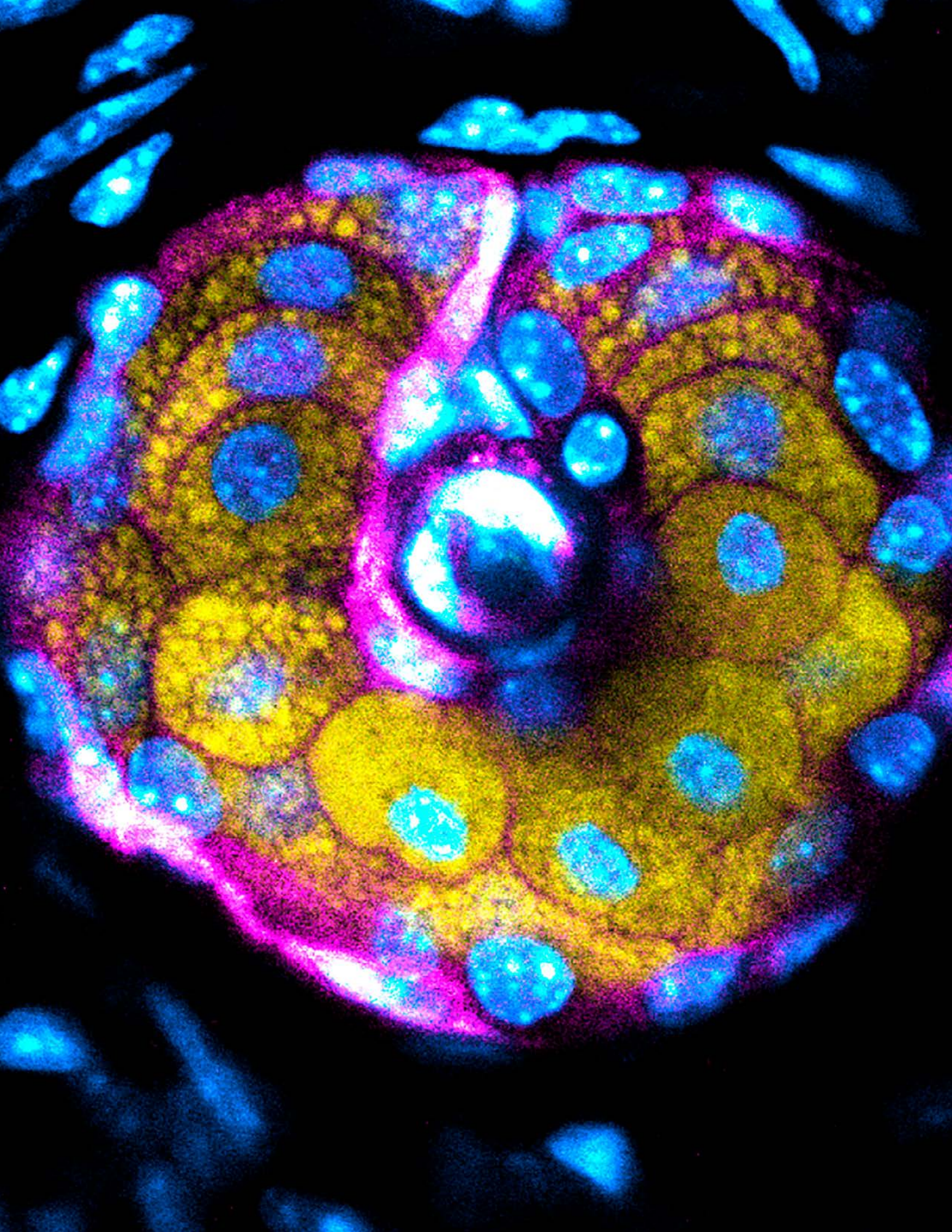
Among the hardest hit patient populations suffering from COVID related challenges were homeless individuals. This report, spearheaded by Dr. Jennifer Tan (who leads MGH Dermatology's homeless care initiative) reports on specific challenges and strategies towards helping to meet the needs of this population.

Katarkar, A., Bottoni, G., Clocchiatti, A., Goruppi, S., Bordignon, P., Lazzaroni, F., Gregnanin, I., Ostano, P., Neel,V., and G.P. Dotto (2020) NOTCH1 gene amplification promotes expansion of Cancer Associated Fibroblast populations in human skin. Nature Comm. doi: 10.1038/s41467-020-18919-2

Cancer associated fibroblasts are established to play key effects in promoting tumor behaviors. This study identified genomic amplifications in the NOTCH1 gene in these fibroblasts, and demonstrated the ensuing consequences in blocking growth arrest responses after DNA damage which thereby promote skin cancer progression after UV.

Shibata S, Kashiwagi M, Morgan B, Georgopoulos K. Functional interactions between Mi-2Beta and AP1 complexes control response and recovery from skin barrier disruption. J Exp Med 2020 Mar 2;217(3)

One of the key functions of healthy skin is to provide a functional barrier against environmental stresses. This study identified genomic loci that response to barrier disruption and defined a role for the chromatin remodeling factor Mi-2ß in directly repressing genes induced by barrier disruption, thereby establishing an epigenetic response with anticipated memory, that controls recovery.



Emergency Medicine

Department Report

DAVID F. M. BROWN, MD, CHIEF

Mission

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

Focus

The role of the emergency physician is to provide rapid diagnostics and therapies for those with acute illness and injury, all while providing compassionate and efficient care. Our clinical environment is challenged with ever-increasing patient volume, digital information overload, and particularly in 2020 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 2020.

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, physiologic monitoring, pediatric emergencies and health services research.

The COVID-19 pandemic of 2020 touched essentially all of these areas of investigation, which is 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 investigative infrastructure was well-equipped to pivot to COVID-19 research and contribute significantly in answering relevant clinical and research questions. Our contributions to COVID-19 research have included active enrollment in national and multinational clinical trials, mobilization of multi-departmental teams to create the largest biorepository of acutely-ill patients with blood samples available for multi-omic analytics for the Harvard scientific community, leadership in national COVID-19 clinical data registries and multi-site COVID-19 cohort investigation, local and national leadership with a research footprint in disaster preparedness and COVID-19 healthcare systems response, as well as numerous clinical and operational innovations employed locally and translated into clinical research in order to inform the greater community.

Amongst the over 300 peer-reviewed publications in 2020 by over 30 contributing faculty, our department published 44 COVID-19-related manuscripts within the span of 6 months. This number eclipses the annual peer reviewed manuscript total (on any topic) for nearly every

academic Department of Emergency Medicine in the country. We are proud of our accomplishments and highlight several of these works below.

Goals for 2021:

1. Continue to develop a strong pipeline of clinical investigations, and clinician and non-clinician researchers, to support a robust research infrastructure that drives forward the departmental research mission.
2. Increase expertise in sample processing to facilitate expanded investigation in proteomics, metabolomics, genomics, and human microbiome.
3. Work on obtaining 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 all investigators at MGH and within the Harvard community.
4. Continue to develop a consistent mechanism for providing electronic clinical data to investigators to carry out health record-based research.
5. Continue to hone departmental resources available to support and optimize our research infrastructure, including grants administration and finance, statistical support, and mentoring for young investigators.

Achievements in 2020:

1. *Plasma proteomics reveals tissue-specific cell death and mediators of cell-cell interactions in severe COVID-19 patients. Filbin MR, Mehta A, …, Parry BA, Villani AC, Sade-Feldman M, Hacohen N, Goldberg MB. BioRxiv. 2020 Nov 3:2020.11.02.365536. doi: 10.1101/2020.11.02.365536.*

   As the COVID-19 pandemic swept over Boston, both clinical and research operations in the Emergency Department rapidly shifted to the clinical care and investigation of patients with severe COVID-19 disease. The Division of Clinical Research led by Dr. Michael Filbin and Blair Parry, along with collaborators in the Division of Infectious Diseases and MGH Center for Cancer Immunotherapy, organized a blood sample collection study that enrolled 400 patients in the span of 6 weeks, including over 300 patients with COVID-19. A team of 20 research coordinators and technicians worked almost around the clock to collect and process samples for single cell RNA sequencing at the Broad Institute, proteomics panel assays provided at no cost by industry collaborators, and other assays including viral load, SARS-coV-2 surface protein and neutralizing

antibody titers. Samples and data have been shared with scientists throughout the Harvard system to facilitate rapid discovery. The highlighted work here leverages over 5,000 measured serum proteins to characterize signatures associated with severe COVID-19 illness, death, and recovery. These signatures are mapped to both immune cells and organ-specific cells, thus providing a model of immune response and tissue damage in severe COVID-19 and elucidating potential targets for therapies.

2. *Association of obesity and its genetic predisposition with the risk of severe COVID-19: Analysis of population-based cohort data. Zhu Z, Hasegawa K, Ma B, Fujiogi M, Camargo CA Jr, Liang L. Metabolism. 2020 Aug 22;112:154345. doi: 10.1016/j.metabol.2020.154345.*

   During the pandemic, many EM investigators leveraged established collaborations, both nationally and internationally, to contribute to the emerging knowledge base about SARS-CoV-2 infection. The Emergency Medicine Network (EMNet), based at MGH and led by Prof. Carlos Camargo, joined collaborators in the United Kingdom to analyze data on 489,769 adults enrolled in a population-based biobank study that included genomic as well as clinical data. Of these patients, 641 developed severe COVID-19 during the pandemic surge. Investigators demonstrated that body mass index (BMI) had a dose-response association with odds of developing severe COVID-19; obese adults had more than 3x higher odds compared to those with normal BMI. Furthermore, genetic obesity trait was associated with severe COVID-19 independent of BMI, implicating potential genetic predisposition for developing severe disease. These data provided conclusive support for clinical observations and smaller retrospective studies as to the relation between obesity and risk of developing severe COVID-19.

3. *Delirium in Older Patients With COVID-19 Presenting to the Emergency Department. Kennedy M, Helfand BKI, Gou RY, Gartaganis SL, Webb M, Moccia JM, Bruursema SN, Dokic B, McCulloch B, Ring H, Margolin JD, Zhang E, Anderson R, Babine RL, Hshieh T, Wong AH, Taylor RA, Davenport K, Teresi B, Fong TG, Inouye SK. JAMA Netw Open. 2020 Nov 2;3(11):e2029540. doi: 10.1001/jamanetworkopen.2020.29540.*

   This national group of investigators pivoted their work in the aging emergency department population to study 817 older patients with COVID-19 at 7 different centers around the country. Dr. Maura Kennedy and colleagues found a surprisingly high rate of delirium associated with COVID-19—28% of older ED patients with COVID-19 had delirium. In more than one-third of COVID-19 patients with delirium, there were no other typical COVID-19 sign or symptoms such as fever or shortness of breath. Delirium was independently associated with ICU admission and death. This study highlights the importance of an assessment for delirium in elderly patients with COVID-19 and to strongly consider admission in these patients regardless of respiratory criteria that typically drive admission.

4. *Feasibility and Safety of Prone Position Transport for Severe Hypoxemic Respiratory Failure Due to Coronavirus Disease 2019. Seethala RR, Frakes MA, Cocchi MN, Cohen JE, Dargin J, Friedman F, Grant C Jr, Kaye A, Wilcox SR. Crit Care Explor. 2020 Dec 3;2(12):e0293. doi: 10.1097/CCE.0000000000000293.*

Lastly, the pandemic has forced us to adapt new operational strategies both in the ED and prehospital settings to address new clinical and operational challenges. The majority of change has occurred in the ED itself; however, this study exemplifies operational leadership in the prehospital setting, translated rapidly to research that informs COVID-19 prehospital operations globally. The air medical transport environment is the most confined with the most critically ill, and if ventilated proning for COVID-19 can work here, it can work anywhere. Dr. Susan Wilcox, the associate chief medical officer of Boston MedFlight, demonstrated in this study that it can work safely on 25 critically-ill, COVID-19 patients undergoing air medical transport. This proof-of-concept study is the largest series of prone transports in the literature and has widely influenced air medical transport protocols for critically-ill COVID-19 patients in need of emergent transport.

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.

Achievements:

The **Division of General Internal Medicine** has been actively involved in rapidly generating new evidence about our clinical understanding of COVID-related illness, the spread of the coronavirus, and the broader implication of the pandemic on how we deliver care for other health conditions. **Chana Sacks, MD** and colleagues analyzed data early in the pandemic from the MGH occupational health clinic to investigate which symptoms experienced by health care workers (HCW) are associated with a positive COVID-19 test result; those with a positive test were more likely to have reported anosmia (OR 11.9, 95% CI 5.9, 24.3), fever (OR 2.7, 95%CI 2.0, 3.8), or myalgias (OR 2.7, 95%CI 1.9, 3.7) (1). Sore throat was associated with decreased odds of a positive test (OR 0.6, 95%CI 0.4, 0.8). This work indicates that a large hospital system can develop and implement a mandatory, large-scale program with capacity to test all symptomatic health care workers and that while some symptoms, such as sore throat, were associated with decreased odds of a positive test, no singular symptom seemed likely to effectively exclude a diagnosis of COVID-19 given the relatively small magnitude of an effect that each symptom had on the odds of a positive test. Those with a positive test reported a greater number of symptoms.

Dr. Sacks and colleagues extended this work by establishing a centralized scientific review committee at MGH to oversee the portfolio of Covid-19–related trials and continuously evaluate newly proposed studies (2). By establishing formal criteria for evaluation, this process ensures that selected trials are diverse in approach, targeted

at multiple viral and host pathways, and structured to maximize the chance that the research question will be definitively answered. This type of infrastructure is invaluable to all of the trials being conducted in our system during a time when we need rapid deployment and recruitment for diverse needs

The pandemic has been an unfortunate reminder of the social vulnerabilities that many individuals in the US face on a daily basis. The Division of General Internal Medicine has an active research portfolio focused on vulnerable populations. Travis Baggett, MD, MPH and colleagues, in a longstanding partnership with the Boston Health Care for the Homeless Program (BHCHP), rolled out a COVID-19 response strategy that includes respiratory symptom screening at shelter front doors, expedited referrals for SARS-CoV-2 testing and isolation for those with respiratory symptoms, dedicated treatment settings for individuals with positive test results, and contact tracing of confirmed COVID-19 cases early in the course of the pandemic (3). They found that universal SARS-CoV-2 PCR testing of an adult homeless shelter population in Boston early in the pandemic yielded a 36% positivity rate. The majority of individuals with newly identified infections had no symptoms and no fever at the time of diagnosis, suggesting that symptom screening in homeless shelters may not adequately capture the extent of disease transmission in this high-risk setting.

Benjamin Bearnot, MD and colleagues conducted multiple geospatial analyses of a crowdsourced database of service requests for needle reports in San Francisco to examine spatial relationships between needle reports and needle disposal boxes, needle disposal kiosks, and homeless shelters (4). Among 34,912 needle reports, 45.6% originated in the five downtown neighborhoods with the highest needle report density, and 33.8% were identified within 200 meters of boxes, kiosks, or homeless shelters. They found that reports of discarded needles in San Francisco increased dramatically over the last decade, and more than one third of 2019 reports were adjacent to harm reduction and homeless shelter locations. Using geospatial methods to examine needle reports provide an opportunity to understand changes in public injection drug use and target harm reduction services.

The serological response to infection with SARS-CoV-2 is marked by development of antibodies to the receptor-binding domain (RBD) of the SARS-CoV-2 spike protein. **Richelle Charles, MD, Jason Harris, MD, Edward Ryan, MD, Galit Alter, PhD, Regina LaRocque, MD, MPH, Sarah Turbett, MD,** and **Stephen Calderwood, MD** from the **Division of Infectious Diseases** characterized the kinetics of this response in a longitudinal cohort of 343 North American patients with COVID-19, 93% of whom required hospitalization (5). They estimated sensitivities of 95% for IgG, 90% for IgA, and 81% for IgM for detecting infection in infected individuals between 15 and 28 days after symptom onset. The mean time to seroconversion was 12 days for all three antibody isotypes. IgA and IgM seropositivity to SARS-CoV-2 RBD were relatively short-lived, with median time to seroreversion of 71 and 49 days, respectively; in contrast, IgG antibodies to the RBD decayed slowly through 90 days. IgG

antibodies to SARS-CoV-2 RBD were strongly correlated with anti-spike protein neutralizing antibody titers, which demonstrated little to no decrease over 75 days since symptom onset. No cross-reactivity to other widely circulating coronaviruses was detected. These data indicate that among hospitalized patients, RBD-targeted antibodies are excellent markers of previous and recent infection, that differential isotype measurements can help distinguish between recent and older infections, and that IgG responses persist over the first few months after infection and are highly correlated with neutralizing antibodies. The findings indicate that with the appropriate timing, antibody-based assays can add to nucleic acid-based diagnostic approaches. They can also inform the design and interpretation of seroepidemiologic studies.

Sepsis, life-threatening organ dysfunction due to a dysregulated host response to infection, is prevalent and highly lethal. A major challenge is early detection, largely because sepsis is a heterogeneous syndrome, with many patients presenting with vague symptoms and signs; improved biomarkers would enable earlier diagnosis, especially of these patients. A second major challenge is the shortage of effective treatments, as the mechanisms of immune dysfunction and vascular leakage in sepsis are poorly understood, limiting therapeutic development. Here, using transcriptional profiling of single circulating immune cells, **Roby Bhattacharyya, MD, PhD, Marcia Goldberg, MD,** and their colleagues discovered a unique monocyte cell state (MS1) that is significantly expanded in patients with sepsis and absent in patients with milder responses to infection and healthy controls, and validated this discovery in external datasets (6). They showed that MS1 monocytes express a module of immunosuppressive genes, consistent with the immunosuppressive state present during sepsis, and displayed blunted responses to bacterial stimulation, which recapitulates the known dysfunctional phenotypes of monocytes in patients with sepsis. They showed that MS1 monocytes arise from hematopoietic stem cells, suggesting that MS1 monocytes in the circulation of septic patients are newly generated in the bone marrow. In sum, by identifying the sepsis-associated new monocyte cell state MS1 and MS1 gene modules, they identify new biomarkers that are likely to be useful for earlier detection of sepsis in patients. Their characterization of the MS1 transcriptome provides new insights into pathways that may contribute to the underlying immune dysfunction and vascular leak that are key hallmarks of sepsis. And their analysis of MS1 derivation suggests a new mechanism through which hematopoietic adaptation plays a role in the pathophysiology of sepsis.

In the **Division of Rheumatology, Allergy, and Immunology,** the **Robert Anthony, PhD** lab studies how glycosylation of antibodies has profound effects on their function. In this study published *Nature,* they addressed the clinical observation that while allergen-specific IgE is required for allergies they do not always correlate with allergic diseases (7). Robert's lab found that glycosylation of IgE profoundly affects its function and that glycosylation of IgE differed between allergic and non-allergic subjects. Further, modifying the sugars on IgE converted pathogenic IgE into non-pathogenic IgE opening the

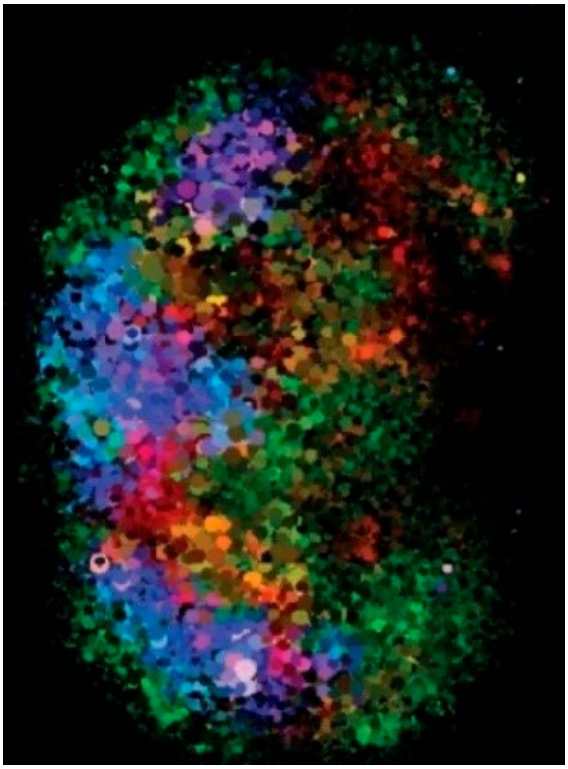
way for an entirely new therapeutic approach to treat IgE-mediated allergic disease.

Regulatory T cells are well known to suppress adaptive immune responses. In this study from the **Andrew Luster, MD, PhD** lab published in *Nature Immunology*, they describe an unexpected function of regulatory T cells in suppressing the innate immune response in the lung to environmental allergens without altering the adaptive immune response (8). This study found that a subset of lung regulatory T cells is activated by the alarmin interleukin-33, which is released by the epithelium in response to injury. These activated regulatory T cells suppress the innate γδ T cell response, resulting in less eosinophil and neutrophil recruitment into the lung, which is beneficial to the host in reducing inflammation induced by allergen.

Dendritic cells can initiate allergic immune responses, but how allergens activate dendritic cells is not known. Using a mouse model in which the allergen papain was injected into the skin, the **Caroline Sokol, MD, PhD** lab reported in *Immunity* that TRPV1^{+} sensory neurons are required for an immune response to allergens (9). Allergen-driven activation of TRPV-expressing neurons caused the release of the neuropeptide substance P, which induced the migration of dendritic cells to the draining lymph nodes where they initiated T helper type 2 cell differentiation. Thus, sensory neurons act as primary sensors of allergens, linking exposure to activation of allergic-skewing dendritic cells and the initiation of an allergic immune response.

Generating a robust T helper cell type 1 response is important for generating protective vaccine-induced immunity. The Luster lab, in a study published in *Cell Reports,* demonstrated that emulsifying an immunogen in oil improved its delivery to specific regions within lymph nodes called interfollicular regions that they had previously found specialize in generating protective type 1 immune responses (10). Activation of this region resulted in the production of the chemokine CXCL10 by inflammatory monocytes that recruited T cells into these areas, which promoted their differentiation into polyfunctional helper T cells and the generation of stronger protective immune responses. Formulations able to deliver immunogens to this specialized region of the lymph node and activate the immune system in a similar manner may improve vaccine efficacy.

Ischemic acute kidney injury (AKI), a complication that frequently occurs in hospital settings, is often associated with hemodynamic compromise, sepsis, cardiac surgery, or exposure to nephrotoxins. In a recent study from the **Division of Nephrology, Agustina Battistone, PhD,** and **Sylvie Breton, PhD, Charles and Ann Sanders MGH Research Scholar,** described a novel mechanism of sterile inflammation that is triggered by ischemic AKI, a finding that provides new mechanistic insight and highlights a new therapeutic target for this condition (11). Using a murine renal ischemia/reperfusion injury model, they showed that intercalated cells rapidly adopted a proinflammatory phenotype after ischemia/reperfusion injury and that during the early phase of AKI either blockade of the proinflammatory P2Y14 receptor located on the apical membrane of intercalated cells or ablation of the gene encoding the P2Y14 receptor in intercalated



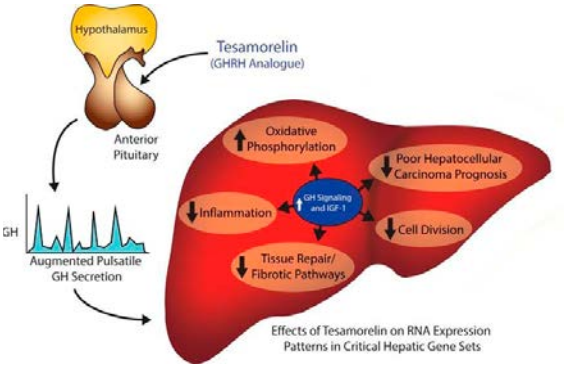
Distribution of a model antigen (ovalbumin), in green, in the mouse draining lymph node after immunization formulated in oil. Follicular dendritic cells in the B cell follicle are in blue, and high endothelial venules are in red. Lian et al. show that immunization in oil formulation promotes antigen targeting to the interfollicular regions of the draining lymph node, which leads to enhanced polyfunctional CD4+ T cell priming and type 1 immunity. Artwork by Aleksandra J. Ozga.

cells reduces neutrophil and monocyte renal infiltration, reduces the extent of kidney dysfunction, and attenuates proximal tubule damage. These observations indicate that the P2Y14 receptor participates in the very first inflammatory steps associated with ischemic AKI. In addition, they showed that the concentration of the P2Y14 receptor ligand UDP-glucose (UDP-Glc) was higher in urine samples from intensive care unit patients who developed AKI compared with patients without AKI. Thus, this study identifies the UDP-Glc/P2Y14 receptor axis as a potential target for the prevention and/or attenuation of ischemic AKI.

Fibroblast growth factor-23 (FGF23) is a bone-derived hormone that controls blood phosphate levels by increasing renal phosphate excretion and reducing 1,25-dihydroxyvitamin D3 [1,25(OH)2D] production. Disorders of FGF23 homeostasis are associated with significant morbidity and mortality, but a fundamental understanding of what regulates FGF23 production is lacking. Because the kidney is the major end-organ of FGF23 action, **Petra Simic, MD, PhD** and **Eugene Rhee, MD** hypothesized that it releases a factor that regulates FGF23 synthesis (12). Using aptamer-based proteomics and liquid chromatography-mass spectrometry (LC-MS) based metabolomics, they profiled >1600 molecules in renal venous plasma obtained from human subjects. Renal vein glycerol-3-phosphate (G-3-P) had the strongest correlation with circulating FGF23 (r^2 = 0.76, P = 5.2x10^{-6}). In mice, exogenous G-3-P stimulated bone and bone marrow FGF23 production through local glycerol-3-phosphate acyltransferase (GPAT)-mediated lysophosphatidic acid (LPA) synthesis. Further, the stimulatory effect of G-3-P and LPA on FGF23 required the LPA receptor 1 (LPAR1). Acute kidney injury (AKI), which increases FGF23 levels, rapidly increased circulating G-3-P in humans and mice, and the effect of AKI on FGF23 was abrogated by GPAT inhibition or Lpar1 deletion. Together, these findings establish a novel mechanism in mineral metabolism and outline potential targets to modulate FGF23 production during kidney injury.

In the **Division of Palliative Care and Geriatrics, Juliet Jacobsen, MD** and the **Continuum Team** continues to make substantial accomplishments in promoting generalist palliative care communication skills, in particular with respect to serious illness conversations. Publications related to this work have been in palliative care journals, the *Journal of Hospital Medicine,* the *New England Journal of Medicine,* a Health Affairs blog and the *Boston Globe* (13-17).

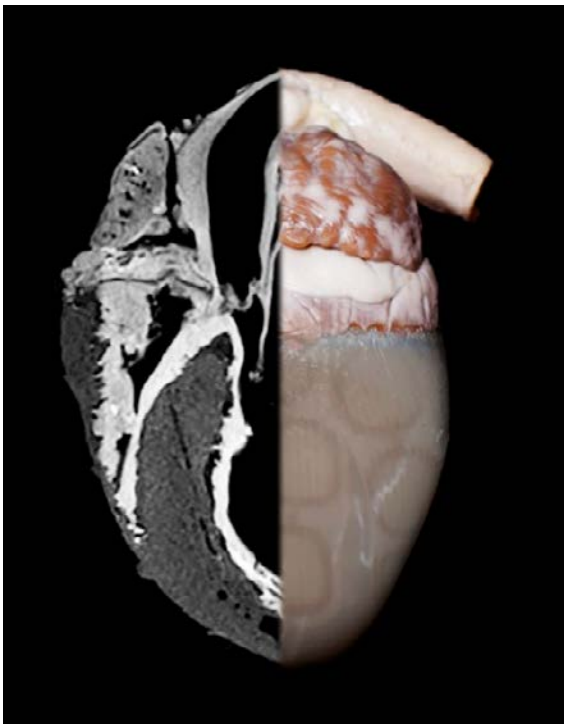
Laura Petrillo, MD received the ASCO Conquer Cancer Career Development Award, a three-year award for early career researchers in clinical research in oncology, to support a project titled “Improving Patient and Caregiver Understanding of Risks and Benefits of Immunotherapy for Lung Cancer or Melanoma.” Her work at the interface of cancer and palliative care has led to publications in Cancer, where she described performance status and end-of-life care among adults with non–small cell lung cancer receiving immune checkpoint inhibitors, and in the Oncologist (18-28).



Effects of Tesamorelin on RNA Expression Patterns in Critical Hepatic Gene Sets

In translational work from the **Metabolism Unit** in the **Endocrine Division, Lindsay Fourman, MD** led a whole transcriptome analysis on paired liver biopsy specimens to elucidate mechanisms of a novel agent to treat nonalcoholic fatty liver disease (NAFLD) in HIV (29). To our knowledge, this study is the first to utilize high-throughput gene expression technology to investigate the biologic underpinnings of a NAFLD therapy in humans, and particularly to understand the cellular changes that constitute a clinical response. In a randomized placebo-controlled trial, she recently demonstrated that the growth hormone-releasing hormone (GHRH) analogue tesamorelin reduced liver fat and prevented fibrosis progression over 1 year among individuals with HIV-associated NAFLD *(Stanley and Fourman, Lancet HIV 2019).* Building upon this prior work, she now examined the relationship of differential changes in hepatic gene expression patterns by treatment status to changes in liver phenotype *(Fourman, JCI Insight 2020).* She found that tesamorelin upregulated hepatic genes involved in oxidative phosphorylation and downregulated genes contributing to inflammation, tissue repair, and cell division. The leading edge of the oxidative phosphorylation gene set included genes critical to the electron transport chain and mitochondrial function. Tesamorelin also reciprocally up- and downregulated genes associated with favorable and poor hepatocellular prognosis, respectively. Notably, among tesamorelin-treated participants, changes in hepatic gene expression signatures correlated with improved fibrosis-related gene scores. These findings provide a mechanistic basis for the observed clinical effects of tesamorelin and inform our knowledge of the biology of pulsatile growth hormone action on the liver. This work has led to the development of a large international Phase III trial of this novel agent for NAFLD/NASH in the general population.

Although puberty is considered a universal human experience, approximately 5% of the population do not enter puberty at the proper time. Half of those children are “delayed.” These individuals initiate sexual maturation on their own, but much later than their peers, creating 1) anxiety 2) decreased self-esteem and 3) long term health risks. Unfortunately, a subset of delayed patients never enter puberty. These patients have a rare disease (congenital hypogonadotropic hypogonadism) in which the reproductive centers of the brain fail to function. These children have more serious long-term health risks and are required to take hormone medications for the rest of their lives, as if untreated, the disorder results in sexual infantilism and infertility. There has never been a diagnostic test that can differentiate children who are late but will eventually enter puberty (a self-limited condition), from the children who are late yet will never start puberty. However, investigators from the **Reproductive Endocrine Unit,** have developed a new diagnostic test to differentiate between these two groups. The neuropeptide kisspeptin, which stimulates GnRH release, can be used to probe the integrity of the reproductive endocrine axis. A large investigative team including **Stephanie Seminara, MD, Bob and Laura Reynolds MGH Research Scholar,** and **Margaret Lippincott, MD** from MGH and Dr. Chan from BCH sought to determine whether responses to kisspeptin can predict outcomes for individuals with pubertal delay (30). They administered kisspeptin



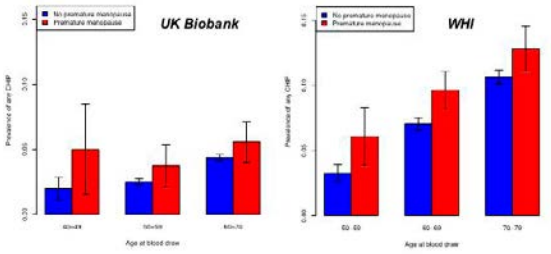
Biohybrid, functioning robotic heart using *in vivo* cardiac diffusion magnetic resonance imaging to improve biomimicry

to children with pubertal delay, determined the GnRH response, and then followed the children for up to 5 years to determine whether they entered puberty spontaneously or not. The responses to kisspeptin accurately predicted later pubertal outcomes. Specifically, those who responded to kisspeptin initiated puberty on their own. Those who did not respond to kisspeptin did not initiate puberty. Thus, kisspeptin-stimulation testing can assess future reproductive endocrine potential in prepubertal children and is a promising novel tool for predicting pubertal outcomes for children with delayed puberty. This work was published in 2020 and the authorship team is the recipient of the 2021 Top 10 Clinical Research Achievement Award from the Clinical Research Forum.

Bone is a dynamic tissue that constantly responds to mechanical cues. It has long been appreciated that osteocytes are the primary mechano-sensors in bone. However, the signaling pathways used by osteocytes to transduce mechanical cues have been poorly understood. In this work, osteocytes were studied in their physiologic context: buried deep within mineralized bone matrix. This technically challenging approach allowed the group of **Marc Wein, MD** to understand how cell/matrix signaling regulates mechano-transduction. The authors demonstrated that constitutive cell/matrix association drives high levels of basal focal adhesion kinase (FAK) activity (31). Mechanical cues transiently disrupt cell/matrix interaction, and therefore reduce FAK function. This work went on to define how FAK regulates gene expression; in osteocytes, FAK phosphorylates the key co-repressor HDAC5 at a specific tyrosine residue that controls HDAC5 subcellular localization. HDAC5 localization had previously been reported to be controlled by hormonal/cAMP-dependent cues via serine phosphorylation. Therefore, this work demonstrates that HDAC5 can integrate hormonal and mechanical cues to regulate cell type-specific gene expression. These findings have major implications for mechano-biology beyond bone; the model that changes in constitutive cell/matrix interactions drives mechano-transduction will be applicable to many other biologic systems. Finally, these findings suggest that targeting FAK inhibitors to bone represents a novel therapeutic strategy to simulate osteocyte mechano-transduction in order to prevent immobilization-induced bone loss.

From the **Division of Cardiology, Chris Nguyen, PhD** of the MGH **Cardiovascular Research Center** and Ellen Roche, PhD of MIT have developed a biohybrid, functioning robotic heart using *in vivo* cardiac diffusion magnetic resonance imaging to improve biomimicry. The heart model combines organic endocardial tissue from a preserved explanted heart with synthetic myocardium comprised of soft robotic actuators adhered to the organic endocardial tissue in a helical fashion to form a flexible, conformable, and watertight organosynthetic interface (32). Potential applications of the model include facilitating testing of a broad range of cardiac devices and other therapeutic interventions. Ultimately this approach could lay a foundation for the development of customizable artificial hearts and/or assist devices for advanced heart failure patients. The work was published in *Science Robotics.*

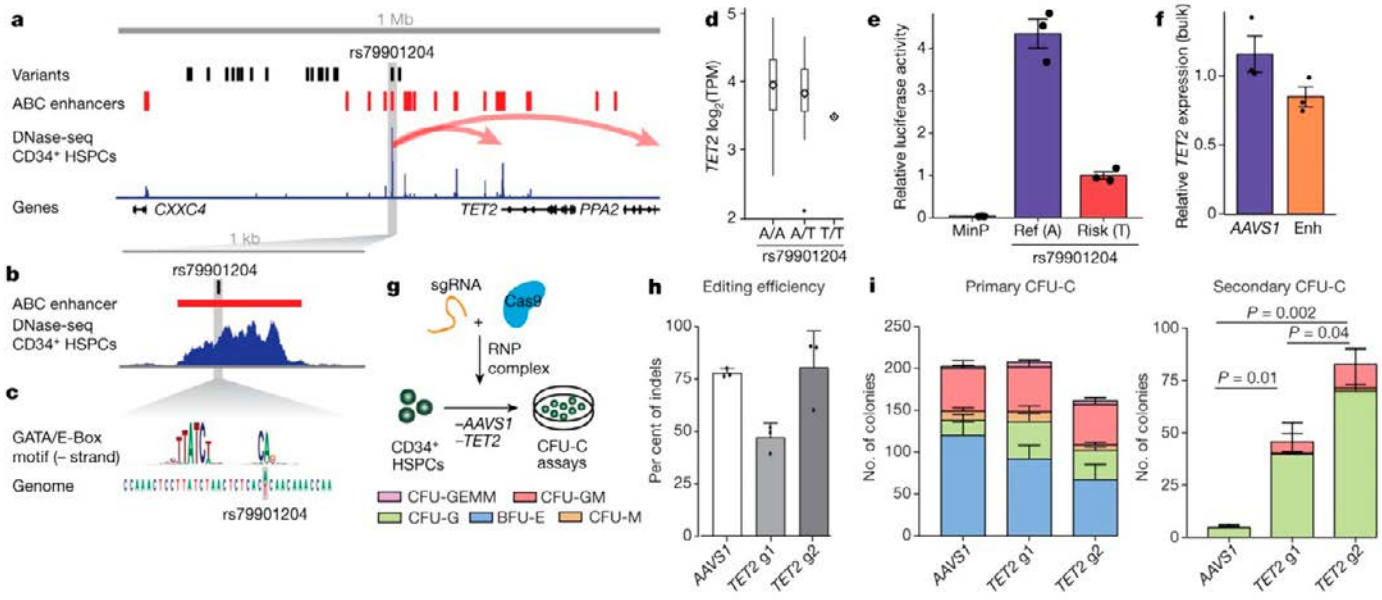
Aortic aneurysm predisposes to dissection, an important cause of sudden death. **James Pirruccello, MD** (a junior faculty member working with **Patrick Ellinor, MD, PhD**) developed a machine learning approach to quantitatively analyze the ascending and descending thoracic aorta in ~40,000 UK Biobank participants with MRI data (33). This enabled a large-scale genetic analysis of aortic diameter that identified 103 genetic loci, including known loci, such as Fibrillin1, and dozens of novel loci that provide a roadmap for future investigation and potential therapeutic targets. The team developed a polygenic score that strongly predicted the diagnosis of aortic aneurysm (HR = 1.43 per standard deviation of the score). This work has been provisionally accepted at *Nature Genetics* and was posted as a preprint on bioRxiv. In addition to Drs. Pirruccello and Ellinor, other MGH Cardiology contributors include **Mark Lindsay, MD, PhD, Steven Lubitz, MD, MPH, Jennifer Ho, MD,** and **Shaan Khurshid, MD.**



Prevalence of clonal hematopoiesis of indeterminate potential (CHIP) by age at blood draw and premature menopause status in the UK Biobank and Women's Health Initiative (WHI)

Clonal hematopeoisis of indeterminate prognosis (CHIP) has emerged as a major risk factor for atherosclerotic coronary disease that, in part, explains its association with age. Premature menopause is also a risk factor for vascular disease and **Michael Honigberg, MD, MPP, Pradeep Natarajan, MD** and colleagues examined the prevalence of CHIP in women with premature menopause (34). Interestingly they found an increase in CHIP in women with premature menopause in 2 large cohorts. This work was published in *Circulation* in 2020 and Dr. Honigberg received the Stamler Award at the 2020 Northwestern Cardiovascular Young Investigators' Forum for this work.

Pradeep Natarajan, MD led a simultaneous germline and somatic whole genome sequence analysis comprised of 97,691 individuals from 51 cohorts across the United States sponsored by NHLBI (35). His team identified 4,229 individuals without blood cancer who had clonally-expanded blood cancer mutations indicative



Simultaneous germline and somatic whole genome sequence analysis

of clonal hematopoiesis, a risk factor of both blood cancer and cardiovascular disease. His team identified multiple germline genetic variants associated with clonal hematopoiesis. Using silico-informed functional assays, they found that an African American-specific variant associated with clonal hematopoiesis disrupted the transcription of TET2, an epigenetic regulator. Reduced TET2 transcription promoted proliferation and vitality of hematopoietic stem cells. Overall, the study yielded insights toward causal factors simultaneously promoting hematologic cancer and coronary artery disease. This work was published in *Nature* in 2020.

An enormous contribution the **Division of Pulmonary and Critical Care Medicine** to the research community during the emergence of SARS-CoV-2 and through the pandemic has been the Fast Literature Assessment and REview (FLARE) newsletter. Initially launched by **C. Corey Hardin, MD, PhD** as an internal communication to our staff, FLARE rapidly expanded outside the walls of MGH and then Harvard, ultimately reaching thousands of people worldwide. Published daily for nearly 70 consecutive days from March through May and intermittently since then, each FLARE newsletter provided a detailed, succinct and rigorous review of the rapidly evolving evidence around COVID-19 epidemiology, diagnosis and treatment. With the explosion of anecdotal data and research of varying rigor, FLARE was an anchor to busy clinicians and scientists across the globe. Dr. Hardin, along with the rest of the FLARE team, truly provided a north star of evidence-based medicine at a time when experimental therapies were being promoted and adopted widely, and when individual providers were too stretched to analyze the literature on daily basis. Lastly, this incredible volume of very high-quality work was produced at a time when these individuals were also pulled in to work clinically with critically ill COVID patients. Their contribution has been profound and appreciated by many.

This first author Cell paper by **Michael Gillette, MD** describes an innovative multi-omics approach to defining subgroups and subphenotypes within lung adenocarcinoma and provides a roadmap for novel diagnostic and therapeutic approaches (36). By characterizing both cancerous tissue and normal adjacent tissue (NAT), and by utilizing multiple –omic toolkits, Dr. Gillette and co-authors identified four defined subgroups within lung adenocarcinoma and have provided a unique public resource for future investigation.

Although observational, this report on the physiology and outcomes of our initial COVID-19 ARDS cohort has been downloaded over 27 thousand times since publication six months ago (37). This report shifted the conversation around patients with COVID-19 and ARDS, emphasizing their similarity to prior ARDS cohorts and among the best outcomes reported worldwide. This investigation thereby disrupted a growing narrative both that COVID-19 ARDS was a unique, never before seen entity, and that our prior evidence-based care may not apply. Additionally, it provided a key counterpoint to contemporaneous reports of very high mortality in the ICU, which had been widely publicized.

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†equal contribution.

