Celebration of SCIENCE

Executive Committee on
RESEARCH

MGH 1811
MASSACHUSETTS GENERAL HOSPITAL
RESEARCH INSTITUTE

Welcome

Welcome to the annual Celebration of Science. In past years, the Celebration of Science has been held as a prelude to the annual meeting of the MGH Scientific Advisory Committee (SAC).

This year the Celebration of Science is being held on the morning of April 5th and we will be forgoing our traditional SAC meeting in lieu of hosting the 2017 Warren Triennial Prize and Symposium.

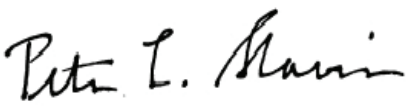
As in past years, our Celebration will begin with welcoming remarks from Dr. Peter L. Slavin, President of MGH. Dr. David N. Louis, Chair of the Executive Committee On Research (ECOR), will then deliver the annual ECOR report, highlighting notable research accomplishments and events over the past year and introducing the newly selected 2017 class of MGH Research Scholars.

The outstanding MGH researchers who will be presenting their work in our symposium this year are the 2017 Martin Research Prize recipients, Daniel G. MacArthur, PhD, and Alexander A. Soukas, MD, PhD, and the 2017 Howard Goodman Award recipient , Mario L. Suvà, MD, PhD.

The Martin Research Prizes are awarded annually in honor of HMS Dean Emeritus Joseph B. Martin, who was Dean of Harvard Medical School from July 1997 to July 2007. The prize was first awarded in 2009, and it recognizes outstanding research achievements published by MGH investigators in the previous calendar year. One award is given for excellence in Clinical Research and the other for excellence in Fundamental Research. Presenting first is the Clinical Research awardee, Daniel G. MacArthur, PhD. He will present his paper, "Analysis of protein-coding genetic variation in 60,706 humans," which was published in Nature. The Fundamental Research awardee, Alexander A. Soukas, MD, PhD, will present his paper, "An Ancient, Unified Mechanism for Metformin Growth Inhibition in C. elegans and Cancer," which was published in Cell.

The Celebration of Science will conclude with a presentation by the winner of the 2017 Howard M. Goodman Fellowship. The Fellowship honors Howard M. Goodman, PhD, founder of the MGH Department of Molecular Biology in 1982 and Chief of that Department until 2004. The 2017 awardee, Mario L. Suvà, MD, PhD, will present on his project "Leveraging single-cell analyses to dissect the tumor micro-environment of human gliomas and design highly specific immunotherapies."

We look forward to an engaging and stimulating morning of presentations and discussion and appreciate your participation. We hope you will return to Simches Auditorium this afternoon for the 2017 Warren Triennial Prize Symposium, which is honoring Dr. James Allison for his breakthrough research in cancer immunology.



Peter L. Slavin, MD
President

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

Harry W. Orf, PhD
Senior Vice President for Research

Agenda

Wednesday, April 5, 2017
Simches 3.110

Celebration of SCIENCE

9:00 - 9:15 am

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

Opening Comments and Introductions
David N. Louis, MD, Chair, Executive Committee on Research (ECOR)

2017 MGH Research Scholars
Dr. Louis

9:15 - 10:00 am

ECOR Report
Dr. Louis

10:00 - 10:30 am

2017 Goodman Fellowship
Leveraging single-cell analyses to dissect the tumor micro-environment of human gliomas and design highly specific immunotherapies
Mario L. Suvà, MD, PhD

10:30 - 10:50 am

BREAK

10:50 - 11:20 am

2017 Martin Prize for Clinical Research
Analysis of protein-coding genetic variation in 60,706 humans
Daniel G. MacArthur, PhD

11:20 - 11:50 am

2017 Martin Prize for Fundamental Research
An Ancient, Unified Mechanism for Metformin Growth Inhibition in C. elegans and Cancer
Alexander A. Soukas, MD, PhD

Goodman & Martin Award Winners

2017 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.