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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:

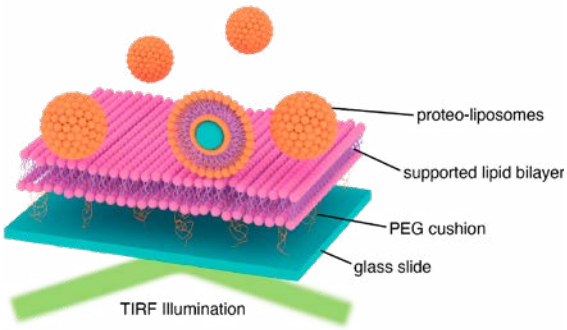
- Chromatin remodeling, long noncoding RNAs, X-chromosome inactivation (Kingston, Lee, Sadreyev), epigenetics, (Hochedlinger, Kingston, Lee, Sadreyev), reprogramming & pluripotency (Hochedlinger).
- Human genetics, mitochondrial physiology and disease (Mootha), and mitochondrial membrane structure and 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:

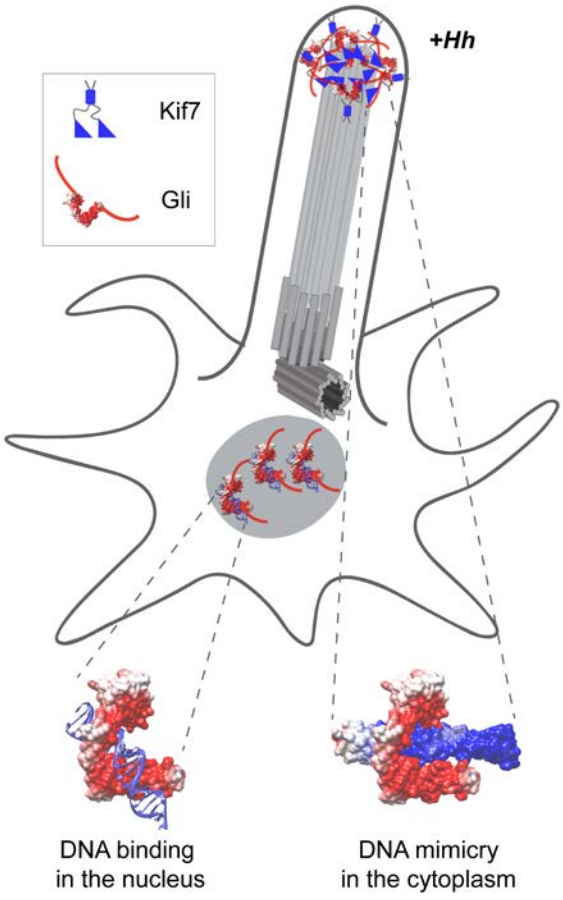
The Department of Molecular Biology is excited to bring world-class cryoelectron microscopy (Cryo-EM) to MGH through its collaborative initiatives with Harvard and MIT. Together with Harvard Medical School, Boston Children's Hospital, and DFCI, the Harvard Cryo-EM Center for Structural Biology has three high-end instruments (1 Talos Arctica and 2 Titan Krios) with staff-assisted training, screening and data collection (https://cryoem.hms.harvard.edu/). With MIT Biology and MIT.nano, the Department of Molecular Biology has also launched a program in electron cryo-tomography (cryo-ET), supporting a Aquilos cryo-FIB/SEM instrument that allows windows to be cut into frozen, hydrated cellular samples (https://biology.mit.edu/tile/center-for-automated-cryogenic-electron-microscopy/). These technologies open incredible new opportunities to visualize proteins and cells in stunning new detail. We congratulate Luke Chao for his successful effort in building these partnerships. Dr. Chao's laboratory, among others, use these new facilities to study macromolecular cellular assemblies with the goal of advancing the fundamental science that underlies devastating diseases.

One such program of study from the Chao lab focuses on mitochondrial membrane dynamics. The merger of mitochondria is essential for cell health, buffering oxidative damage and important in the transmission of maternally inherited traits. Major neurodegenerative conditions (including Charcot Marie Tooth 2A and Dominant Optic Atrophy) result from mutation in the proteins that control this process. It has remained a mystery how this merger is regulated. The Chao lab recently recreated the essential elements of this process using sophisticated membrane systems that can control the lipid and protein levels (figure 1). Using this system, they are able to watch molecular events with new detail and precision *(Ge et al., eLife 2020, doi: 10.7554/eLife.50973)*. These systems open up tremendous new opportunities to probe new areas of subcellular membrane architecture (*Ge et al., JoVE 2020, doi: 10.3791/61620)*.

Following the theme of macromolecular cellular dynamics, recent work from Radhika Subramanian's lab illuminates how aberrances in these processes may lead to tumorigenesis. During embryo development, cells divide from a single fertilized egg and organize into the exquisite structures that are tissues and organs. The timing of these developmental processes is precisely governed by cellular switches that turn "on" for specific durations of time. When the very same switch that helps achieve this developmental process is erroneously turned "on" post-development, it can result in unchecked growth of cells leading to the formation of tumor masses. In a recent study submitted for publication in *Nature Cell Biology,* Farah Haque and colleagues, working in Dr. Subramanian's lab, focused on one such switch, the Hedgehog (Hh) signaling pathway, which is essential for embryonic development and erroneously "switched on" in numerous cancers, including medulloblastoma and basal cell carcinoma. The final step of Hh signaling is gene regulation by Gli (Glioma associated oncogene) transcription factors. Therefore, strategies that can flip the



The Chao lab constructed a membrane system allowing the observation molecular events with new detail and precision *(Ge et al., eLife 2020, doi: 10.7554/eLife.50973).*



DNA molecular mimicry by the Kif7 coiled-coil, discovered in recent work by the Subramanian lab, underlies the tethering of Gli in the cytoplasm and the cilia tips. The zinc-finger domain of Gli that binds DNA in the nucleus is co-opted for binding the Kif7 coiled-coil out of the nucleus.

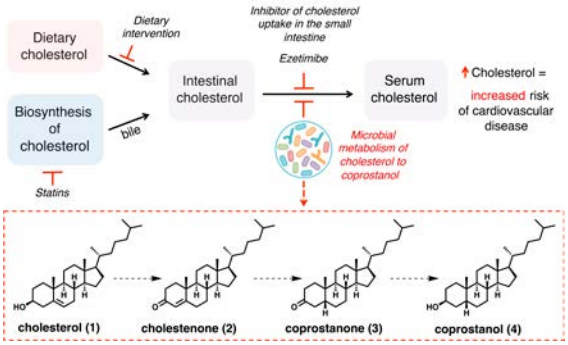
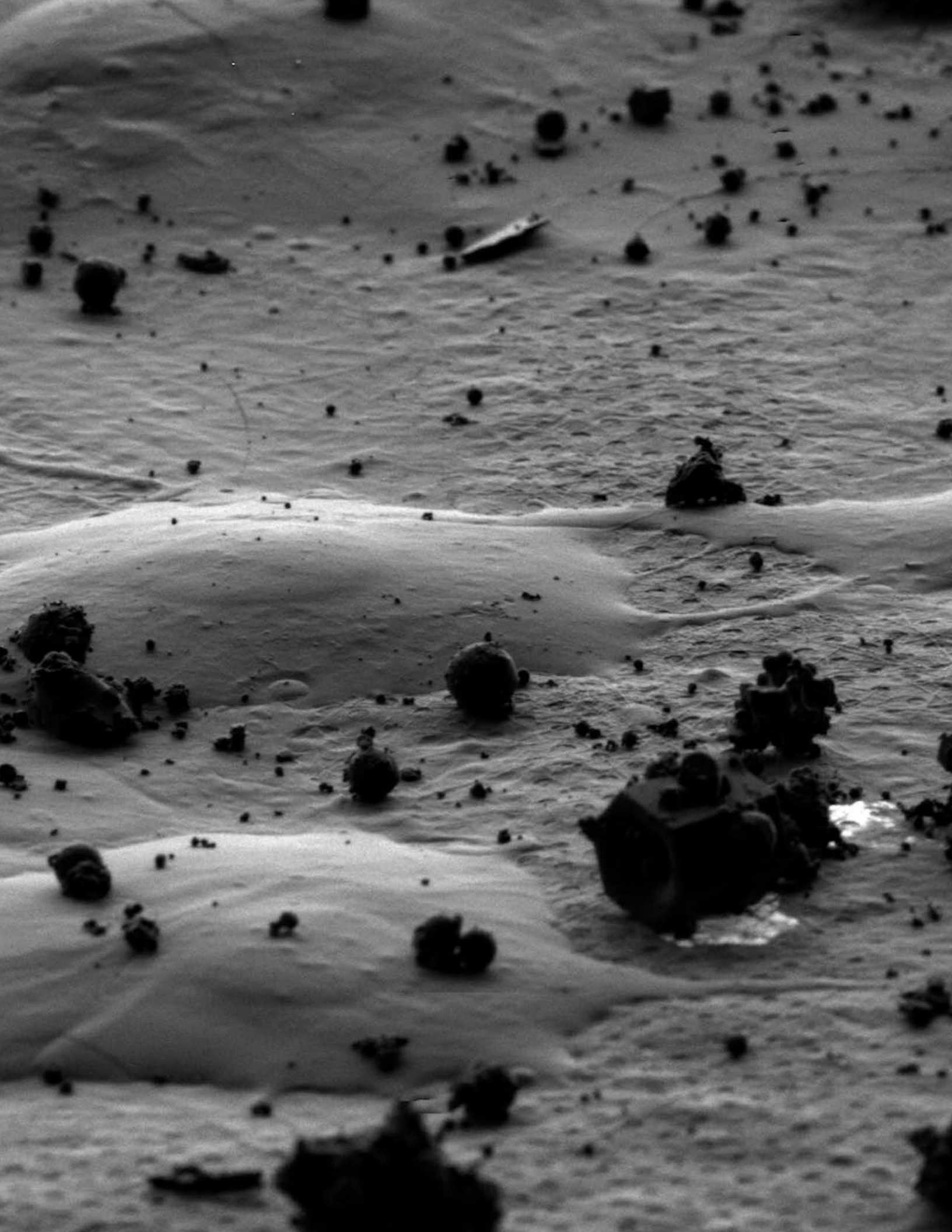


Figure 3. Ramnik Xavier's lab published a report showing that levels of serum cholesterol are important for human health and can be modulated by a variety of factors, including metabolism of cholesterol by the gut microbiota *(Kenny et al., Cell Host Microbe 2020, doi: 10.1016/j.chom.2020.05.013)*

switch and "turn off" Gli in cancer cells have tremendous therapeutic potential. In this study, they discovered that a peptide from Kif7, a conserved kinesin protein of the Hedgehog pathway, masquerades as DNA in the cytoplasm (figure 2). This mode of DNA mimicry can be used to trick the transcription factor to be tethered to cytoplasm and prevent its nuclear entry. This is the first example of DNA mimicry in the eukaryotic cytoplasm and provides a potential "off switch" that could be exploited to control the Hh pathway. The Subramanian lab hopes that this work will act as a starting point for treating aggressive cancers in novel ways.

Our department takes pride in the breadth of our work, including our translational research. In one recent example *(Kenny et al., Cell Host Microbe 2020, doi: 10.1016/j.chom.2020.05.013)*, the Xavier lab found that people who have cholesterol metabolizing bacteria in their intestines have lower cholesterol levels in their blood than those without the microbes (figure 3). The discovery suggests a possible reason why some people can consume more cholesterol in their diet with minimal effect on their blood cholesterol levels. It also hints that boosting populations of these bacteria, through diet, probiotics, or another kind of treatment, may one day be an effective way to help lower cholesterol levels.



Neurology

Department Report

MERIT E. 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 and to solve brain diseases. More specifically, the Department of Neurology research revenue continues to grow, securing over $142M in research funds annually. Our greatest asset in achieving our goals is our talented faculty. As an example, last year we were fortunate to recruit Craig Blackstone, MD, PhD, from a leadership position at the NIH. Dr. Blackstone, an expert in hereditary spastic paraplegias, is our new division Chief of Movement Disorders. Similarly, we promoted 16 gifted postdoctoral fellows to Instructors, and had 31 faculty promotions. Several of our world-renowned faculty members serve on NIH councils, are members of the National Academy, the National Alzheimer Prevention Act council, and editorial boards of the leading journals in Neuroscience. In addition, they are leaders of major disease consortiums (e.g. amyotrophic lateral sclerosis (ALS), Huntington's disease (HD), Parkinson's, adrenoleukodystrophy, Stroke, and Alzheimer's disease (AD)).

The department offers numerous resources to support our research faculty 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. We also offer a new lecture series to introduce alternative career paths to our postdoctoral fellows and junior faculty and to further forge and strengthen our relationship with our industry partners.

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. As an example, our department launched a new internship program, the MGH Youth Neurology Education and Research Program, in partnership with the Biogen Foundation, to provide research mentorship and career training for 31 underrepresented high school and undergraduate students in the Boston area. The students worked across 10 MGH neurology labs including those of faculty members underrepresented in neurology.

Departmental Strategic Research Priorities

1. Unite department around a common vision: leadership in therapeutic research to better understand/treat diseases
2. Build a cohesive partnership community, 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 work productively and creatively
6. Expand revenue streams through strategic pursuit of philanthropy and other funding sources

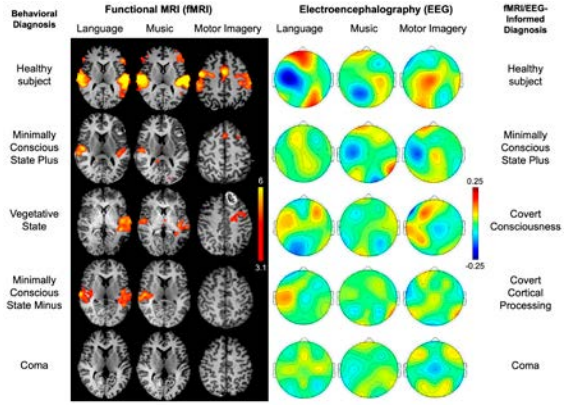
Achievements:

We are proud to share the Department of Neurology published more than 1,400 papers in FY20, with many in high profile journals! Of the 1,400 published, 387 were high impact papers with several NEJM articles and the strongest concentration in Neurology, JAMA Neurology, and Stroke.

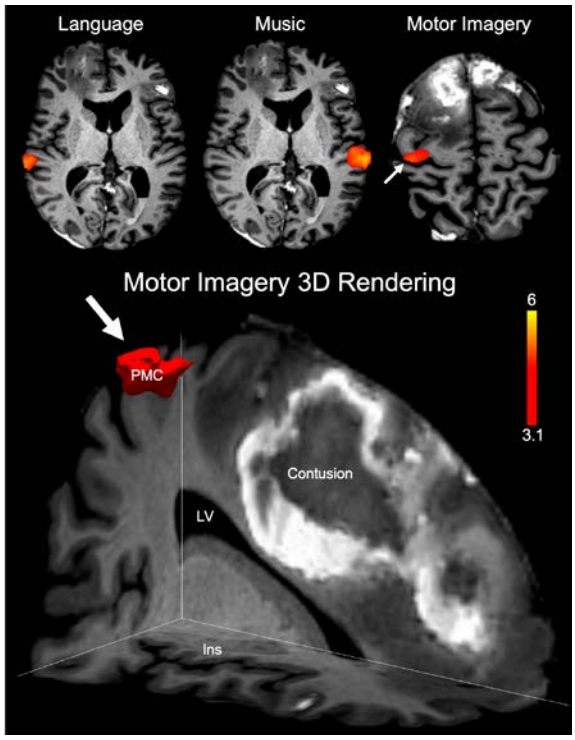
Breakthroughs in Research and Therapeutics

Tau molecular diversity contributes to clinical heterogeneity in Alzheimer's disease. Alzheimer's disease (AD) causes unrelenting, progressive cognitive impairments, but its course is heterogeneous, with a broad range of cognitive decline. The spread of tau aggregates (neurofibrillary tangles) across the cerebral cortex parallels symptom severity. We hypothesized the kinetics of tau spread may vary if the properties of propagating tau proteins vary across individuals. We found striking patient-to-patient heterogeneity in the hyperphosphorylated species of soluble, oligomeric, seed-competent tau. Tau seeding activity correlates with the aggressiveness of the clinical disease, and some post-translational modification sites appear to be associated with both enhanced seeding activity and worse clinical outcomes, whereas others are not. These data suggest that different individuals with 'typical' AD may have distinct biochemical features of tau. This data is consistent with the possibility that individuals with AD may have multiple molecular drivers, and emphasize the potential for personalized therapeutic approaches for slowing clinical progression of AD.

Dujardin S, Commins C, Lathuiliere A, Beerepoot P, Fernandes AR, Kamath TV, De Los Santos MB, Klickstein N, Corjuc DL, Corjuc BT, Dooley PM, Viode A, Oakley DH, Moore BD, Mullin K, Jean-Gilles D, Clark R, Atchison K, Moore R, Chibnik LB, Tanzi RE, Frosch MP, Serrano-Pozo A, Elwood F, Steen JA, Kennedy ME, Hyman BT. Tau molecular diversity contributes to clinical heterogeneity in Alzheimer's disease. Nat Med. 2020 Aug;26(8):1256-1263. doi: 10.1038/



A team of investigators in the MGH Department of Neurology is developing task-based functional MRI and EEG tools to detect covert signs of consciousness in patients who are unresponsive on bedside examination. By detecting covert consciousness in the intensive care unit, clinicians may be able to provide families with a more accurate prognosis that will inform time-sensitive, life-or-death decisions about goals of care.



These images are from a functional MRI scan performed in a 51-year-old man who was unresponsive eight days after experiencing a severe traumatic brain injury. Despite showing no signs of awareness on the bedside examination, his brain responded to language and music, and he showed evidence of volitional brain activity when asked to perform a motor imagery task, suggesting that he was covertly conscious.

s41591-020-0938-9. Epub 2020 Jun 22. PMID: 32572268; PMCID: PMC7603860.

Replay of Learned Neural Firing Sequences during Rest in Human Motor Cortex. The offline ‘‘replay’’ of neural firing patterns underlying waking experience is thought to be a mechanism for memory consolidation. Researchers tested for replay in the human brain by recording spiking activity from the motor cortex of two participants who had intracortical microelectrode arrays placed as part of a brain-computer interface pilot clinical trial. Participants took a nap before and after playing a neurally controlled sequence-copying game that consists of many repetitions of one ‘‘repeated’’ sequence sparsely interwoven with varying ‘‘control’’ sequences. Both participants performed repeated sequences more accurately than control sequences. We compare the firing rate patterns that caused the cursor movements to firing rate patterns throughout both rest periods. Correlations with repeated sequences increase more from pre- to post task rest than do correlations with control sequences, providing direct evidence of learning-related replay in the human brain.

Eichenlaub JB, Jarosiewicz B, Saab J, Franco B, Kelemen J, Halgren E, Hochberg LR, Cash SS. Replay of Learned Neural Firing Sequences during Rest in Human Motor Cortex. Cell Rep. 2020 05 05; 31(5):107581.

A structural variation reference for medical and population genetics. Structural variants (SVs) rearrange large segments of DNA and can have profound consequences in evolution and human disease. As national biobanks and clinical genetic testing have grown increasingly reliant on genome sequencing, population references such as the Genome Aggregation Database (gnomAD) have become integral in the interpretation of single-nucleotide variants (SNVs). However, there are no reference maps of SVs from high-coverage genome sequencing comparable to those for SNVs. We present a reference of sequence-resolved SVs constructed from 14,891 genomes across diverse global populations (54% non-European) in gnomAD. We discovered a rich and complex landscape of 433,371 SVs, from which we estimate that SVs are responsible for 25–29% of all rare protein-truncating events per genome. We found strong correlations between natural selection against damaging SNVs and rare SVs that disrupt or duplicate protein-coding sequence, which suggests that genes that are highly intolerant to loss-of-function are also sensitive to increased dosage. We also uncovered modest selection against noncoding SVs in cis-regulatory elements, although selection against protein-truncating SVs was stronger than all noncoding effects. Finally, we identified very large, rare SVs in 3.9% of samples, and estimate that 0.13% of individuals may carry an SV that meets the existing criteria for clinically important incidental findings. This SV resource is freely distributed via the gnomAD browser and will have broad utility in population genetics, disease-association studies, and diagnostic screening.

Collins RL, Brand H, Karczewski KJ, Zhao X, AlfÃldi J, Francioli LC, Khera AV, Lowther C, Gauthier LD, Wang H, Watts NA, Solomonson

M, O'Donnell-Luria A, Baumann A, Munshi R, Walker M, Whelan CW, Huang Y, Brookings T, Sharpe T, Stone MR, Valkanas E, Fu J, Tiao G, Laricchia KM, Ruano-Rubio V, Stevens C, Gupta N, Cusick C, Margolin L, Taylor KD, Lin HJ, Rich SS, Post WS, Chen YI, Rotter JI, Nusbaum C, Philippakis A, Lander E, Gabriel S, Neale BM, Kathiresan S, Daly MJ, Banks E, MacArthur DG, Talkowski ME. A structural variation reference for medical and population genetics. Nature. 2020 05; 581(7809):444-451.

Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis. Sodium phenylbutyrate and taurursodiol have been found to reduce neuronal death in experimental models. The efficacy and safety of a combination of the two compounds in persons with amyotrophic lateral sclerosis (ALS) are not known. In this multicenter, randomized, double-blind trial, we enrolled participants with definite ALS who had had an onset of symptoms within the previous 18 months. Participants were randomly assigned in a 2:1 ratio to receive sodium phenylbutyrate–taurursodiol (3 g of sodium phenylbutyrate and 1 g of taurursodiol, administered once a day for 3 weeks and then twice a day) or placebo. The primary outcome was the rate of decline in the total score on the Amyotrophic Lateral Sclerosis Functional Rating Scale–Revised (ALSFRS-R; range, 0 to 48, with higher scores indicating better function) through 24 weeks. Secondary outcomes were the rates of decline in isometric muscle strength, plasma phosphorylated axonal neurofilament H subunit levels, and the slow vital capacity; the time to death, tracheostomy, or permanent ventilation; and the time to death, tracheostomy, permanent ventilation, or hospitalization. Sodium phenylbutyrate–taurursodiol resulted in slower functional decline than placebo as measured by the ALSFRS-R score over a period of 24 weeks. Secondary outcomes were not significantly different between the two groups. Longer and larger trials are necessary to evaluate the efficacy and safety of sodium phenylbutyrate–taurursodiol in persons with ALS.

Paganoni S, Macklin EA, Hendrix S, Berry JD, Elliott MA, Maiser S, Karam C, Caress JB, Owegi MA, Quick A, Wymer J, Goutman SA, Heitzman D, Heiman-Patterson T, Jackson CE, Quinn C, Rothstein JD, Kasarskis EJ, Katz J, Jenkins L, Ladha S, Miller TM, Scelsa SN, Vu TH, Fournier CN, Glass JD, Johnson KM, Swenson A, Goyal NA, Pattee GL, Andres PL, Babu S, Chase M, Dagostino D, Dickson SP, Ellison N, Hall M, Hendrix K, Kittle G, McGovern M, Ostrow J, Pothier L, Randall R, Shefner JM, Sherman AV, Tustison E, Vigneswaran P, Walker J, Yu H, Chan J, Wittes J, Cohen J, Klee J, Leslie K, Tanzi RE, Gilbert W, Yeramian PD, Schoenfeld D, Cudkowicz ME. Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis. N Engl J Med. 2020 09 03; 383(10):919-930.

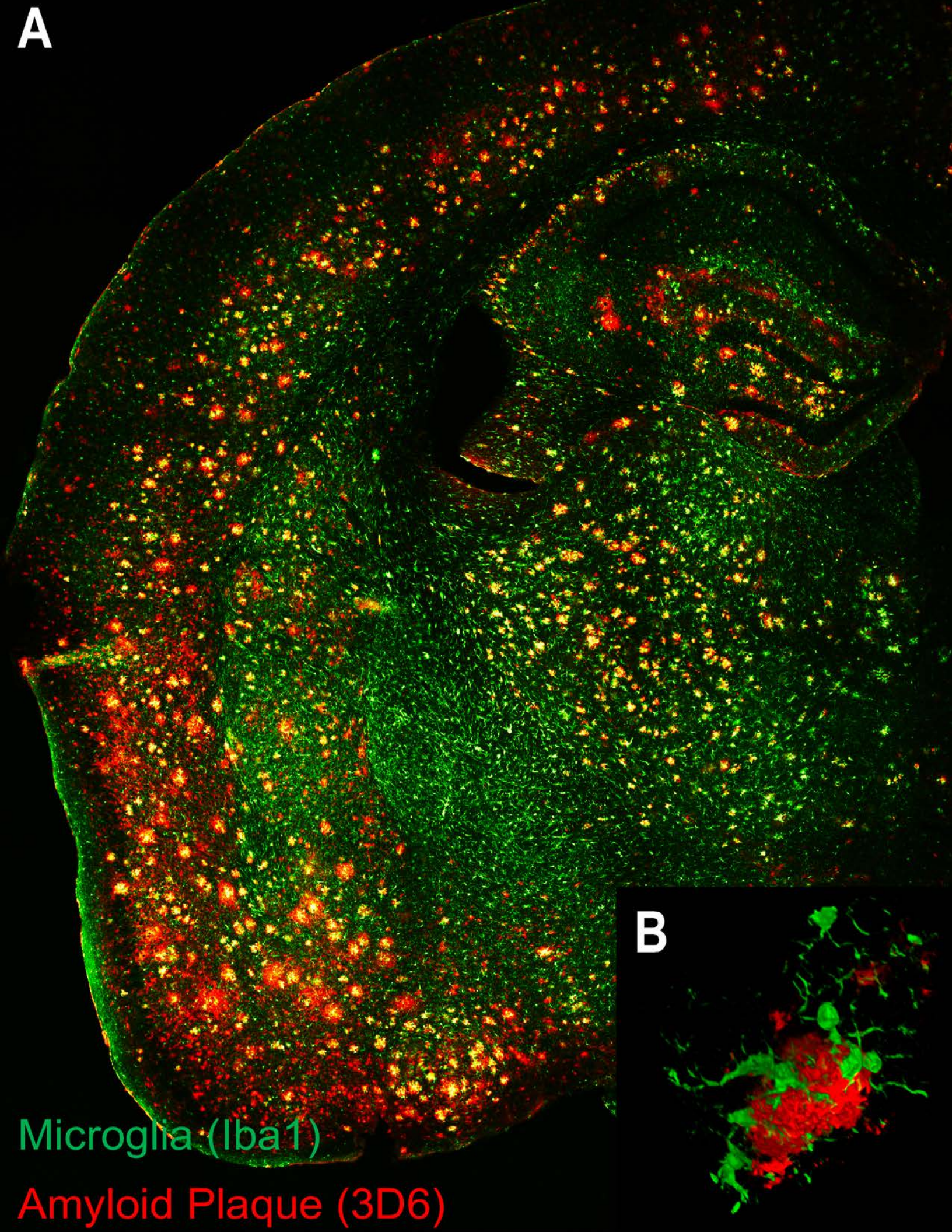
Aß-accelerated neurodegeneration caused by Alzheimer's-associated ACE variant R1279Q is rescued by angiotensin system inhibition in mice. The pathogenic mechanism by which *ACE* causes AD is unknown. Using whole-genome sequencing, we identified rare *ACE* coding variants in AD families and investigated one, ACE1 R1279Q, in knockin (KI) mice. ACE1 was increased in neurons, but not microglia or astrocytes, of KI brains, which became elevated further

with age. Angiotensin II (angII) and angII receptor AT1R signaling were also increased in KI brains. Autosomal dominant neurodegeneration and neuroinflammation occurred with aging in KI hippocampus, which were absent in the cortex and cerebellum. Female KI mice exhibited greater hippocampal electroencephalograph disruption and memory impairment compared to males. *ACE* variant effects were more pronounced in female KI mice, suggesting a mechanism for higher AD risk in women. Hippocampal neurodegeneration was completely rescued by treatment with brain-penetrant drugs that inhibit ACE1 and AT1R. Although *ACE* variant-induced neurodegeneration did not depend on ß-amyloid (Aß) pathology, amyloidosis in 5XFAD mice crossed to KI mice accelerated neurodegeneration and neuroinflammation, whereas Aß deposition was unchanged. KI mice had normal blood pressure and cerebrovascular functions. Our findings strongly suggest that increased ACE1/angII signaling causes aging-dependent, Aß-accelerated selective hippocampal neuron vulnerability and female susceptibility, hallmarks of AD that have hitherto been enigmatic. We conclude that repurposed brain-penetrant ACE inhibitors and AT1R blockers may protect against AD.

Cuddy LK, Prokopenko D, Cunningham EP, Brimberry R, Song P, Kirchner R, Chapman BA, Hofmann O, Hide W, Procissi D, Hanania T, Leiser SC, Tanzi RE, Vassar R. A?-accelerated neurodegeneration caused by Alzheimer's-associated ACE variant R1279Q is rescued by angiotensin system inhibition in mice. Sci Transl Med. 2020 Sep 30; 12(563).

Intact Brain Network Function in an Unresponsive Patient with COVID-19. Many patients with severe coronavirus disease 2019 (COVID-19) remain unresponsive after surviving critical illness. Although several structural brain abnormalities have been described, their impact on brain function and implications for prognosis are unknown. Functional neuroimaging, which has prognostic significance, has yet to be explored in this population. This article describes a patient with severe COVID-19 who, despite prolonged unresponsiveness and structural brain abnormalities, demonstrated intact functional network connectivity, and weeks later recovered the ability to follow commands. When prognosticating for survivors of severe COVID-19, clinicians should consider that brain networks may remain functionally intact despite structural injury and prolonged unresponsiveness.

Fischer, D., Threlkeld, Z.D., Bodien, Y.G., Kirsch, J.E., Huang, S.Y., Schaefer, P.W., Rapalino, O., Hochberg, L.R., Rosen, B.R. and Edlow, B.L. (2020), Intact Brain Network Function in an Unresponsive Patient with COVID-19. Ann Neurol, 88: 851-854. https://doi.org/10.1002/ana.25838


A
B
Microglia (Iba1)
Amyloid Plaque (3D6)

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:

Functional neurosurgery

Dr. Ziv Williams, Co-Director of Functional Neurosurgery, and Director of the Neuronal Communication and Restoration Laboratory, led an exciting study entitled *Single-neuronal predictions of others' beliefs in humans,* which examined recordings from single cells in the human dorsomedial prefrontal cortex, to identify neurons that reliably encode information about others' beliefs across richly varying scenarios and that distinguish self- from other-belief-related representations. Since human social behavior crucially depends on the ability to reason about others, the identification of these candidate neurons provides a foundation for theory of mind as a vital role in social cognition, enabling us not only to form a detailed understanding of the hidden thoughts and beliefs of other individuals but also to understand that they may differ from our own. This work was recently published in *Nature*.

In May of 2020, **Dr. Jeffrey Schweitzer,** Director of the Neurosurgery Stem Cell Therapeutics Laboratory, reported the implantation of patient-derived midbrain dopaminergic progenitor cells, differentiated *in vitro* from autologous induced pluripotent stem cells (iPSCs), in a patient with idiopathic Parkinson's disease. The patient-specific progenitor cells were implanted into the putamen (left hemisphere followed by right hemisphere, 6 months apart) of a patient with Parkinson's disease, without the need for immunosuppression. Clinical measures of symptoms of Parkinson's disease after surgery stabilized or improved at 18 to 24 months after implantation. This work was published in the *New England Journal of Medicine.*

Together, Drs. Williams and Schweitzer work with **Dr. Mark Richardson,** the Director of Functional Neurosurgery, to create one of the nation's most innovative centers for functional neurosurgery, with leading clinical programs in surgical based care for epilepsy, movement disorders, psychiatric, and pain conditions.

Tumor Neurosurgery

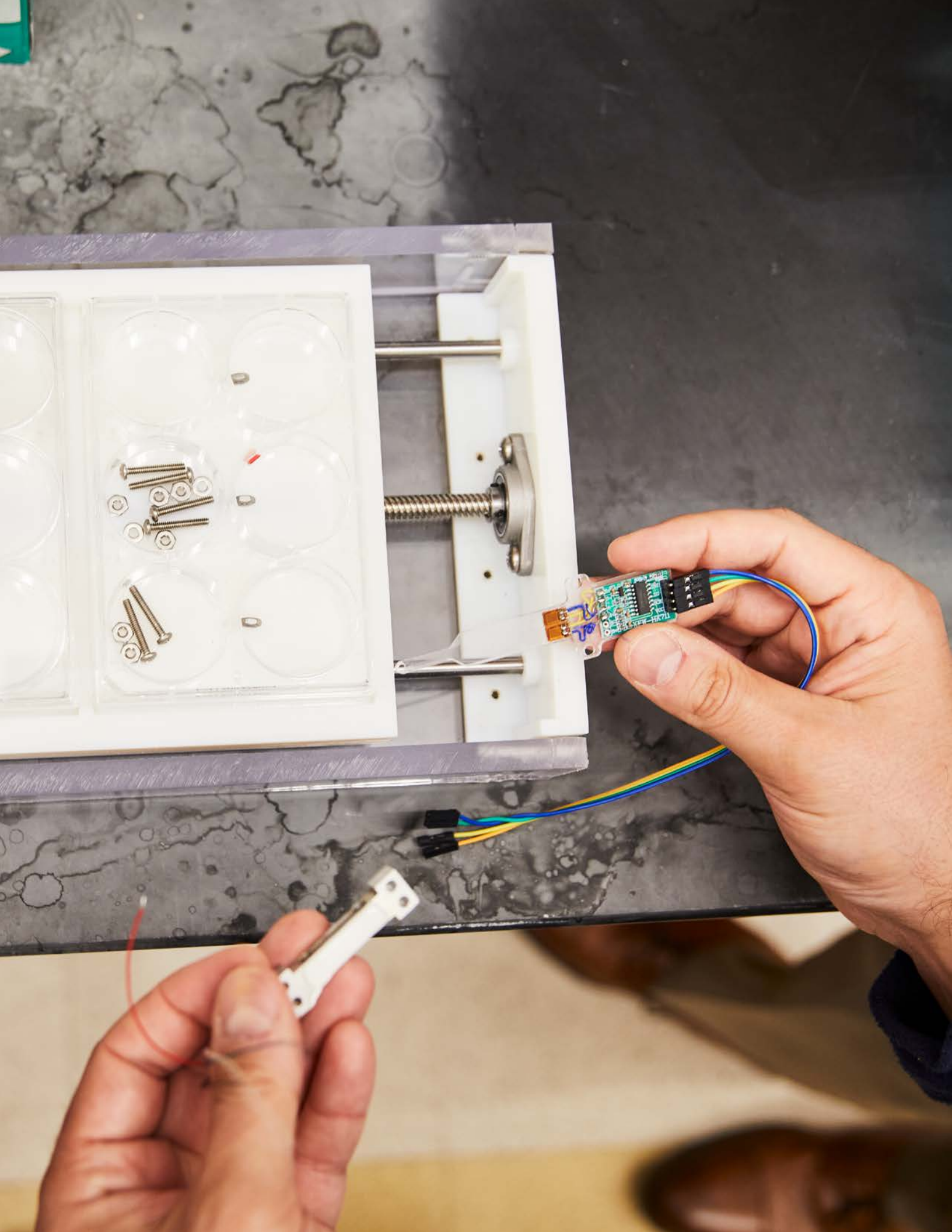
In the Brain Tumor Center, **Drs. Christine Lee, Hiroaki Wakimoto** and **Daniel Cahill,** collaborating with Dr. Julie Miller of Neuro-Oncology, have focused on the study of gliomas that have mutations in the isocitrate dehydrogenase (IDH) genes, which are the most common primary brain cancer in younger adults. The laboratory had previously reported in *Cancer Cell* that IDH-mutant cancer cells have low levels of nicotinamide adenine dinucleotide (NAD+), a ubiquitous metabolic molecule that's vital to cell survival. Subsequently, they showed that temozolomide treatment of IDH-mutant glioma can cause NAD+ to be critically depleted, resulting in a metabolically vulnerable state in these cancer cells. The consumption of NAD+ is driven by activation of poly(ADP-ribose) polymerases (PARPs), which catalyze the joining of monomeric NAD+ into polymeric poly(ADP-ribose) (PAR). PAR is a key molecular signal of DNA damage. PARylation is regulated by an enzyme called poly(ADP-ribose) glycohydrolase (PARG), which causes breakdown of PAR. The research team theorized that combination of temozolomide with a PARG inhibitor for IDH-mutant glioma would cause a simultaneous "two-hit" disruption of NAD+ metabolism. Using IDH-mutant glioma cell lines and an IDH-mutant xenograft mouse model, the team was the first to demonstrate that such PARG inhibition enhances the alkylating effectiveness of chemotherapy. As hypothesized, temozolomide treatment promoted PARP activation and consumption of NAD+, while PARG inactivation froze NAD+ as polymerized PAR by blocking subsequent breakdown. PARylation recruited the DNA repair machinery to the sites of chemotherapy-induced DNA damage. Thus, the combination therapy also limited the escape avenues available for the emergence of subclonal resistance mutations. These non-overlapping mechanisms, metabolic cytotoxicity and DNA damage, represent a novel strategy for improving the treatment of IDH-mutant glioma. This work was published in *Cancer Discovery* in November 2020.

Drs. Ganesh Shankar, Brian Nahed, William Curry, Pamela Jones, Daniel Cahill, Leonora Balaj and **Bob Carter** have pursued studies of liquid biopsy, which offers a minimally invasive tool to diagnose and monitor the heterogeneous molecular landscape of tumors over time and therapy. In *Clinical Cancer Research,* they recently reported the development of a novel digital droplet PCR (ddPCR) assay that incorporates features to improve sensitivity and allows for the simultaneous detection and longitudinal monitoring of two common TERT promoter mutations (C228T and C250T) in cfDNA from the plasma of patients with glioma. Importantly, upon longitudinal monitoring in 5 patients, they noted that peripheral TERT-mutant allele frequency reflects the clinical course of the disease, with levels decreasing after surgical intervention and therapy and increasing with tumor progression. These results demonstrate the feasibility of detecting circulating cfDNA TERT promoter mutations in patients with glioma with clinically relevant sensitivity and specificity.

Drs. Myron Rolle and **Brian Nahed** aimed to explore the current status of global neurosurgery education in residency programs across the United States. Global neurosurgery encompasses the social and surgical practices that effect the neurological health of vulnerable and underserved populations in domestic and international resource-limited settings. They surveyed ACGME-accredited residency programs in the U.S. on global neurosurgery education. While the majority of respondents offered funding for research and educational opportunities in global neurosurgery, programs tended to support global neurosurgery conferences, periodic dedicated lectures, and rotations in resource-constrained or marginalized communities domestically or abroad. Some programs offer continuity clinics in marginalized settings, supplementary reading material, core curricula or a designated residency track in global neurosurgery. Overall, the majority of programs had low levels of engagement in global neurosurgery, with only three residency programs categorized as having high levels of engagement. These investigators concluded that formal global neurosurgery training within US residencies is limited. With rising trends in neurosurgical disease burden globally, it may benefit residency programs to develop training paths to equip the next generation of neurosurgeons to address such needs. This work was published in *World Neurosurgery* in June of 2020.

Spine Neurosurgery

Complex spine surgery carries a high complication rate that can produce suboptimal outcomes for patients undergoing these extensive operations. However, multidisciplinary pathways introduced at multiple institutions have demonstrated a promising potential towards reducing the burden of complications in patients being treated for spinal deformities. **Drs. Gabriel Friedman, Vijay Yanamadala, John Shin,** and **Jean Valery Coumans** systematically collated and reviewed the multidisciplinary approaches in use at various institutions. Key aspects of multidisciplinary approaches to complex spine surgery included extensive pre-operative workup and interdisciplinary conferencing, intra-operative communication and monitoring, and post-operative floor management and discharge planning. These strategies produced decreases in surgical duration and complication rates, and provides a roadmap towards reducing the elevated complication rate for patients undergoing complex spine surgery. This work was published in the *Spine Journal* in April 2020.



Nursing

Department Report

Munn Grants: Principal investigator: Phoebe Wells, RN, for her study, “Do Non-Pharmacologic Interventions Decrease Stress in Antepartum/ Postpartum Patients or Special Care Nursery Mothers.” (Not pictured: mentor, Kim Francis, RN, and team member, Kelli Thomas, RN.)

Munn Grants: Principal investigator: Jeanne Dolan, RN (left), with mentor, Paul Arnstein, RN, and (not pictured) team members Aynsley Forsythe, RN, and Karen Szcesiul, RN, for their study, “Mindfulness-Based Intervention for PACU Nurses.”

GAURDIA BANISTER, RN, PHD

Overview:

The Yvonne L. Munn Center for Nursing Research continues to advance nursing research that is dedicated to improving patient and family care outcomes and fostering a work environment that promotes satisfaction, health and healing for staff, patients and families. Nurses with research-intensive doctoral preparation (e.g. PhD) are involved in the development of original research, mentor other nurses, and collaborate with other disciplines to generate interdisciplinary research initiatives. Nurses with a doctorate in practice (DNP) lead, mentor, develop, use and facilitate the translation of evidence into practice.

The Munn Center's **strategic goals for 2020 include** 1) Facilitating nurses’ participation in and development of nursing knowledge that aligns with the goals of MGH and Patient Care Services; 2) Fostering opportunities to enhance the unique contributions of nursing science; 3) Partnering with academic, clinical settings, and industry to improve the health and wellbeing of the communities we serve; 4) Expanding the impact of nursing science through the development of resources that improve patient care delivery; and 5) Strengthening nursing’s contribution to patient outcomes through the use of large data sets.

Over the past year, the work of nurse scientists was impacted by a global pandemic with ongoing investigations placed on hold and new inquiry focused on COVID-19 and its effect on professional practice and patient care experiences. During this time, Nurse Scientists working in Munn Center along with nurse scholars across the MGH and the MGB network continued to promote inquiry designed to understand the impact of COVID-19 on patients, families and care providers. This work generated knowledge, fostered innovative approaches to care, promoted new measures to evaluate professional practice and looked to uncover the patient and provider experience in the midst of a growing international pandemic.

Achievements:

Highlights from the work of the Munn Center can be clustered into four major areas including but not limited 1) Nursing research and response to the pandemic; 2) New funding opportunities; 3) research awards and recognition and 4) leadership and inquiry during challenging times.

Nursing research and the pandemic

During the height of the COVID-19 pandemic, a recurring feature was added to the *PCS COVID-19 Newsletter* by the Munn Center faulty. The publication presented the latest research articles, guidelines, standards and evidence for practice on the Munn Center website and accessible to staff caring for COVID-19 patients, their families and providers. In addition, Nurse Scientists in the Munn Center are involved in an investigation to explore data in an effort to better understand population responses to the COVID-19 pandemic.

In addition, Jen Cahill PhD, RN was the only nurse co-investigator to participate in research lead by John Iafrate MD of (MGH Pathology) to lead a series of community-based serology studies that sought to identify the prevalence of antibodies to COVID across Boston. These studies were the first to identify viral hotspots with residents who had been already exposed to the COVID-19 virus but were asymptomatic and provided data to public health departments nationally to improve responsiveness to the pandemic.

New Grant Funding Opportunities
Additional funding opportunities became available during 2020, to initiate or extended funding for nurses interested in advancing research and inquiry. They include:

1. **The Massachusetts General Hospital Nurses' Alumni Association (MGHNAA) Grant** is a new funding opportunity supported by the MGH School of Nursing Nurses Alumni Association that provides 2 years of funding ($3,000) to nurses enrolled in a Master of Science in Nursing or Doctor of Nursing Practice (DNP) Program developing projects to advance nursing science and improve outcomes for the nursing workforce, patients, or families.
2. **The Dorothy A. Jones Endowed Nursing Research Fund**, sponsored Frances and Stephen Foster, will be an annual grant award ($4-5K) designed to support PhD prepared nurse researchers at the MGH advancing a program of research that explores patient experience within a holistic approach to nursing assessment and clinical reasoning to uncover individual response to illness and nursing interventions that promote outcomes focusing on health and well-being.
3. **The Connell Nursing Research Scholars (CNRS)** program with additional funding from the Connell family provides research intensive experiences for PhD prepared nurses at the MGH. The CNRS spends two days each week, *over an 18 month period,* to build nursing science through the investigation of issues that influence the delivery of cost effective, safe, efficient, high quality patient/family-centric care as well as care redesign and health policy. Participation in the CNRS program is available to an *Early or Mid–Career Nurse Researchers* and offers each scholar the active mentoring needed to generate funding and disseminate knowledge to advance interdisciplinary health care for all.

2020 Munn Research Grants
2020 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 MGH staff 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.

(From left to right) Gregory Conklin, RN, Virginia Capasso, RN, Janet Gail Umphlett, RN, Franchesca Carducci, RN, Cyndi Bowes, RN, and Lisa Philpotts *won in the category of Evidence-Based Practice* for their poster, "Skin Care Guidelines: What is The Evidence Regarding Topical Agents on Skin during Radiation Delivery."

(Shown in photo) Esteban Franco Garcia, MD, Susan Maher, RN, (missing from photo) Carmen Zhou, MD, Marilyn Heng, MD, Maria Van Pelt, RN, Oluwaseun Akeju, MD, and Sadeq Quraishi, MD, *won in the category of Original Research* for their poster, "Nutritional Status is Associated with New-Onset Delirium in Elderly, Acute Care, Orthopedic Trauma Patients: A Single-Center Observational Study."

Nursing

Department Report

(Front row): Stephanie Qualls, RN, Michelle Crocker, RN, Karen Miguel, RN, Sean Wang, (back row): Colleen Snydeman, RN, Virginia Capasso, RN, Mary Ann Walsh, RN, (missing from photo): Mark Vangel, Zackery Chornnoby, RN, and John Murphy, RN, *won in the category of Advanced/Mid-Career Nurse Researcher* for their poster, "Pressure-Injury Development, Mitigation, and Outcomes in Patients Proned for ARDS due to COVID-19."

Kim Francis, RN, and Margaret Settle, RN, (pictured above) along with Elizabeth Farland, Sergei Roumiantsev, MD, and Paul Lerou, MD, (not pictured) *won in the category of Advanced/Mid-Career Nurse Researcher* for their poster, "Comparison of Salivary Biomarkers with Infant-Driven Feeding® (IDF) scores."

The 2020 recipients of the Munn Grants are:

1. Principal investigator: Eli Bobrowich, RN; mentor, Sara Looby, RN, and team member, Robert Goldstein, MD, for their study, "An Exploratory Study Evaluating Clinical, Psychosocial, and Environmental Care Needs of Gender Minorities at a Transgender Health Program."
2. Principal investigator: Phoebe Wells, RN, for her study, "Do Non-Pharmacologic Interventions Decrease Stress in Antepartum/Postpartum Patients or Special Care Nursery Mothers." (Not pictured: mentor, Kim Francis, RN, and team member, Kelli Thomas, RN.)
3. Principal investigator: Jeanne Dolan, RN (left), with mentor, Paul Arnstein, RN, and (Not pictured team members Aynsley Forsythe, RN, and Karen Szcesiul, RN,) for their study, "Mindfulness-Based Intervention for PACU Nurses."

2020 Poster Awards–selected by a team of interdisciplinary judges out of 58 posters accepted for presentation. These were disseminated virtually during Nursing Research Day and beyond are as follows:

1. Janet Umphlett RN; Cyndi Bowes, NP; Virginia Capasso, NP; Franchesca Carducci, RN; Gregory Conklin, RN; and Lisa Philpotts RN, *won in the category of Evidence-Based Practice* for their poster, "Skin Care Guidelines: What is The Evidence Regarding Topical Agents on Skin during Radiation Delivery."
2. Susan Maher, RN; Esteban Franco Garcia, MD; Carmen Zhou, MD; Marilyn Heng, MD; Maria Van Pelt, RN; Oluwaseun Akeju, MD; and Sadeq Quraishi, MD, *won in the category of Original Research* for their poster, "Nutritional Status is Associated with New-Onset Delirium in Elderly, Acute Care, Orthopedic Trauma Patients: A Single-Center Observational Study.
3. Virginia Capasso, NP; Colleen Snydeman, RN; Karen Miguel, RN; Michelle Crocker, RN; Zachary Chornoby, RN; Mark Vangel; Mary Ann Walsh, RN; John Murphy, NP; Stephanie Qualls, RN; and Xianghong Wang *won in the category of Advanced/Mid-Career Nurse Researcher* for their poster, "Pressure-Injury Development, Mitigation, and Outcomes in Patients Proned for ARDS due to COVID-19."
4. Margaret Settle, RN; Kim Francis, RN; Elizabeth Farland; Sergei Roumiantsev, MD; and Paul Lerou, MD, *won in the category of Advanced/Mid-Career Nurse Researcher* for their poster, "Comparison of Salivary Biomarkers with Infant-Driven Feeding® (IDF) scores."
5. Jennifer Duran, RN, *won in the category of Quality Improvement* for her poster, "Nurse-Driven Implementation of Bubble CPAP in a Ugandan Nursery."

6. Chris Curtis, RN, *won in the category of Emerging Researcher* for the poster, "Implementation of a Standardized Electronic Hand Off Tool for Advanced Practice Provider Patient Transfer."

Leadership and inquiry during challenging times–During 2020 Nurse Scientists in the Munn Center provided leadership by promoting the translation of research evidence into practice, mentoring nurses in advancing research and inquiry, promoting partnerships and disseminating research through international, virtual presentations and publications in impact journals to promote the delivery of safe, effective, high quality care to patients and families at the MGH. 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 MGH Nursing.

Through mentoring of research experiences along with participation in international seminars the Munn Center offers nurses research opportunities to advance knowledge and improve patient care. Partnerships with interdisciplinary research teams, hosting nursing grand rounds and outreach to nurse researchers in other sites (e.g. Wentworth-Douglass Hospital) promote collaboration and increase shared opportunities for advancing nursing science. In addition, many scholars have disseminated their research findings in international impact journals. Examples include:

Flanagan, J., Read, C. Y. & Shindul-Rothschild, J. (2020). Factors associated with the rate of sepsis post-surgery. Critical Care Nurse. 40 (5): e1–e9.

Leets, L. L., Cahill, J., Sprenger, A. M., Thomas, J. S., Hartman, R., Reed, M. E. P., & Klaus, S. (2020). Nudging discharge readiness with a poster: A sequential, exploratory mixed methods pilot study of patient caregivers. Journal of Patient Experience, 2374373520968976.

Paige, E., Flanagan, J. & Matthew, P. (2020). The last day narratives: an exploration of the end of life for patients with cancer from a caregivers' perspective. Journal of Palliative Care Medicine, 23(9), 1172–1176. https://doi.org/10.1089/jpm.2019.0648

JH, Sherman JB, Stanley TL, Corey KE, Fitch KV, Looby SE, Robinson JA, Lu MT, Burdo TH, Lo J. Sim JH, et al. Pro-inflammatory Interleukin-18 is associated with Hepatic Steatosis and Elevated Liver Enzymes in people with HIV Monoinfection. AIDS Res Hum Retroviruses. 2020 Dec 15. doi: 10.1089/AID.2020.0177. Online ahead of print. AIDS Res Hum Retroviruses. 2020. PMID: 33323025

Jennifer Duran, RN, *won in the category of Quality Improvement* for her poster, "Nurse-Driven Implementation of Bubble CPAP in a Ugandan Nursery."

Chris Curtis, RN, and Laura Andrews, RN, (not pictured) *won in the category of Emerging Researcher* for the poster, "Implementation of a Standardized Electronic Hand Off Tool for Advanced Practice Provider Patient Transfer."

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 from the perspectives of 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.

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.

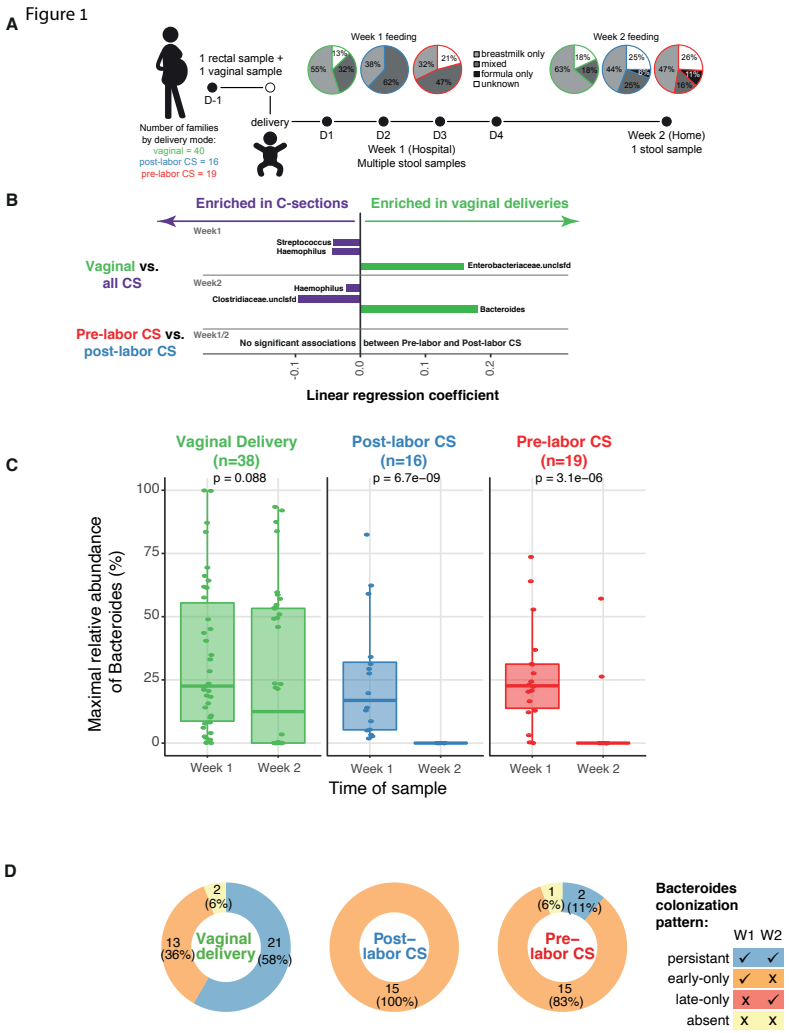
Achievements:

1. *Mitchell CM, Mazzoni C, Hogstrom L, Bryant A, Bergerat A, Cher A, Pochan S, Herman P, Carrigan M, Sharp K, Huttenhower C, Lander ES, Vlamakis H, Xavier RJ, Yassour M. Delivery mode impacts stability of early infant gut microbiota. Cell Reports Medicine 2020 December 22;1(9):100156. PMID 33377127*

Abstract
Mode of delivery strongly influences the early infant gut microbiome. Children born by Cesarean section (C-section) lack *Bacteroides* species until 6-18 months of age. One hypothesis is that these differences stem from lack of exposure to the maternal vaginal microbiome. Here, we re-evaluate this hypothesis by comparing microbial profiles of 75 infants born vaginally or by planned versus emergent C-section. Multiple children born by C-section have high abundance of *Bacteroides* in their first few days of life, but at two weeks, both C-section groups lack *Bacteroides* (primarily according to 16S-sequencing), despite their difference in exposure to the birth canal. All C-section delivered infants were exposed to pre-operative antibiotics, but vaginally delivered infants exposed to antibiotics for Group B streptococcus prophylaxis demonstrated similar *Bacteroides* colonization as vaginally delivered infants not exposed to antibiotics. All analyses were controlled for breastmilk vs. formula feeding. Finally, comparison of microbial strain profiles between infants and maternal vaginal or rectal samples finds evidence for mother-to-child transmission of rectal rather than vaginal strains. These results suggest differences in colonization stability as an important factor in infant gut microbiome composition rather than birth canal exposure. Additionally, these results suggest that "vaginal seeding," or smearing vaginal fluid on infants born via C-section, is unlikely to be a successful strategy for preventing the changes in infant microbiota seen after C-section.

2. *Edlow AG, Li JZ, Collier AY, Atyeo C, James KE, Boatin AA, Gray KJ, Bordt EA, Shook LL, Yonker LM, Fasano A, Diouf K, Croul N, Devane S, Yockey LJ, Lima R, Shui J, Matute JD, Lerou PH, Akinwunmi BO, Schmidt A, Feldman J, Hauser BM, Caradonna TM, De la Flor D, D'Avino P, Regan J, Corry H, CoxenK, Fajnzylber J, Pepin D, Seaman MS, Barouch DH, Walker BD, Yu XG, Kaimal AJ, Roberts DJ, Alter G. Assessment of Maternal and Neonatal SARS-CoV-2 Viral Load, Transplacental Antibody Transfer, and Placental Pathology in Pregnancies During the COVID-19 Pandemic. JAMA Netw Open. 2020 Dec 1;3(12):e2030455. doi: 10.1001/jamanetworkopen.2020.30455. PMID: 33351086; PMCID: PMC7756241*

Figure 1



Cohort description and key differential taxa across delivery modes. (A) Cohort information about delivery mode, feeding practices and sampling. Women presenting to Labor and Delivery at term (≥ 37 weeks) with singleton gestation were enrolled, and had a rectal and vaginal sample collected prior to delivery. A stool sample was collected from the infants' diaper daily while in hospital, and parents sent a single stool sample from home at 2 weeks of life. Feeding practices were abstracted from inpatient charts for week 1 and obtained from parent questionnaires for week 2. **(B) Impact of delivery mode on early life microbial composition.** Multivariate linear regression was used to identify taxa that were enriched in vaginally delivered vs. C-section delivered infants and pre- vs. post-labor C-section (using the results of 16S rRNA sequencing). Analyses were adjusted for feeding practices in the week of interest. A positive coefficient represents a taxon more abundant in vaginally delivered infants. Only associations with absolute coefficients ≥ 0.015 are included here. **(C) Loss of *Bacteroides* colonization in C-section delivered infants.** Maximal abundance of *Bacteroides* in week 1 (i.e. the sample with the highest relative abundance) vs. week 2 samples by 16S sequencing was compared within delivery mode using t-test. **(D) Differences in patterns of *Bacteroides* colonization by delivery mode.** The *Bacteroides* colonization phenotype was assigned based on detection at ≥ 0.1% in week 1 samples only *(early-only),* both week 1 and week 2 *(persistent),* or neither *(absent)*. Results are presented for the 67 infants with samples available from both time points.

Abstract

Importance: Biological data are lacking with respect to risk of vertical transmission and mechanisms of feto-placental protection in maternal SARS-CoV-2 infection.

Objective: To quantify SARS-CoV-2 viral load in maternal/neonatal biofluids, transplacental passage of anti-SARS-CoV-2 antibody, and incidence of feto-placental infection.

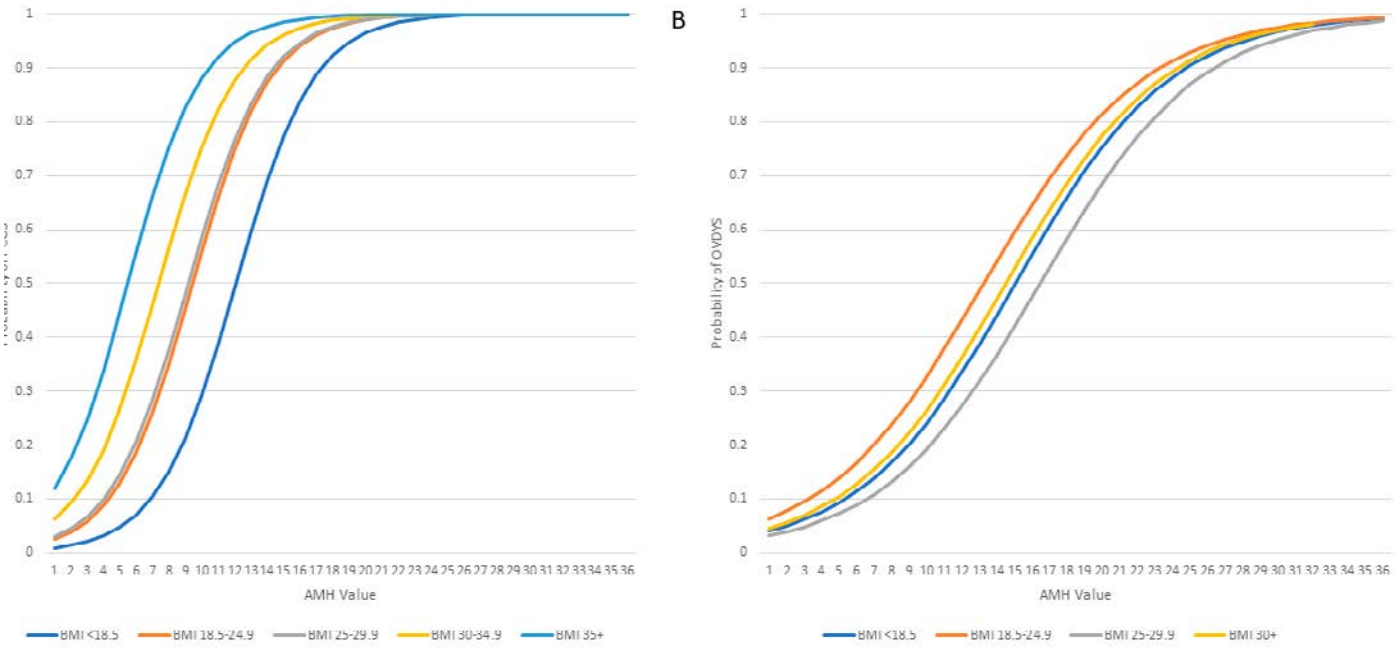
Design: Pregnant women with confirmed SARS-CoV-2 infection and contemporaneous uninfected participants, were enrolled in a prospective cohort study. Follow-up occurred through July 10, 2020.

Setting: Three tertiary care centers in Boston, Massachusetts.

Participants: Pregnant women positive for SARS-CoV-2 presenting for hospital care between April 2, 2020 and June 13, 2020. Unexposed participants were enrolled as a convenience sample from women negative for SARS-CoV-2.

Exposure: SARS-CoV-2 infection in pregnancy defined by nasopharyngeal swab RT-PCR.

Main Outcomes: SARS-CoV-2 viral load in maternal plasma/respiratory fluids and umbilical cord plasma; quantification of anti-SARS-CoV-2 antibodies in maternal and cord plasma; presence of SARS-CoV-2 RNA in the placenta.



Body mass index (BMI) strata-specific estimates of predicted diagnoses as generated by postestimation from series of multivariate logistic regression models. (A) Probability of polycystic ovary syndrome (PCOS) diagnosis versus other causes of infertility for various antimüllerian hormone (AMH) values, after controlling for age. (B) Probability of ovulatory dysfunction disorders (OVDYS) versus other causes of infertility for various AMH values, after controlling for age (DOI: 10.1016/j.fertnstert.2020.07.023)

Results: Among 127 pregnant participants, 64 SARS-CoV-2 positive (mean age 31.6 (SD, 5.6) years) and 63 SARS-CoV-2 negative (33.9 (5.4) years) provided samples for analysis. Of women with SARS-CoV-2, 36% (N=23) were asymptomatic, 34% (N=22) had mild disease, 11% moderate (N=7), 16% severe (N=10), 3% critical (N=2). In viral load analyses (N=107), there was no detectable viremia in maternal or cord blood and no evidence of vertical transmission. 1/77 neonates had detectable IgM to N-antigen in cord blood. SARS-CoV-2 RNA was not detected in any placentas (N=88). In antibody analyses (N=77), anti-RBD IgG was detected in 65% (24/37) of pregnant women with SARS-CoV-2, anti-N in 70% (26/37). Mother-to-neonate transfer of anti-SARS-CoV-2 antibodies was significantly lower than transfer of anti-influenza (HA) antibodies (mean±SD cord-to-maternal ratio for anti-RBD IgG 0.72±0.57, anti-N 0.74±0.44, versus anti-HA transfer ratio 1.44±0.80, p<0.001). Non-overlapping placental expression of SARS-CoV-2 receptors ACE2 and TMPRSS2 was noted.

Conclusions and Relevance: In this cohort study, there was no evidence of placental infection or definitive vertical transmission of SARS-CoV-2. Transplacental transfer of anti-SARS-CoV-2 antibodies was inefficient. Lack of viremia and reduced co-expression of placental ACE2 and TMPRSS2 may serve as protective mechanisms against vertical transmission.

3. *Vagios S, James KE, Sacha CR, Hsu JY, Dimitriadis I, Bormann CL, Souter I. A patient-specific model combining antimüllerian hormone and body mass index as a predictor of polycystic ovary syndrome and other oligo-anovulation disorders. Fertil Steril. 2021 Jan;115(1):229-237. doi: 10.1016/j.fertnstert.2020.07.023. Epub 2020 Oct 16. PMID: 33077236.*

Abstract

Objective: To determine whether a patient-specific predictive model combining antimüllerian hormone (AMH) levels and body mass index (BMI) can aid in the diagnosis of polycystic ovary syndrome (PCOS) and other ovulatory dysfunction disorders (OVDYS) among infertile women.

Design: Retrospective cohort study.

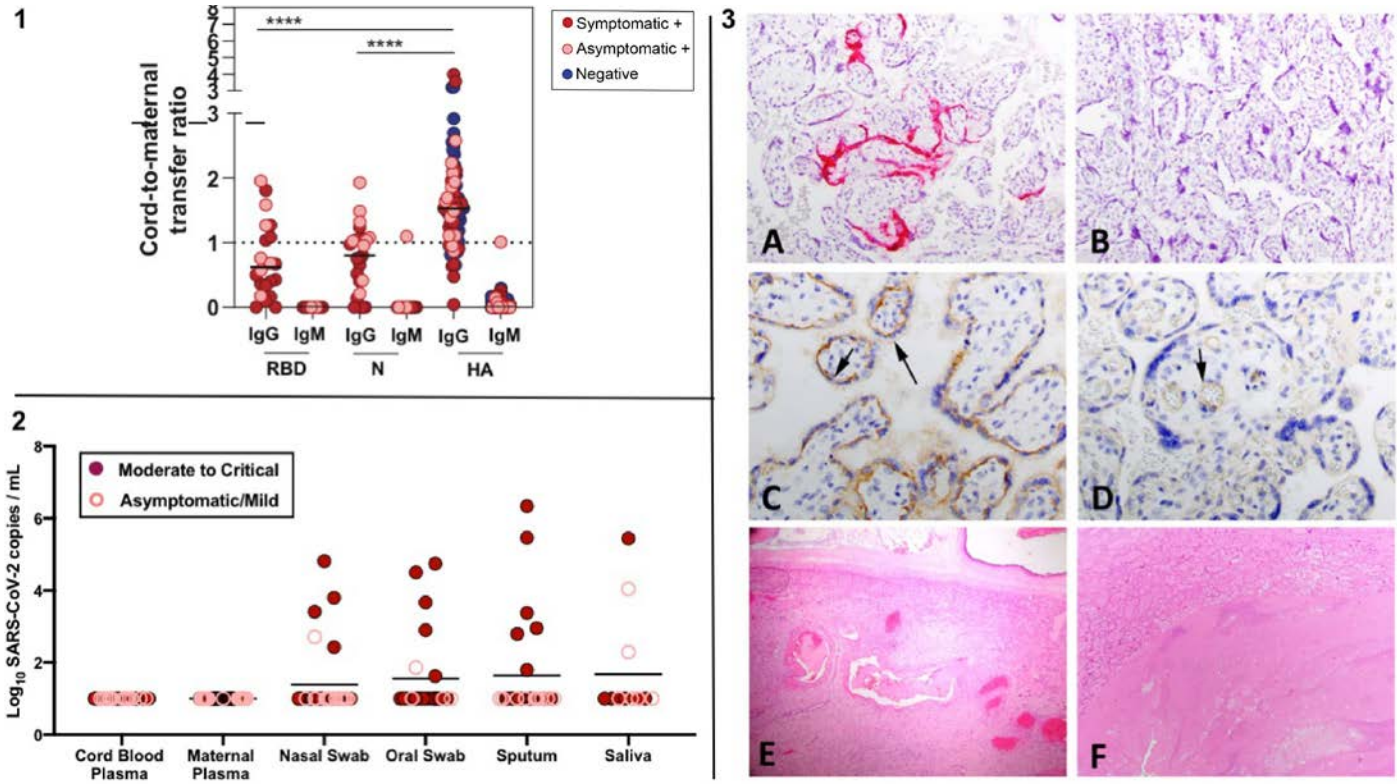
Setting: Academic fertility center.

Patient(s): One thousand and ten infertile women undergoing 3,160 intrauterine insemination (IUI) cycles, stratified by diagnosis in three groups: PCOS, OVDYS, and other etiologies.

Intervention(s): Ovulation induction followed by IUI or ultrasound-monitored natural cycles.

Main outcome measure(s): The probability of either PCOS or OVDYS diagnosis based on AMH levels alone and a patient-specific predictive model that combines serum AMH and patient's BMI.

Result(s): Median and interquartile range (IQR) for the serum AMH levels (ng/mL) were the highest in women with PCOS, and lowest in those with other infertility causes. Overall, for every 1 ng/mL increase in AMH, the odds of PCOS and OVDYS versus other causes

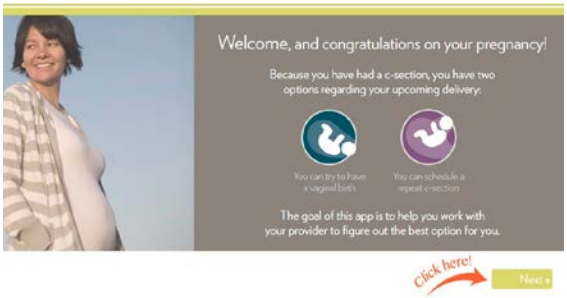


Maternal SARS-CoV-2 Infection is Associated with Reduced Transplacental Antibody Transfer, and Absence of Maternal Viremia or Placental Infection

1. Cord-to-Maternal Transplacental Antibody Transfer Ratios for Influenza and SARS-CoV-2: The blue, light red and dark red dots depict the cord-to-maternal transfer ratio, calculated as (OD450-570 cord)/(OD450-570 maternal) for antibodies against influenza (hemagglutinin or HA) and SARS-CoV-2 RBD and N. Significance was assessed with a one-way ANOVA followed by Tukey's post hoc testing to determine the source of significant differences in antibody transfer ratios between HA, RBD and N. ****p<0.0001

2. SARS-CoV-2 viral load in maternal and neonatal biofluids and tissues by maternal disease severity: The dot plot shows viral loads across samples by RTqPCR. No significant differences in viral load between any respiratory fluid were detected by Wilcoxon signed rank test. Respiratory fluids contained detectable virus, but there was no detectable virus in maternal blood or cord blood.

3. Placental findings in maternal SARS-CoV-2 infection: (A and B): RNAish (*in situ* hybridization) results: (A): Control positive placenta at 20x original. Magneta red signal is visualized in the syncytiotrophoblast. (B) Representative placenta from a mother with SARS-CoV-2, no detectable SARS-CoV-2 virus in any placental tissue at 20x original. **(C and D):** SARS-CoV-2 receptor expression by immunohistochemistry. (C) ACE2 at 40x original. Expression is restricted to the villous trophoblast with a polarity such that the highest expression is stromal side of the syncytiotrophoblast (short arrow) with minimal to absent expression in the maternal vascular side (long arrow). (D) TMPRSS2 at 40x original. Weak expression limited to the villous endothelial cells (arrow). Resident placental macrophages (Hofbauer cells) expressed neither ACE2 nor TMPRSS2. **(E and F):** Maternal vascular malperfusion (MVM) pathology. (E) Decidual arteriopathy. H&E 4x original. (F) Infarction hematoma. H&E 10x original.



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increased by 55% and 24%, respectively. Postestimation from multivariate logistic regression models showed that PCOS diagnosis can be predicted with lower AMH values in women with a higher BMI compared with the AMH values predicting PCOS in normal-weight or underweight patients. The receiver operating characteristic curves reinforced these findings, and the best cutoffs for PCOS diagnosis were 7.5, 4.4, and 4.1 ng/mL for women belonging to the BMI groups 18.5-24.9, 25.0-29.9, and ≥30.0 kg/m2, respectively.

Conclusion(s): Taking into account AMH and BMI, we developed a model that predicts the probability of an oligo-anovulation diagnosis, thus facilitating patient-specific counseling in the infertility setting.

4. *Kuppermann M*, Kaimal AJ*, Blat C, Gonzalez J, Thiet MP, Bermingham Y, Altshuler AL, Bryant AS, Bacchetti P, Grobman WA. Effect of a Patient-Centered Decision Support Tool on Rates of Trial of Labor After Previous Cesarean Delivery: The PROCEED Randomized Clinical Trial. JAMA. 2020 Jun 2;323(21):2151-2159. doi: 10.1001/jama.2020.5952. PMID: 32484533; PMCID: PMC7267848.*

Summary: Reducing cesarean delivery rates in the US is an important public health goal; despite evidence of the safety of vaginal birth after cesarean, most women have scheduled repeat cesareans. This randomized trial tested the hypothesis that women eligible for trial of labor after cesarean would be more likely to opt for this delivery approach, have a vaginal delivery, and experience better decision quality if they had the opportunity to use a decision support tool that offered consistent and reliable information regarding the processes and potential outcomes of trial of labor after cesarean and elective repeat cesarean delivery, included explicit consideration of their values and preferences, and provided a personalized assessment of their likelihood of having a vaginal birth if they underwent trial of labor.

1485 English- or Spanish-speaking women with one prior cesarean and no contraindication to trial of labor were enrolled between January 2016 and January 2019; follow up was completed in June 2019. Participants were randomized to use a tablet-based decision support tool prior to 25 weeks' gestation or to receive usual care (without the tool). Among 1485 patients (mean [SD] age 34.0 [4.5] years), 1470 (99.0%) completed the trial (n=735 in both randomization groups) and were included in the analysis.Trial of labor rates did not differ significantly between intervention and control groups (43.3% versus 46.2%; adjusted absolute risk difference (aARD), -2.78%, 95% CI, -7.80 to 2.25; adjusted relative risk (aRR), 0.94, 95% CI 0.84 to 1.05). There were no statistically significant differences in vaginal birth rates or any of the decision quality measures. Overall, study participants experienced relatively high trial of labor and vaginal birth rates and good decision quality regardless of exposure to the decision tool. Given this, further increasing the trial of labor rate in the study population may not be appropriate or desirable, as it may already reflect the true informed preference-based demand for this delivery.

*Kuppermann and Kaimal contributed equally to the creation of this manuscript.

Ophthalmology

Department Report

JOAN W. MILLER, MD, FARVO, CHIEF

Overview:

The research mission of the Mass Eye and Ear/MGH Department of Ophthalmology is focused on eliminating blinding diseases and disorders of the eye and visual system. Tackling blinding diseases using a multifaceted, multidisciplinary approach has been the mainstay of the Department's past success in translational medicine. This approach has led to groundbreaking advancements such as proton beam irradiation 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. 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 10 (LCA10).

Today, scientific collaboration and information—leveraged from modern genetics and genomics—are accelerating our understanding of blinding diseases and revealing new targets for therapy. Capitalizing on this momentum, the department's research strategy focuses on areas of greatest unmet medical need, including retinal degenerations, macular degeneration, and diabetic eye disease, as well as optic neuropathies, particularly glaucoma. Programs in other areas—cornea and ocular surface, oncology, immunology, infectious disease, and vision rehabilitation—are also an important focus.

Going forward, we are pursuing a range of promising research areas, including artificial intelligence, big data, genetics and gene-based therapy, imaging, and other diagnostic technologies. We are confident that treatment breakthroughs and cures are imminent for many blinding diseases.

Highlighted accomplishments for the Department of Ophthalmology in 2021 are grouped thematically below:

Achievements:

Response to COVID-19

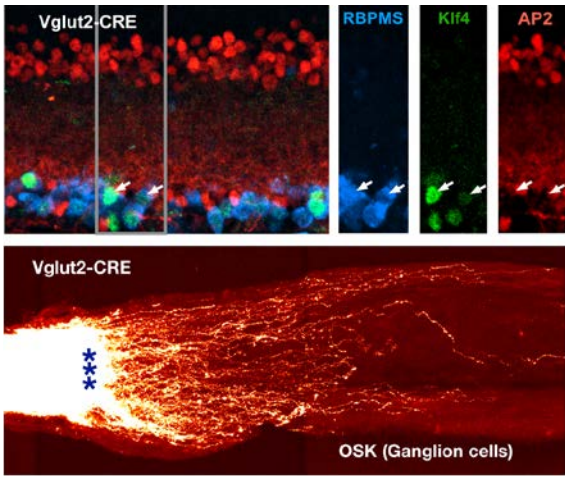
In response to the COVID-19 pandemic, researchers and clinician scientists from the Mass Eye and Ear/MGH Department of Ophthalmology quickly adapted to lead many innovative and collaborative initiatives. While onsite research activities were immediately limited to essential activities, faculty and staff continued to analyze data, submit grant applications, author manuscripts, and conduct virtual clinical research visits.

On March 23, 2020, Governor Charlie Baker ordered the closure of nonessential businesses and issued a stay-at-home advisory on March 24. With this, all elective and non-urgent cases were

temporarily postponed. A study led by **John B. Miller, MD, Alice C. Lorch, MD, MPH, Matthew F. Gardiner, MD,** and **Grayson W. Armstrong, MD, MPH,** investigated the impact of the COVID-19 pandemic on ophthalmic care at the Mass Eye and Ear Emergency Department (ED), a 24-hour ophthalmology-specific ED, during the first COVID-19 surge in Massachusetts. Results showed a decrease in the median number of daily visits to the ED (18 fewer visits per day), accounting for a 32% decrease in the total volume of ED visits in 2020 compared to a similar time frame in prior years *(Moon, Miller, et al., Clinical Ophthalmology. 2020 14:4155-4163).* Additionally, there was a 9% increase in the proportion of primary diagnoses considered urgent, with the proportion of visits requiring urgent surgery increased by 39%. The findings from this study suggest that patients were likely more reluctant to seek eye care during the COVID-19 pandemic, choosing to defer less urgent evaluation.

With the cancellation and/or postponement of elective and non-urgent cases, the Department of Ophthalmology implemented virtual and hybrid visits, combining remote imaging with video conferencing. These telehealth approaches allow for shorter in-person interactions and enable clinicians to meet patient care needs while following social distancing protocols. A review by **Deep Parikh, MD, Grayson W. Armstrong, MD, MPH, Victor Liou, MD,** and **Deeba Husain, MD,** provided a comprehensive overview of telemedicine in ophthalmology. While there are still barriers to implementation, such as cost of equipment and physicians' lack of confidence in their ability to assess from a distance, ongoing advances may lead to improved detection and earlier treatment, resulting in better care and improved visual outcomes. *(Parikh, et al., Seminars in Ophthalmology. 2020 35(4):210-215).*

And, while most on-site research ramped down during this time, COVID-19 related research projects accelerated quickly. Multiple investigators in the Department of Ophthalmology broadened their research focus to include COVID-related research efforts into potential therapeutics, and are pursing COVID-treatment strategies in addition to vaccine development. The laboratory of **Luk Vandenberghe, PhD,** (Mass Eye and Ear) is working to develop a novel gene-based vaccine candidate against SARS-CoV-2, the virus that causes COVID-19. The vaccine uses an adeno-associated viral (AAV) vector, a clinically established gene transfer technology leveraging the properties of a harmless viral carrier, to deliver genetic sequences of the SARS-CoV-2 spike antigen to initiate an immune response to COVID-19. **Mason Freeman, MD,** (MGH) a key collaborator on this project, is leading the efforts to develop the clinical studies necessary to establish safety and efficacy of the experimental vaccine. The program brings together an academia-industry consortium from groups across MGH and MGB, Harvard Medical School, and the University of Pennsylvania. Additionally, Mass Eye and Ear/MGH have entered into manufacturing agreements with AveXis (a Novartis company), Viralgen, Aldevron, and Catalent, to support the manufacturing of the experimental vaccine for



Regenerative and pro-survival effects of OSK in retinal ganglion cells (RGCs). Confocal image stack demonstrating delivery of AAV-OSK to intact Vglut2-Cre transgenic retinas, resulting in RGS-specific OSK expression (top panel) and robust axon regeneration in the optic nerve (bottom panel). White arrows indicate RBPMS+ (AP2-)-labeled RGCs that express *Klf4* (green).

Figure adapted from *Lu, et al., Nature. 2020 588(7836): 124-129.*

clinical trials. The AAVCOVID vaccine program also just received an award from the Bill & Melinda Gates Foundation that will aid the effort to bring further preclinical validation to the AAV vaccine platform. An AAVCOVID vaccine candidate is set to enter clinical trials in 2021.

Turning Back Time

In collaboration with **David A. Sinclair, PhD,** and colleagues at Harvard Medical School, **Bruce Ksander, PhD, Meredith Gregory-Ksander, PhD,** and **Zhigang He, PhD, BM,** successfully restored vision in elderly mice by reestablishing youthful DNA methylation patterns and transcriptomes in aged retinal ganglion cells to restore their youthful function. The team used an adeno-associated virus as a vehicle to deliver three of the four Yamanaka factors—*Oct4, Sox2,* and *Klf4* (OSK)—to drive ectopic expression of these genes in the retina, which promoted axon regeneration after injury and reverse vision loss in aged mice and a mouse model of glaucoma. *(Lu, et al., Nature. 2020 Dec;588(7836):124-129)*. The findings from this study provide proof-of-principle for safely reprogramming complex tissues, such as the retina, and may ultimately lead to a new class of therapeutics that could restore vision.

Regenerating the Ocular Surface

In September of 2020, surgeons from Mass Eye and Ear replaced the ocular surface of four patients each with chemical burns to one eye using cultivated autologous limbal epithelial stem cell transplantation (CALEC), as part of an ongoing clinical trial supported by the NIH National Eye Institute. Developed by a team of researchers from Mass Eye and Ear, Boston Children's Hospital, and Dana-Farber Cancer Institute and led by **Ula V. Jurkunas, MD,** the CALEC technique takes a small biopsy of stem cells from the limbus of the patient's healthy eye, expands them in tissue culture, and grows them on a membrane substrate until ready for transplantation. Dr. Jurkunas then performs extensive scar tissue removal and transplants the CALEC onto the damaged cornea. Shortly after the CALEC grafting procedures, the four recipients no longer experienced pain from their initial chemical injuries. These patients will continue to be monitored long-term to follow their progress. With feasibility and safety of the CALEC procedure established, additional patients with corneal damage are being recruited into a second phase of the trial which will continue through 2021. The success of CALEC in these early cases holds great promise for a safe treatment option for those who have lost vision from chemical burns and corneal infections.

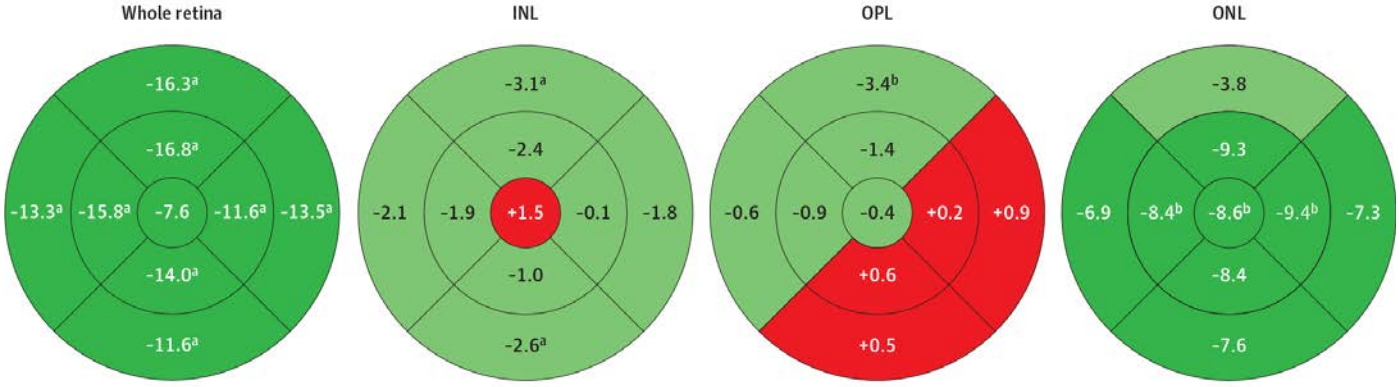
First Use of CRISPR-Cas9 Directly in Humans

In a landmark new clinical trial, co-led by **Eric Pierce, MD, PhD,** and **Jason Comander, MD, PhD,** CRISPR-Cas9 gene-editing techniques are being utilized to delete a mutation in the gene *CEP210* that causes a rare condition called Leber congenital amaurosis 10 (LCA10), a leading cause of blindness. The *CEP20* gene is too large for conventional gene therapy, which uses a viral vector to insert a healthy copy of the mutated genes into affected cells. In contrast,

CRISPR-Cas9 genome editing technology can be programmed to target specific stretches of genetic code and to edit DNA at precise locations, making it possible to permanently modify genes in living cells and to correct mutations at precise locations in the human genome in order to treat genetic causes of disease. This trial represents the first use of CRISPR-Cas9 gene therapy directly in patients for any condition, and the first therapeutic for LCA10. The work is based on early discoveries from the laboratory of Dr. Pierce, which identified that *CEP290* was heavily involved in LCA risk and that a targeted gene therapy might offer benefits as shown in cellular and preclinical models. It is hoped that the therapy will eventually restore vision to patients with the LCA10 inherited retinal disorder.

The Eye Provides Insights into Alzheimer's Disease

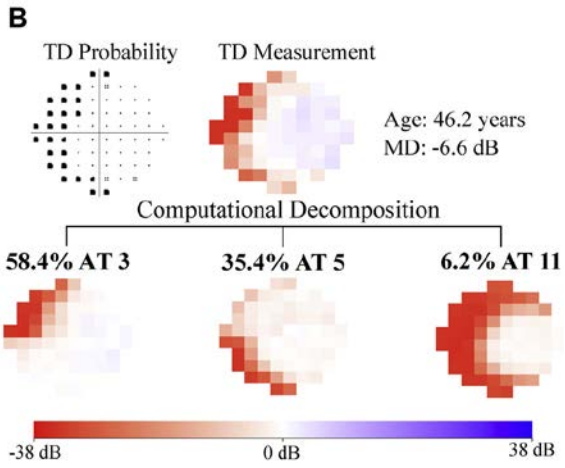
A recent study led by **Milica A. Margeta, MD, PhD,** and **Janey L. Wiggs, MD, PhD,** sought to identify genetic associations between primary open-angle glaucoma (POAG) and *APOE* and *TREM2* genetic variants, known to be associated with Alzheimer's disease, and also contribute to a microglial activation signature involved in neurodegeneration. As previous studies have demonstrated commonalities among glaucoma and other neurodegenerative diseases of the brain, and microglial activation is involved in the pathogenesis of POAG, the authors speculated that these genes may contribute to glaucoma risk. Study results identified that the *APOEe4* allele is associated with a reduced risk of POAG, whereas *TREM2* variants associated with Alzheimer's disease did not significantly contribute to POAG risk *(Margeta, et al., IOVS, 2020 61(8):3).* Interestingly, the same *APOEe4* allele is a known risk factor for Alzheimer's disease, suggesting mechanistic differences between neurodegenerative diseases of the eye and the brain.



Estimated Difference in Thickness of Retinal Layers in *PSEN1* Carriers vs. Controls. Grids developed by the Early Treatment Diabetic Retinopathy Study (ETDRS) showing estimated difference (regression coefficient) in the thickness of various retinal layers of PSEN1 carriers compared with the controls. Left side of the grid represents nasal retina; right side represents temporal retina (light green, -0.1 to -5.0; dark green, -5.1 to -10.0). INL = inner nuclear layer; OPL = outer plexiform layer; ONL = outer nuclear layer. [a]p<0.05; [b]p<0.01

Figure adapted from *Armstrong, et al., JAMA Ophthalmology, 2020 Nov 12;e204909.*

A research team from Mass Eye and Ear, consisting of **John B. Miller, MD, Grayson W. Armstrong, MD, MPH, Leo A. Kim, MD, PhD,** and **Joseph F. Arboleda-Velasquez, MD, PhD,** along with collaborators from MGH, evaluated the possible use of optical coherence tomography (OCT) to detect early retinal alterations in carriers of the Alzheimer's gene presenilin 1 *(PSEN1)* E280A mutation who are



Example of a patient's central VF decomposed quantitatively into a linear combination of the 17 central VF patterns. All VFs are plotted in right-eye format. AT = archetype; MD = mean deviation; TD = total deviation.