Mario L. Suvà, MD, PhD
Assistant Professor
Department of Pathology

2017 Martin Research Prize for Clinical and Fundamental Research

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

Clinical Research
Daniel G. MacArthur, PhD
Assistant Professor
Department of Medicine, Analytic and Translational Genetics Unit
Center for Genomic Medicine (formerly Center for Human Genetic Research)

Fundamental Research
Alexander A. Soukas, MD, PhD
Assistant Professor
Department of Medicine, Endocrine Division, Diabetes Unit
Center for Genomic Medicine (formerly Center for Human Genetic Research)

Executive Committee on Research

Officers and Members 2017

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

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

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

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

Galit Alter, PhD
Ragon Institute
Alternative representative

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

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

Dennis A. Ausiello, MD*
Medicine
April 2013 - March 2019

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

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

Sylvie Breton, PhD
Program in Membrane Biology/ Nephrology
Elected Representative
January 2014 - December 2017

James A. Brink, MD*
Chief, Imaging
April 2013 - March 2019

Dennis Brown, PhD
Director, Office for Research Career Development
Ex-officio

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

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

Iain Drummond, PhD
Nephrology
Co-Chair, Subcommittee on Review of Research Proposals (SRRP)
Ex-officio

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

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

Marcia Goldberg, MD*
Infectious Diseases
April 2012 - March 2018

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

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

Kurt J. Isselbacher, MD
Honorary Member

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

Anne Klibanski, MD
Chief Academic Officer, Partners Healthcare
Director, Center for Faculty Development
Ex-officio

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

*Chair Appointment, ‡ Chiefs Council

Executive Committee on Research
Officers and Members 2017

Andrew Luster, MD, PhD
Chief, Rheumatology, Allergy and Immunology
Chair, Subcommittee on Animal Resources (SAR)
Ex-officio

Thomas J. Lynch, Jr., MD
CEO & Chairman, MGPO
Ex-officio

Joren Madsen, MD, DPhil*
Director, MGH Transplant Center
April 2012 - March 2018

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

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

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

Christopher Newton-Cheh, MD, MPH
Cardiology
Committee on Clinical Research (CCR) Representative
Ex-officio

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

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

Bruce Rosen, MD, PhD
Director, MGH Martinos Center
Ex-officio

Jerrold Rosenbaum, MD‡
Chief, Psychiatry
April 2012 - March 2018

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

Harry E. Rubash, MD‡
Chief, Orthopaedics
April 2012 - March 2018

Paul S. Russell, MD
Honorary Member

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

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

Brian Seed, PhD
Director, Center for Computational & Integrative Biology
Ex-officio

Stephanie Seminara, MD
Reproductive Endocrine
Elected Representative
January 2015 - December 2017

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

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

Elsie M. Taveras, MD, MPH
Population Health Management/Pediatrics
Elected Representative
January 2017 - December 2019

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

Korkut Uygun, PhD
Center for Engineering in Medicine/ Surgery
Elected Representative
January 2017 - December 2019

Bruce Walker, MD
Director, Ragon Institute
Ex-officio

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

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

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

*Chair Appointment, ‡ Chiefs Council

The Research Institute Comes of Age...

2016 marked the second full year of operation of the MGH Research Institute, the entity created as the cornerstone element within the Research Strategic Plan approved by our trustees in 2014. In the Institute's first year of operation, from 2014 -2015, research revenues grew from $786M to an all-time high of $800M. This past year, we are pleased to report that revenues again reached a new high, coming in at just under $850M.

As we look back over the Institute's first 24 months of operation, we are starting to see the initiatives proposed under the strategic plan taking shape and coming to realization. The $11 million, 18-bed Translational Research Center (TRC) formally opened its doors with a ribbon-cutting ceremony on November 30, 2016. The Partners Biobank at MGH exceeded its enrollment targets with over 55,000 subjects consented and 40,000 samples collected by the end of 2016. Our Strategic Alliance Committee to engage industry has brought together multiple investigators and assembled broad-based programs in epigenetics, cancer immunology, neurodegeneration in neuroinflammation, and the microbiome. And the Institute's development team has, in addition to continuing its successful donor recruitment work for the Research Scholars Program, produced the first Research Institute Endowed Chair.