Figure adapted from *Wang, et al., Ophthalmology. 2020 127(6): 731-738*.

cognitively unimpaired. Comparisons of retinal thickness between carriers of the mutation and non-carrier family members found that cognitively unimpaired *PSEN1* carriers had a generalized decrease in thickness of the whole retina as well as individual retinal layers. The findings suggest that OCT can detect functional and morphologic changes in the retina of carriers of familial Alzheimer's disease who are cognitively unimpaired several years before clinical onset, suggesting the use of retinal OCT findings as a biomarker *(Armstrong, et al., JAMA Ophthalmology, 2020 Nov 12;e204909)*.

Big Data, Artificial Intelligence, and Predicting Glaucoma Progression

Using data from a large healthcare claims database, a team led by **Lucia Sobrin, MD, MPH,** examined if female hormonal therapy (FHT) is associated with an increased risk of noninfectious uveitis—an immune-mediated disease that has an increased prevalence among women. Results revealed that exposure to FHT was associated with increased rates of incident noninfectious uveitis as defined by the International Classification of Diseases (ICD) diagnostic codes and documented corticosteroid treatment *(Sobrin, et al., Ophthalmology. 2020 127(11): 1558-1566)*. However, the absolute risk is low, suggesting that FHT is generally safe with regard to uveitis risk for the majority of patients.

Tobias Elze, PhD, Mengyu Wang, PhD, and collaborators quantified the central visual field (VF) loss patterns in glaucoma patients using artificial intelligence (AI). In a cross-sectional analysis of central VF patterns using unsupervised AI methods, 17 distinct central VF patterns were identified for the nearly 14,000 eyes across the spectrum of disease severity. These VF patterns quantitatively confirmed previous findings of arcuate defects and less vulnerable zones in central VF. The researchers also demonstrated the clinical usefulness of the central VF patterns by using them to track central VF changes longitudinally and to predict central VF mean deviation. As previous studies have shown that the central VF is most relevant to the quality of life for glaucoma patients, improving prediction of future central VF loss based on earlier VF patterns is an important advance. By better identifying high-risk patients for more aggressive management based on early VF loss patterns, central VF loss and the associated decrease in quality-of-life may be averted *(Wang, et al., Ophthalmology. 2020 127(6): 731-738)*.

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.

- **Biogen** exclusively licensed technology from Mass Eye and Ear based on work led by **Eric Pierce, MD, PhD,** to develop AAV-mediated gene augmentation therapy for *PRPF31* to treat autosomal dominant retinitis pigmentosa.

- **Claris Biotherapeutics,** founded in 2020, is focused on the preclinical development of gene therapy-based therapeutics for corneal scarring and hazing. Claris exclusively licensed technology from Mass Eye and Ear 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 $60M Series A funding in March 2020 and entered into a sublicense agreement with Vertex in April 2020 for collaboration on novel genetic therapies.
- **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 raised a $213M IPO in June 2020.

Oral and Maxillofacial Surgery

Department Report

WILLIAM G. AUSTEN, JR., MD, INTERIM CHIEF

Overview:

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

Achievements:

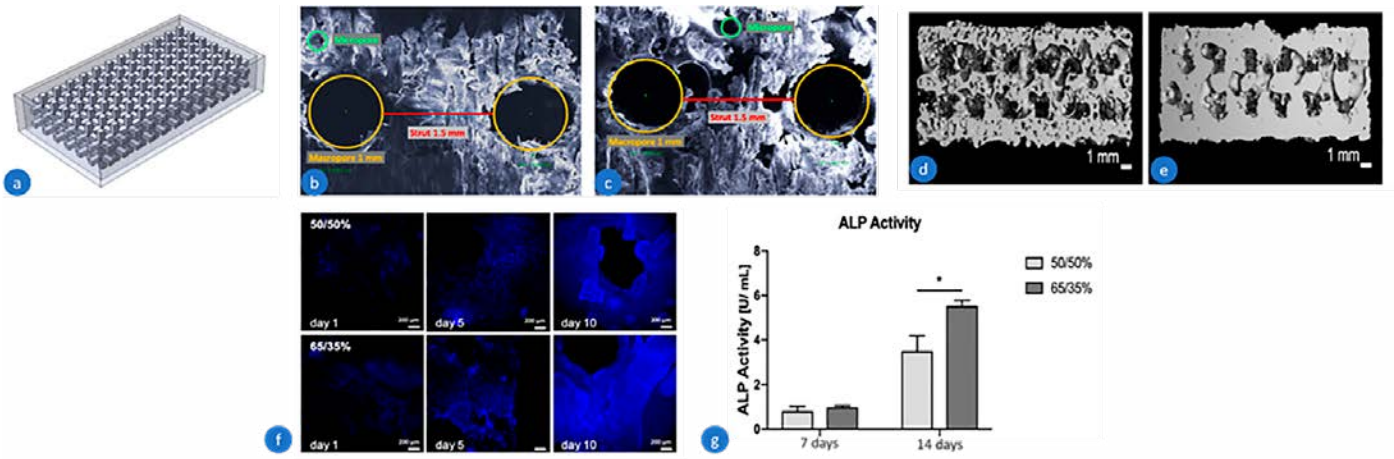
Division/Center: Skeletal Biology Research Center

Scaffolds with different beta-tricalcium phosphate/ polycaprolactone ratios for bone tissue engineering: Characterization and *in vitro* study

Dr. Max-Laurin Mueller (Research Fellow), Dr. Mark Ottensmeyer (Simulation Group CIMIT, MGH), Dr. Maria Troulis, Dr. Fernando Guastaldi (PI)

Description

The treatment and regeneration of maxillofacial bone defects is complex and poses significant challenges to surgeons and scientists. Several techniques are available in the clinical setting for surgeons to treat large bone defects of the jaws, including autogenous bone grafting (i.e. non-vascularized and vascularized bone grafts), reconstruction plates, titanium mesh combined with growth factors and biomaterials, and distraction osteogenesis. Three-dimensional (3D) printing and bone tissue engineering (BTE) strategies is an exciting minimally invasive alternative to bone harvesting techniques to replace missing bone of the mandible and the maxilla. Advances in the fields of computer-assisted planning, 3D printing technology, and BTE over the past few decades offer promising new treatment alternatives using biocompatible scaffold materials, autologous mesenchymal stem cells and growth factors. The use of these techniques might have the potential to profoundly improve patients' function, form, and quality of life. These approaches have provided a new platform for basic and translational research and has shown promising results for maxillofacial regeneration. Previous studies at our Laboratory (Sharaf et al., 2012) investigated 3D printed (20x20x7 mm) 50/50% ß-TCP/PCL scaffolds seeded with porcine bone marrow stem cells (pBMPCs) *in vitro* and found cellular proliferation, depth of cell penetration throughout the scaffold, and early bone formation. To further expand on previous work performed the aims of this study were (1) to develop scaffolds with high ß-TCP ratio (65/35%) of large size (40x20x8 mm), (2) to perform a thorough characterization of both 50/50% and 65/35% ß-TCP/ PCL scaffolds, and (3) to evaluate cellular growth, distribution and viability as well as osteogenic differentiation throughout both groups seeded with pBMSCs *in vitro*. Our results showed that the mechanical



Summary of the results: (a) Scaffold design (CAD). Scaffold morphology: Scanning Electron Microscopy of (b) 50/50% ß-TCP/PCL scaffold and (c) 65/35% ß-TCP/PCL scaffold. Micro-CT evaluation: cross-section of (d) 50/50% ß-TCP/PCL scaffold and (e) 65/35% ß-TCP/PCL scaffold. Scaffold surface staining over time: (f) DAPI. (g) Alkaline phosphatase analysis.

properties of the developed 65/35% scaffolds were within the range of natural trabecular bone. Also, the 65/35% scaffolds showed biological advantages, such as higher cell growth and osteogenic potential, as well as higher ALP activity. Higher ALP activity of the 65/35% scaffolds proof a developed stage of osteogenic differentiation.

Presented at the 2019 AAOMS (American Association of Oral and Maxillofacial Surgeons) Annual Meeting. Submitted to the *Journal of Biomedical Materials Research Part B: Applied Biomaterials* (2020; unpublished data).

Chondrogenic differentiation of mouse CD105+ stem/ progenitor cells on amino-group-functionalized biosilica-hydrogel scaffolds
Dr. Janis Thamm (Research Fellow), Dr. Youssef Jounaidi (MGH), Dr. Vicki Rosen (HSDM), Dr. Maria Troulis, Dr. Fernando Guastaldi (PI)

Description
Temporomandibular disorders (TMDs) are widely spread within the population, and a subgroup have progressive degenerative changes including cartilage degeneration and subchondral bone remodeling. In 10–17% of patients with TMD symptoms, temporomandibular joint (TMJ) osteoarthritis is present. Chondrocytes senescence follows a stagewise turnover while under the process of endochondral ossification. Chondrocytes become pre-hypertrophic, hypertrophic, entering a post-mitotic state, and finally apoptotic. Morphologically, flattening of TMJ condyle can be observed. Mesenchymal stem progenitor cells (MSPCs), populating the proliferative zone of the TMJ, are critical for the cartilage's homeostasis in the process of cartilage maintenance. The regeneration of tissues may be achieved by approaches which activate the body's own intrinsic capacities to restore native tissue. In the field of tissue engineering this approach can be augmented using a scaffold functioning as a template for cell interactions under differentiation stimulus. In a previous study at our Laboratory (unpublished data), we found that CD105+ MSPCs derived from the mouse temporomandibular joint (TMJ) cartilage (mCoSPCs105+), have increased chondrogenic potential compared to a CD105- control. Biosilica is reported to strengthen

the mechanical properties tissue engineered scaffolds. NH2-functionalization of scaffolds surfaces was reported to improve stem cell differentiation abilities. The aim of this study was to investigate cartilage forming abilities of a mouse TMJ derived CD105+ MSPC subgroup (mCoSPC) on functionalized biosilica-hydrogel scaffolds, under chondrogenic stimulus, *in vitro*. In conclusion, we demonstrated the successful manufacture of a hydrogel-based biosilica scaffold that provides a viable environment for cell growth and differentiation of stable chondrocytes. Also, our findings imply that preselecting of CD105+ phenotype in MSPCs may enhance tissue regeneration of fibrocartilage.

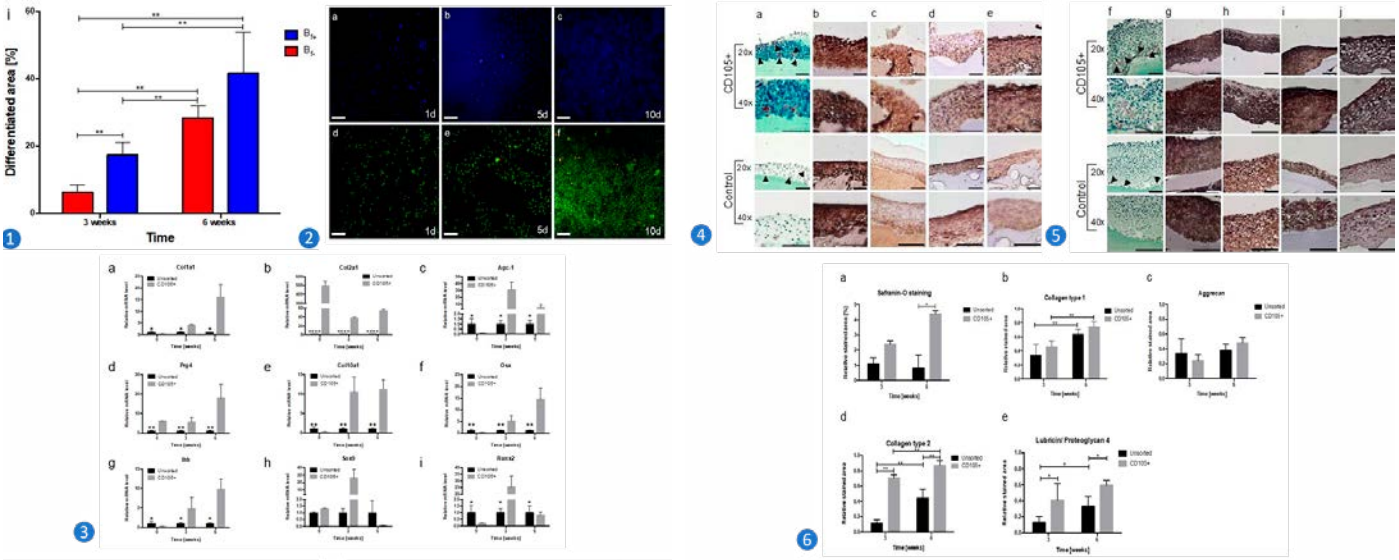
Presented at the 2020 AAOMS (American Association of Oral and Maxillofacial Surgeons) Annual Meeting. Submitted to the *Journal of Oral and Maxillofacial Surgery* (2020; unpublished data).

The impact of cannabis on alveolar bone remodeling in orthodontic treatment

Dr. Katherine Klein (PI), Dr. Fernando Guastaldi (Co-PI), Dr. Yan He (Postdoctoral Research Fellow), Dr. Scott Lukas (Collaborator; Director, McLean Imaging Center, HMS)

Description

Marijuana remains the most widely used recreational drug in the world. Clarifying the impact of increased exposure to cannabis products is important as THC binds to cannabinoid receptors which play a role in bone homeostasis, and early studies suggest a link to bone remodeling. The movement of teeth with orthodontic treatment is

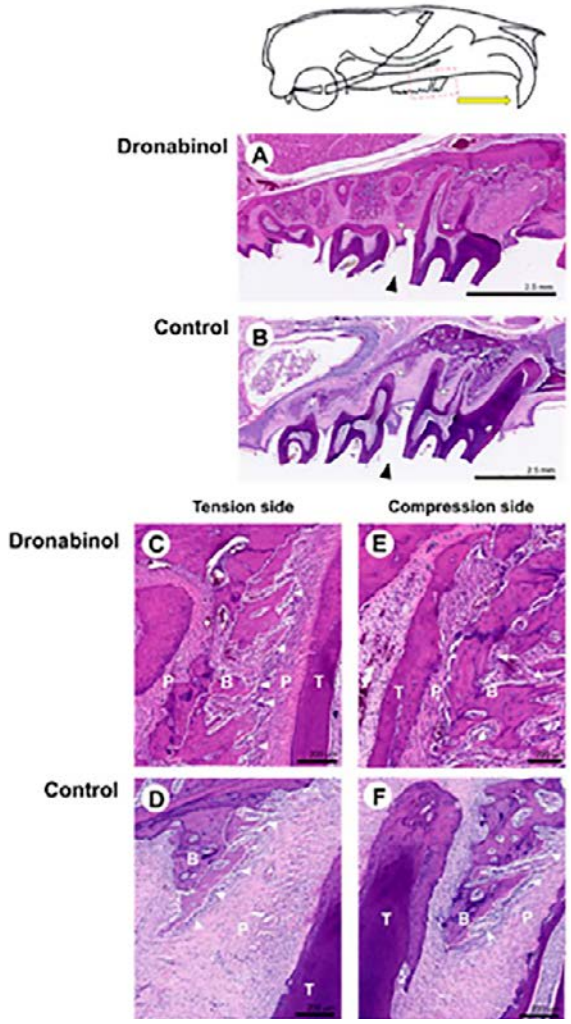


(1) Alcian blue staining of cell-seeded scaffolds. (2) DAPI staining of cell seeded scaffolds after 1d (a), 5d (b) and 10d (c). Live/dead staining (d-f). (3) Quantitative real-time PCR of cell-seeded scaffolds. Gene expression relevant for cartilage ECM and chondrocyte function. (4,5) Histology and immunohistochemistry. Safranin-O staining after 3 weeks (4) and increased staining at 6 weeks (5). (6) Evaluation of histological staining and immunostaining after 3 and 6 weeks of scaffold incubation.

reliant on the process of bone remodeling, and a variety of medications impact the ability of teeth to move through bone. Assess the impact of dronabinol on alveolar bone remodeling in rats who were subjected to orthodontic force. Despite the greater prevalence of marijuana use, especially in the adolescent and young adult populations who most often seek out orthodontic treatment, and the clinical administration of Marinol® in treating chronic diseases, there is no research on the impact of dronabinol on bone remodeling and orthodontic tooth movement. Dental research to date has only focused on the oral soft tissue effects of cannabis use. Therefore, the aim of the present study was to assess the impact of dronabinol on alveolar bone remodeling in rats with otherwise healthy tissue when subjected to orthodontic force. This is the first study showing that dronabinol decelerated orthodontic tooth movement by interfering with bone resorption. A variety of drugs impact orthodontic tooth movement and statistically significant results from this study demonstrate that cannabis should be added to the category of medications that decelerate tooth movement and promote bone regeneration. As marijuana use becomes more prevalent, especially in the adolescent and adult populations who often seek out orthodontic treatment, clinicians should identify patients who are using any cannabis product and this knowledge should be taken into consideration when developing a treatment plan, estimating treatment length and conducting informed consent. With current results, we claimed that cannabis consumption influenced the alveolar bone remodeling initiated by orthodontic force at cell and tissue levels.

Presented at the 2020 AAOMS (American Association of Oral and Maxillofacial Surgeons) Annual Meeting. Presented at the Forsyth Scientific Symposium: My Teeth = My Health 2020.

Submitted to the *American Journal of Orthodontics and Dentofacial Orthopedics* (2020; unpublished data).



Histological observations on periodontium and alveolar bone around the distal root of upper first molar after 21-day orthodontic tooth movement.

Orthopaedics

Department Report

The Mass General/Newton-Wellesley Hospital Orthopaedic Foot and Ankle Research and Innovation Laboratory (FARIL) is located at the James C. Alex M.D. Innovation Center. The 13,000 square feet laboratory is a first of its kind endeavor that unites foot and ankle specialists from across the globe under one roof with the singular goal of advancing the care of foot and ankle patients.

Educational sessions for residents, clinical fellows, surgeons, and research fellows are frequently held at FARIL. This figure shows an educational course using portable ultrasound (left) and application of minimal invasive surgery (right).

MITCHEL B. HARRIS, MD, CHIEF

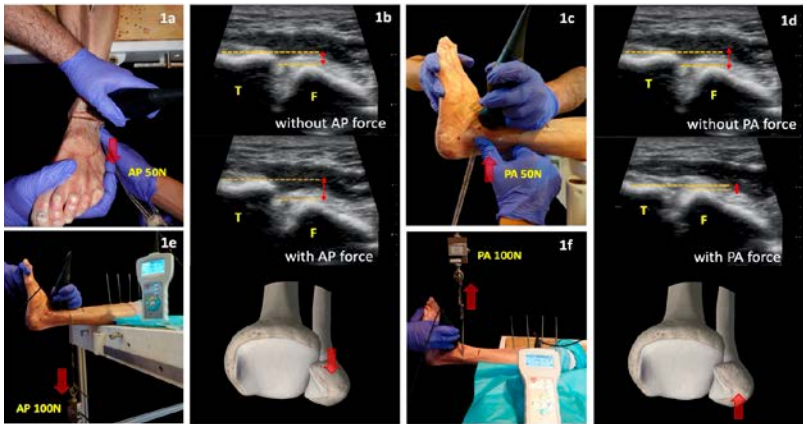
Overview:

Hand
Our Hand Surgery Research group is dedicated to analyzing the outcomes of our clinical practice, identifying concepts that can improve clinical practice and delivery of care, and mentoring future researchers.

Harris Orthopedics Lab
The pioneering efforts of the Harris Orthopaedics Laboratory have positively impacted the quality of life of millions of patients through innovation since its inception in 1969. The mission of the laboratory is to improve patient outcomes through materials science, implant design and clinical research. In 2020, our Associate Director Ebru Oral, PhD, was elected to the National Academy of Inventors based on the laboratory's impactful work on novel joint replacement materials.

Foot & Ankle
The Foot & Ankle Research and Innovation Laboratory (FARIL) is a first of its kind endeavor aiming to improve the care of foot and ankle patients through world-leading scientific investigation, translational product design, and surgeon education rooted in international collaboration and patient-focused research. FARIL fosters cross-department collaborations with other orthopaedic subspecialties and creates opportunities for Harvard Combined Orthopaedic Residents and Clinical Fellows to participate in research and educational activities. Under the leadership of Christopher W. DiGiovanni, MD, Chief of the Division of Foot & Ankle at MGH and NWH, Bart Lubberts, MD, PhD, Director of the MGH-NWH Foot & Ankle Research and Innovation Laboratory, and Mitchel Harris, MD, Chief of the Department of Orthopaedic Surgery at MGH, FARIL has been honored with several national and international awards for scientific discovery—and these have quickly translated into patient benefit around the world through innovative product solutions and surgeon education.

Trauma
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 Boston 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.



Portable ultrasound assessment of the syndesmosis in the sagittal plane under a 50-N manual force (1a,1c) or a 100-N hook force (1e,1f) applied from anterior to posterior or from posterior to anterior direction. The force was measured and standardized using an electronic force gauge. (1b) The portable ultrasound images showing the position of the tibia and fibula before and after the AP force was applied. (1d) The portable ultrasound images showing the position of the tibia and fibula before and after the PA force was applied. One-headed arrows represent the direction of force applied. Broken lines represent the tibial and fibular positions. These lines were drawn parallel to the portable ultrasound probe, at the most anterior aspect of the distal tibia and the distal fibula. Two-headed arrows represent the distances in mm measured between the lines representing tibial and fibular position at before and after the force was applied.

(N=newton; AP=anterior to posterior; PA=posterior to anterior; T=tibia; F=fibula; P-US=portable ultrasound)

Arthroplasty
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. Dr. 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 orthopaedic 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.

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.

Shoulder
Our service continues to lead by pushing the envelope of knowledge not only in pioneering novel and new approaches to unsolved problems of the shoulder girdle, but application of new technologies to improve outcomes and value of care.

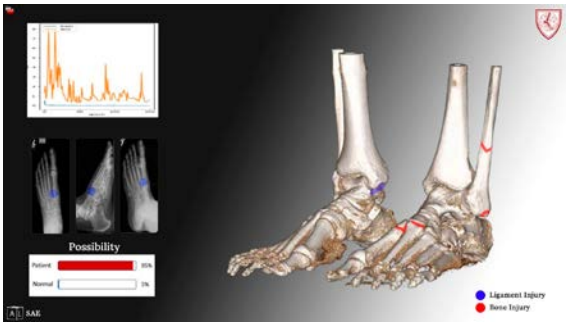
Achievements:

Hand
Since 2010, we have published over 500 peer-reviewed articles. Notable recent developments are:

Orthopaedics

Department Report

Weightbearing computed tomography 3D volumetric measurement in a patient with right sided Lisfranc instability. (A) Lisfranc joint area (shaded area) in the coronal plane. (B) Anterior view. After measuring the Lisfranc joint area in each coronal slice, the volumetric measurement of the Lisfranc joint was created and measured. This figure shows the bilateral Lisfranc volumetric measurement on the weightbearing computed tomography. Abbreviations: L, left; R, right.



Automated msuculoskeletal image interpretation system (AMIIS) uses machine learning and image analysis methods to detect and annotate orthopaedic illnesses using X-rays and CT scan images.

FARIL Researchers Fellows presenting their work at the Orthopaedic Research Society 2020 Annual Meeting.

1. **Demonstration that radial head resection leads to asymmetric arthritic change in the ulnohumeral joint.** There is substantial debate among surgeons whether isolated comminuted radial head fractures should undergo excision or radial head arthroplasty. This study provides the strongest evidence to date that radial head resection leads to ulnohumeral arthritis, and that arthroplasty may be warranted to optimize outcomes.
2. **Identification that bone density on computed tomography to predict non-union in scaphoid fractures treated with immobilization after delayed presentation.** Prior studies suggest that after scaphoid fracture, the bone density of the proximal and distal fragments change over time. We hypothesized that these density changes may predict healing. Using pre-treatment CT data, we identified that increases in bone density of both the proximal and distal scaphoid fragments are associated with non-union after cast immobilization.
3. **A double-blind randomized controlled trial evaluating the effect of Vitamin C on CRPS after distal radius fracture.** A number of prior studies claim that vitamin C administration reduces the incidence of CRPS after distal radius fracture. We performed a randomized controlled trial evaluating the effect of Vitamin C on finger range of motion (an objectively measurable surrogate for CRPS) and found no difference in outcomes in patients who received Vitamin C versus placebo.
4. **Identification that use of a fibular strut graft in the fixation of proximal humerus fractures increases risk of greater tuberosity resorption.** Fibular strut grafting is a technique that is being more frequently utilized in proximal humerus surgery. We identified that fibular strut grafting increases the odds of greater tuberosity resorption by 4.5 times.

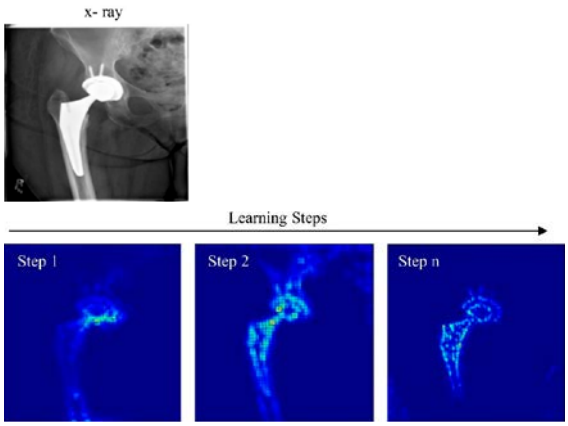
Harris Orthopedic Lab

1. **The first prototype of a gentamycin sulfate eluting polyethylene tibial knee spacer intended to treat periprosthetic joint infection in total knee replacement patients**
   Periprosthetic joint infection (PJI) occurs in about 2% of total knee replacement (TKR) patients with devastating outcomes. This implant offers both increased anti-microbial protection and superior wear resistance compared to PJI spacer implants in clinical use. We are collaborating with an orthopaedic implant manufacturer and expect to have FDA clearance for this device within a year.
2. **AI model for detection of the design of total hip replacement implant components before revision surgery**
   In recent years artificial intelligence (AI) has revolutionized the way medical data are being processed achieving higher accuracy and efficacy than medical experts in many applications. Harris Orthopaedics Laboratory has been the pioneer of developing novel AI models for orthopaedic applications. Among these applications is the first-ever AI model to detect the design of total hip replacement (THR) implant components before revision surgery. The figure above shows how the machine analyzes a given x-ray and “learns”

to identify the design of THR implant components. Automated and accurate identification of implant components is a valuable addition to the tool-kit of revision arthroplasty surgeons, which can save significant time and effort, and reduce the likelihood of incorrect pre-operative device identification. This work has been featured in the Journal of Bone & Joint Surgery 2020 editorial and has received the Orthopaedic Research Society 2021 William H. Harris Award.

3. **New NIH-funded project on customizing joint replacements according to infection risk**
   Our pioneering work in using polyethylene joint replacement bearing surfaces as drug delivery devices was expanded this year with new grant funding exploring the customization of drug synergies and release profiles for local infection therapy. Preliminary results on methods for stratifying infection risks according to resistant clinical bacterial strains and synergies of antibiotics with other drugs to address these risks was accepted for presentation at the Annual Meeting of the Orthopaedic Research Society in February 2021.
4. **Collaborations on decontamination methods for N95 respirators in the COVID era**
   Our laboratory played a prominent role in the MGB task force evaluating different methods of decontamination for the emergency use of N95 respirators by healthcare workers. We collaborated with many MGB researchers as well as virologists at Boston University's NIEDL laboratory for live testing of the SARS-COV2 virus and Charles River Laboratories for testing with surrogate viruses. This work led to the decontamination of N95 respirators by using vapor hydrogen peroxide across the MGB system. We published three preprints and were part of various consortiums to aid others across the US and internationally to evaluate their resources for the emergency use of N95 respirators.
5. **New rodent models of periprosthetic infection and tibia fracture/plating**
   We developed two new preclinical rodent models to evaluate the translational aspects of local drug delivery devices, on which we have been recently focusing. The first is a chronic peri-prosthetic infection and the second is a tibia fracture/plate fixation model. These models aim to capture the post-surgical course of injury and treatment in a clinically relevant manner to comparatively evaluate novel therapies. The latter is a candidate for an award of the International Section of Fracture Repair at the annual Meeting of the Orthopaedic Society in February 2021.

The first prototype of a gentamycin sulfate eluting polyethylene tibial knee spacer intended to treat periprosthetic joint infection in total knee replacement patients.

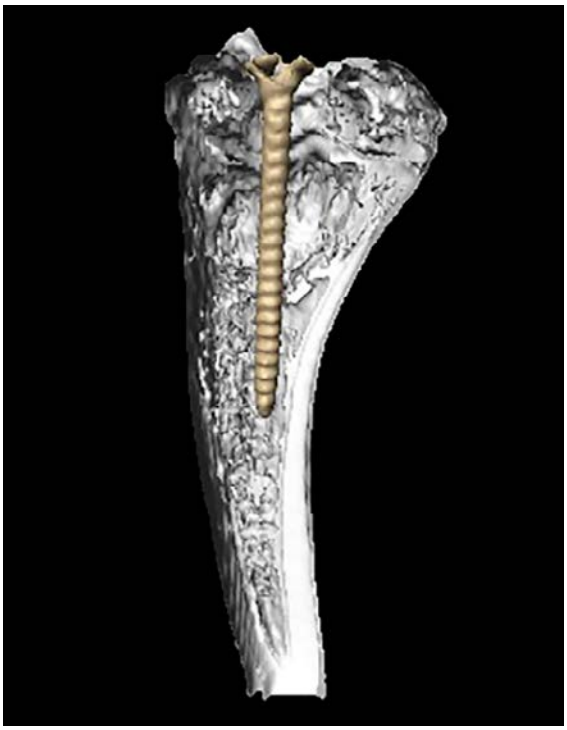


AI model for detection of the design of total hip replacement implant components before revision surgery.

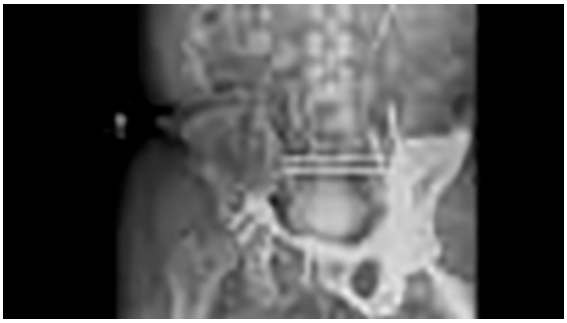
Machine "learning" to identify the design of a total hip replacement implant from a given x-ray.

Foot & Ankle

1. **Cross-department collaboration**
   In our efforts to foster cross-department collaborations we have completed numerous research projects with other orthopaedic subspecialties. Examples hereof are; 1) Translational arthroscopic and portable investigations of the medial patellofemoral complex and lateral meniscal fascicle injuries led by Miho Tanaka, MD, Sports Medicine Orthopaedic Surgeon; 2) Analysis of weight-



Established peri-prosthetic joint infection. New rodent models of periprosthetic infection and tibia fracture/plating.



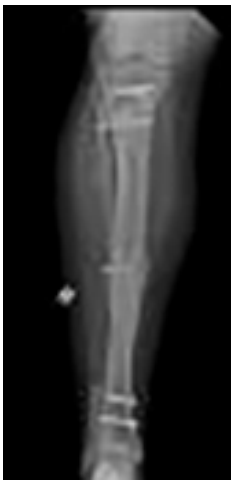
3D custom made implant to reconstruct the pelvis in a patient facing an external hemipelvectomy. Our upcoming research is focusing in the complications, function, predictors of success and PROMs when using this type of implants.

bearing CT scans for the diagnosis of syndesmotic and Lisfranc instability using deep learning algorithms in collaboration with the Harris Orthopaedics Laboratory led by Orhun K. Muratoglu, PhD; 3) Development of open access educational videos on the diagnosis and treatment of ankle fractures initiated by the Harvard Global Orthopaedic Collaborative led by Kiran Agarwal-Harding, MD, MPH; and 4) A collaboration with the Skeletal Oncology Research Group (SORG) directed by Joseph H. Schwab, MD, MS, for creating a comprehensive orthopaedic patients data registry.

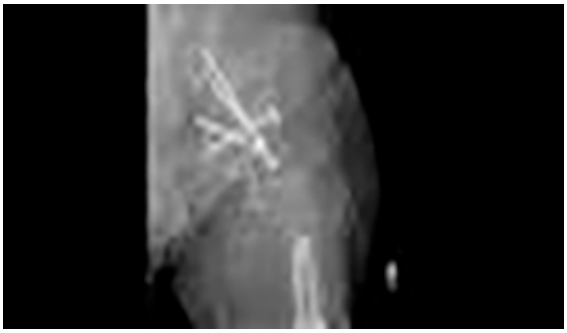
2. **Education**
   Another primary mission of FARIL is becoming the national and international educational resource for evolving orthopaedic technologies. In 2020, we initiated five educational courses for Harvard Combined Orthopaedic Residents and Clinical Fellows, focusing on minimally invasive surgery, fixation methods for Jones fractures and unstable syndesmotic injuries, and total ankle replacement. Additionally, we have created three open-access educational videos describing the use of portable ultrasound to evaluate musculoskeletal pathology of the upper and lower extremities. In collaboration with the Harvard Global Orthopaedic Collaborative, three educational videos on the diagnosis and treatment of ankle fractures were created. These are accessible for free through YouTube and the FARIL website: faril.mgh.harvard.edu.
3. **Research and innovation**
   FARIL members have produced research that has improved our understanding of how to optimize care of common injury patterns suffered by active patients and athletes, including syndesmotic ligament injuries of the ankle, Lisfranc injury of the foot, and Jones fractures. This includes provisional patents on implant technologies that are intended to make their way into the operating room. In 2020, FARIL emerged as one of the recognized leaders in the U.S. for the development and utility of dynamic portable ultrasound techniques and weight-bearing computed tomography for musculoskeletal conditions that affect both the foot and ankle. As diagnostic instability measures play an important role in the treatment decision process, FARIL prioritizes imaging modalities that can assess and evaluate the instability of the foot and ankle. Additionally, our lab members applied artificial intelligence and created machine learning algorithms to help recognize injury patterns of the foot and ankle on radiographic imaging techniques. More specifically, we have focused on increasing the accuracy of the currently used imaging modalities and hastening the interpretation process. Starting with the most common foot and ankle traumas, including ankle fractures, syndesmotic instability, fifth metatarsal fractures, and tarsometatarsal (Lisfranc) instability, we utilized complex machine learning and image analysis algorithms to create an automated musculoskeletal image interpretation system (AMIIS). The outcome of our research using AMIIS on X-rays and weight-bearing computed tomography scans showed an accuracy of higher than 90% with ten times faster speed in detecting these orthopedic conditions. AMIIS was depicted to be a

promising diagnosis assistant that can help healthcare providers, particularly those with less experience and knowledge, detect even the most complex orthopedic conditions and decide for appropriate management.

4. **Dissemination**
   FARIL has blossomed into a team of world-class students, surgeons, engineers, and post-doctorate researchers from over a dozen countries who embrace one common mission—finding innovative solutions to the clinical problems faced by foot and ankle patients everywhere. In 2020, members of our lab published 17 peer-reviewed journal articles and delivered 32 scientific presentations at national and international medical meetings.



Carbon fiber rod used to safe a fracture allograft in a patient with remote history of osteosarcoma. Our upcoming research will evaluate the properties of these implants when imaged with different modailites for follow of oncologic patients. We will also evaluate their properties when exposed to radiation and their performance in gait training.



Patient treated in the ICAN network with a “tibial turn up surgery.” This procedure is executed in a multidisciplinary fashion and allows patients to become functional above the knee amputees instead of receiving hip disarticulations, which have a worse functional outcome. In this surgery the tibio-talar joint is used to recreate or reconstruct the hip joint.

Trauma

Does surgical approach influence the risk of postoperative infection after surgical treatment of tibial pilon fractures?

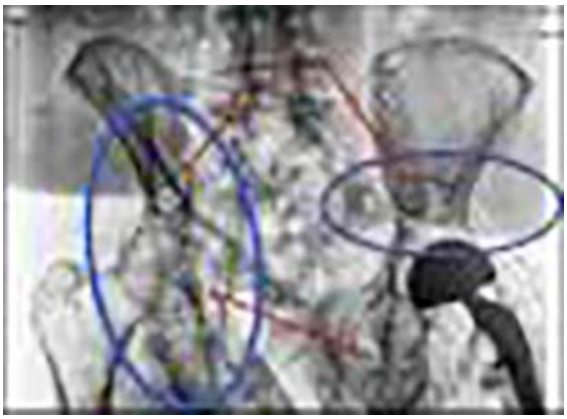
The primary goal of the study was to determine whether a particular surgical approach or combination of approaches is a risk factor for infection after open reduction internal fixation (ORIF) of pilon fractures. There was no association between primary surgical approach and development of infection. Surgical approach does not appear to be a significant risk factor for postoperative infection after open reduction internal fixation of distal tibial pilon fractures. When treating tibial pilon fractures, surgeons should select the approach they feel best addresses the specific fracture pattern.

Pelvic packing and angio-embolization after blunt pelvic trauma: A retrospective 18-year analysis

Treatment of pelvic trauma related hemorrhage is challenging and remains controversial. In hemodynamically unstable patients suspected for massive bleeding, pre-peritoneal packing (PPP) with temporary external fixation (EF) and subsequent trans-arterial embolization (TAE) can be performed in order to control bleeding. In hemodynamically stable patients suspected for minor to moderate bleeding, primary TAE with EF may be performed. The goal of this study was to determine effectiveness and safety of both strategies. Primary TAE appears to be an effective and safe adjunct for (minor) pelvic hemorrhage in hemodynamically stable patients. Primary PPP followed by EF and adjunct bilateral unselective TAE with gelfoam appears effective for those suspected of massive pelvic bleeding. This unselective embolization approach using gelfoam might be related to (ischemic) complications. When considering the amount and severity of complications and the severity of pelvic trauma, these might not outweigh the benefit of fast hemorrhage control.

Association of patient-reported outcomes with clinical outcomes after distal humerus fracture treatment

In this study, we assessed the patient-reported outcomes of distal humerus fracture treatment using Patient-Reported Outcomes Measurement Information System (PROMIS) or QuickDASH (Disabilities of the Arm, Shoulder, and Hand) scores and the association between patient-reported outcomes and clinical



Intramedullary polymer stabilization is an alternative that we are developing for the management of metastatic disease in pelvis. This procedure with small incision and faster recovery seems to be more effective and simpler than other more traditional and invasive techniques for management of metastatic disease in the pelvis. In this specific case of a patient with multiple myeloma, we were able to prophylactically stabilize both acetabulums in a single surgery with a 24 hour stay in the hospital. Upcoming research is going to analyze the impact of this implants in quality of life and gait as evaluated in a gait analysis.

outcomes. We found that clinical factors (the arc of flexion-extension) and patient psychological factors (PROMIS Global [Mental] score) were independently associated with PROMIS measures of PF after distal humerus fracture treatment. These data can be used to contextualize patient outcomes and guide patient expectations.

Defining the mean angle of diaphyseal long bone non-unions—Does shear prevail?

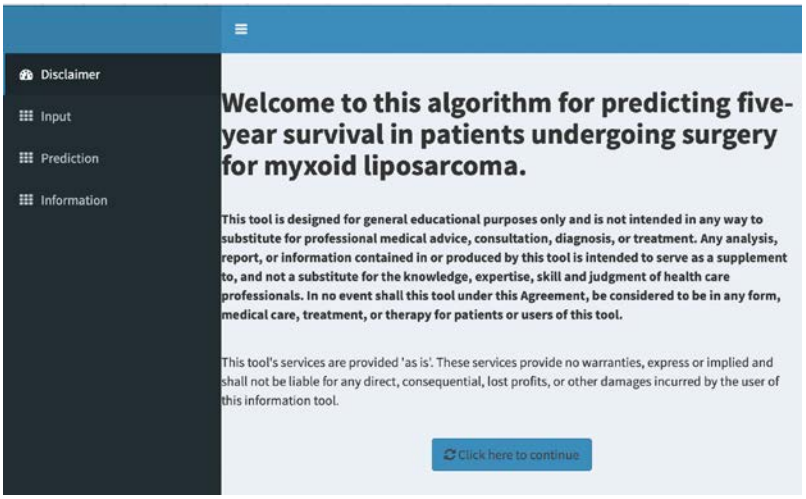
Diaphyseal non-unions of the lower limb are a clinically significant and costly problem in orthopaedics. Patients with non-union have poor quality of life, including pain, functional limitation and restriction in returning to work. It is hypothesised non-union formation may be because of the concentration of shear strain in this plane. This study aims to define the mean angle of a series of diaphyseal non-unions based on radiographic analysis. We investigate the orientation of a large series of diaphyseal non-unions of the lower limb. This study demonstrates the mean angle of diaphyseal non-unions from long bones of the lower limb approaches 45 degrees. This is noted in all types of fractures and is irrespective of anatomic location or sex. This confirms the hypothesis that shear is likely to play a role in the development of a non-union. This study provides further evidence that non-unions occur primarily due mechanical instability.

Arthroplasty

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 which are 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

This is a sample of one of the calculators created with artificial intelligence algorithms in order to assist patients and clinicians in decision making in terms of treatment given the risk of local recurrence after treatment or risk of metastatic disease given an overall survival probability.



knee and the surgical management of these potentially catastrophic complications.

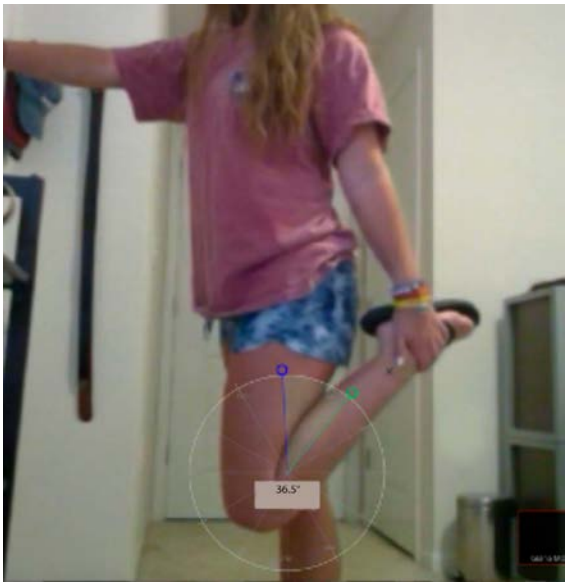
Bioengineering Laboratory

At the **Bioengineering Laboratory,** 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 48 accepted abstracts presented at the 2020 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 learned 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.

The Bioengineering Laboratory also 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-reviewed publications. 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



Range of motion of the knee is quantified on screen during a virtual orthopaedic visit.

Orthopaedics

Department Report

Markers are placed on a high school pitcher to allow optical motion analysis cameras to create 3D visualizations of pitches.

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.

Shoulder

This year Dr. Bassem Elhassan has joined us as the Co-Director of the Shoulder Service. He has pioneered many novel techniques of tendon transfer in order to improve shoulder function. These techniques have been applied to address shoulder paralysis and muscle insufficiency. Our research program will assess outcomes going forward.

Dr. Warner has assisted with the application of mixed reality guidance for shoulder replacement using holographic referencing in the operating room in order to improve accuracy of component placement

Drs. Evan O'Donnell and Jon JP Warner have spearheaded an effort in value-based health care and shoulder pathology. Their research has focused on improving meaningful patient outcomes while decreasing costs in all phases of care including office consultations, follow-up visits, as well as surgical procedures. Drs. O'Donnell and Warner have shown there is significant value in telemedicine, when virtual visits were compared to standard in-person visits. Via a novel cost accounting approach, time-driven activity-based costing (TDABC), the authors have shown the introduction of new implants in shoulder arthroplasty may reduce operative times and lead to decreased cost in the OR episode. Lastly, a primary aim of 2021 is to study through multicenter collaboration the value of transitioning from inpatient shoulder arthroplasty to an outpatient model.

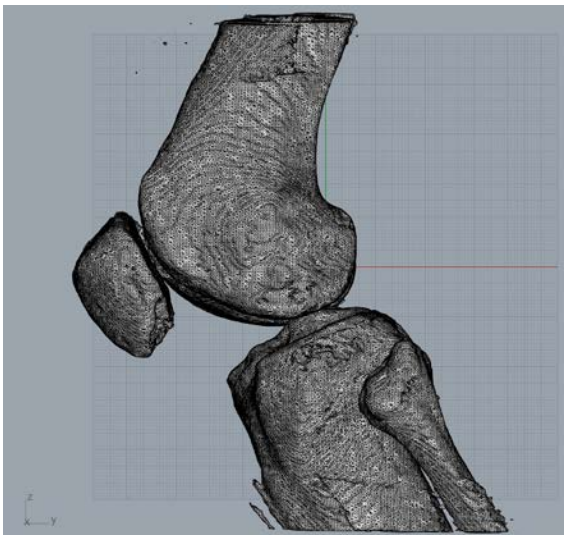
Musculoskeletal Oncology Service

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.

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.



3D model created from 4D imaging of a knee with patellar instability allows for computational analysis and surgical simulations to assess for kinematic changes in patellar tracking.

Achievements:
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.

Otolaryngology, Head and Neck Surgery

Department Report

MARK A VARVARES, M.D., F.A.C.S., INTERIM CHAIR

Overview:

Massachusetts Eye and Ear and Massachusetts General Hospital
The Department of Otolaryngology, Head and Neck Surgery, is home to one of the largest research groups devoted to the study of areas relevant to our field. Our research foci include cochlear and middle ear mechanics, inner ear biology, hereditary and acquired deafness, cochlear regeneration, central auditory processing and plasticity, processing of neurological voice and speech disorders, facial paralysis, head and neck cancer, and vestibular function and dysfunction. The department's strategic goal is to leverage the culture of close collaborations among clinical practitioners and basic scientists to advance our understanding of the mechanisms underlying normal and disordered function, and to translate that understanding into the development of new treatments for diseases and disorders of the ear, nose, throat, head, and neck. Disorders impacting this area have direct impact on how we interact as humans. Using a broad portfolio of approaches to investigate diseases of the head and neck and skull base, the department continues to be a global leader of research in this area. Below are some of the highlights from different divisions within the Department from the past year.

Achievements:

Basic Science Laboratories
Basic research in our department includes 28 investigators, and spans most of the subfields of Otolaryngology Head and Neck Surgery, including, hearing and deafness, balance and vestibular, laryngology and voice disorders, head & neck cancer and facial nerve disorders.

Of the 134 peer-reviewed basic-science publications from our department in 2020, some of the most salient highlights include the following:

1. **Treatments for Sensorineural Hearing Loss:** Several Departmental investigators published preclinical studies on the therapeutic potential of a number of strategies for regenerating sensory cells and their primary neural innervation in animal models of sensorineural hearing loss. **Albert Edge, PhD,** and his laboratory reported on three different types of drugs that can regenerate synapses between auditory neurons and hair cells, providing mechanistic insights into synaptic repair that are applicable to treatments for hearing loss, as well as neurodegenerative disease more broadly. The lab of **Zheng-Yi Chen, DPhil,** identified an FDA-approved drug that shows robust protection against noise-induced hearing loss, and in collaboration with Qiaobing Xu, PhD, at Tufts, identified lipid nanoparticles capable of delivering mRNA, protein and ribonucleoproteins into the mammalian inner ear, providing new avenues for genome editing and gene therapy. The laboratory of **Artur Indzhykulian, MD, PhD,** continues to study the structural

biology of the cadherin protein that is defective in Usher syndrome, with the aim of designing a truncated, yet fully functional, version of the protein small enough to be coded within a single AAV vector.

2. **Hidden Hearing Loss:** A number of audiological studies were published by **Stephane Maison, PhD, CCC-A,** and colleagues further probing the mechanisms of "hidden hearing loss", i.e. people with normal audiometric thresholds who nevertheless have difficulty understanding speech in noisy environments. Maison's electrophysiological results from over 100 "normal-hearing" subjects show a strong correlation between metrics of cochlear neural function and performance on difficult words-in-noise tasks, adding further support for the notion that hidden hearing loss can arise when inner-ear neural degeneration outpaces the loss of inner ear sensory cells. The laboratory of **M. Charles Liberman, PhD,** published studies of histopathopathology in human autopsy specimens showing, in the normal-aging human inner ear, that sensory neurons die back well before the sensory cells themselves, as predicted from studies of hidden hearing loss in animal models. **Dan Polley, PhD,** and colleagues showed that changes in pupil diameter during difficult words-in-noise tasks, and the ability to detect subtle changes in frequency modulation, represent simple and rapid ways to identify subjects with normal audiograms who will have difficulty understanding speech in difficult listening environments.
3. **Conductive Hearing Loss:** Several departmental laboratories focus their research on the mechanics of hearing, i.e. the conduction of sound through the middle and external ears. A group led by **Bradley Welling, MD, PhD, FACS,** published results of a clinical trial investigating the therapeutic benefit of topical administration of fibroblast growth factor 2 for chronic tympanic membrane perforation. **Aaron Remenschneider, MD, MPH,** and colleagues continued their studies of 3D printed materials as grafts for a perforated eardrum. **Jeffrey Tao Cheng, PhD,** and **John Rosowski, PhD,** published on their use of optical coherence tomography to better understand the vibration modes of the tympanic membrane that enable high-frequency hearing, and **Heidi Nakajima, MD, PhD,** along with **John Guinan, PhD,** and **Joe Nadol, MD,** reported on the fundamental differences in the modes of sound-evoked mechanical vibration in the human inner ear compared to all the extensively studied animal models.
4. **Central Processing in Hearing and Balance:** The lab of **Anne Takesian, PhD,** studies neural mechanisms underlying auditory cortical plasticity. Recent studies have shown that cortical layer 1 (L1), a sparse layer of inhibitory interneurons located directly underneath the pial surface, plays a key role as master regulators of cortical plasticity and auditory learning. **Faisal Karmali, PhD,** studies vestibular feedback and postural control, and his recent studies, focusing on healthy human subjects with no known vestibular pathology or symptoms, showed that vestibular encoding of lateral translation cues is a key contributor to balance control.

5. **Head and Neck Cancer:** Mutations in histone modifying enzymes and histone variants have been identified in multiple cancers in The Cancer Genome Atlas (TCGA) studies. However, very little progress and understanding has been made in identifying the contribution of epigenetic factors in head and neck squamous cell carcinoma (HNSCC). **Derrick Lin, MD, FACS, Vinod Saladi, PhD,** and colleagues recently reported the identification of RUVBL1 (TIP49a), a component of the TIP60 histone modifying complex, as being amplified and overexpressed in HNSCC, playing a key role in regulating transcription of key genes involved in differentiation, cancer cell proliferation and invasion. Using patient data analysis of multiple cohorts including TCGA and single cell HNSCC data their findings indicated that RUVBL1 overexpression is a poor prognostic marker and predicts poor survival. *In vitro* experiments indicate a pro-proliferative role for RUVBL1/H2AZ in HNSCC cells, making it a key contributor to tumorigenesis and a vulnerable therapeutic target in HNSCC patients.

Pediatric Otolaryngology
Quantitative evaluation of the human vocal fold extracellular matrix using multiphoton microscopy and optical coherence tomography (Chris Hartnick, MD, MS)

To be able understand human pathology, there is a need to understand the normal anatomic state. Since 1975, the field of laryngology has been driven by Dr. Hirano's landmark description of the histologic structures of the three level structure of the human fold. However, despite remarkable histological contributions, our understanding of the vocal fold (VF) physiology has remained murky. Why does phonotrauma induce formation of vocal nodules in classic regions of the vocal folds and not at other areas? Where are the most likely sites of invasion of laryngeal cancer from the superficial epithelium and why? The more we know about the underlying anatomic structures, where there are changes in morphology that might predispose to disease development or anatomic disruption, the more we can learn to understand (and in the future perhaps treat) pathology. The emerging field of non-invasive 3D optical imaging may be well-suited to unravel the complexity of the VF microanatomy. This study focused on characterizing the entire VF Extracellular matrix (ECM) in length and depth with optical imaging. A quantitative morphometric evaluation of the human vocal fold lamina propria using two-photon excitation fluorescence (TPEF), second harmonic generation (SHG), and optical coherence tomography (OCT) was investigated. The evidence acquired in this study suggests that the VF is not a strict discrete three-layer structure as traditionally described but instead a continuous assembly of different fibrillar arrangement anchored by predominant collagen transitions zones. This study demonstrated that the VF composition is distinct and markedly thinned in the anterior one-third of itself, which may play a role in the development of some laryngeal diseases.

Rhinology and Skull Base Surgery
In recent years, biologic therapies such as dupilumab have emerged as promising yet expensive options in the treatment of recalcitrant chronic sinusitis with nasal polyps (CRSwNP). **George Scangas, MD,** and his colleagues from 5 academic institutions across the country performed a rigorous cost utility analysis to assess the relative benefits and costs of endoscopic sinus surgery versus dupilumab for patients with CRSwNP. They found that an endoscopic sinus surgery strategy for upfront management of CRSwNP was much more cost effective than one that employed dupilumab.

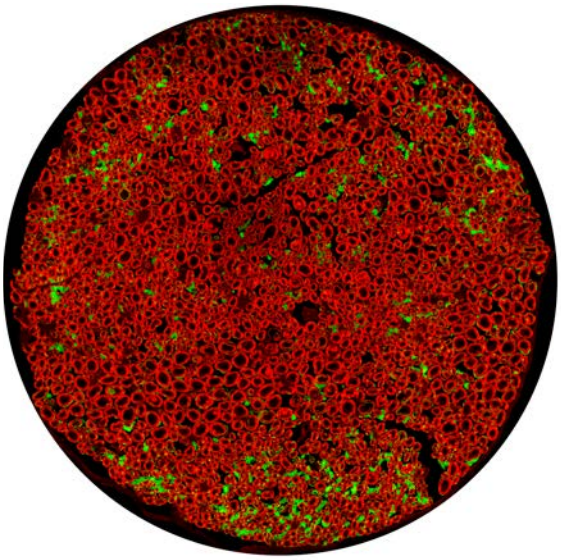
For patients undergoing endoscopic sinus surgery for chronic rhinosinusitis without evidence of infection at the time of surgery and without use of intranasal packing or stents, the use of antibiotics did not improve symptoms or rates of infection in the post-op period. However, antibiotic use increased the rate of gastrointestinal complications. **Marlene Durand, MD, Stacey Gray, MD,** and **Eric Holbrook, MD,** were key contributors to this study that supports the limitation of antibiotic use for prophylactic purposes in routine endoscopic sinus surgery.

COVID-related research
The MEE Department of Otolaryngology emerged as a global leader early in the COVID-19 pandemic at identifying the risks of ENT procedure related aerosolization in both the clinical and surgical setting across a range of subspecialities. Building on this work, the faculty not only helped to develop international guidelines on safety protocols for outpatient visits, but also innovated a variety of novel barrier technologies to help protect both the provider team and other patients.

A highlighted article from this body of work was “Airborne Aerosol Generation During Endonasal Procedures in the Era of COVID-19: Risks and Recommendations," with primary authors Alan Workman, MD, MTR, and Ben Bleier, MD, FACS, *(Otolaryngol Head Neck Surg. 2020 Sep;163(3):465- 470. doi: 10.1177/0194599820931805. Epub 2020 May 26).* The objective of this investigation was to quantify airborne aerosol production under clinical and surgical conditions and examine efficacy of mask mitigation strategies. Airborne aerosol quantification with an optical particle sizer was performed in real time during cadaveric simulated endoscopic surgical conditions, including hand instrumentation, microdebrider use, high-speed drilling, and cautery. Aerosol sampling was additionally performed in simulated clinical and diagnostic settings. Their findings that transnasal drill and cautery use is associated with significant airborne particulate matter production in the range of 1 to 10 μm under surgical conditions—and that during simulated clinical activity, airborne aerosol generation was seen during nasal endoscopy, speech, and sneezing—were critical in our understanding of viral transmission in common clinical settings. In addition, the finding that intact or VENT-modified N95 respirators mitigated airborne aerosol transmission, while standard surgical masks did not, were significant findings for the otolaryngology

Otolaryngology, Head and Neck Surgery

Department Report



High resolution imaging of myelinated and unmyelinated fibers of axial cryosections of sciatic nerve in Sox10-Venus mice, stained with FluoroMyelin Red.

community worldwide. The results of this study became one of the primary references for the development of strategies to mitigate viral spread during otolaryngologic procedures.

Facial Plastic and Reconstructive Surgery

Nanoscale intravital imaging of cranial nerves. High-resolution imaging of nerves regulating vital functions in the head and neck is challenging, yet critical for understanding their structure, function, and response to therapeutic intervention. A team of investigators within the Surgical Photonics & Engineering Laboratory including **Iván Coto Hernández, PhD, Nate Jowett, MD,** are developing means for intravital three-dimensional imaging of peripheral nerves to advance knowledge and outcomes in the field of motor and sensory rehabilitation of the head and neck. Recently, the team established means for resolving nanoscale unmyelinated axons in murine nerve using light microscopy, circumventing the need for resource-intensive electron microscopy. They then demonstrated the feasibility of intravital three-dimensional imaging of intact human nerve without need for chemical staining by means of stimulated Raman scattering microscopy, employing machine learning algorithms for automated highly-quantitative assessment of nerve structure. These approaches could yield means for non-ablative nerve biopsy to guide diagnosis and intraoperative decision making in nerve transfer procedures, as they report in the *Journal of Neuropathology & Experimental Neurology and Muscle & Nerve Research*.

Otology, Neurotology and Skull Base Surgery and Division of Vestibular and Balance Disorders

The Neurotology and Vestibular Divisions are widely known for their research programs investigating disorders effecting the temporal bone and lateral skull base. Research foci include temporal bone histopathology, middle ear mechanics, and multiple aspects of the results of cochlear implantation, the pathophysiology of balance disorders, inner ear hair cell regeneration and the potential novel therapeutic targets of vestibular schwannoma. There is considerable overlap and collaboration between this division and the basic science laboratories.

One study to highlight is that done by **Tina Stankovic, MD, PhD, FACS,** and colleagues studying MMP-14 (MT1-MMP) as a biomarker of surgical outcome and a potential mediator of hearing loss in patients with vestibular schwannomas (VS). Factors such as tumor size or growth rate do not shed light on the pathophysiology of associated sensorineural hearing loss (SNHL) and suffer from low specificity and sensitivity, whereas histological markers only sample a fraction of the tumor and are difficult to ascertain before tumor treatment or surgical intervention. Using a combination of in silico, *in vitro*, and *ex vivo* approaches, these investigators identified matrixmetalloprotease 14 (MMP-14; also known as MT1-MMP), from a panel of candidate proteases that were differentially expressed through the largest meta-analysis of human VS transcriptomes. The abundance and proteolytic activity of MMP-14 in the plasma and tumor secretions from VS patients correlated with clinical parameters

and the degree of SNHL. Further, MMP-14 plasma levels correlated with surgical outcomes such as the extent of resection. Finally, the application of MMP-14 at physiologic concentrations to cochlear explant cultures led to damage to spiral ganglion neuronal fibers and synapses, thereby providing mechanistic insight into VS-associated SNHL. Taken together, MMP-14 represents a novel molecular biomarker that merits further validation in both diagnostic and prognostic applications for VS.

Laryngology

The division of laryngologyinvestigates topics related to voice and swallowing as related to the larynx, upper trachea and entire phonatory mechanism.

Phil Song, MD, and colleagues have developed a laryngeal force sensor to help improve the postoperative sequelae experienced by patients who undergo suspension microlaryngoscopy in the course of diagnosis or treatment of disorders involving the larynx and trachea. The laryngeal force sensor measures the tissue pressure delivered to the mouth and throat during phonosurgery. The measurements derived from the sensor include maximal force, average force, total impulse, and suspension time and these metrics have correlated with extra-laryngeal complications including pain, dysguesia, dysphagia, and neuropathy. The measurements have also demonstrated a strong correlation with postoperative pain requirements, with a significant predictive variable for perioperative narcotic administration and an incremental increase of 0.273 mg of morphine equivalents per minute of total suspension time. The latest paper published in Otolaryngology Head and Neck Surgery reports the results of a prospective controlled trial that demonstrates active intraoperative tissue pressure monitoring (IOTPM) reduces the likelihood of postoperative complications by almost 30% (29.1%). *Feng AL, Puka E, Ciaramella A, Rao VM, Wang TV, Naunheim MR, Song PC. Laryngeal Force Sensor for Suspension Microlaryngoscopy: A Prospective Controlled Trial. Otolaryngol Head Neck Surg. 2021 Jan 5:194599820982635. doi: 10.1177/0194599820982635. Online ahead of print.*

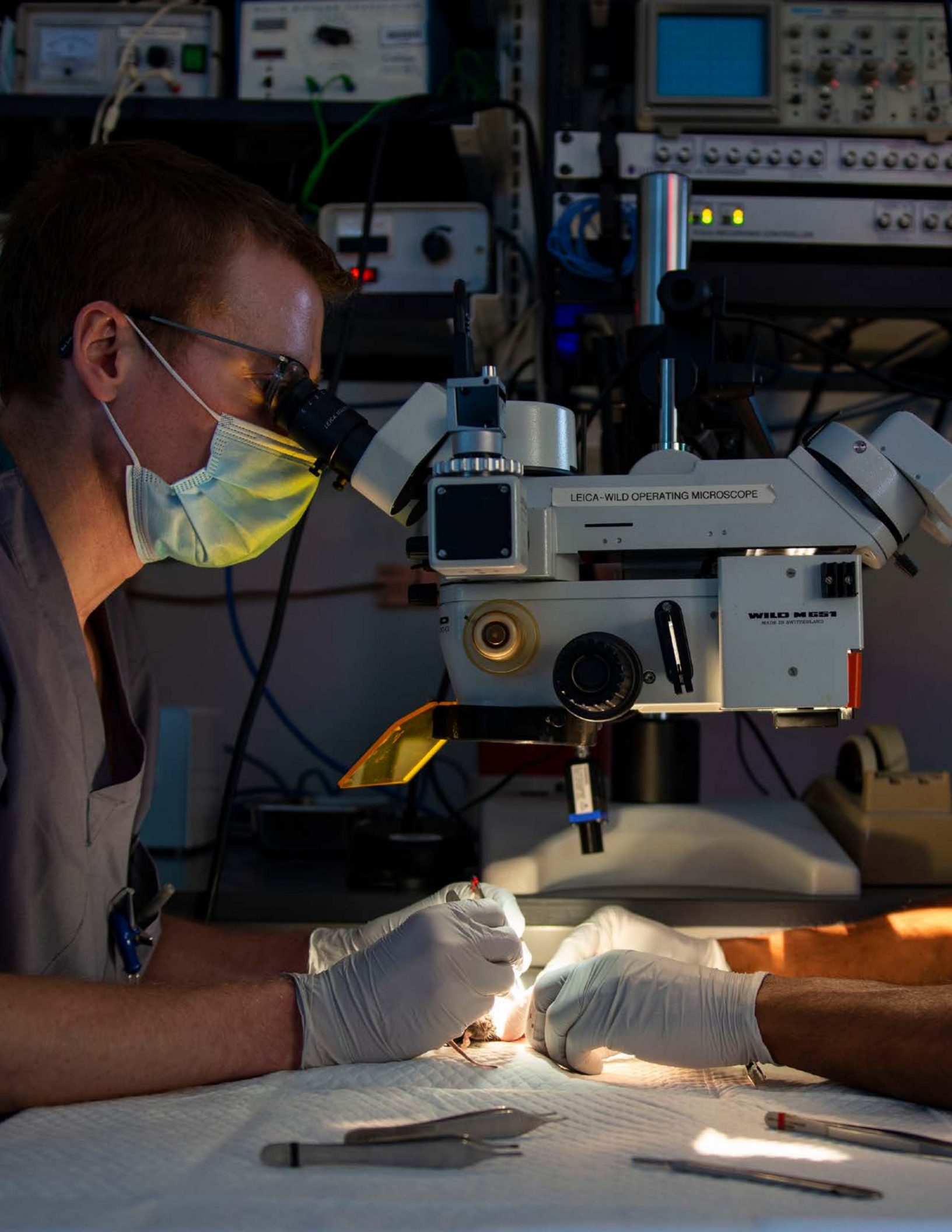
Kristina Simonyan, MD, PhD, contributed substantially to the diagnosis and treatment of laryngeal dystonias with recent work on microstructural neural network biomarkers for dystonia diagnosis identified by a DystoniaNet, a deep learning platform. Isolated dystonia is a neurological disorder of heterogeneous pathophysiology, which causes involuntary muscle contractions leading to abnormal movements and postures. Its diagnosis is remarkably challenging due to the absence of a biomarker or gold standard diagnostic test. This leads to a low agreement between clinicians, with up to 50% of cases being misdiagnosed and diagnostic delays extending up to 10.1 years. Dr. Simonyan and colleagues developed a deep learning algorithmic platform, DystoniaNet, to automatically identify and validate a microstructural neural network biomarker for dystonia diagnosis from raw structural brain MRIs of 612 subjects, including 392 patients with three different forms of isolated focal dystonia and 220 healthy controls. DystoniaNet identified clusters in corpus

callosum, anterior and posterior thalamic radiations, inferior fronto-occipital fasciculus, and inferior temporal and superior orbital gyri as the biomarker components. The DystoniaNet-based biomarker showed an overall accuracy of 98.8% in diagnosing dystonia and significantly outperformed shallow machine-learning algorithms in benchmark comparisons, showing nearly a 20% increase in its diagnostic performance. The translational potential of this biomarker is in its highly accurate, interpretable, and generalizable performance for enhanced clinical decision-making.

Thyroid and Parathyroid Surgery
Divisional research has focused on a variety of topics related to surgery of the thyroid and parathyroid glands, in addition to gender disparities in academic head and neck surgical programs.

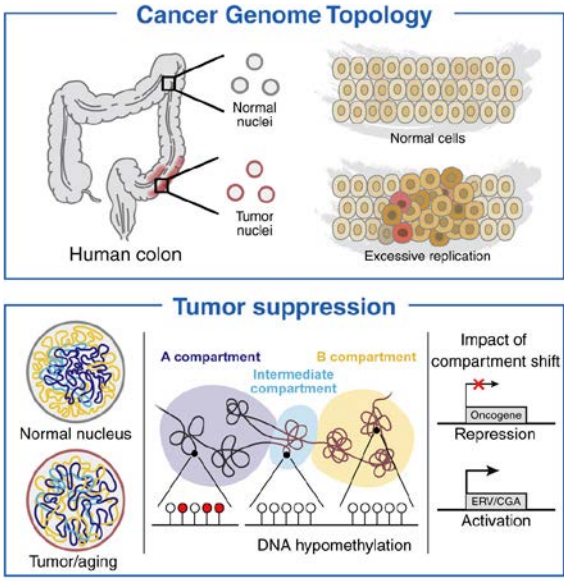
Greg Randolph, MD, FACS, FACE, and colleagues surveyed 37 AHNS accredited head and neck fellowships and quantitated the activities of 732 faculty members associated with those fellowships. Leadership positions were found to be held by females in only 10% of cases. However when they studied the academic productivity of senior faculty members they found no difference between men and women. They describe that the ultimate productivity of men and women are the same but that the time frame of their contributions vary through the faculty's career and that this timed nuance in academic productivity should be taken into account by department leadership in regards to leadership positions, promotion and compensation.

Alan Workman, MD, MTR, and **Greg Randolph, MD, FACS, FACE,** and colleagues developed a proposal for improved preoperative diagnosis for optimal initial medullary thyroid carcinoma specific surgery. This study investigated the ability, through standard cytology, to preoperatively identify medullary cancer of the thyroid (MTC). The investigators found between one third and one half of patients are not clearly identified by preoperative cytology. This has major implications in terms of the correct surgery being offered to the patient with safety and with optimal patient outcomes, which are historically poor for MTC. The group proposed algorithms that would allow the definitive and complete detection of all cases of medullary cancer of the thyroid given lack of sensitivity of cytological evaluation.


LEICA-WILD OPERATING MICROSCOPE
WILD M651

Pathology

Department Report



Spatial partitioning of the open and closed genome compartments is profoundly compromised in tumors. This reorganization is accompanied by compartment-specific hypomethylation and chromatin changes. Remarkably, similar shifts were evident in aged, non-malignant cells. These analyses suggest that the topological changes found in aging also repress stemness and invasion programs in cancer while also inducing anti-tumor immunity genes to restrain malignant progression *(Johnstone et al., Cell 2020).*

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, genomics, and epigenetics as well as with single-cell and genome editing technologies. Over the past several years, we have implemented initiatives identified from our departmental strategic planning process: leveraging our world-class expertise in genome editing and clinical genome sequencing to expand our understanding of the functional significance of DNA sequence variants; expanding computational biology and bioinformatics faculty, personnel, and infrastructure to accelerate the development of the novel discipline of Computational Pathology; and building collaborations and interactions throughout the MGH through our Center for Integrated Diagnostics. We believe that these efforts will help to ensure that MGH Pathology faculty remain at the forefronts of their fields, enabling them to continue advancing our understanding and diagnosis of human diseases.

Achievements:

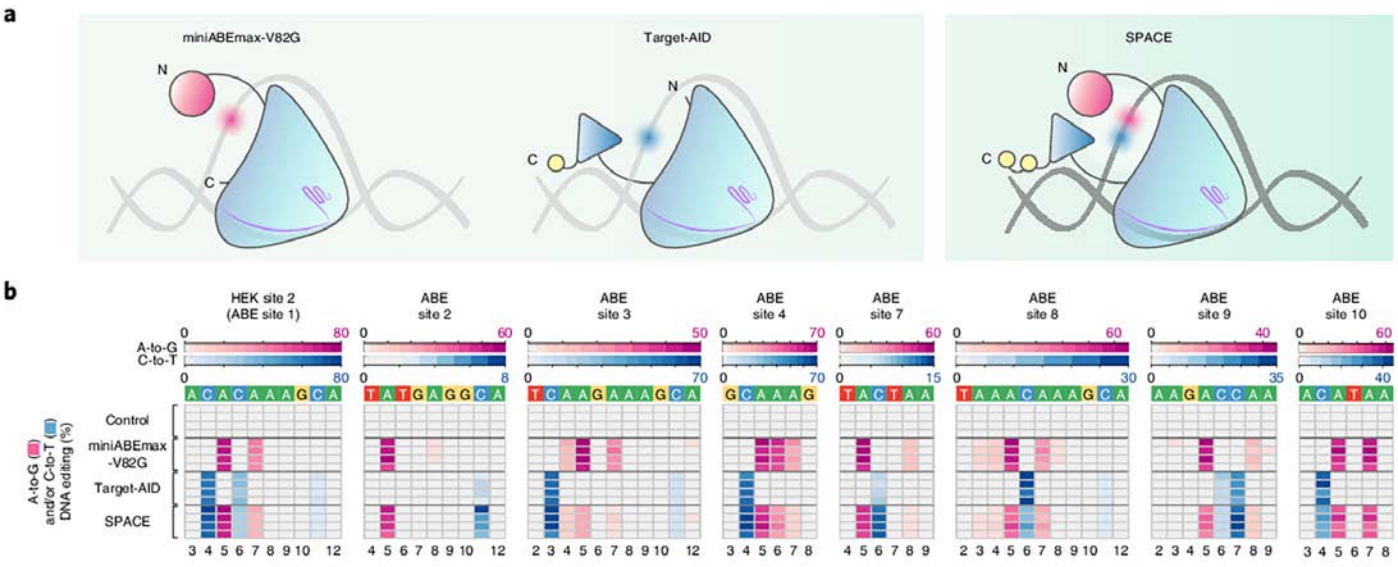
Large-Scale Topological Changes Restrain Malignant Progression in Colorectal Cancer.
Johnstone SE, Reyes A, Qi Y, Adriaens C, Hegazi E, Pelka K, Chen JH, Zou LS, Drier Y, Hecht V, Shoresh N, Selig MK, Lareau CA, Iyer S, Nguyen SC, Joyce EF, Hacohen N, Irizarry RA, Zhang B, Aryee MJ, Bernstein BE*. Cell. 2020;182(6):1474-1489. PMID: 32841603*

This study was the first to map the 3D nuclear DNA structure of the cancer genome, combining experimental epigenomic techniques with the development of novel computational approaches for 3-D modeling that involved the processing of over 28 billion sequencing reads. The work revealed that colon cancer cells undergo large scale reorganization and compaction of repressive chromatin. The reorganized segments of DNA, representing almost half of the genome, correspond to those that undergo hypomethylation in cancer. Although loss of DNA methylation in solid tumors was the first described cancer-associated epigenetic change, its function has been

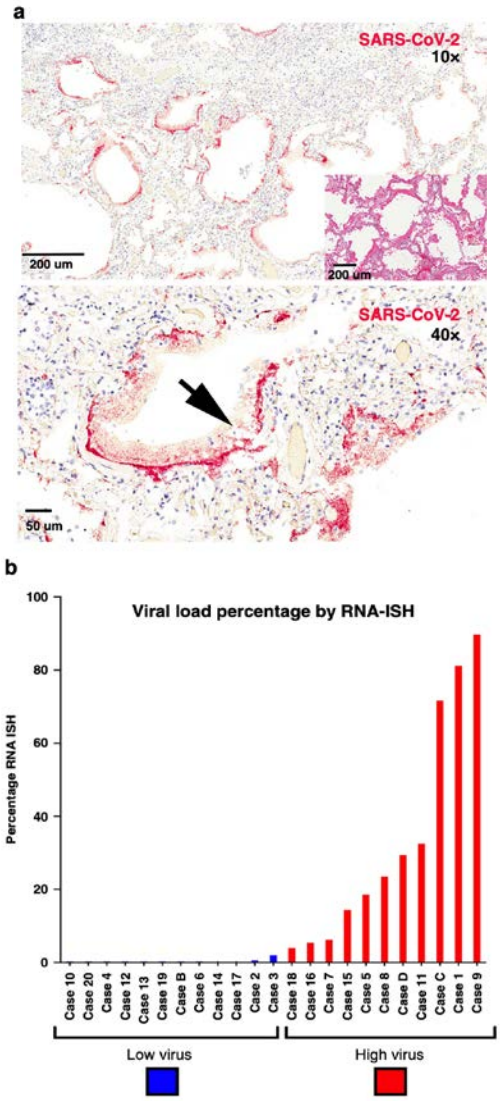
poorly understood. This study showed that DNA methylation loss only happens in specific physical nuclear compartments and linked it to functional changes in chromatin compaction and repression. A key surprising finding of the paper is that these characteristic epigenetic changes seen in all solid tumors, are in fact not oncogenic, but rather appear to be tumor suppressive. The same changes can be seen in normally aging cells, and are associated with repressed stemness, invasion and proliferative gene expression programs. Cancer cells are able to circumvent this tumor suppressive effect, through mechanisms that include genetic mutations, to facilitate tumor growth.

A dual-deaminase CRISPR base editor enables concurrent adenine and cytosine editing.
Grünewald J, Zhou R, Lareau CA, Garcia SP, Iyer S, Miller BR, Langner LM, Hsu JY, Aryee MJ, Joung JK. Nat Biotechnol. 2020;38(7):861-864. PMID: 32483364

Existing adenine and cytosine base editors induce only a single type of modification, limiting the range of DNA alterations that can be created. Here, Grünewald et al. describe a CRISPR-Cas9-based synchronous programmable adenine and cytosine editor (SPACE) that can concurrently introduce A-to-G and C-to-T substitutions with minimal off-target edits. SPACE expands the range of possible DNA sequence alterations, broadening the research applications of CRISPR base editors. For example, SPACE adds 60 additional codon changes (resulting in 18 amino acid substitutions) that cannot be created with existing editing approaches. In addition, SPACE could be useful



A CRISPR-Cas9-based synchronous programmable adenine and cytosine editor (SPACE) concurrently introduces A-to-G and C-to-T substitutions with minimal RNA off-target edits. a, Schematic illustrating adenine base editor miniABEmax-V82G, cytosine base editor Target-AID, and dual-deaminase base editor SPACE. A-to-G (pink halo) and C-to-T (blue halo) base edits are illustrated. Light blue shape indicates Steptococcus pyogenes Cas9 (D10A) nickase, purple structure in Cas9 represents the guide RNA, pink circle represents the TadA 7.10 (V82G) adenosine deaminase monomer, blue triangle indicates the cytidine deaminase pmCDA1, and yellow circles represent uracil glycosylase inhibitors (UGIs). b, Heat maps showing on-target DNA A-to-G (pink) and C-to-T (blue) editing frequencies across gRNAs *(n= 4 independent replicates; Grünewald et al, Nat Biotechnol. 2020).*



Detection of SARS-CoV-2 in human autopsy samples identifies two distinct pathologies associated with infection. a, Paraffin embedded sections from the lung show abundant SARS-CoV-2 extracellular RNA-ISH signal (red) predominantly localization to the hyaline membranes (arrow). The inset shows the corresponding hematoxylin and eosin stained section with histologic features of exudative diffuse alveolar damage with prominent hyaline membranes. b, Percentage of viral load in the lung identifies two subsets of patients that die from complications related to SARS-CoV-2 as determined by a quantitative analysis by RNA-ISH. This work went on to evaluate the spatiotemporal relationship of viral load and host microenvironment response to this disease that will help inform the design of new trials *(Desai et al., Nature Communications 2020).*

for creating or reverting multi-nucleotide variants (MNVs), a newly emerging category of sequence variants associated with disease. Notably, among MNVs, TG-to-CA and CA-to-TG (both inducible by SPACE) are the most frequent consecutively arising adjacent dinucleotide MNVs. Furthermore, the greater combinatorial diversity of mutations that result with SPACE as compared with single-deaminase base editors could make it attractive for molecular recording systems (e.g., lineage tracing) as well as for saturation mutagenesis screens, directed evolution, and protein engineering.

Simultaneous Identification of Cell of Origin, Translocations, and Hotspot Mutations in Diffuse Large B-Cell Lymphoma Using a Single RNA-Sequencing Assay.
Crotty R, Hu K, Stevenson K, Pontius MY, Sohani AR, Ryan RJH, Rueckert E, Brauer HA, Hudson B, Berlin AM, Rodenbaugh M, Licon A, Haimes J, Iafrate AJ, Nardi V, Louissaint A. Am J Clin Pathol. 2020:aqaa185. PMID: 33258912

Diffuse large B-cell lymphoma (DLBCL) is an aggressive non-Hodgkin lymphoma with a heterogenous genetic landscape that can require multiple assays to characterize. Here, Crotty et al. report an RNA-based assay to determine cell of origin, detect translocations, and identify mutations. Using a single custom Archer FusionPlex Lymphoma panel, anchored multiplex polymerase chain reaction-based RNA sequencing was performed on 41 cases of de novo DLBCL. This FusionPlex assay offers a robust, single method for cell of origin classification, mutation detection, and identification of important translocations in DLBCL.

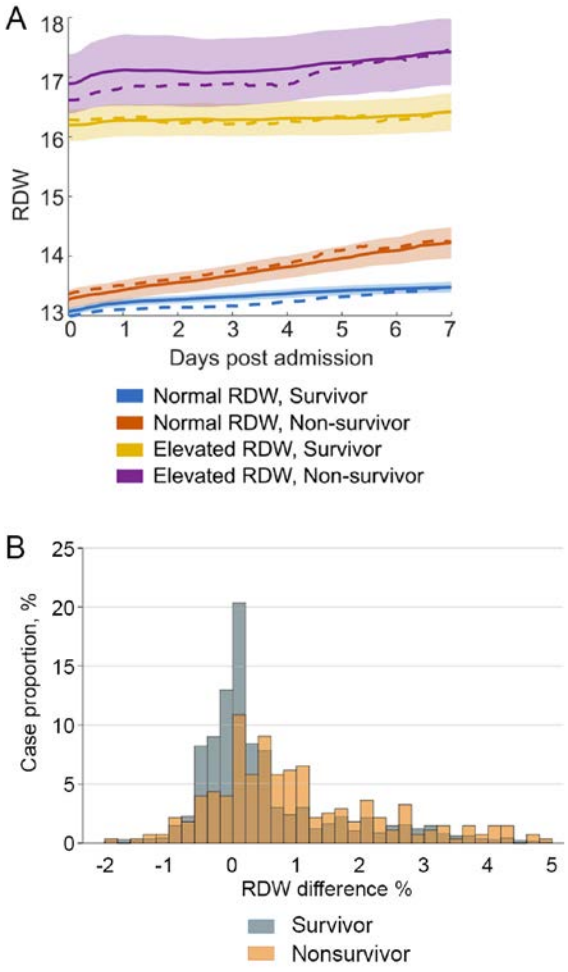
Temporal and spatial heterogeneity of host response to SARS-CoV-2 pulmonary infection.
Desai N, Neyaz A, Szabolcs A, Shih AR, Chen JH, Thapar V, Nieman LT, Solovyov A, Mehta A, Lieb DJ, Kulkarni AS, Jaicks C, Xu KH, Raabe MJ, Pinto CJ, Juric D, Chebib I, Colvin RB, Kim AY, Monroe R, Warren SE, Danaher 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 relationship of SARS-CoV-2 pulmonary infection and severity of disease is not fully understood. Here, Desai et al. analyzed autopsy specimens from 24 patients who succumbed to SARS-CoV-2 infection using a combination of different RNA and protein analytical platforms to characterize inter-patient and intra-patient heterogeneity of pulmonary virus infection. There is a spectrum of high and low virus cases associated with duration of disease. High viral cases have high activation of interferon pathway genes and a predominant M1-like macrophage infiltrate. Low viral cases are more heterogeneous likely reflecting inherent patient differences in the evolution of host response, but there is consistent indication of pulmonary epithelial cell recovery based on napsin A immunohistochemistry and RNA expression of surfactant and mucin genes. Using a digital spatial profiling platform, the authors found that the virus corresponds to distinct spatial expression of interferon response genes demonstrating

the intra-pulmonary heterogeneity of SARS-CoV-2 infection. This work identified two distinct clinical presentations of infection, both of which led to patient mortality. This work provides the foundation to evaluate the spatiotemporal relationship of viral load and host microenvironment response to this disease, findings that are likely to inform the design of future interventional trials.

Association of Red Blood Cell Distribution Width With Mortality Risk in Hospitalized Adults With SARS-CoV-2 Infection.
Foy BH, Carlson JCT, Reinertsen E, Padros I Valls R, Pallares Lopez R, Palanques-Tost E, Mow C, Westover MB, Aguirre AD, Higgins JM. JAMA Netw Open. 2020;3(9):e2022058. PMID: 32965501

Red Blood Cell Distribution Width (RDW) is a standard component of the routine complete blood count (CBC) that measures the amount of variation in the size of a patient's red blood cells. Higher RDW means more difference in the size of one red blood cell compared to another. In the past decade, many studies have found that elevated RDW is associated with poor prognosis in a very wide range of disease including infection, cancer, heart disease, and autoimmunity. Here, Foy et al. found that patients whose RDW was elevated when they were admitted to the hospital for COVID-19 had a 31% mortality rate, while patients whose RDW was not elevated had an 11% mortality rate. This work identified a widely available biomarker that was associated with an overall 2.7x increased risk of death. This work also identified that hospitalized COVID-19 patients whose RDW increased during hospitalization had a 2-4x increased risk of death. The association between RDW and COVID-19 mortality remained significant after adjusting for patient age and other identified risk factors including some pre-existing illnesses. The association reported by Foy et al. uses a widely-available test to identify COVID-19 patients who are at elevated risk of mortality and should be prioritized for close monitoring and aggressive interventions.



Increased Red Blood Cell Distribution Width (RDW) following admission identifies high mortality risk among patients with SARS-CoV-2. A, Stratifying patients based on admission RDW and mortality reveals that, among patients with an RDW of 14.5% or less at admission, those who do not survive have an average RDW increase of 1.5% during their first week of hospitalization. Shading represents the 95% CI. Mean trajectories when including patients with shorter hospital stays (< 7 days) are also included (dashed line). B, A histogram showing that nonsurvivors were more likely than survivors to experience an RDW increase during hospitalization. Change in RDW is reported in percentage points. For instance, a change in RDW from 14.0% to 15.0% is reported as 1.0% *(Foy et al., JAMA Netw Open. 2020).*

Pediatrics

Department Report

RONALD E. KLEINMAN, MD, CHIEF

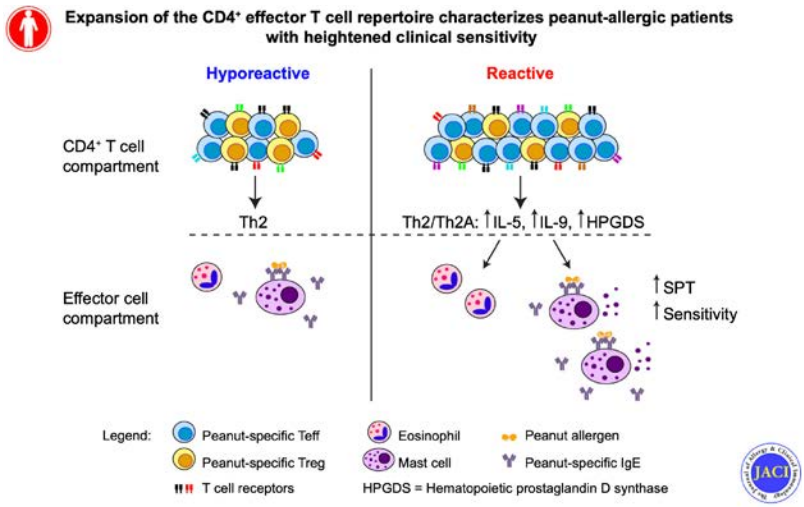
Overview:

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 MGHfC recognizes the challenges and opportunities for child health research dictated by the changing social, economic and health care policy landscape in the US, including the shift toward Precision Medicine. Across the Department, our research integrates multidisciplinary clinical and scientific expertise with local, regional, national and international collaborations.