In addition to the programs growing out of our strategic plan, other important events and developments have had a significant impact on our research enterprise in 2016. Among the most notable of these are the creation of a new Postdoctoral Fellow Division within the Office for Research Career Development, several new programs to improve the state of research safety, dramatic growth in the Isuggest Program that resulted in the implementation of over 100 process improvement suggestions this past year, and a major expansion of research job titles within Human Resources that now allows us to identify and communicate with much more role specificity to the thousands of members our research community. These and other important developments from the past year are reported below, this year in a new sectional format that aligns with the organizational components (Guide, Promote, Support) of the governance structure of the Institute.

The Research Institute Steering Committee (RISC)

The MGH Research Institute is led by a Steering Committee whose structure is shown in the diagram below. The hospital President, Chief of Medicine, and Chief of Surgery sit ex-officio on the committee. The Executive Committee on Research (ECOR), which is the body chartered by the hospital's General Executive Committee to set science policy (i.e., GUIDE the research enterprise), is represented on RISC by the ECOR Chair, Vice Chair, and Immediate Past Chair. ECOR administers the hospital's internal research grant programs, awarding over $12M annually to MGH investigators, and effectively serves as the legislative branch of the Research Institute. The MGH Research Management Department serves as the executive branch of the Institute, directing all SUPPORT departments and managing the administrative and financial components of the entire research enterprise. It is represented on RISC by the Senior Vice President for Research. Finally, the newest elements of Research Institute leadership were born out of the MGH Research Strategic Plan and created to PROMOTE the research enterprise. They are the Scientific Director of the Research Institute and the Director of the Division of Clinical Research whose offices, respectively, PROMOTE science across the entire research enterprise and at the clinical-research interface.

Leadership Structure of Research at MGH

GUIDE

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

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

Leadership of ECOR

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

ECOR Membership

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

ECOR's broad areas of focus include:

Meetings and Events

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

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 nearly 70 years the committee members have served as a sounding board for the hospital's leadership, helping us evaluate our research mission and address problems we are facing. SAC membership has included Nobel laureates and leaders in science and medicine from academia, industry and government. Current membership includes:

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

Mark C. Fishman, MD
Past President and CEO
Novartis Institutes of Biomedical Research

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

Chris Kaiser, PhD
Professor of Biology
MacVicar Faculty Fellow
Massachusetts Institute of Technology

Vivian S. Lee, MD, PhD, MBA
Senior Vice President for Health Sciences
Dean, School of Medicine
CEO, University of Utah Health Care

Richard P. Lifton, MD, PhD
President and Head of Laboratory of Human Genetics and Genomics
The Rockefeller University

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

Daniel K. Podolsky, MD
President
University of Texas Southwestern Medical Center

E. Albert Reece, MD, PhD, MBA
Vice President for Medical Affairs
University of Maryland, Baltimore
Dean and Akiko K. Bowers Distinguished Professor
University of Maryland School of Medicine

Initiatives and Subcommittees

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

- The Research Space Advisory Committee (RSAC) makes recommendations on the allocation and management of research space.
- The Subcommittee on Animal Resources (SAR) 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.

ECOR also plays a vital role in facilitating communication within the MGH research community via its website, e-newsletters and targeted mailing campaigns.

Recent Initiatives

Post Doctoral Division (PDD)

At the recommendation of our SAC in 2015, ECOR began the process of creating a Division to serve the post doctoral community. The newly formed Post Doctoral Division (PDD), located within the Office for Research Career Development (ORCD), was officially implemented in 2016 with Marcia Goldberg, MD, serving as the inaugural Director of the Division. The goals of the PDD include: serving the career advancement needs of post doctoral fellows in all research settings, providing professional development programs, services, counseling and resources - while enhancing the existing sense of community, as well as the overall experience of post doctoral fellows affiliated with MGH.

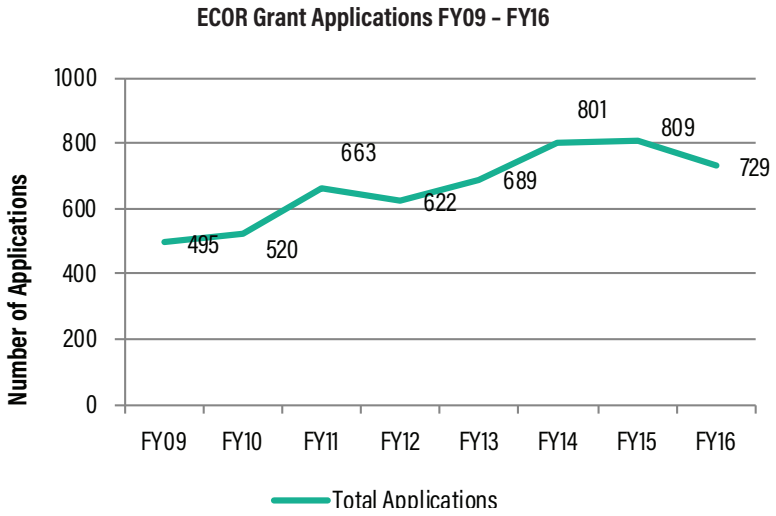
Research Council Departmental Representatives