With the appreciation that biological events beginning during gestation and continuing into childhood can strongly influence disease onset during childhood and beyond, we intend to expand our integrated models focused on pre-clinical/early and translational clinical studies to provide the rationale for possible therapeutic and/or preventive interventions. Our overarching **goal** is to improve the lives of children and families through science. A current strategic **priority** is to develop new effective personalized and preventive strategies for disorders *starting in childhood* by integrating multi-level, multisystem data ranging from the molecular to the whole child in order to prevent or reverse development of disease. To better coordinate our effort and to integrate our scientific mission within the MGH Research Institute we have established the Pediatric Translational Research Center (PTRC) in which basic, translational, clinical, and community-based research are blended to deliver state-of-the-art clinical care, to provide superb training opportunities, and foster cutting-edge discoveries to achieve our mission. Furthermore, since the beginning of the COVID-19 pandemic and during the initial lockdown, we have repurposed our research enterprise to support the MGH effort in developing 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). Once we have regained access to the labs and resumed clinical trials, our research faculty has gradually returned to routine research, however we 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



Expansion of the CD4+ effector T cell repertoire characterizes peanut-allergic patients with heightened clinical sensitivity.

research effort, The Food Allergy Center at Massachusetts General Hospital (FAC@MGH) was established in 2010 as a multi-disciplinary research and clinical care virtual center with the recruitment of Dr. Shreffler to provide leadership, and the core participation of clinicians and investigators from Allergy / Immunology, Rheumatology, Gastroenterology, Dermatology, Pathology, Psychology, Nutrition, Child Life and the Harvard CTSA-supported, MGH Clinical Research Center (CRC). At the time of its inception, there were no clinical trials, interventional or otherwise, focused on food allergy at MGH. To date, the FAC@MGH has initiated more 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 cohorts / 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, Dr. Michael Pistiner leads our program on Prevention, Education and Advocacy. This program is one of the largest in the country targeting high risk infants by

collaborating with primary care pediatricians in the MGH/Mass General Brigham network to lower the barriers of access in order to expand the early childhood diet to include common allergens—the most effective means of allergy prevention currently proven—and to develop a national model for doing this in other settings. Because of Dr. Pistiner's efforts, effective Dec 2018, we have also become the second site for an NIAID-funded prevention study, led by our colleagues at Johns Hopkins University and have attracted other new extramural funding for education and prevention as well. 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.

Cardiology

The Pediatric/Congenital Cardiology division is involved in research in basic science and health services research to understand the causes of congenital heart disease and to study clinical interventions to improve the provision of pediatric cardiovascular care and foster a patient centered environment. We are fortunate to have a robust clinical and academic environment to promote these research endeavors. Members of our service are engaged in basic science research understanding the genetic etiologies of vascular pathology such as aortopathies (e.g. Marfan and Loeys Dietz syndromes). We are also involved in health services research specifically in the area of patient safety and quality as it pertains to pediatric cardiology. We have ongoing investigations evaluating diagnostic accuracy of cardiac imaging, investigations evaluating of parental health literacy among congenital heart disease families, and studies of resource use among patients undergoing congenital heart surgery. Our preventative cardiology service has collaborated with the Harvard T.H. Chan School of Public Health on projects to examine outpatient and wireless means to track physical activity and caloric intake.

Critical Care Medicine

A major focus of the division of Pediatric Critical Care Medicine is preventing and understanding mechanisms of pediatric traumatic brain injury. Our neurocritical care research efforts include basic science and translational studies to understand cellular and molecular events that occur following brain trauma, with the goal of finding new therapies that mitigate specific maladaptive responses and improve outcome. In addition, we seek to inform public health trauma prevention strategies to reduce pediatric traumatic brain injury through our Trauma and Injury Prevention Outreach Project (TIPOP). This multidisciplinary group focuses research, community outreach, and education on the most common causes of pediatric injuries leading to emergency department visits and PICU admissions,

including motor vehicle accidents, window falls, firearms violence, burns and recreational-related trauma. Our division is also dedicated to better understanding the long-term neurological sequelae of critical illness to better inform our practice, particularly as it relates to long-term exposure to pain and sedation medications. Finally, the division is committed to better understanding existing modalities that deliver non-invasive respiratory support during critical illness and to developing innovative technologies for use in low-resource settings.

Endocrinology

The focus of research in the Division of Endocrinology is to enhance the understanding of endocrine systems and endocrine disease during the childhood, adolescent and transition years. Areas of particular interest include investigations into the neurobiology of conditions that span the weight spectrum from obesity to exercise induced amenorrhea to anorexia nervosa utilizing state-of-the-art neuroimaging techniques coupled with investigations of circulating hormones important in appetite regulation, and carbohydrate, fat and bone metabolism. Other areas of interest include investigations of novel technologies related to diabetes care, and the impact of administration of the growth hormone releasing hormone analog, tesamorelin, on carbohydrate and fat metabolism. We will continue to foster an environment of inquiry and investigation among our faculty and fellows, work on optimizing funding opportunities to maintain a strong research base within the division. This includes intra- and extra-mural collaborations with other laboratories actively engaged in these areas to create a rich and interactive reinforcing environment that will lead to changes in medical care paradigms for children with endocrine disorders.

Gastroenterology, Hepatology & Nutrition

Mucosal Immunology and Biology Research Center

Our mission is to expand clinical, basic and translational research in pediatric gastroenterology and nutrition to provide better outcomes for pediatric patients. Using a multidisciplinary approach, our major basic research mission is to characterize the role of the enteric mucosa and its mucosal barrier function at the interface between microbial luminal stimuli and lymphoid effector responses. We focus on the enterocyte and its involvement in microbial “crosstalk,” lymphoid-nerve-epithelial interactions and inappropriate developmental responses secondary to epigenetic pressure by the gut microbiota during the first 1000 days of life. We also look at host-pathogen interactions during infection as well as how the enterocyte functions both as a barrier to antigen trafficking and as a site for the beneficial effects of probiotics in chronic inflammation. Finally, we are interested in the gut-brain axis, particularly as concerns small intestinal and blood brain barriers in the contest of neuroinflammatory diseases. Our researchers examine strategies used by gut microbiota to affect the host and how these interactions lead to both local and systemic chronic inflammation and autoimmunity in the Mucosal Immunology and Biology Research Center (MIBRC). The MIBRC

tool also lead to repurpose the research of many of its members to work on COVID-19-related research, mainly focusing the effort in establishing a large pediatric biobank collecting samples (including urine, nasal swabs, saliva, urine, stools) for more than 500 children and almost 40 children affected by MIS-C, so creating one of the largest pediatric COVID-19 biobank in the nation. In addition, active clinical and translational research to implement personalized and primary preventive medicine is carried out in our Airway, Voice and Swallowing Center for Children; the Center for Celiac Research and Treatment; the Center for Diagnostic, Therapeutic and Interventional Endoscopy; the Center for Inflammatory Bowel Disease; the Center for Nutrition; the Center for Pediatric Hepatobiliary and Pancreatic Disease; the Food Allergy Program; the Liver Transplantation Program; the Lurie Center for Autism Pediatric Gastroenterology Program; the Neurogastroenterology Program and the Pediatric Weight Center.

General Academic Pediatrics

Our internationally-known academic research division continues to be dedicated to improving the health of children and adolescents through research on prevention and reduction of the burden of chronic disease among children; reduction and elimination of disparities in children's health and healthcare; evaluating the costs and cost-effectiveness of interventions and screening guidelines; and improving the health of populations across the life course through innovations in research, patient care, education, and community advocacy. We also conduct research to prepare and support primary care pediatricians in the delivery of health care innovations, leveraging clinical and community partnerships to implement and sustain effective interventions.

Division faculty have a wide variety of research specialties, including:

- Childhood obesity prevention and treatment, including understanding the role physical activity and other health behaviors play in chronic disease prevention, the development of new, innovative childhood obesity interventions, and the dissemination and implementation of proven-effective programs.
- Providing comprehensive, high quality care to children with special health care needs, including autism spectrum disorder through collaborations such as the Autism Intervention Research Network on Physical Health (AIR-P), Autism Speaks Autism Treatment Network (ATN), and the newly created Autism Learning Health Network (ALHN).
- Strategies to address tobacco use and exposure in families, including the development of the Clinical Effort Against Secondhand Smoke Exposure (CEASE) program available in all 50 states for free, thirdhand smoke, electronic cigarettes, regulating smoking in multiunit housing, and raising the purchase age of tobacco to 21.
- Maternal-child health throughout the life course, including how substance use in pregnant and parenting women impacts the health of children and families, obesity prevention efforts beginning pre-conception and in pregnancy, and the role and influence of fathers in the early life period.

- How the built environment, such as architecture and urban planning, can affect individual and population health.
- Health outcomes of HIV-infected adolescents and adolescents at risk for HIV infection.

Genetics and Metabolism
The Division of Medical Genetics and Metabolism at MGHfC provides diagnostic analyses and cares for individuals with developmental, congenital and metabolic disorders affecting the entire life course. We are actively engaged in basic science at the cellular and sub-cellular level at the bench and as well in translational and clinical studies. We perform counseling, diagnostic and management services helping patients and physicians to better understand the genetic contributions to their health and disease and to diagnose and treat a wide variety of genetic/metabolic conditions. We have established specialty clinics in metabolism, lysosomal storage diseases, mitochondrial disease, Turner syndrome, William syndrome, 22q deletion syndrome, Stickler syndrome, Klinefelter syndrome, hereditary hemorrhagic telangiectasia, CHARGE syndrome, a multidisciplinary Sensorineural Hearing Loss Clinic at the MEEI, an Autism Genetics Clinic at the Lurie Center, Pitt Hopkins Syndrome Clinic and Pediatric Cancer Predisposition Clinic. Our multidisciplinary Down Syndrome Clinic leads the way in care and research including participation in groundbreaking clinical therapeutic trials of agents to improve cognitive function in people with Down syndrome. Our Williams syndrome and Pitt Hopkins syndrome clinics are world renown the largest experience with these patients of any site in the world and regularly have international referrals seeking our expertise. Active clinical trials are also underway with lysosomal storage diseases and mitochondrial diseases. The MGH Genetics Division has been at the forefront of applying clinical whole exomic sequencing for diagnosis and new gene discovery in selected patients and participates in the NIH sponsored Undiagnosed Diseases Network. Our services impact every field of pediatric and adult medicine. We have active engagement throughout the hospital in advisory and teaching capacities assisting other providers and committees in the implementation of genetics in medicine.

Global Health
Founded in 2010, the Division of Global Health at MassGeneral Hospital is actively engaged in interdisciplinary research, education and clinical care aimed at improving the wellbeing of the most vulnerable children in our global community. The Division includes faculty, research fellows and staff with diverse experiences and interests but a shared dedication to the health and development of children across the globe. Building upon MassGeneral Hospital for Children's long-standing commitment to scientific and clinical innovation, our faculty and staff work to combat prematurity, birth asphyxia, neonatal sepsis, childhood pneumonia, cholera transmission, and HIV at several sites across the globe.

Pediatrics

Department Report

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. Dr. Verena Göbel in our division has been a leading basic science investigator studying lumenogenesis and cell polarity. These studies have important implications for tumor invasion and metastasis Dr. David Sweetser's lab is focusing on the interaction of the bone marrow microenvironment and leukemic stem cells. The tumor microenvironment has become important to the 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 Dr. Miguel Rivera's research in the Department of Pathology using epigenome editing tools to examine the genetic drivers in Ewing sarcoma and medulloblastoma and Dr. Shannon Stott's research in the MGH Cancer Center isolating exosomes and circulating tumor cells ("liquid biopsy") from the peripheral blood of patients with brain tumors and sarcomas for diagnosis and a noninvasive method to monitor response to therapy.

Infectious Disease

The Pediatric Infectious Disease Unit has been active in both basic science and in translational/clinical research. Dr. Harris's externally funded cholera research efforts encompass investigation of the immune response to Vibrio cholerae infection with an emphasis on vaccine response and development, and exploration of the molecular epidemiology and ecology of V. cholerae. He has also initiated a series of studies relating to the serologic response to SARS-CoV 2 infection. Dr. Warren's pivotal discovery over the past several years of the differential genomic responses between humans and mice to sepsis and inflammation has led to the establishment of a large multicenter project to investigate mechanisms responsible for species-specific sensitivity to inflammation and to develop novel therapies to treat human sepsis. Dr. El Saleeby has been developing refined vancomycin dosing algorithms for hospitalized children. Dr. Pasternack has been part of a clinical and research consortium focused on the study of children with PANDAS (pediatric autoimmune neuropsychiatric

disorder associated with streptococcal infection). Dr. Pierce is engaged in the development of novel molecular diagnostic tools for the clinical microbiology laboratory.

Lurie Center for Autism

At the Lurie Center for Autism, the primary focus is to partner with individuals and families to incorporate groundbreaking research into the practice of clinical medicine. The integration of clinical care and clinical research through the initiation of clinical treatment trials continues to be a focus. There are exciting clinical studies looking at new molecules for the treatment of Angelman syndrome (Dr. Chris Keary), and, along with researchers at the Lincoln Lab of MIT, Dr. Lisa Nowinski has initiated a study of movement and gait in children with ASD. Our collaborative research project with Dr. Jacob Hooker, Phyllis and Jerome Lyle Rappaport MGH Research Scholar, and Dr. Nicole Zurcher (Martinos Center) aims to identify an "inflammatory subtype" of autism and has produced very exciting preliminary findings. To identify inflammation within the brains of patients with autism spectrum disorder (ASD), we are assessing translocator protein 18 kDA (TSPO) expression in individuals using [^{11}C]PBR28 positron emission tomography (PET) imaging. Preliminary results show a striking decrease in the expression of this protein in males with ASD compared to age- and gender-matched typically developing controls, indicating a change in neuroimmune activity within the brains of patients. Our publications on methods for preparing adults with ASD for MR/PET scanning highlights our commitment to engaging and preparing patients for success in research. Ongoing work in this model aims to incorporate females in these studies based on evidence in mice and in postmortem human brains that immune system function within the brain differs between males and females, which we believe has relevance for the sex bias in ASD (4:1 males to females). Our ongoing work is to develop an animal model to determine the function of TSPO protein changes, both in the brain and in the peripheral (blood) cells of males and females, and these studies are underway in Dr. Marcie Kingsbury's lab. Finally, the pre-clinical arm of the Lurie Center and the clinical arm (researchers and clinicians) have established a monthly "think tank" for consistent interaction and cross-fertilization of ideas.

Neonatology and Newborn Medicine

The research effort in the Neonatology and Newborn Medicine Unit is multifaceted and ranges from basic science to epidemiology. 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 including birth asphyxia 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 and to improve 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. 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. 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 large amounts of GMP-grade PTH-IA is now well underway, which will be used to conduct toxicology studies in animals. If no evidence for side effects is obtained, the first clinical trials in adult patients affected by Jansen's disease will be started in 2022. 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.

Neurology
The Neurology Department seeks to directly improve child health through cutting-edge translational projects. These include a bench-to-bedside effort to find more effective therapies for neonatal seizures, improving the detection of active disease in adrenoleukodystrophy, and optimizing genetic therapies and response metrics for leukodystrophies and spinal *muscular* atrophy, and dietary therapy for hereditary sensory and autonomic neuropathy type 1. Basic studies are focused on metabolic disorders including sulfite oxidase deficiency and the genetic origins of mitochondrial disorders; corticothalamic dysfunction underlying comorbidities of epilepsy including learning disabilities and sleep disorders; the driving forces for neurotransmitter-mediated neuronal inhibition. Clinical studies include characterizing genetically-based epilepsies and neurocutaneous syndromes and testing new therapies for intractable childhood epilepsies. Highlights for 2019 include a paper in *Neurology* describing MRI findings in adrenoleukodystrophy, a study published in the *Journal of Neuroscience* describing how seizures start and stop; a trial of dietary therapy for hereditary sensory and autonomic neuropathy type 1 published in *Neurology;* a paper describing the phenotype of a mitochondrial disorder manifesting with ataxia; and a study describing EEG measures of seizure recurrence risk published in *Brain*.

Pediatric Palliative Care
In 2019, we embarked on a pilot of a novel model of care for children with serious illness. We have combined the medical home model of the Coordinated Care Clinic with the predominantly inpatient palliative care service to provide more comprehensive and seamless care to a small population of children whose care represents the most expensive and intensive. These patients are characterized by frequent or prolonged admissions to hospital and repeated transitions from home to hospital to outpatient and community services.

Pulmonary
The research focus of the Pulmonary Division has broadened this past year to include research related to COVID-19. The first area of research, led by Drs. Lael Yonker and Bernard Kinane is the mechanism of spread of COVID-19 and the immunological basis of MIS-C. The second area, led by Dr. Lael Yonker, is an effort to develop new models of the cystic fibrosis (CF) airway. She is also leveraging this model system to develop an understating of how COVID-19 induces lung inflammation. The third area lead by Drs. Lael Yonker and Bethany Bartley focuses on CF palliative care. They designed primary palliative care interventions to provide chronic symptom management at all stages of the disease. The fourth area of

research, led by Drs. Bernard Kinane and Lael Yonker is the genetic basis of lung disease including interstitial lung disease and non-cystic fibrosis bronchiectasis. In collaboration with the Mass General Brigham Center for Personalized Medicine, they have developed standard diagnostic approaches that are used across the Nation. Finally, in the area of education research, Dr. Ben Nelson established a CPC type program that publishes in cases in Pediatric Pulmonology.

Rheumatology
Investigators in the Pediatric Rheumatology Program lead and participate in clinical research that include observational research studies and randomized clinical trials, as well as investigator-initiated outcomes and adverse event studies, across a wide range of childhood-onset rheumatic diseases. As part of such research efforts, we enroll patients as a member site of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, which is a long-term, multi-site prospective observational study focused on safety and disease outcomes that combines FDA Phase IV post-marketing surveillance with outcomes research. In addition, MGH will be an enrolling site for the LIMIT-JIA clinical trial, funded by Patient-Centered Outcomes Research Institute—this is the first FDA Phase III study of prevention of disease progression in patients with limited Juvenile Idiopathic Arthritis (JIA), the most common subtype of JIA. As part of these studies, MGH is also participating in the development of advanced clinical informatics strategies, including development of computable phenotypes for JIA, to improve the efficiency of enrolment for rare disease studies, under the leadership of Marc Natter as site PI.

Other research in our program focuses on creating and improving guidelines for the safety monitoring of children receiving rituximab and strategies for preventing immunosuppression-related infections among high-risk patients with pediatric-onset rheumatologic diseases. Deborah Rothman has received a grant from CARRA to study the association between rituximab and infection risk. We are currently performing a retrospective study of children (<18 years old) who received rituximab using data using EHR data from subjects at MGH and other sites that assesses risk factors such as the immunoglobulin deficit to infection risk following rituximab treatment. During the COVID-19 pandemic we have partnered with our Infectious Disease, Cardiology, and other colleagues to develop guidelines for the management of MIS-C, Multisystem Inflammatory Syndrome in Children at MGHfC. We also have been participating in daily multidisciplinary rounds to discuss the management of these children.

Achievements:

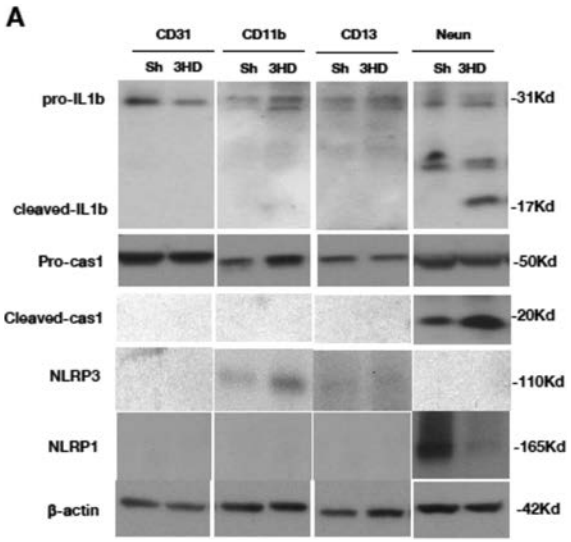
1. Identification of allergen-specific T cell repertoire expansion is a biomarker of clinical allergic sensitivity.
Ruiter B, Smith NP, Monian B, Tu AA, Fleming E, Virkud YV, Patil SU, Whittaker CA, Love JC, Shreffler WG. Expansion of the CD4+ effector T-cell repertoire characterizes peanut-allergic patients with heightened clinical sensitivity. J Allergy Clin Immunol. 2020 Jan;145(1):270-282.

Some individuals with confirmed peanut allergy can ingest more than a gram of peanut before experiencing any symptoms while others suffer systemic reactions to less than 100 times that amount. Current diagnostic testing (specific IgE and skin testing) does not predict this enormous clinical variability. As they play a central role in antigen-specific immunity, we hypothesized that a quantitative measure of the antigen-specific CD4 effector T cell response might be a biomarker capable of capturing some of this heterogeneity. We studied the T-cell receptor ß-chain (TCRß) usage and phenotypes of peanut-activated, CD154+ CD4+ memory T cells from patients who were stratified by their clinical sensitivity. We employed a novel approach to statistically identify likely peanut-specific clones based on their enrichment in the peanut-activated fraction (CD154+/CD154-) after *in vitro* stimulation. Consistent with antigen-specific selection, these putatively specific clones were significantly more homologous than the overall CD154+ population; in fact for 17% of them, the full CDR3 was 'public' among peanut allergic individuals and several sequence motifs within the CDR3 were highly ubiquitous. Consistent with our hypothesis of immune progression within CD4 effector cells, putatively specific clones were significantly expanded among the reactive over the hyporeactive patients, and this expansion was identified within effector, but not regulatory T-cell populations. The ratio of peanut-specific clones in the effector versus regulatory T-cell compartment, which distinguished these clinical groups, was independent of specific IgE concentration. Expansion of the peanut-specific effector T-cell repertoire is correlated with clinical sensitivity—an observation that may be useful to inform our assessment of disease phenotype and that is consistent with immune progression as a mechanism of more severe disease.

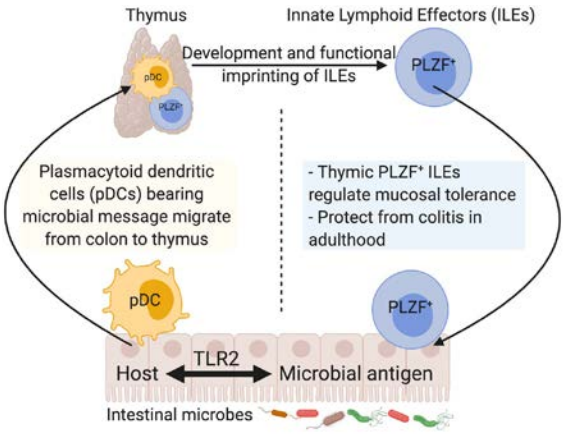
2. Repetitive concussions in an adolescent brain injury model is linked to later neurodegeneration and highlight IL-1R1 signaling as a potential therapeutic target to prevent dementia later in life in young athletes who sustain multiple head impacts playing contact sports.

Whalen, MW. Modeling single and repetitive concussive TBI in mice and a possible role for IL-1R1. Oral presentation. National Neurotrauma Society. October 14, 2020.

Work in the Whalen lab has shown that adolescent mice injured with three concussive closed head injuries develop progressive cognitive deficits associated with microgliosis at 6 months and neuronal accumulation of activated IL-1 beta, hyperphosphorylated and misfolded Tau, cleaved caspase-1 and NLRP1 (implying inflammasome activation), and display chronic mTOR pathway activation, CAMKII activation, and pEif2-alpha activation. Single cell nuclear RNA sequencing confirms a neuronal genetic signature of impaired proteostasis. Notably, IL-1R1 knockout mice did not accumulate phospho-Tau and do not develop cognitive impairment in this model. The data are the first to link repetitive concussions in an adolescent brain injury model to neurodegeneration and highlight IL-1R1 signaling as a potential therapeutic target to prevent dementia



(a) Western blot and (b-g) densitometry data for IL-1ß, caspase-1, NLRP1, NLRP3 in isolated CD31+ endothelial cells, CD11b+ myeloid cells, CD13 + pericytes and neurons in sham vs 3HD WT mice brain at 14 months after injury, showing inflammasome activation in neurons in the chronic phase after CHI (n = 4-6/group, *p < 0.05 vs. sham).



Early life entero-thymic communication: Complex interplay between the host immune cells and intestinal microbes in early life influence the development and functional imprinting of ILEs in the thymus. This has consequences on disease suscrptibility in later life.

later in life in young athletes who sustain multiple head impacts playing contact sports.

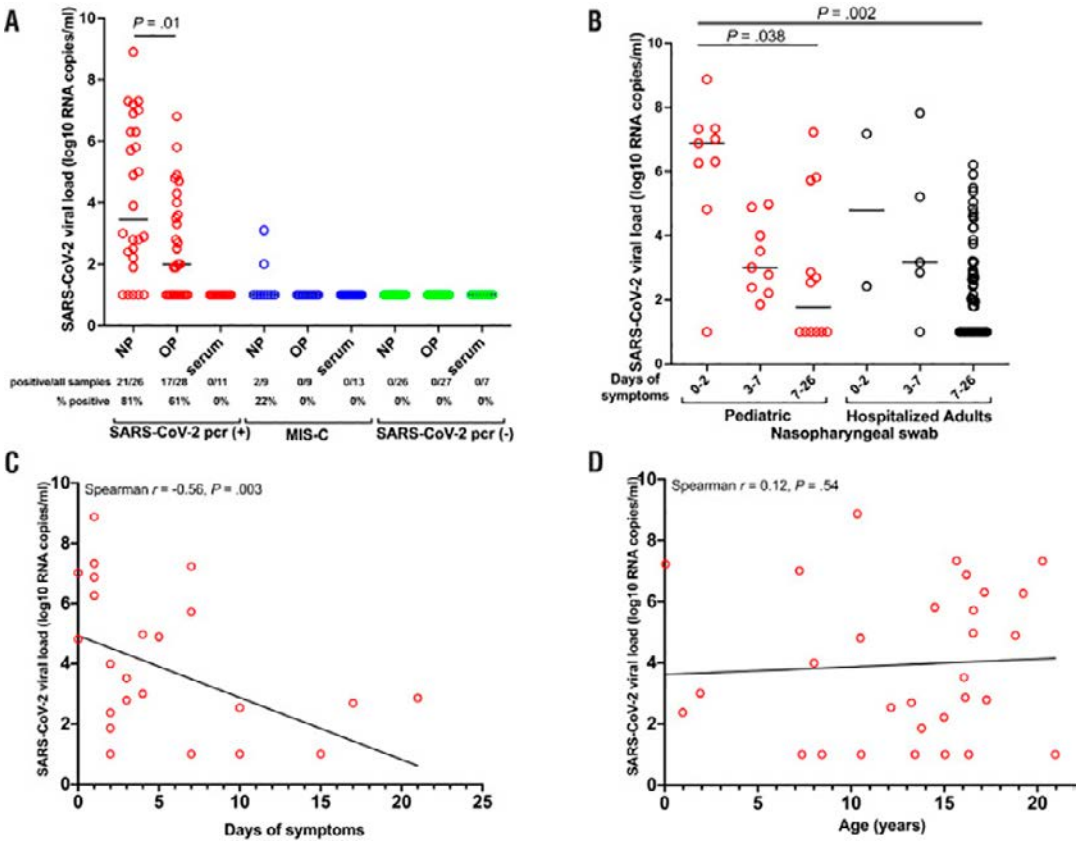
3. Intestinal microbes influence development of thymic lymphocytes in early life.
Ennamorati, M., Vasudevan C., Clerkin K., Halvorsen, S., Verma, S., Ibrahim, S., Prosper, S., Porter, C., Yeliseyev, V., Kim, M., Gardecki, J., Sassi, S., Tearney, G., Cherayil, B.J., Bry, L., Seed B., Jain, N. Intestinal microbes influence development of thymic lymphocytes in early life. Proc. Natl. Acad. Sci. USA. 2020; 117: 2570-2578.

The early life represents a period of unique immune development during which the foundation for lifelong immunity is laid. Microbial exposures during early life have the potential to influence the development and functionality of immune cells that can have consequences on diseases susceptibility in later life. In their study published in PNAS [PMID: 31964813], Dr. Jain's lab in collaboration with Dr. Brian Seed and colleagues, demonstrate an early life entero-thymic communication where intestinal microbes impinge on the thymic development of transcription factor PLZF expressing innate lymphoid effector cells (ILEs). These ILEs typically function at the gut mucosal interface and provide protection at barrier sites. Offspring of animals treated with broad-spectrum antibiotics or those reared in a germfree environment had altered development of thymic ILEs. This early life microbial imprint on PLZF+ ILEs persisted into adulthood and contributed to their increased susceptibility to colitis. Protection from colitis could be initiated by the transfer of PLZF$^+$ cells from mice that developed with normal microbiota in early life. These studies provide proof of concept for the regulation of immune development by intestinal microbes and affirm the existence of a 'window of opportunity' that may be exploited to program long-lasting host protective immune responses.

4. An understanding of the potential role children play in the coronavirus infectious disease 2019 (COVID-19) pandemic and the factors that drive severe illness in children
Yonker LM, Neilan AM, Bartsch Y, Patel AB, Regan J, Arya P, Gootkind E, Park G, Hardcastle M, St John A, Appleman L, Chiu ML, Fialkowski A, De la Flor D, Lima R, Bordt EA, Yockey LJ, D'Avino P, Fischinger S, Shui JE, Lerou PH, Bonventre JV, Yu XG, Ryan ET, Bassett IV, Irimia D, Edlow AG, Alter G, Li JZ, Fasano A. Pediatric Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2): Clinical Presentation, Infectivity, and Immune Responses. J Pediatr. 2020 Dec;227:45-52.e5.

Dr. Yonker and her colleagues defined an understanding of the potential role children play in the coronavirus infectious disease 2019 (COVID-19) pandemic and the factors that drive severe illness in children is critical. They established a COVID-19 Biorepository for children with confirmed/suspected SARS-CoV-2 infection or multisystem inflammatory syndrome in children (MIS-C). Forty-nine children (26%) were diagnosed with acute SARS-CoV-2 infection; an additional 18 children (9%) met the criteria for MIS-C. Only 25

children (51%) with acute SARS-CoV-2 infection presented with fever; symptoms of SARS-CoV-2 infection, if present, were nonspecific. Nasopharyngeal viral load was highest in children in the first 2 days of symptoms, significantly higher than hospitalized adults with severe disease (*P* = .002) [Figure]. Age did not impact viral load, but younger children had lower angiotensin-converting enzyme 2 expression (*P* = .004). Immunoglobulin M (IgM) and Immunoglobulin G (IgG) to the receptor binding domain of the SARS-CoV-2 spike protein were increased in severe MIS-C (*P* < .001), with dysregulated humoral responses observed. This study reveals that children may be a potential source of contagion in the SARS-CoV-2 pandemic despite having milder disease or a lack of symptoms; immune dysregulation is implicated in severe postinfectious MIS-C. This study is defining the policies for the return of children to schools during the COVID-19 pandemic.



Infective SARS-CoV-2 viral load in children. **A,** Viral loads from nasopharyngeal, oropharyngeal, and blood were quantified within SARS-CoV-2 (+), MIS-C, and SARS-CoV-2 (–) cohorts. Viral load in nasopharyngeal and oropharyngeal specimens from SARS-CoV-2 (+) children were compared with the Mann-Whitney *U* test, median presented. **B,** SARS-CoV-2 viral loads were categorized by symptom duration, including asymptomatic period to day 2 of symptoms, days 3-7 of symptoms, and days 7-26 of symptoms. The median is presented and comparisons are by the Kruskal-Wallis test. Nasopharyngeal viral load was correlated with, **C,** days of symptoms and, **D,** age; Spearman correlation. *NP*, nasopharyngeal; *OP*, oropharyngeal

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 disorder, 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 26 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 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 across neuroscience, research psychology, and a variety of other fields train with us.

In addition, our educational efforts reach tens of thousands of health professionals through the 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. 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 FY20, Department faculty had $70 million in research support, continuing its record of successful funding despite a challenging funding environment, and published over 1200 original articles in 2020.

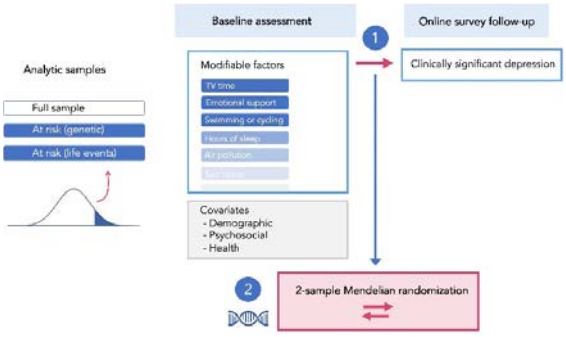
MGH Department of Psychiatry Publications in 2020	
Journal Articles	1202

Key Recruitment in Pediatric Depression

This year, the Department was pleased and excited to recruit from Brown University a well-published researcher in child and adolescent depression. Richard Liu, PhD is a clinical psychologist whose work focuses on characterizing dynamic processes of risk underlying onset and recurrence of self-injurious thoughts and behaviors and depression in youth and young adults and has published over 80 papers on these and related topics. He is the new director of suicide research in the Division of Child and Adolescent Psychiatry and director of big data studies at the Depression Clinical and Research Program. His work has been continuously supported with NIMH funding since 2014, and he is currently the principal investigator of two NIMH-funded studies involving mobile assessments of psychosocial stress, physiological arousal, and sleep, as well as neurocognitive markers of short-term risk for suicidal behavior in adolescents.

Important New Research Initiative-Precision Psychiatry

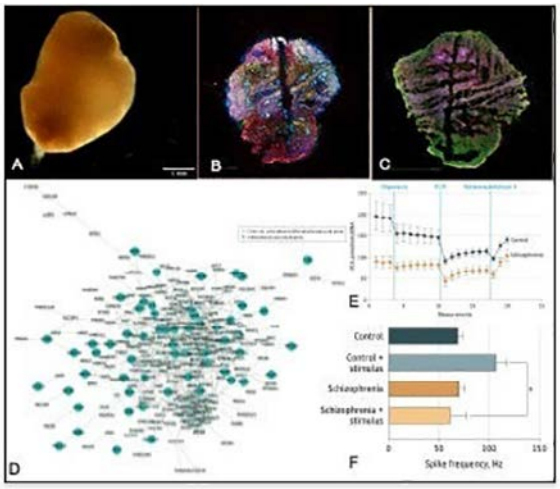
This year, the Department launched a new, interdisciplinary center, the Center for Precision Psychiatry (CPP), to drive the transformation of the field of psychiatry towards a new and rapidly emerging paradigm, “precision psychiatry.” Led by Dr. Jordan Smoller, Tepper Family MGH Research Scholar, and drawing on our world class expertise in big data analytics, genomics, neuroscience and clinical trials, the CPP integrates research and clinical practice to enable more accurate risk prediction, targeted prevention, precise diagnosis, and effective treatments for psychiatric disorders. A major focus of the Center will be a deep investment in addressing the problem of suicide, including the prediction and prevention of suicidal behaviors and the care of patients across all areas of medicine who are affected by this growing public health crisis that is the second leading cause of death among young people. The CPP will take a learning health system approach to suicide prevention, systematically bringing evidence-based risk prediction and prevention tools into clinical practice expeditiously, while establishing mechanisms to track outcomes and inform future research.



Overview of two-stage analytic design to test prospective associations between modifiable factors and subsequent depression. Associations were tested in three analytic samples: (a) full sample; (b) at-risk individuals based on polygenic risk; and (c) at-risk individuals based on reported traumatic life events.

Psychiatry

Department Report



A. Brain organoid grown from a human stem cell. B. Cross-section of a brain organoid showing markers for different types of cortical neurons. C. Cross-section of a brain organoid showing presence of neural stem cells (red) and mature neurons with synapses (green). D. Overlap of differentially expressed genes in schizophrenia organoids with genes implicated in schizophrenia from genetic studies. E. Mitochondrial respiration in schizophrenia and control organoids under different conditions. F. Multi-electrode array data of neuronal firing in schizophrenia and healthy brain organoids in the presence and absence of electrical stimulation

Achievements:

Choi KW et al, 2020, An Exposure-Wide and Mendelian Randomization Approach to Identifying Modifiable Factors for the Prevention of Depression.
Although depression is the leading cause of disability worldwide, we still have relatively little knowledge about how to prevent depression at a population level. Previous studies have focused on a limited number of potential actionable targets, making it difficult to evaluate and design comprehensive prevention strategies for depression. In this study, we developed a unique two-stage approach to screen the largest set of candidate prevention targets for depression to date. We first leveraged a longitudinal sample of over 100,000 adults from the UK Biobank, with both genomic and wide-ranging lifestyle and environmental measures, to conduct an “exposure-wide association scan” of more than 100 modifiable factors (ranging from diet, physical activity, media use, sleep habits, social interaction, and environmental exposures) to identify those most strongly associated with developing depression over time. Second, we took the top associated factors from the first stage and independently evaluated their causal importance using a statistical method called two-sample Mendelian randomization, which treats genetic differences between people as a kind of natural experiment to help determine whether an association is likely causal. Our two-stage results identified an array of promising targets for depression prevention. The most prominent modifiable factor was confiding in others, a measure of social connection that showed robust risk-lowering effects on depression across both stages of analysis. We also observed risk effects of sedentary screen (e.g., TV) time, daytime sleep, and salt intake, and protective effects of visits with family and friends, and exercises such as swimming or cycling. Interestingly, some initially associated factors such as vitamin B supplementation were not supported at the second stage, suggesting not all factors may be causal nor translate into potent targets for intervention. Overall, this large-scale exposure-wide approach combined with genetically informed causal inference methods points to high-priority targets for depression prevention.

Choi KW, Stein MB, Nishimi KM, Ge T, Coleman JRI, Chen C-Y, Ratanatharathorn A, Zheutlin AB, Dunn EC, 23andMe Research Team, Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium, Breen G, Koenen KC, Smoller JW. An Exposure-Wide and Mendelian Randomization Approach to Identifying Modifiable Factors for the Prevention of Depression. Am J Psychiatry. 2020 Oct 1;177(10):944–954. PMID: 32791893

Kathuria A et al, 2020. Transcriptomic Landscape and Functional Characterization of Induced Pluripotent Stem Cell-Derived Cerebral Organoids in Schizophrenia.
Recent advances in stem cell research enables generation of patient-specific stem cells that can be used to study disease biology in the laboratory. We used patient-derived stem cells to grow brain organoids from eight schizophrenia patients and eight healthy individuals. A comprehensive analysis of gene expression patterns

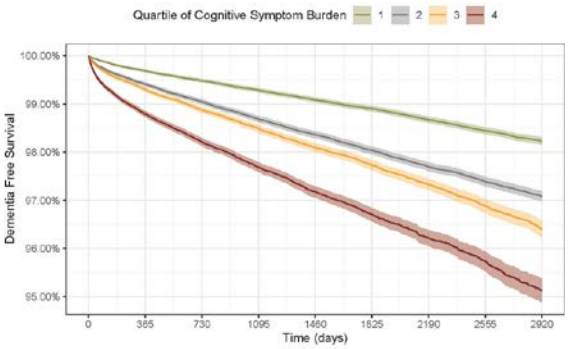
indicated dysregulation of pathways involved in synaptic biology, mitochondrial function and in excitatory/inhibitory balance in schizophrenia. Experiments of mitochondrial function in schizophrenia brain organoids identified specific differences in mitochondrial respiration. In studies of neuronal electrical activity using multi-electrode arrays, schizophrenia brain organoids showed normal electrical activity patterns at baseline but an aberrant response to electrical and chemical stimulation. These results show the power and utility of patient-derived brain organoids to interrogate and understand neurobiological underpinnings of psychiatric disorders such as schizophrenia.

Kathuria A, Lopez-Lengowski K, Jagtap SS, McPhie D, Perlis RH, Cohen BM, Karmacharya R. Transcriptomic Landscape and Functional Characterization of Induced Pluripotent Stem Cell-Derived Cerebral Organoids in Schizophrenia. JAMA Psychiatry. 2020 Jul 1;77(7):745-754.

McCoy TH et al 2020. Stratifying risk for dementia onset using large-scale electronic health record data: a retrospective cohort study.

This article reported the successful use of software applied to hospital discharge summaries to stratify risk of that patient developing a new diagnosis of dementia. The study considered over half a million patients and followed them for up to eight years. The software used to convert discharge summaries into a risk score is a form of natural language processing that was developed using unsupervised machine learning that combined MGH physician expertise with insights about patient illness reached by the software's review of thousands of medical records. The ability to identify patients at increased risk for future dementia diagnosis is an important step in both efficient clinical trials of novel treatments and optimal care using the current state of the art. Validation of this algorithm is a step toward enabling both at the bedside. As the software was designed to capture cognitive symptom burden in general, rather than trained as a dementia predictor in particular, the developers anticipate broad applicability. For example, in a secondary component of this initial study, looking at those who already had a diagnosis of dementia at the time of admission, the higher cognitive symptom burden calculated by the software was associated with shorter time to death.

McCoy TH, Han L, Pellegrini AM, Tanzi RE, Berretta S, Perlis RH. Stratifying risk for dementia onset using large-scale electronic health record data: a retrospective cohort study. Alz & Dementia, 2020; 16(3):531-540.



Kaplan-Meier plot of time to new dementia outcome following hospital discharge by quartile of cognitive symptom burden score (color) estimated by applying natural language processing algorithm to hospital discharge summary. Incident dementia risk is associated with cognitive symptom burden in both unstratified (log-rank chi squared (3df)=1464; p<1e-6) and stratified analysis (log-rank chi squared (3df)=429; p<1e-6) over 2.4 million patient years of follow up.

Radiation Oncology

Department Report

ANTHONY ZIETMAN, MD

Research Overview:

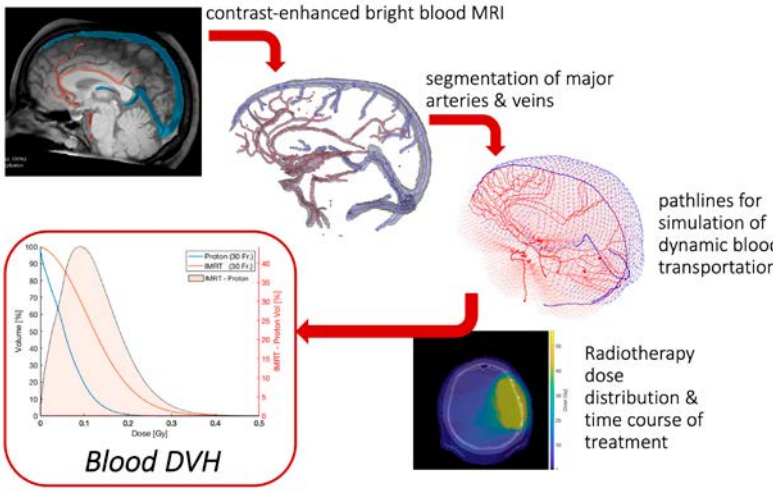
The Mass General Department of Radiation Oncology had approximately **$20.4M** in research expenditures in FY20. Nearly **28%** of this research funding originated from federal support. The department continues to have an impressive record as a highly collaborative research team, reflected in the rich publication record of our faculty with over 268 publications in 2020. Additionally, in 2020, the Department of Radiation Oncology maintained **27** active clinical trials, with an additional 1 that was completed, and **294** 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.

Achievements:

Department General Achievements:

- The 2020 Radiation Oncology Research Retreat, entitled "Milestones in Tumor Biology, New Directions for Radiation Oncology," was held on September 30, 2020 as a virtual symposium celebrating **Rakesh K. Jain, PhD's 30-year anniversary as Director of the Edwin L. Steele Laboratories for Tumor Biology**. The guest keynote speaker was **William G. Kaelin Jr., MD**, the Sidney Farber Professor of Medicine at Dana-Farber Cancer Institute and Harvard Medical School, and the **2019 Nobel Laureate in Physiology or Medicine**. In his inspirational talk entitled "The von Hippel-Lindau Tumor Suppressor Gene: Insights into Oxygen Sensing and Cancer," Dr. Kaelin described his groundbreaking work on how cells sense and respond to changes in oxygen levels, and the clinical applications of his discoveries. The second keynote talk, by **Dr. Rakesh Jain**, was entitled "Normalizing the Tumor Microenvironment to Improve Cancer Immunotherapy: From Bench to Bedside" and summarized



Starting with a contrast enhanced MRI, we segmented major vessels and arteries. Next we interpolated a set of pathlines between these large arteries and veins to fill the entire brain with "path lines", with a maximum distance of 5mm between them. Then these path lines were used for the dynamic simulation of blood flow throughout the entire brain. Together with the radiotherapy dose distribution and accurate information about the time course of treatment, we were able to simulate the dose to the circulating blood during radiotherapy treatments. The purpose of this work is to estimate the dose to circulating lymphocytes traveling in the blood stream, which is linked to the immunosuppressive effects of radiation and needs to be considered in the design of immunotherapy-radiotherapy combination approaches. For details see *Hammi et al. (2020). 4D blood flow model for dose calculation to circulating blood and lymphocytes. Physics in Medicine & Biology, 65(5).*

Dr. Jain's contributions to the field of tumor microenvironment, with focus on normalization of the tumor vasculature and its relevance for cancer therapy in patients. In the afternoon, several brief talks by young investigators in our department comprised the "The Future of Tumor Biology" segment, covering a range of pathologies including medulloblastoma, glioblastoma, breast cancer, pancreatic cancer, liver cancer and liver cirrhosis. **Over 100 participants joined the retreat, our first to be held virtually.**

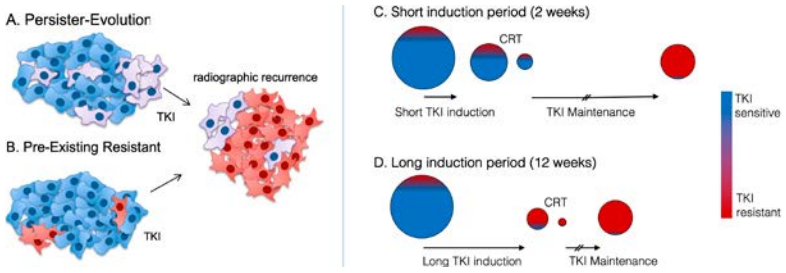
- Radiation Oncology maintained a 28% submission success rate with a during 2020 despite the impact of COVID.
- Prospective clinical trials by Drs. Taghian, Shih, Hong, Delaney, and Efstathiou have resulted in six (6) separate publications in the Journal of Clinical Oncology in 2020, and another by Dr. Chen in Lancet Oncology.
- The Department of Radiation Oncology was awarded Research Grants from the National Cancer Institute (NCI/ NIH) outlined below:
  - **R01 Harald Paganetti:** "Developing whole-body computational phantoms for blood dosimetry to model the impact of radiation on the immune system".
  - **R21 Clemens Grassberger:** "A Computational Method to Calculate the Radiation Dose to Circulating Lymphocytes"

Physics Achievements:

- An October 2020 article in Physics World highlighted a collaboration among Department of Radiation Oncology Physics researchers **Fernando Hueso-González, PhD, Patrick Wohlfahrt, PhD,** and **David Craft, PhD,** and dosimetrist **Kyla Remillard**, to develop RadCollision, an open-source collision detection tool designed to aid dosimetrists in planning photon or proton beam radiotherapy. The team published their work in the August 24, 2020 edition of Biomedical Physics & Engineering Express.
- In July 2020 **Joost Verburg, PhD**, and co-authors received the "Best in Physics" distinction (multi-disciplinary category) for their

Radiation Oncology

Department Report



A/B (left): Graphical illustration of the two main mechanisms that are modeled: evolution of resistance in initially persistant cell populations and pre-existing resistance. TKI sensitive, persistent, and resistant cells are shaded blue, purple, and red, respectively. Note that TKI therapy is not only specific to sensitive cells but also leads to slowed growth of persistent cells. Chemo-radiation however is assumed to have equal effects on each cell subpopulation. The mathematical model takes into account these three cell populations, the transition probabilities between them (probability of a resistance inducing mutation such as T790M), and the effect of chemotherapy and radiation. The distant tumor compartment is only susceptible to systemic agents, in this case chemotherapy and TKI therapy, while the local compartment is also affected by radiotherapy.

C/D (right): Illustration of the results, showing differential evolution of the TKI-resistant and sensitive populations between a short 2 wk. and long 12 wk. induction length. When CRT is done after a significant TKI induction period, the tumor shrinks with the targeted drug killing the TKI sensitive cells (blue), but with more TKI resistant (red) cells at the time of CRT (case D), increasing the chance of a late TKI resistant recurrence if CRT isn't curative. This demonstrates the conceptual differences that have to be taken into account when combining targeted agents with concurrent chemo-radiation in locally-advanced disease. For details see "Modeling Resistance and Recurrence Patterns of Combined Targeted Chemoradiotherapy Predicts Benefit of Shorter Induction Period." *McClatchy DM, Willers H, Hata AN, Piotrowska Z, Sequist LV, Paganetti H, Grassberger C. Cancer Res. 2020 Nov 15;80(22):5121-5133.*

work "First-In-Human Use of Prompt Gamma-Ray Spectroscopy for Proton Range Verification" at the 2020 annual meeting of the AAPM/COMP. The work was also highlighted in physicsworld. For the past seven years, the department has been developing Prompt Gamma, to measure the range of the protons in real-time during patient treatment. This started with small pre-clinical experiments and led to the completion of a first clinical prototype system last year. In February, the department scanned the first proton therapy patient, with plans to continue to scan more patients over the course of the year. The goal of this initial clinical study is to get a better understanding of what the range uncertainties truly are in clinical proton beams.

- **The Paganetti Lab** hosted the CAMPEP approved TOPAS course in livestreams September 16-18. The TOPAS software is part of NCI's Informatics Technology for Cancer Research (ITCR) program and has more than 1000 users worldwide.

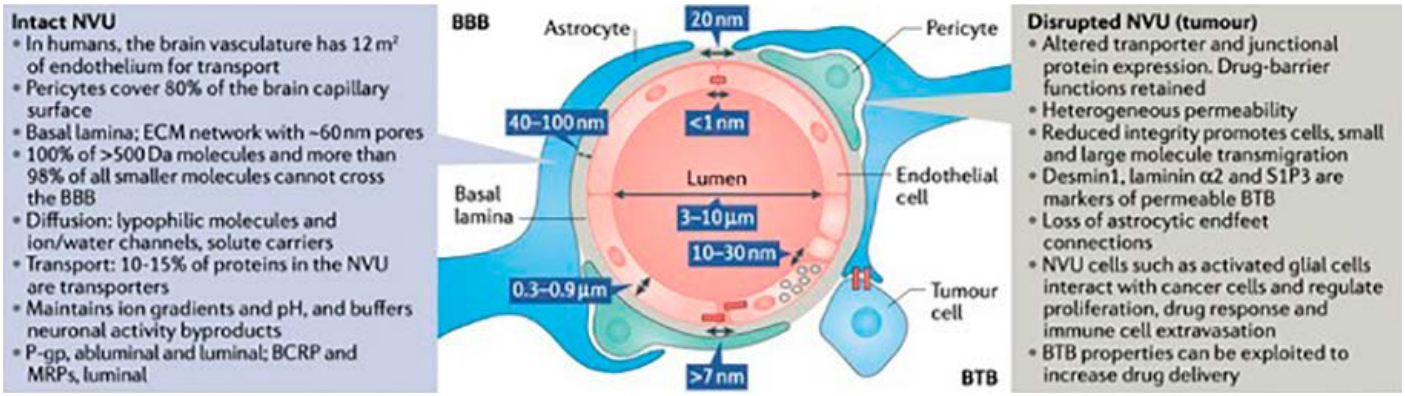
Clinical Research and Radiation Biology Research Achievements:

- The Pediatric Proton/Photon Consortium Registry (PPCR), a consented, multi-center registry established and headed by **Torunn Yock, MD, MCH**, expanded to include 19 radiation centers. The PPCR serves to expedite outcomes research on proton radiotherapy and to better define the role of proton radiation in treating pediatric cancers.
- **Sophia Kamran, MD**, and **Rachel Jimenez, MD**, were both recognized with The Center for Faculty Development's Anne Klibanski Visiting Scholars Award.
- William Hwang, MD, PhD, was among four recipients of the first annual Hopper-Belmont Foundation (HBF) Inspiration Award. Dr. Hwang was recognized for his pancreatic cancer research by receiving this very competitive award which targets the nation's most innovative young cancer investigators.
- **William Hwang, MD, PhD**, was also 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," mentored by Tyler Jacks, PhD of MIT.
- **Alice Ho, MD**, was elected as a representative to The Executive Committee on Research (ECOR) of MGH.

- **Henning Willers, MD**, edited a SpringerNature Book on Molecular Targeted Radiosensitizers featuring investigators from the NCI-funded Preclinical Chemo-Radiotherapy Testing Consortium https://www.springer.com/us/book/9783030497002
- **Li Lan, MD PhD**, received the MGH Claflin Distinguished Scholar Award designed to support women to advance to senior positions in academic medicine

Tumor Biology: Edwin Steele Laboratories Achievements:

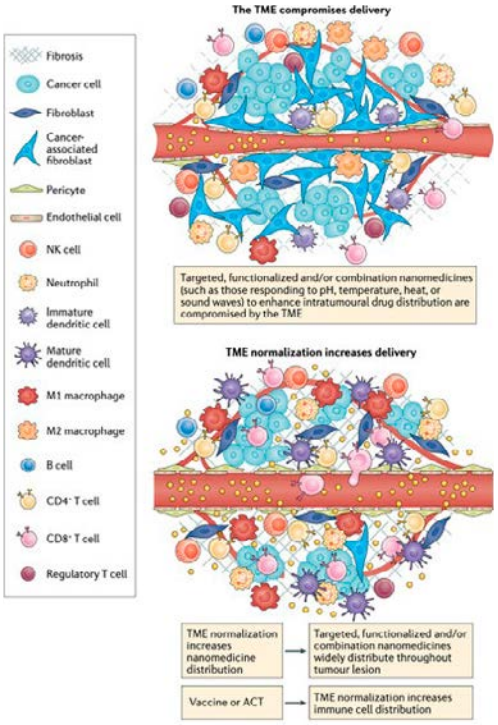
- **Rakesh Jain, PhD**, was named a Fellow of the Academy of the American Association for Cancer Research (AACR) Class of 2020. Election to the Academy is an honor bestowed by the AACR on those whose scientific contributions have propelled significant innovation and progress against cancer.
- **Rakesh Jain, PhD**, and **Dai Fukumura, PhD**, were both named Highly Cited Researchers for 2020 by Clarivate Web of Science. **Rakesh K. Jain, PhD**, was named as a "Highly Cited Researchers 2020" by Clarivate Analytics Web of Science for the 7th year in a row. His publications have been cited >116,000 with an h-index of 165. **Dai Fukumura, MD, PhD**, Deputy Director of the Steele Laboratories and head of the Fukumura Lab in the Steele Laboratory was named as a "Highly Cited Researchers 2020" by Clarivate Analytics/Web of Science for the second year in a row. This designation identifies researchers who have been most frequently cited by their peers over the last decade. In 2020, about 0.1%, of the world's researchers, in 21 research fields and across multiple fields, earned this distinction.



Physical and chemical properties of the BBB. The blood–brain barrier (BBB) structure displays unique physical properties that tightly regulate molecular and cellular flow in the neuroparenchyma. The brain barrier's importance is evident from its functional conservation across organisms, from fruit flies to humans1. As the BBB develops and matures, endothelial cell fenestrations decrease, and the subsequent appearance of tight junctions is followed by a reduction in transcytosis. Centre panel: cross-section of a central nervous system (CNS) capillary depicting estimated distances and spaces within the BBB, which circulating drugs are required to overcome to permeate the brain parenchyma. Left panel: in the non-diseased brain, the neurovascular unit (NVU) includes an intact BBB that displays multiple characteristics that limit drug permeability into the CNS. Right panel: during tumour progression, stroma–cancer cell interactions in the brain tumor microenvironment dictate vessel permeability and cancer cell proliferation. The blood–tumor barrier (BTB) characteristics listed here contribute to the heterogeneous permeability observed in the disrupted NVU. BCRP, breast cancer resistance protein; ECM, extracellular matrix; MRP, multidrug resistance protein; P-gp, P-glycoprotein; S1P3, sphingosine 1-phosphate 3. (from *CD Arvanitis, GB Ferraro and RK Jain. The blood–brain barrier and blood–tumor barrier in brain tumors and metastases. Nature Reviews Cancer 20: 26-41, 2020).*

Radiation Oncology

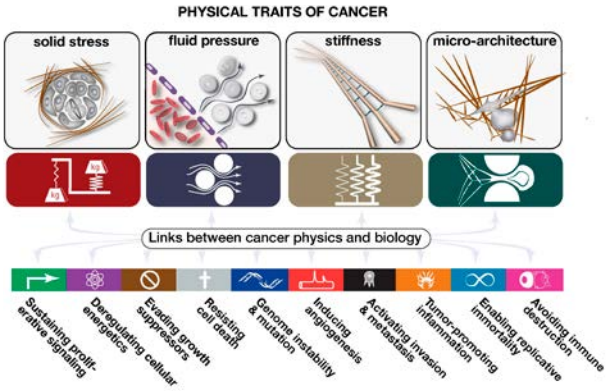
Department Report



Normalizing the TME to increase the penetration of combination therapies. Targeted or stimuli-responsive nanomedicines often have a limited level of distribution within tumors because the tumour microenvironment (TME) limits blood flow and therefore the extent of tumor penetration. With insufficient penetration and a limited density of antitumor immune cells, the advantage of these nanomedicines compared with passively accumulating and releasing nanomedicines is reduced. TME-normalizing therapies increase and homogenize the intratumor distribution of immune cells and nanomedicines. Nanomedicine-based vaccines and autologous transferred T cells carrying nano- medicines increase the number of antitumor T cells in the host. If followed by TME normalization, a larger percentage of these T cells can migrate to the tumor parenchyma. Similarly, functionalized nanomedicines following TME normalization can penetrate the tumor parenchyma in higher fractions thereby reaching their target and/or stimuli and demonstrating a larger improvement over passive nanomedicine. Thus, normalizing the TME could increase the effectiveness of targeted nanomedicines that combine cytotoxic agents and immunotherapies. ACT, adoptive cellular therapy; NK, natural killer. From *JD Martin, H Cabral, T Stylianopoulos and RK Jain. Improving cancer immunotherapy using nanomedicine: Progress, opportunities and challenges. Nature Reviews Clinical Oncology. 17(4):251-266 (2020).*

- **Rakesh Jain, PhD, Lance Munn, PhD, Dai Fukumura, MD, PhD** and **Dan G. Duda, DMD, PhD** are among the top 2 percent of scientists in the world based on a composite score [c-score] of citations, co-authorship and collaborations (https://journals.plos.org/plosbiology/article?id=10.1371/journal.pbio.3000918).
- The American Institute for Medical and Biological Engineering (AIMBE) inducted **Dan Duda, DMD, PhD** into its College of Fellows. The College of Fellows is comprised of the top two percent of medical and biological engineers; membership honors those who have made outstanding contributions to “engineering and medicine research, practice, or education” and to “the pioneering of new and developing fields of technology, making major advancements in traditional fields of medical and biological engineering, or developing/implementing innovative approaches to bioengineering education.”
- **Rakesh K. Jain, PhD** was listed among the top 100 “Highly Cited Researchers” with h-index>100 according to Google Scholar.
- **Rakesh K. Jain, PhD**, received grants from the Advanced Medical Research Foundation, The National Foundation for Cancer Research, the Jane’s Trust Foundation and Harvard Ludwig Cancer Center, and a sponsored research agreement from Boehringer-Ingelheim.
- **Rakesh K. Jain, PhD**, gave Keynote lectures at 21st International Vascular Biology Meeting, Seoul, S. Korea, VIRTUAL (Sept 9 -12, 2020), and 2nd Annual Congress of Immuno-Oncology Society of India, VIRTUAL (October 30- Nov 1, 2020).
- **Rakesh K. Jain, PhD** offered the “35th Annual Critical Issues in Tumor Microenvironment: Angiogenesis, Metastasis and Immunology,” CME course, livestreamed on October 26 - 29, 2020. The course highlighted key gaps in the present knowledge of cancer, and outlined future directions for research at the bench, in the clinic, and in drug development.
- **Dan G. Duda, DMD, PhD**, director of Translational Research in GI Radiation Oncology and head of the Duda Lab of the Steele Laboratories, received an honorary degree (Doctor Honoris Causa) from his Alma Mater, University of Medicine Iasi, Romania.
- **Dan G. Duda, DMD, PhD**, received the 2020 Excellence Award–World Ambassador of Romanian Medicine from Medica Academica, Tarus Media Romania.
- **Dan G. Duda, DMD, PhD**, received sponsored research agreements from Bayer, BMS and Exelixis.
- **Lei Xu, MD, PhD**, head of the Xu Lab of the Steele Laboratories, received a Department of Defense Neurofibromatosis Research Program Impact Award, Children’s Tumor Foundation Drug Discovery Initiative Award, and the Children’s Tumor Foundation Accelerator Award.
- **Franziska Hauth, MD**, postdoctoral fellow, received a German Academic Exchange Service (DAAD) Fellowship.

- **Satoru Morita, MD, PhD**, postdoctoral fellow, received a Japan Society for the Promotion of Science (JSPS) Fellowship.
- **Nilesh Telele, PhD**, postdoctoral fellow, received the Cancer Research Institute-Merck Fellowship.
- **Hengbo Zhou, PhD**, postdoctoral fellow, received K00 from NIH.
- **Meenal Datta, PhD** and **Zohreh Amoozgar, PhD**, Postdoctoral fellows working under **Dr. Rakesh Jain**, received the inaugural Anne Klibanski Postdoctoral Scholars Awards. These awards provide the opportunity to give a lecture/seminar at a national or international institution, organized by the Center for Faculty Development (CFD).
- **Drs. Datta and Amoozgar** were also selected to participate in the Leadership Development Program for Researchers, also sponsored by the Center for Faculty Development; this course aims to prepare investigators for challenges inherent in establishing and maintaining a successful research program.
- **Heena Kumra, PhD**, Steele Lab Research Fellow, was awarded the prestigious American Society for Matrix Biology (ASMB) Founders award. This award recognizes the highest level of scientific excellence in extracellular matrix and cell-matrix interactions in young scientists in transition toward their first independent career positions, and who have demonstrated a visible commitment to a career in matrix research and the activities of the ASMB.
- **Dr. Liqun Gu MD, PhD**, postdoctoral fellow, received a fellowship from Xiangya Stamatological Hospital.
- **Zhenzhen Yin, MD**, postdoctoral fellow, received fellowships from China Scholarship Council and Tianjin Medical University Cancer Institute & Hospital.
- **Jing Den, PhD**, postdoctoral fellow, received fellowships from China Scholarship Council and West China School of Stomatology Sichuan University.
- **Igor Garkavtsev, MD, PhD**, was named one of two runners-up in the Salisbury Award Competition for Entrepreneurial Translational Research conducted by the National Foundation for Cancer Research. The Salisbury Award encourages and promotes innovative scientists and early stage start-up companies to translate their discoveries into therapies that can improve the lives of cancer patients.



In an article published in Science, Rakesh Jain, Lance Munn and Hadi Nia of the Steele Labs propose four physical hallmarks or "traits" of cancer. Emerging studies demonstrate that tumor progression and treatment-outcome depend upon both biological and physical properties of the cancer. Although much research effort has improved our understanding of cancer biology, the physics of cancer has only recently emerged as an important area of study. The review article summarizes the physical features common to tumors that contribute to cancer initiation and make treatment more difficult: (1) solid stresses (forces generated from solid phase of tumor), (2) fluid pressure (forces from fluid phase of tumor), (3) stiffness (rigidity), and (4) architecture and organization of tumor constituents. In this conceptual framework, Jain and co-authors discuss the origins of these distinct physical hallmarks of cancer and how they enable and synergize with aberrant cancer biology to fuel cancer initiation, progression, immune-evasion, and treatment-resistance. *[H Nia, LL Munn, and RK Jain, Science 370: aaz0868 (2020).]*

Radiology

Department Report

JAMES A. BRINK, MD, CHIEF

Overview:

Despite the many challenges of 2020, Radiology Research at Massachusetts General Hospital has continued to produce exciting research with ever-greater impact. The largest radiology research program anywhere in the world, MGH Radiology reported total research activity of $130M for the 2020 fiscal year (FY2020), a roughly 3.5% increase over the year before.

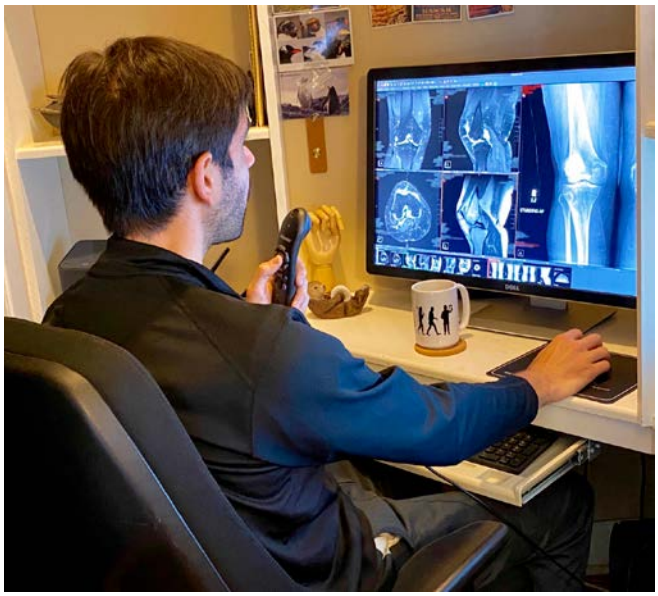
The third-largest department for research funding at Mass General, behind only Neurology and Medicine, Radiology accounted for 11% of the hospital's total research revenue in FY2019. If you factor in research from other Mass General departments that depend on Radiology's incomparable resources—Neurology, Psychiatry and Cardiology, among others—the impact of the Radiology Departments research program on the MGH overall research enterprise is considerably higher.

The department's research revenues exceeded its professional clinical revenues in FY2020 for the second time, representing the critical importance of the departments research effort for the department overall. While a decline in clinical revenues due to the COVID-19 pandemic contributed to this gap in 2020, even stronger research revenue numbers are projected for 2021, with considerable expansion in the works.

Achievements:

From the earliest days of the **COVID-19 pandemic,** Radiology researchers raced to understand the mechanisms of the disease. As the year progressed, they continued to explore ways in which imaging could help with understanding and treating it. Work in the department included, for example, one of the first spectroscopic imaging-based studies of neurological injury in COVID-19 patients, revealing metabolic disturbances in the brain similar to those found in patients who suffered hypoxia from other causes [1], and a functional MRI study showing intact functional brain networks in patients with disorders of consciousness after severe COVID-19, despite the presence of structural brain injury [2]. The findings of the latter suggest that clinicians should exercise caution before presuming a poor neurologic outcome of COVID-19 based on EEG or structural MRI.

Radiology researchers also worked to improve operations and access to care during the pandemic. Two examples: In the Medical Analytics Group (MAG) and the Medically-Engineered Solutions for Healthcare (MESH) Incubator housed in the Radiology department, researchers studied imaging volume trends and recovery models during the pandemic [3][4]. Also, Radiology researchers reported racial/ethnic disparities in the severity of COVID-19 lung disease on admission X-ray, underscoring the need to improve access to care for vulnerable populations [5].

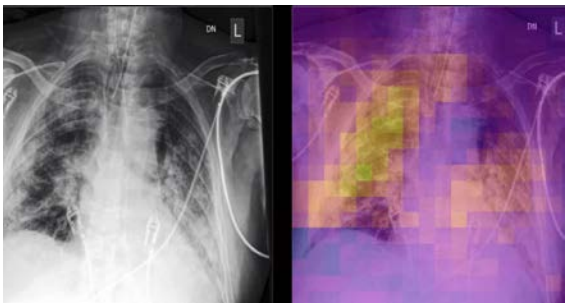


To help maintain social distancing, a number of Mass General radiologists worked from home during the initial surge of the COVID-19 pandemic. Shown here are the hospital's Jad Husseini, MD (left), and Kasra Mojtahed, MD (right).

The use of **artificial intelligence** in COVID-19—for instance, to provide objective measures of disease severity on chest X-rays [6]—reflected a larger trend in radiology research at Mass General. Department researchers published more than 150 studies in 2020 exploring the development and application of artificial intelligence for radiology. In a recent example, a team demonstrated use of AI with chest X-rays to predict lung cancer using only data commonly available in the electronic medical record: a chest X-ray (radiograph) image, the patient's age and sex and whether the patient is currently a smoker [7]. Other studies included a report of an AI tool to accelerate MRI parameter mapping for quantitative assessment of key biophysical properties of tissues [8].

Molecular imaging was another notable area of research in 2020. Work in this area encompassed, for instance, validation of a new PET probe that recognizes type I collagen, following work reported in [9]. The team is using this novel molecular probe to identify disease activity in pulmonary fibrosis and other conditions, critical information for clinicians seeking to establish prognosis and evaluate response to treatment. Molecular assessments were also integral to a newly reported portable fluorescence-based image cytometry analyzer for cancer diagnosis in point-of-care locations, especially in the developing world and in other resource-limited areas [10].

Development of **portable imaging technologies** was by no means limited to molecular imaging, however. Point-of-care evaluation was also introduced this year for a first-of-its-kind portable clinical MRI scanner, based on work done by a Mass General Radiology lab and assessed in a clinical setting in a study led by Department researchers [11] as well as of a prototype portable scanner, developed within the Department, small enough to fit in the back of an ambulance [12]. The latter scanner works by using an innovative array of magnet "cubes" arranged around the head instead of the large superconducting magnet found in conventional MRI scanners, sidestepping the



Mass General researchers have developed an artificial intelligence algorithm that can extract information about lung disease severity from chest X-rays of patients with COVID-19.

substantial power and cooling needs of the conventional MRI magnets and scanners. This device has now been licensed and will be built commercially by a startup which includes its MGH Radiology inventors.

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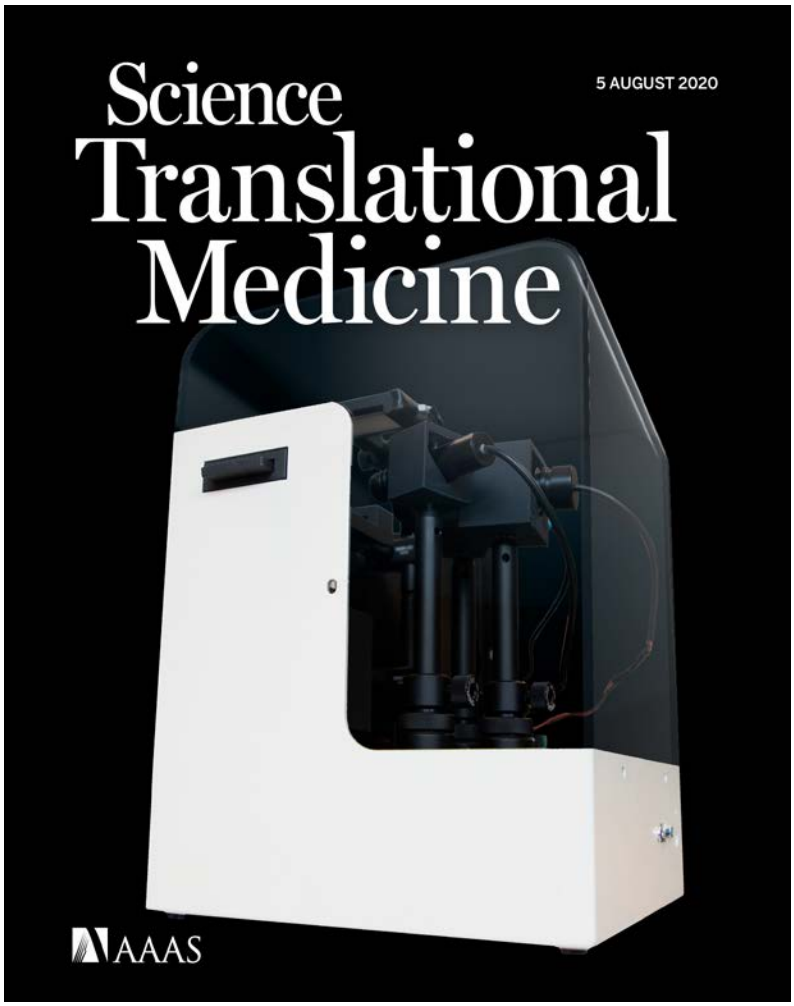
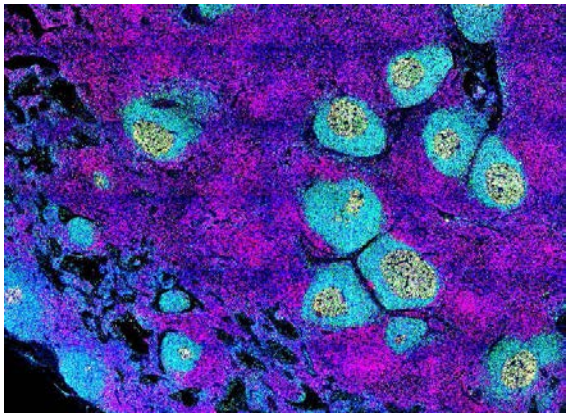


Department researchers reported a portable fluorescence-based image cytometry analyzer to facilitate cancer diagnosis in point-of-care locations, especially in resource-limited areas.

Ragon Institute of MGH, MIT & Harvard

Department Report

BRUCE D. WALKER, MD, DIRECTOR
FACUNDO BATISTA, PHD, ASSOCIATE DIRECTOR



Germinal centers (turquiose) in lymph nodes (purple), taken as a control in the study showing lack of germincal center development may play a significant role in fatal cases of COVID-19, led by Core Member Shiv Pillai, MD, PhD. *(Kaneko, et. al, Cell, 2020)*

Overview:

Ragon Institute
The mission of the Ragon Institute is to harness the immune system to prevent and cure human disease. Our strategy combines cross-disciplinary research with flexible funding to allow the full power of scientific knowledge to be applied in achieving immunologic solutions to global medical problems. Located in the center of the most robust biomedical research ecosystem in the world, our first 11 years of existence have shown, time after time, that this model works. Our initial goal of making an effective global HIV vaccine is in the final stages of phase 3 clinical studies in Africa. We have expanded our focus to additional pathogens such as tuberculosis, influenza, Zika, and malaria. Last January, we rapidly pivoted to the new coronavirus sweeping the globe, relying on the model we have created to contribute swiftly and significantly to COVID-19 research, including developing a COVID-19 vaccine currently in phase 3 trials.

Achievements:

1. Contributions to ending the COVID-19 pandemic
The Ragon Institute began studying COVID-19 as soon as the SARS-CoV-2 genome was sequenced, in January 2020. Core Member Aaron Schmidt, PhD, immediately began producing spike protein, allowing Core Member Galit Alter, PhD, Samana Cay MGH Research Scholar, to develop a robust antibody test well before any were commercially available. Supported by a generous gift from Mark and Lisa Schwartz, the Institute immediately launched an effort to develop a vaccine based on the platform Dan Barouch, MD, developed for our promising HIV vaccine candidate, currently in Phase 3 trials. Alter's antibody assay was used to show immunogenicity of this vaccine in animals *(Chandrashekar et al, Science 2020)*. Following demonstration of robust protection in preclinical studies *(Yu et al Science 2020)* and definition of the correlates of protection *(McMahan et al, Nature 2020),* our COVID-19 vaccine is currently in phase 3 trials sponsored by Johnson and Johnson *(Sadoff et al, NEJM 2021*). This single dose shot does not require extreme cold storage and represents a potential game changer for the vaccine efforts. Ragon faculty efforts in combating COVID-19 have also included, among many others, the work of Core Member Alejandro Balazs, PhD, collaborating with Dr. Galit Alter, to define the role neutralizing antibodies play in disease progression *(Garcia-Beltran, et. al, Cell, 2020; Zohar et al Cell 2020; Chen et al, Cell 2020)*, Alter showing transplacental transfer of COVID-19 antibodies from mother to fetus *(Edlow, et. al, JAMA ON 2020)* and definition of early serological signatures that track with COVID-19 survival *(Atyeo, et. al, Immunity, 2020)*, Core Member Shiv Pillai, MD, PhD, identifying the loss of Bcl-6-expressing T follicular helper cells that may underlie the lack of germinal centers seen in fatal COVID-19 *(Kaneko, et. al, Cell, 2020)*, and Member Bryan Bryson, PhD, using natural language processing algorithms to predict immune escape and viral evolution *(Hie et al, Science 2021)*. In total, the Ragon Institute has been involved in 58 COVID-19 publications over the last year, with many more in review or currently submitted as preprints.

2. Establishment and leadership of the Massachusetts Consortium on Pathogen Readiness

In the past year, we used the Ragon model of cross disciplinary collaboration to help establish the Massachusetts Consortium on Pathogen Readiness (MassCPR). Galit Alter, PhD, Xu Yu, MD, Alex Shalek, PhD, and Bruce Walker, MD, in collaboration with Harvard Medical School, have all taken on leadership roles in this 500+ member consortium, which includes Harvard, MIT, UMass, Tufts, BU, and academic medical centers throughout Massachusetts. Through combined HMS and Ragon efforts, over $15M was raised within three weeks of establishing the consortium on March 2, 2020; an RFA was released; and funding was provided to approximately 70 projects in April of 2020. The COVID-19 Sample Repository, established and led by Xu Yu, has provided hundreds of investigators with critical patient samples, and the Pathogenesis Working Group, led by Dr. Galit Alter, has provided exceptional benefit to the broader community, with biweekly presentations often including over 90 participants representing institutes from all over Massachusetts. These efforts created a broad community of investigators and have transformed the collaborative research environment in Massachusetts for good.

3. Plans for new expanded facilities: Ragon 2.0

In 2020 the Ragon Institute leased a plot of land in Kendall Square for the creation of a new building to support the continued growth and expansion of the Institute, land which is now part of the MIT campus. Plans for the new 5 story facility are nearing completion, and construction is slated to begin later this year

4. Progress toward HIV cure

For the past 25 years, members of the Ragon Institute have focused on trying to understand how a small fraction of HIV infected individuals, known as “elite controllers”, are able to control the virus without the need for medication. Ragon researchers led by Core Member Xu Yu, MD, and Member Mathias Lichterfeld, MD, have shown that these elite controllers are able to eliminate the intact proviruses which make up the latent HIV reservoir integrated in genic, or gene-expressing, regions of the virus, leaving only viruses that have integrated in non-genic regions (“gene deserts”) like the centromere. These non-genic integration sites will not be transcribed and translated, even with cellular activation, meaning the elite controllers have cleared all replication competent virus *(Jiang et al, Nature 2020)*. In one extreme case published, and in other cases since identified, the team has shown complete eradication of all detectable intact provirus in more 1.5 billion cells analyzed from blood and tissues. The mechanism of this exceptional clearance of replicant-competent viral genomes is thought to be HIV-specific CD8+ T cells able to target mutationally intolerant CD8+ T cell epitopes (building on Ragon publication *Gaiha, Rossin et al, Science 2019)*. This finding may open a new path to combatting the HIV reservoir, one of the most difficult blocks to HIV cure. By using the assay developed, and building off the findings of this study, we can now focus on creating the same kind of immune response we see in elite controllers in persons with progressive infection.

Ragon workforce members after returning onsite following lockdown, working under new safety protocols, which include wearing face masks and social distancing.

Ragon workforce members working in the BSL-3 lab, which allows for the safe handling of pathogens such as SARS-CoV-2 and *mycobacterium tuberculosis.* Our BSL-3 lab, led by Member Amy Barczak, MD, was certified for SARS-CoV-2 work shortly after the virus began spreading in Boston.

Surgery

Department Report

Eric C. Liao, M.D., Ph.D., Chief Research Officer

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 Massachusetts General Hospital. We believe that progress is made at the interface of disciplines and that we thrive on working with colleagues outside of surgery to solve problems we treat in the operating room.

Focus and strategic priorities

In recognition of the importance and ever-increasing demands of managing the diverse research activities of our Department, Surgeon-in-Chief, **Keith Lillemoe, MD**, created a Chief Research Officer position in 2020. After a formal committee selection process, **Eric C. Liao, MD, PhD**, was named to lead Massachusetts General Surgery research as the CRO. Dr. Liao is the Laurie and Mason Tenaglia MGH Research Scholar, the Director of Pediatric Plastic Surgery and the Director of the Cleft and Craniofacial Center. Dr. Liao chairs the Surgical Research Council (SRC) and has revamped this committee to enhance resident and faculty mentorship, academic career development, grant writing, equity and health services research. The Department of Surgery is also undertaking a strategic planning process in 2021, where Dr. Liao and Administrative Director of Research **Daniel Salvati** are leading a committee to identify and implement key strategic priorities that will prepare our department to build upon our successes and prepare for future challenges.

Centers of Excellence

The Department of Surgery has four specialized centers of excellence in research and the Surgical Artificial Intelligence and Innovation Laboratory that are designed to enhance the research environment, foster collaboration, and leverage expertise and resources to expand the productivity and output in areas of interest.

Center for Transplantation Sciences (CTS)

The CTS at Massachusetts General Hospital is a multidisciplinary research center working at the interface between basic science and clinical applications in transplantation immunology and related fields. It was established in 2015 by merging the Transplantation Unit Surgery Research Laboratory and the Transplantation Biology

Research Center, with **Joren C. Madsen, MD, DPhil,** and **James F. Markmann MD, PhD,** serving as co-directors and **Richard N. Pierson III, MD,** serving as scientific director.

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:

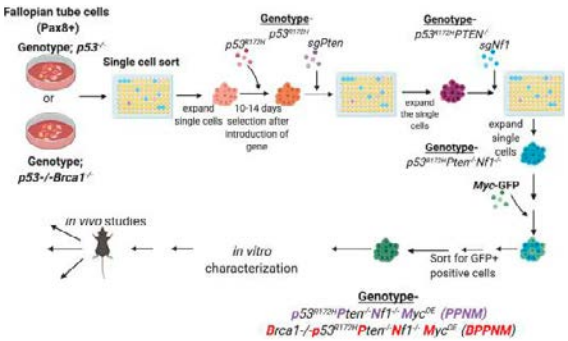
- Better understanding the mechanisms underlying the immune response
- Developing novel means of inducing immune tolerance
- Finding creative ways of increasing the supply of donor organs

Center for Engineering in Medicine & Surgery (CEMS)
The CEMS engages in the basic sciences, clinical medicine, and engineering to solve every day biomedical challenges for patients. Our team of clinically-inspired engineers, physicians and biologists, among others, use creative scientific approaches to improve health care delivery and further the use of personalized medicine, minimally invasive therapies and new technologies for today's and tomorrow's diagnostics and treatments.

The Center's position within the MGH clinical and research environments enables not only the traditional academic triad of sciences, technology, and clinical medicine, but its position also enables a fourth dimension—innovation. Serving as co-directors are **Mehmet Toner, PhD,** and **Martin Yarmush, MD, PhD**.

Center for Organ Engineering
In the Center for Organ Engineering, **Harald Ott, MD, Charles and Sara Fabrikant MGH Research Scholar,** 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.

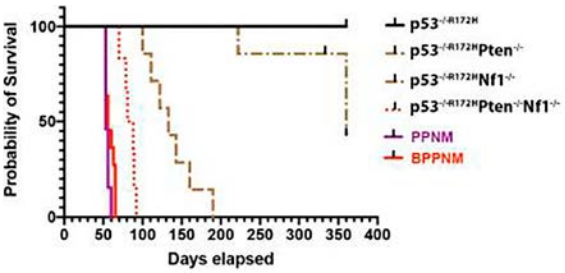
Codman Center for Clinical Effectiveness in Surgery
The Codman Center's mission is to deliver the safest, highest value patient care through innovative research and education. Local, regional and national initiatives analyze and promote the clinical effectiveness of surgical care. The Codman Center collaborates 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.



The BPPNM ($p53^{-/-R172H}Brca1^{-/-}Pten^{-/-}Nf1^{-/-}Myc^{OE}$ genotype) is HR deficient, and the PPNM ($p53^{-/-R172H}Pten^{-/-}Nf1^{-/-}Myc^{OE}$ genotype) cell line does not correspond precisely with a known HR-deficient human HGSC genotype is therefore deemed "non-classified".

Surgery

Department Report



Comparative Kaplan–Meier survival curves of mice bearing the genetically defined engineered cell lines.

Spotlight on Research: The Surgical Artificial Intelligence and Innovation Laboratory (SAIIL)

SAIIL is a multidisciplinary group composed of surgeons, engineers and data scientists who are passionate about redesigning the delivery of surgical care. The team, led by **Ozanan Meireles, MD,** and **Daniel Hashimoto, MD,** is comprised of surgeons in Mass General's Department of Surgery, scientists from the Massachusetts Institute of Technology Computer Science and Artificial Intelligence Laboratory (CSAIL), and students from Harvard University. SAIIL's primary research goals focus on utilizing computer vision to investigate the intraoperative phase of care through real-time, automated analysis of operative video for laparoscopic, robotic, and endoscopic procedures. Other research efforts include investigating quantitative signal from the electronic medical record associated with the surgical video data and their correlation with clinical outcomes, investigation of the value of robotic kinematics in minimally invasive surgery, and co-development of video annotation software.

In 2019, SAIIL presented results of its computer vision system's automated analysis of laparoscopic sleeve gastrectomy videos at the 139th meeting of the American Surgical Association and subsequently published in Annals of Surgery. SAIIL members were also invited lecturers at several other meetings last year, including the Intelligent Health Summit (Basel, Switzerland); European Association of Endoscopic Surgeons (Seville, Spain). SAIIL's research was also covered by the media, including the Financial Times, PBS News, Harvard Medicine Magazine, and TED.

Furthermore, SAIIL has partnered with the Society of American Gastrointestinal and Endoscopic Surgeons (SAGES) to lead an international, multi-institutional collaboration among surgeons and engineers from academia and industry, with 60+ invited participants from North America, Asia, and Europe to create a consensus surgical video annotation framework to allow for international collaboration in surgical AI research (aka, surgical data science).

Achievements:

Defining and optimizing a better recovery from burn injury

People with larger burn size are at higher risk for death. This information guides medical decisions during acute care. **Colleen Ryan, MD,** Director of Burn Outcomes in the Sumner Redstone Burn Center, published one of the first attempts to measure whether the effects of larger burn size extend past the initial hospitalization and impact on long-term quality of life. Using the LIBRE-Profile, a tool developed by her team of Massachusetts General Hospital researchers, in collaboration with colleagues from Spaulding Rehabilitation Hospital, Boston University School of Public Health, Shriners Hospitals for Children, and importantly, burn survivors, identified complex differences related to burn size in work and social spheres. This information may help guide treatments to improve burn recovery.

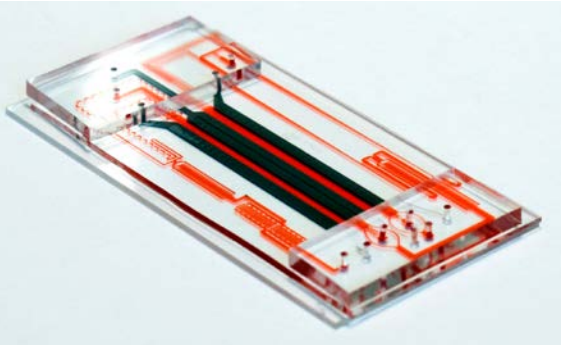
Genetically defined syngeneic mouse models of ovarian cancer as tools for the discovery of combination immunotherapy
Despite advances in immuno-oncology, the relationship between tumor genotypes and response to immunotherapy remains poorly understood, particularly in high-grade serous tubo-ovarian carcinomas (HGSC). We developed a series of mouse models that carry genotypes of human HGSCs and grow in syngeneic immunocompetent hosts to address this gap. We transformed murine-fallopian tube epithelial cells to phenocopy homologous recombination-deficient tumors through a combined loss of p53, Brca1, Pten, Nf1, and overexpression of Myc and p53R172H, which was contrasted to an identical model carrying wild-type Brca1. For homologous recombination proficient tumors, we constructed genotypes combining loss of p53, and overexpression of Ccne1, Akt2, p53R172H, and driven by KRASG12Vor Brd4 or Smarca4 overexpression. These lines form tumors recapitulating human disease, including genotype-driven responses to treatment, and enabled us to identify follistatin as a driver of resistance to checkpoint inhibitors. These data provide proof of concept that our models can identify new immunotherapy targets in HGSC.

Patricia Donahoe, MD, and her team in the Pediatric Surgical Research Laboratory, engineered a panel of murine fallopian tube epithelial cells bearing mutations typical of high grade serous tubo-ovarian carcinomas and capable of forming tumors in syngeneic immunocompetent hosts. These models recapitulate tumor microenvironments and drug responses characteristic of human disease. In a Ccne1-overexpressing model, immune checkpoint resistance was driven by follistatin.

Massachusetts General Hospital performs first successful DCD heart transplant in New England
The demand for heart transplantation increases significantly each year, however donor organ availability remains a limitation to those seeking heart transplantation to treat their end-stage heart disease. Until recently, the only donor hearts utilized for transplantation were those donated after brain death (DBD) and preserved statically using cold storage. Ex-vivo heart perfusion (EVHP) offers new opportunities to expand the donor pool to include hearts donated after circulatory death (DCD), which would otherwise be discarded due to the damaging effects of warm ischemia. The use of EVHP minimizes the effects of warm ischemia by allowing the heart to be resuscitated to a metabolically active and beating state. Most importantly, EVHP allows the heart to be perfused with warm blood, oxygen, and nutrients, which ultimately allows the transplant team to assess the metabolic health of the heart and determine its suitability for transplantation.

David D'Alessandro, MD, and his team were the first in New England and second in the U.S. to perfuse and transplant a human DCD heart as part of an investigational device clinical trial conducted by a local company (TransMedics). Trial enrollment was completed in 2020 by 25 US sites. Of the 90 DCD hearts transplanted study-wide, 20 were transplanted at MGH. The MGH site experience using DCD hearts perfused using EVHP clearly indicates that the technology can reduce

The TransMedics Perfusion Machine



Ultra-high throughput microfluidic chip, LPCTC-iChip, that rapidly processes an entire leukapheresis product.

the time recipients wait to be successfully transplanted. Due to this success, MGH has activated a continued access protocol allow patients to resume using DCD hearts despite the close of the initial trial.

Liquid biopsy using leukapheresis products

Investigators from the MGH Surgery and Center for Engineering in Medicine & Surgery in collaboration with the MGH Cancer Center, led by **Mehmet Toner, PhD, Shyamala Maheswaran, PhD,** and **Daniel Haber, MD, PhD,** together with the fellows **Avanish Mishra, PhD**, and **Taronish Dubash, PhD,** have developed a new approach for liquid biopsy.

Circulating tumor cell (CTC)-based liquid biopsies have emerged as a promising tool for cancer diagnostics, treatment selection, and response monitoring. However, despite advanced technologies for rare cell detection, the very low number of CTCs (0 to 5) present in standard 10 mL peripheral blood samples have significantly limited their clinical utility. In a series of experiments, published in PNAS, we demonstrate a new microfluidic technology enabling highly sensitive liquid biopsy by screening whole human blood volume (5 liter). This is accomplished via leukapheresis, a well-tolerated routine clinical procedure, in which large volumes of blood (5 liter) is processed, with centrifugal enrichment of peripheral blood mononuclear cells into a leukopak of approximately 65 mL volume during an hour-long procedure. The remaining constituents of the blood are returned to the patient, including plasma, RBCs and most neutrophils. CTCs by virtue of having a similar density as mononuclear cells become enriched in the leukapheresis product. While leukapheresis allows for initial cell density-based sorting of entire blood volumes, current CTC isolation technologies can only process up to 3 to 5% of a leukopak, significantly limiting the ultimate benefit of processing leukapheresis products.

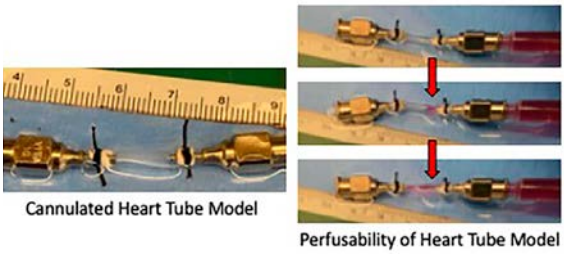
To address this challenge, we developed an ultra-high throughput microfluidic chip, LPCTC-iChip, that rapidly processes an entire leukapheresis product (> 6 billion nucleated cells in 65 mL sample). For effectively depleting massive numbers of antibody-tagged WBCs, we established permeability-enhanced magnetic sorting. In this technique, high magnetic field gradients are achieved through soft magnetic iron-filled channels, which act as magnetic microlenses and intensify the field gradient within the sorting channels. In proof of principle experiments, the LPCTC-iChip achieved 86% CTC recovery with 105 enrichment. The negative depletion of antibody-tagged leukocytes enables isolation of potentially viable CTCs without bias for expression of specific tumor epitopes, making this platform applicable to all solid tumors. Thus, the initial enrichment by routine leukapheresis of mononuclear cells from very large blood volumes, followed by rapid flow, high gradient magnetic sorting of untagged CTCs, provides a technology for noninvasive isolation of 100-fold higher number of cancer cells than standard 10 mL blood samples. Thus, microfluidic technology for ultra-high throughput magnetic sorting of rare cells within very large blood volumes will provide

exceptional opportunities, ranging from real-time pharmacokinetic monitoring of drug response to tissue-of-origin determination in early-stage cancer screening.

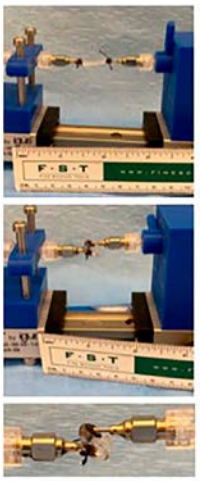
With robust technologies such as presented here, CTC analyses performed on leukapheresis products will extend the reach of liquid biopsies in metastatic cancer, enabling a broad range of additional molecular analyses, including RNA and protein-based determinations and whole-cell analyses, which currently require direct biopsies of metastatic lesions. These include quantitation of cell-surface proteins on cancer cells to guide immune checkpoint therapies or antibody–drug conjugates; pharmacokinetic measurements to assess the effect of therapeutic interventions on their targeted intracellular signaling pathways and defining molecular mechanisms of acquired cancer drug resistance; and real-time generation of tumor-cell-derived cultures for individualized functional drug sensitivity testing. Single-cell-resolution analyses also enable critical studies of cancer heterogeneity, including the detection of early resistant colonies that foretell the emergence of clinical drug resistance and molecular analyses of heterogeneity among metastatic precursors that underlie the blood-borne spread of cancer. Importantly, since CTCs may be shed by invasive cancers long before metastases are established, leukapheresis combined with CTC detection may play a critical role in screening high-risk patients for early cancer, identifying the tissue of origin and reducing the need for invasive biopsies. In this context, CTC-based analyses may be combined with plasma-based screening for mutations or aberrant DNA methylation patterns, providing a comprehensive approach to noninvasive early cancer detection.

Engineering Development: A Tissue Model of Congenital Heart Defects

The heart is the first organ to develop during embryogenesis. It starts out as a simple tube that then undergoes a looping phenomenon which transforms the tubular structure into the beginnings of the adult four-chambered organ. Incomplete looping causes misalignment of the developing heart resulting in congenital heart disease (CHD). In order to better study the development of CHD, MGH Research Scholar **Harald Ott, MD,** and his team have begun to create a tissue engineered model of the embryonic heart tube which will be subjugated to external mechanical forces that lead to looping through a specially designed bioreactor. The long-term goal of this project is to create a three-dimensional tissue model system that recapitulates cardiac development to act as a tool to examine the pathophysiology of CHD. To build such a model, tissue engineering principles will be combined with knowledge from developmental biology. Through this approach of "engineered development", we hypothesize that a tissue model of early cardiac development can be established and used to examine and predict the induction of congenital heart disease. This project was awarded funding through a Discovery Award from the Department of Defense's Congressionally Directed Medical Research Program.


Cannulated Heart Tube Model

Perfusability of Heart Tube Model


Heart Tube in Bioreactor Undergoing Looping

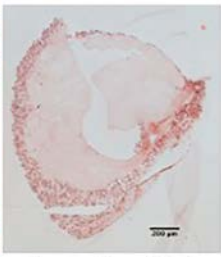
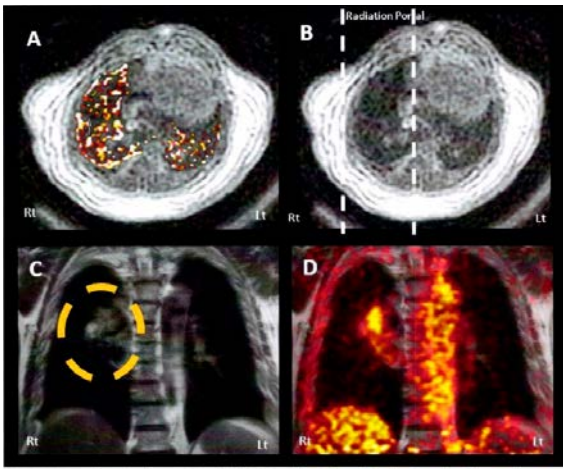
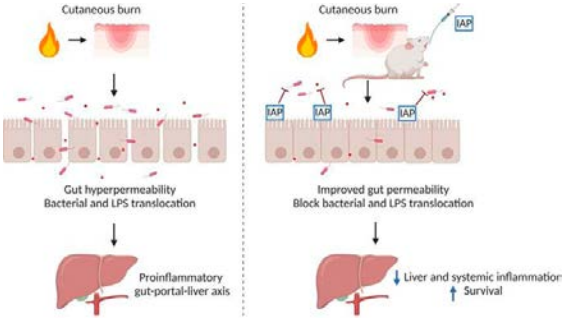

Hematoxylin and Eosin Staining of Cross Section of Engineered Heart Tube

Figure 1: Cannulated Heart Tube Model
Figure 2: Perfusability of Heart Tube Model
Figure 3: Heart Tube in Bioreactor Undergoing Looping
Figure 4: Hematoxylin and Eosin Staining of Cross Section of Engineered Heart Tube



(A) MRI image of murine lungs Rx'ed with 21Gy with enhanced probe signa in R lung normal signal (B) in control mouse (C) MRI of human subject with RILI in RUL. (D) Fused PET/MR depicting localization of collagen PET probe with an area of established RILI



Targeting the gut to prevent sepsis from a cutaneous burn. *JCI Insight DOI: 10.1172/jci.insight.137128*

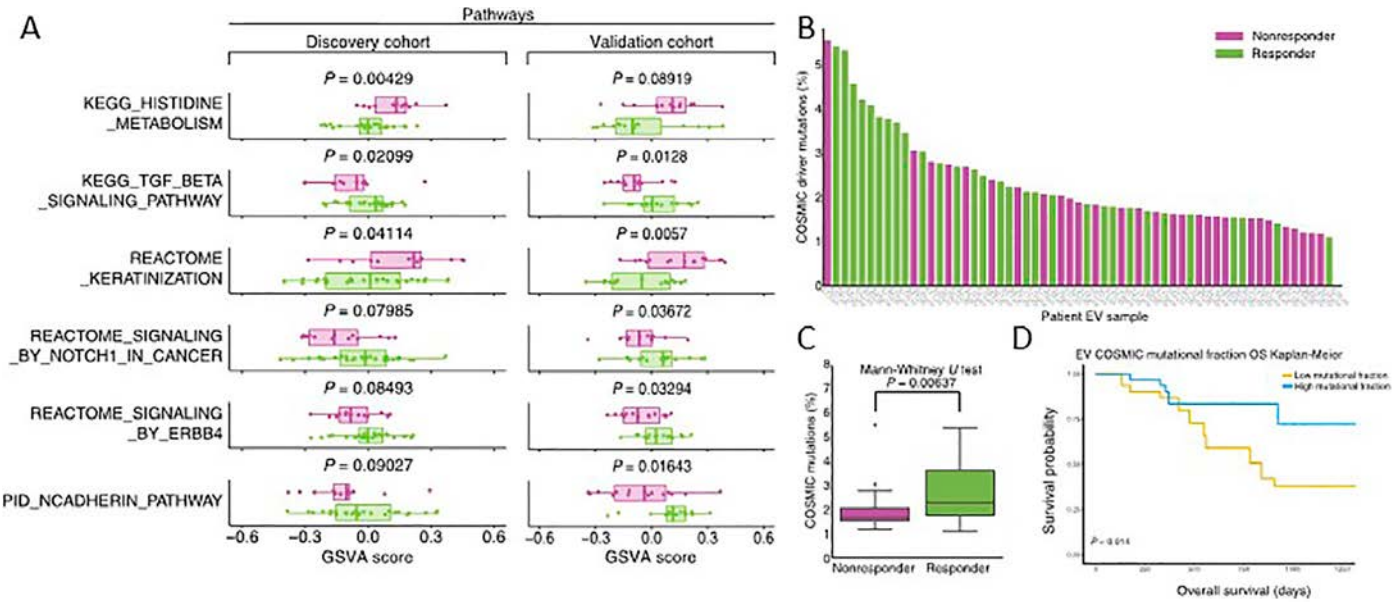
CHEST Foundation Research Grant in Pulmonary Fibrosis

Michael Lanuti, MD, won the CHEST Foundation Research Grant in Pulmonary Fibrosis for his project titled, "PET Imaging of Pulmonary Fibrosis." Dr. Lanuti served as a co-principal investigator. The CHEST Foundation supports research projects, "that aim to champion the prevention, diagnosis, and treatment of chest diseases." This project funds a clinical trial to noninvasively quantify Pulmonary Fibrosis and Radiation Induced Lung Injury using [68Ga]CBP8 Type 1 Collagen Probe.

Developing new strategies to detect and prevent trauma induced bacterial infections

Laurence Rahme, MSc, PhD, was named an MGH Research Scholar for her work focusing on infections associated with sepsis and burns. Severe trauma renders patients highly susceptible to multiple independent infection episodes (MIIE). MIIE incidence varies across individuals, suggesting the importance of considering individual patients' underlying susceptibility. In collaboration with trauma and burn surgeons the Rahme lab has been working on developing methods to identify increased MIIE risk before clinical signs appear, which is fundamentally different from existing approaches of detecting infections after they are established. In their recent *iScience* publication, by applying machine learning algorithms to genome-wide transcriptome data of early blood collected within 48 hours of injury, the team identified a panel of biomarkers that were highly predictive of future MIIE cases. Moreover, using clinical data, in their *PLoS One* publication, the team showed that Denver and Marshall scores ascertained at admissions could be a predictor of MIIE. Methods to identify trauma patients with increased risk of infection could be advantageous for ensuring timely and appropriate delivery of preventative measures, improving surveillance, and promoting antibiotic stewardship to limit the emergence of multi-drug resistance bacteria, reduce toxicity to patients and decrease health care costs. The unique biomarker development method and precision medicine approach can be widely applicable to different patient populations and a variety of outcomes. Moreover, it could help elucidate underlying molecular mechanisms, thus opening avenues for potential preventative and therapeutic interventions.

Severe burn injury induces gut barrier dysfunction and subsequently a profound systemic inflammatory response. The laboratory of **Richard Hodin, MD** investigated the role of the small intestinal brush border enzyme, intestinal alkaline phosphatase (IAP), in preserving gut barrier function and preventing systemic inflammation after burn wound infection in mice. Both endogenously produced and exogenously supplemented IAP significantly reduced gut barrier damage, decreased bacterial translocation to the systemic organs, attenuated systemic inflammation, and improved survival in this burn wound infection model. IAP attenuated liver inflammation and reduced the proinflammatory characteristics of portal serum. These results indicate that oral IAP therapy may represent an approach to preserving gut barrier function, blocking proinflammatory triggers from entering the



(A) Pretreatment transcriptomic signatures distinguish ICI responders from nonresponders in both the discovery and validation cohorts. (B, C) The responder group had more COSMIC mutations suggestion a correlation with mutational load as inferred from RNAseq. (D) Patients with a higher mutational load as assessed from plasma-derived EV had longer OS than those with a lower mutational load.

portal system, preventing gut-induced systemic inflammation, and improving survival after severe burn injuries.

Extracellular vesicles for cancer detection and therapeutic monitoring

Historically, blood-based biomarkers for immunotherapy focused on cell-free DNA (cfDNA) or circulating tumor cells, which solely reflect tumor-based properties and not changes in the immune system during treatment. To improve prediction and tracking of immune checkpoint inhibitor (ICI) resistance, simultaneous capture of transcriptomic features from both the tumor and immune system is critical. Extracellular vesicles (EVs) are produced by many cell types including tumor and immune cells, which contain a subtranscriptome of their cell of origin. EVs are involved in oncogenesis and immune modulation and serve as communicators of genetic and epigenetic signals. In cancers, tumor-secreted EVs modulate the tumor microenvironment and elicit antitumoral immune responses, and plasma-derived EV transcripts are markers of antitumor immune activity. EVs are also secreted by many immune cell types implicated in immune checkpoint inhibitor (ICI) response including CD4+/CD8+ T cells, dendritic cells, regulatory T cells, and macrophages. During tumor progression, both overall and tumor-specific EVs are elevated in plasma.

Genevieve Boland, MD, PhD, and her laboratory hypothesized that bulk, non-enriched plasma-derived EVs capture both tumor-derived EVs and non-tumor-derived EVs, reflecting tumor-intrinsic and nontumor signals. Their recent publication in Science Advances utilized a transcriptome microarray and RNAseq to analyze pretreatment and on-treatment peripheral blood–derived bulk EV RNA from 50 patients with metastatic melanoma (discovery cohort; n = 33 responders and n = 17 nonresponders) treated with ICI. A subset of patients had posttreatment plasma samples (n = 15) and tumors (n = 26). In addition, four melanoma cell lines and paired EV were analyzed. Results were validated in a separate cohort of 30 patients (n = 14

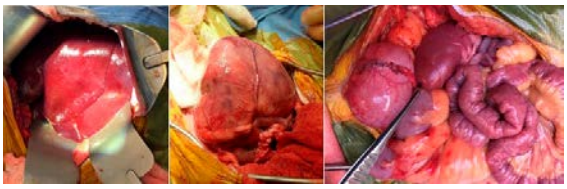


Figure 1: Pig Liver
Figure 2: Pig Heart
Figure 3: Pig Kidney

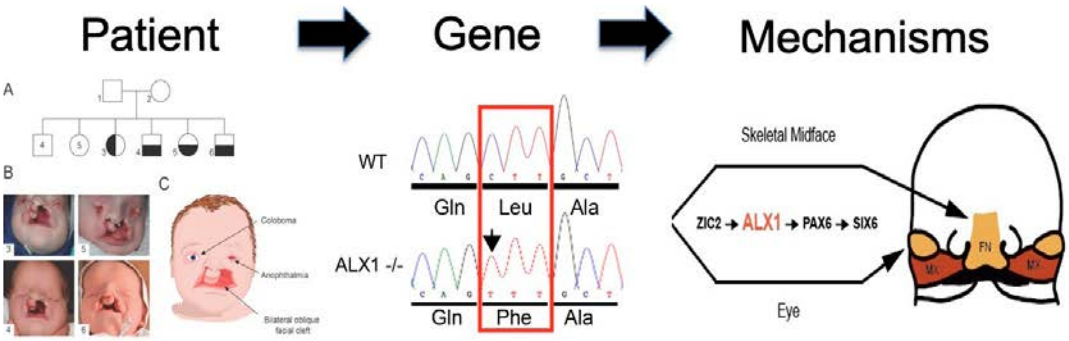
responders and n = 16 nonresponders) using EV RNA sequencing (evRNA- seq). To integrate transcriptomic data from two sequencing platforms, a multipronged statistical strategy was utilized to minimize cross-platform variance. To interpret mixed plasma-derived EV data, a novel Bayesian deconvolution computational model was created to partition transcripts into tumor and nontumoral sources. This work demonstrated that EVs serve as a non-invasive biomarker to jointly probe tumor-intrinsic and immune changes to ICI, function as predictive markers of ICI responsiveness, and monitor tumor persistence and immune activation.

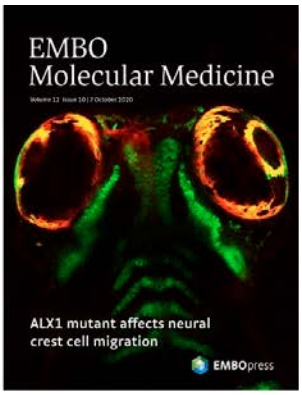
In addition to their use in monitoring therapeutic responses, EVs have the potential to serve as a blood-based biomarker for early detection of cancer. Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are known precursor lesions of pancreatic cancer that often present as cysts. Although IPMNs can progress to invasive cancer, most of these tumors are benign and pose no immediate risk to the patient. Monitoring these tumors in patients by frequent imaging (CT, MRI, EUS, etc) is costly and often does not provide a clear indication of when the tumor has progressed from a benign low grade tumor to one that is advancing towards invasive cancer. Teaming up with **Ralph Weissleder, MD, PhD, Carlos Fernandez, MD,** and **Andrew Liss, PhD,** sought to investigate if specific extracellular vesicles, exosomes, could be used to identify patients with high-risk IPMNs. They found that the presence of MUC5AC in circulating EVs can predict the presence of invasive carcinoma within IPMN (specificity of 82%, sensitivity of 100%). The use of MUC5AC+ EVs as a biomarker has the potential to improve the management and follow-up of patients with IPMN including avoiding unnecessary surgery. This project is now NIH funded, and additional markers are being evaluated to identify patients who have IPMNs with high-grade dysplasia.

MGH Center for Transplantation Sciences is Leading in Xenotransplantation

An inadequate supply of donor organs to treat patients with end stage organ failure is a critical unmet need in medicine and addressing this problem is the highest goal of the transplant research community. The list of patients awaiting life-saving transplants exceeds 100,000 and the wait for organs incurs untold morbidity and mortality. However, the potential demand for organs is far greater than the number currently listed as many potential candidates never make it to the list given the limited supply. And, while the organ has increased by 30% over the last decade, the tremendous success of transplantation to save lives has only further increased demand. Perhaps the only potential solution on the near-term horizon that could provide a limitless organ supply is xenotransplantation, the transplantation of organs from animals.

Although xenotransplantation has been considered for many years, what has changed to revolutionize the field is the advent of multiplex gene editing using CRISPR. This has dramatically increased the efficiency and specificity with which the pig genome can be modified to render pig organs more compatible with human recipients. Three years ago, the MGH transplant research team initiated a broad collaboration with a local start-up company founded





by George Church and Luhan Yang (eGenesis) from Harvard which is using CRSPR based gene editing technology to design pigs for transplantation. Key targets for modification include eliminating 3 carbohydrate antigens expressed by pigs to which humans have natural antibodies, as well as addition of human genes to correct species incompatibilities in the complement cascade, coagulation, and inflammation.

The partnership with MGH takes advantage of our depth of expertise in preclinical models to transplant heart, lung, liver, kidney and islets and a recent investment by MGH in a large animal facility in CNY. The MGH initiative is likely the largest and most concerted effort to date to bring xenotransplantation forward to date and has already resulted in two NIH R-level grant awards to support the work. While full success has not yet been achieved, great progress has been made with modified pig hearts and kidneys; pig kidneys have survived in nonhuman primates for more than 300 days. Shown below are recent CRISPR modified porcine- liver, heart and kidney xenografts transplanted into nonhuman primates.

Identifying the genetic basis of craniofacial development using human iPSC and zebrafish models

MGH Research Scholar **Eric C. Liao, MD, PhD,** from the Division of Plastic Surgery and Center for Regenerative Medicine investigates the genetic basis of cleft and craniofacial development, and aims to harness regenerative approaches to improve diagnosis and treatment. Graduate student **Janina Kueper, MD** discovered the role of ALX1, a homeodomain transcription factor that serves as a master switch for pathways that regulate how midface takes shape. This research leveraged our ability to create human stem cell models (iPSC) from our patients with craniofacial anomalies, to recapitulate the stem cell formation of neural crest cells that contribute to facial structures. Molecular and cellular studies in the human iPSC models then generate hypotheses that can be interrogated in a zebrafish model. This work was published in *EMBO Molecular Medicine* journal and was featured on the cover of the October 2020 issue.

Current work leverages the human iPSC and animal models toward defining ALX1 downstream pathways, and to elucidate epigenetic determinants of craniofacial morphogenesis.

This work was published in *EMBO Molecular Medicine* journal and was featured on the cover of the October 2020 issue.

Current work leverages the human iPSC and animal models toward defining ALX1 downstream pathways, and to elucidate epigenetic determinants of craniofacial morphogenesis.

Urology

Department Report

MICHAEL L. BLUTE, SR., MD, CHIEF

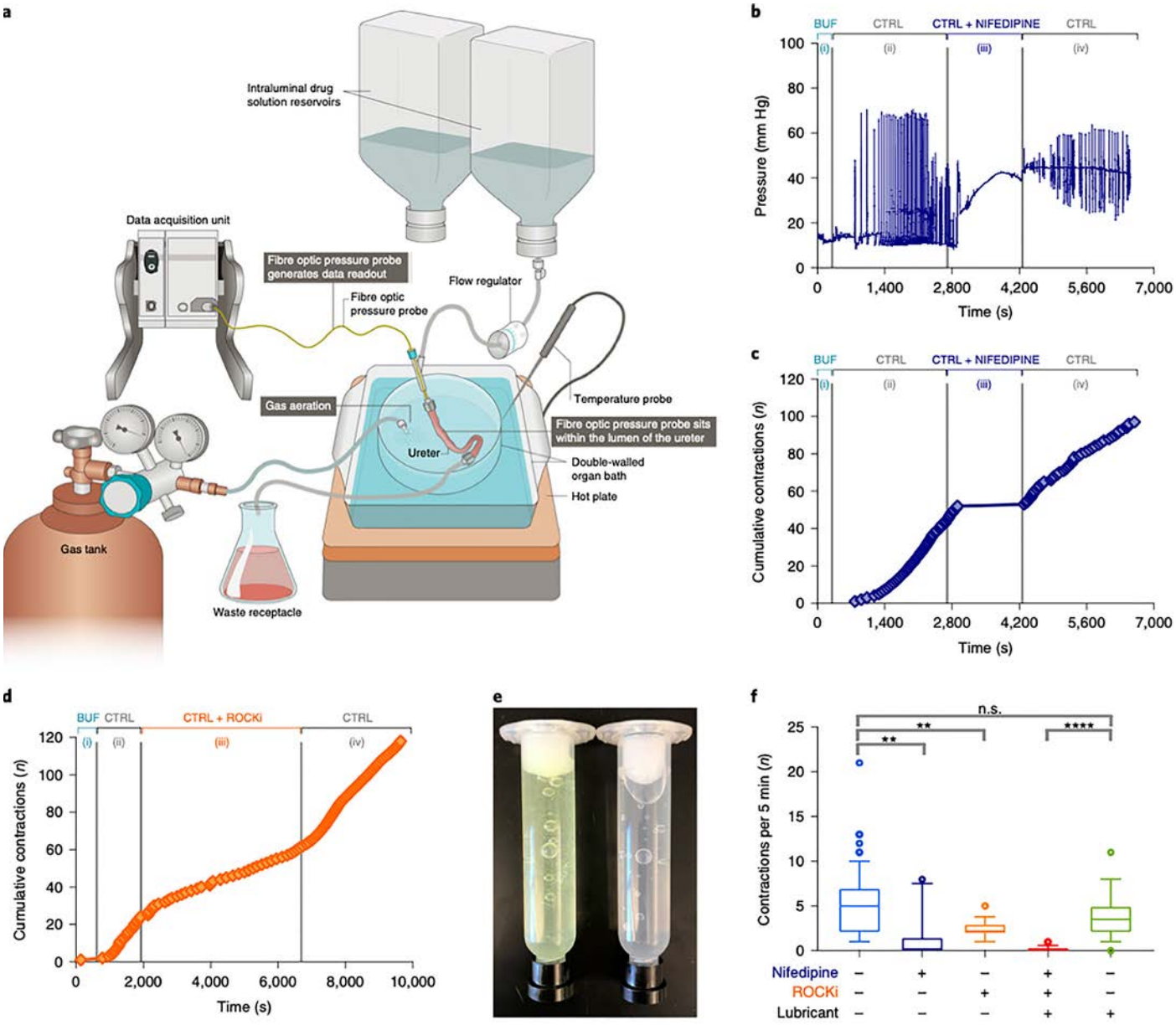
Overview:

Introduction:
Our research program in the Department of Urology at the MGH continues to thrive and grow. We have a wide breath of funded and unfunded research 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 lower urinary tract dysfunction. The department supports research efforts that focus on health sciences and patient outcomes, advances in surgical technique and translational research. We have recently hired three Urology faculty, Keyan Salari, MD, PhD, Michelle Kim, MD, PhD and Jason Michaud, MD, PhD, all dedicated to research activity in addition to clinical care.

Our active dedicated research laboratories include the Urologic Clinical Outcomes and Translational Research Laboratory, under the direction of Adam Feldman, MD, MPH, the Urology-Pathology Research Laboratory, directed by Chin-Lee Wu, MD, PhD, and the Pediatric Urological Research Laboratory, directed by Siam Oottamasathien, MD. 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.

In addition to active labs within the department, our busy clinical surgeons actively collaborate with translational and basic science researchers at MGH and around the Harvard-MIT community. Dr. Douglas Dahl 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 an circulating tumor cell analysis of high-grade prostate cancers and correlation with genomic evaluation of the primary tumor. Dr. Brian Eisner continues his collaborative basic science work in ureteral physiology and kidney stones with researchers at MIT, as outlined in his highlighted study below.



Vasodilators delivered *ex vivo* into the ureteral lumen inhibited ureteral contraction amplitude and frequency.

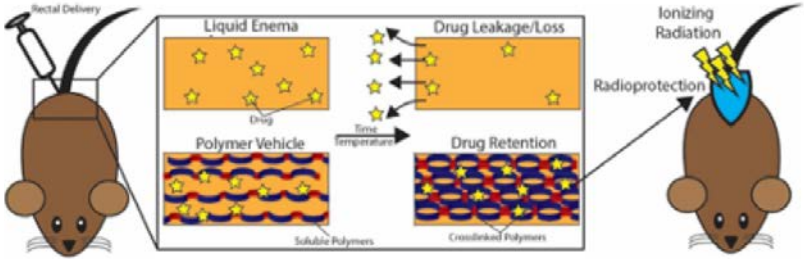
Department Research Strategy For The Future:
As we move forward, we aim to continue to build our research infrastructure to allow our faculty to more effectively pursue meaningful research that will improve patient care. Our continued commitment to translational and basic science research is evident by the hiring of Dr. Salari, who is studying genomics in urologic cancers and Dr. Michaud, whose lab studies body's response to bacterial infections of the urinary tract (UTIs) and aims to develop novel treatments for UTIs in both children and adults. Dr. Michelle Kim is helping to develop our health services research endeavors. As a department, we are building collaborative relationships with other MGH research centers, including the Clinical Data Animation Center (CDAC) and the Center for Outcomes & Patient Safety in Surgery

Urology

Department Report

Glycosaminoglycan ethers delivered via a heat-sensitive polymer into the rectal vault may serve as a protective mechanism during external beam radiation.

GRAPHICAL ABSTRACT



(COMPASS). These collaborative relationships will improve our efficiency in continuing to advance our clinical database development. We also look to develop our infrastructure for participation in Urology-based clinical trials, both in urologic oncology and benign urologic diseases.

Achievements:

Notable Research Projects And Accomplishments In 2020:

- The management of ureteral stones is an ongoing clinical challenge in Urology. Dr. Brian Eisner has developed a collaborative study with Dr. Michael Cima and his team at MIT to assess the feasibility of local delivery of vasodilators into the ureter to reduce the pain associated with ureteral stones and the stents used as part of the treatment of those stones. Their paper, “Identification and local delivery of vasodilators for the reduction of ureteral contractions” was published in *Nature, Biomedical Engineering.* His team demonstrated that vasodilators delivered *ex vivo* into the ureteral lumen inhibited ureteral contraction amplitude and frequency. They went on to further demonstrate in an *in vivo* pig model, that retrograde intraureteral delivery of these vasodilators via ureteral catheter again reduced the ureteral contraction amplitude and frequency, as compared to the clinical gold standard of the orally administered alpha-blocker, tamsulosin. These findings suggest that the intraureteral use of these drugs may benefit patients in the management of nephrolithiasis with medical expulsive therapy and treatment of symptomatic ureteral stent pain.
- The management of the incidentally discovered small renal mass is a clinical dilemma in urologic oncology. 20-25% will be benign, and even many malignant renal tumors may remain indolent for many years. There are currently no clinically available biomarkers to assist clinicians in the decision making between active surveillance or active treatment of small renal masses and small Stage I renal cell carcinoma (RCC). Dr. Adam Feldman has continued his collaborative research with colleagues at the University of Michigan and Myriad Genetics, Inc. in their investigation of genomic predictors of clinical outcomes for RCC. Their latest work, “Biopsy Cell Cycle Proliferation Score Predicts Adverse Surgical Pathology in Localized Renal Cell Carcinoma” was published in the journal, European Urology and builds on prior published investigation of genomic

markers in nephrectomy RCC specimens. The genomic panel, cell cycle proliferation (CCP) score was assessed in renal mass percutaneous needle biopsy specimens and was used to predict adverse pathologic features in eventual surgical specimens. The CCP score was integrated with relevant baseline clinical data in a predictive model and was found to be a significant predictor of adverse surgical pathology. Furthermore, CCP score improved the performance of the predictive model. These findings further suggest that this predictive genomic score could aid clinicians in medical decision making in the management of RCC.

- Radiation cystitis and proctitis can be a challenging clinical problem for patients undergoing pelvic radiation for treatment of various urologic, gynecologic and colorectal malignancies. Dr. Siam Oottamasathien has dedicated much of his basic science laboratory work to the investigation of cystitis and radiation induced cystitis and proctitis. His RO1 funded work, "Localized Delivery of Glycosaminoglycan Ethers for the Treatment of Radiation-Induced Proctitis" is a collaborative effort between his lab and colleagues at the University of Utah. As outlined in Figure 2, his work investigates the delivery of glycosaminoglycan ethers via a heat-sensitive polymer into the rectal vault as a protective mechanism during external beam radiation. Positive results from this innovative work may help develop novel products and methodologies for protecting patients from collateral adjacent tissue damage often caused by therapeutic radiation.

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Table 2 – Multivariable logistic regression for adverse surgical pathology in the overall cohort (*n* = 202) and patients with low-grade tumor on biopsy (*n* = 175).

	Model 1: CCP omitted	Model 2: binary CCP	Model 3: cont. CCP
	OR (95% CI; *p* value)	OR (95% CI; *p* value)	OR (95% CI; *p* value)
Overall cohort (n = 202)			
Age (per 1 yr)	1.02 (1.00–1.05; 0.08)	1.03 (1.00–1.06; 0.05)	1.02 (1.00–1.05; 0.07)
Male sex (vs female)	2.25 (1.18–4.37; 0.02)	2.06 (1.07–4.05; 0.03)	2.13 (1.11–4.17; 0.03)
Nonwhite race (vs white)	1.19 (0.48–2.91; 0.71)	1.21 (0.49–2.99; 0.67)	1.21 (0.49–2.98; 0.67)
Lesion size (per 1 cm)	1.35 (1.16–1.61; <0.001)	1.36 (1.16–1.64; <0.001)	1.34 (1.15–1.60; 0.001)
Bx clear cell (vs non–clear cell)	0.71 (0.36–1.41; 0.33)	0.44 (0.19–0.98; 0.05)	0.48 (0.21–1.04; 0.07)
Bx grade (1, 2, 3–4)	1.98 (1.13–3.59; 0.02)	1.80 (1.00–3.30; 0.05)	1.82 (1.02–3.33; 0.05)
Bx CCP > 0 (vs ≤0)	–	2.44 (1.18–5.22; 0.02)	
Bx CCP (per 1 unit)	–	–	1.72 (1.03–2.92; 0.04)
Low-grade biopsy (n = 175)			
Age (per 1 yr)	1.02 (0.99–1.05; 0.12)	1.03 (1.00–1.06; 0.07)	1.03 (1.00–1.06; 0.10)
Male sex (vs female)	3.00 (1.45–6.51; 0.004)	2.77 (1.32–6.10; 0.01)	2.87 (1.38–6.28; 0.01)
Nonwhite race (vs white)	1.41 (0.55–3.57; 0.47)	1.41 (0.55–3.61; 0.47)	1.41 (0.55–3.59; 0.47)
Lesion size (per 1 cm)	1.41 (1.19–1.71; <0.001)	1.44 (1.21–1.77; <0.001)	1.40 (1.18–1.71; <0.001)
Bx clear cell (vs non–clear cell)	0.73 (0.35–1.52; 0.40)	0.46 (0.19–1.06; 0.07)	0.52 (0.22–1.19; 0.13)
Bx grade 2 (vs grade 1)	0.68 (0.31–1.52; 0.35)	0.62 (0.27–1.42; 0.26)	0.64 (0.28–1.46; 0.29)
Bx CCP > 0 (vs ≤0)	–	2.52 (1.18–5.66; 0.02)	–
Bx CCP (per 1 unit)	–	–	1.64 (0.95–2.90; 0.08)

Bx = biopsy; CCP = cell cycle progression score; CI = confidence interval; OR = odds ratio.

CCP score was integrated with relevant baseline clinical data in a predictive model. The genomic score was found to be a significant predictor of adverse surgical pathology and improved the performance of that predictive model.

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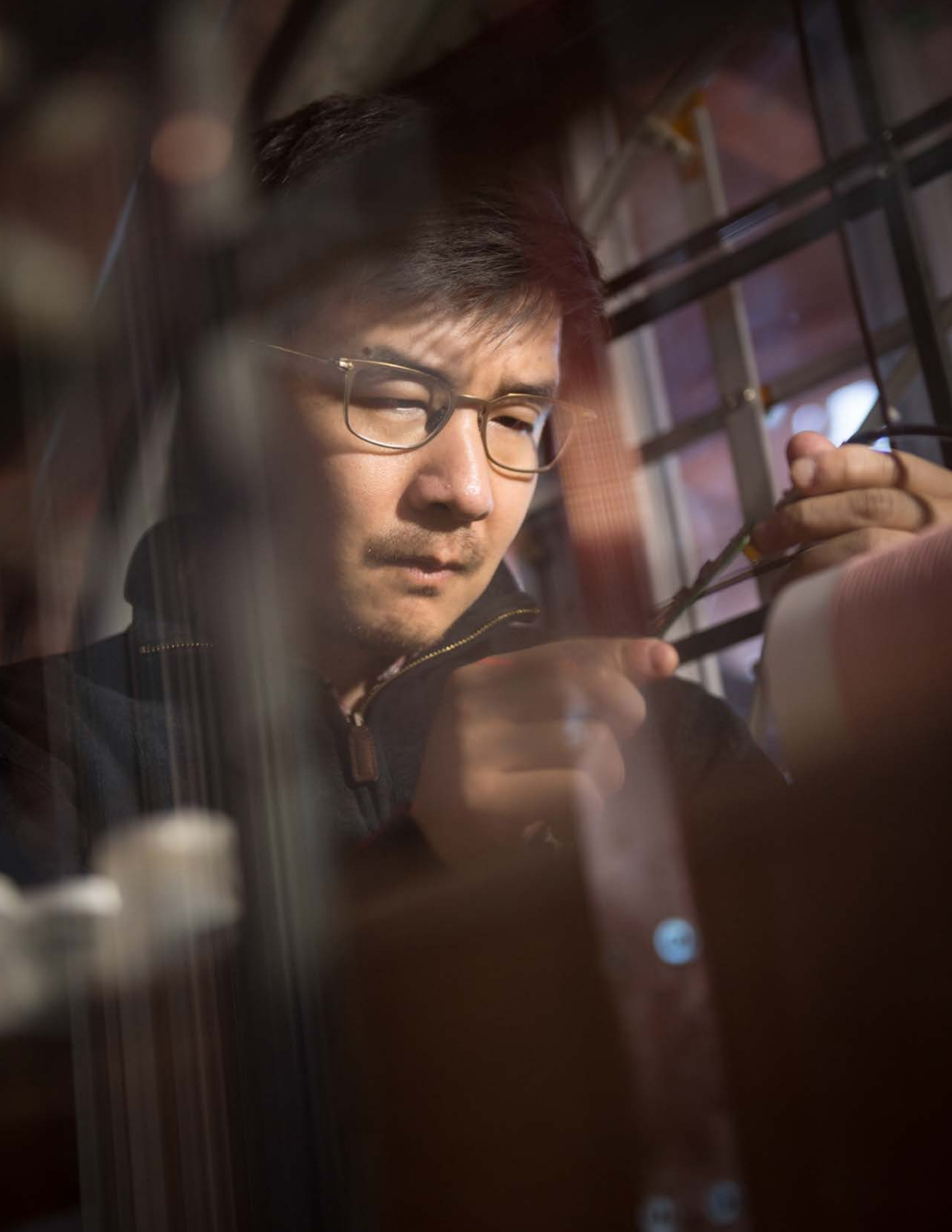

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