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

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

Awards and Grants

ECOR manages a multi-million-dollar grant program, virtually a mini-foundation, which annually reviews nearly 800 applications from MGH investigators and fellows, and awards approximately 150 internal grants. Over the past several years, there has been a significant increase in the number of grant mechanisms offered by ECOR, along with an increase in applications to these opportunities. To meet the needs of an increasing application pool, we established an online grant management system where we manage the entire life-cycle of an ECOR application from the start of an application, through the review process, and to the notification of funding.



Subcommittee on Review of Research Proposals

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, training environment, 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 110 members - 31 Professors, 51 Associate Professors, and 28 Assistant Professors. Approximately 30 SRRP members are eligible to review Deliberative Interim Support Fund (ISF) applications, as we require prior study section experience to participate in the panel.

In FY16, $12.3M was awarded to 134 investigators.

Grants	$	PIs
Interim Support (Deliberative & Formulaic)	$5.8M	78
MGH Research Scholars	$3.0M	6
Claflin Distinguished Scholars	$690K	6
FMD & Tosteson Postdoctoral Awards	$1.8M	26
Other Awards*	$973K	18

**Other Awards include Goodman, Martin, PSDA and SAC Abstracts*

Interim Support Program
ECOR launched a major grants program in 2006 to provide interim/bridge support to faculty whose NIH or other federal funding was delayed or otherwise interrupted. The Interim Support Program is intended to preserve valuable research programs at MGH that are suffering due to the harsh funding climate, giving investigators a chance to retool their applications for resubmission. This program serves a vital role in supporting researchers at MGH: over 90% of investigators who received funding from the Interim Support Program from 2006-2016 are still working within the institution. Since the program's inception in 2006, ECOR has awarded $47M of interim support funding. Our investigators have gone on to leverage these funds nine-fold, bringing in over $486M of federal funding to the institution. Within this program are two grant mechanisms, Formulaic Bridge Support and Deliberative Interim Support Funding, which provide similar funding under different guidelines.

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

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

Tosteson & Fund for Medical Discovery Fellowship Awards
The Tosteson & Fund for Medical Discovery (FMD) Fellowship Awards are intended to support junior investigators (MD and PhD fellows/postdocs) at MGH pursuing clinical or fundamental research. The award is offered three times per year, with one cycle dedicated solely to clinical research. Each award includes a salary stipend of $47,500.

Claflin Distinguished Scholar Awards
Although women scientists are recruited to MGH programs, their advancement to senior faculty positions is still far less frequent than that of their male counterparts. In 1993, The Women in Academic Medicine Committee, originally chaired by Mrs. R. Morton Claflin, Honorary Trustee, was established to facilitate the academic careers of women in science at MGH. Recognizing that a significant obstacle to career advancement is the difficulty of maintaining research productivity during the child-rearing years, this committee, with the sponsorship of ECOR, established the Claflin Distinguished Scholar Awards. It is intended that this funding will increase opportunities for women to advance to senior positions in academic medicine. Among those who received the award between 1997-2015 and are still at MGH, 79% have been promoted, while 82% of recipients have received additional grants. In FY16, six women received the Claflin Award.

MGH Physician-Scientist Development Award
The MGH Physician/Scientist Development Award (PSDA) is designed for MD and/or PhD investigators at MGH to support the development of research investigators who are considered underrepresented in medicine (URM), and thereby increase opportunities for URM researchers to advance to senior positions in academic medicine at MGH. In FY16, three investigators received this award.

MGH-MIT Grand Challenges
The MGH-MIT Grand Challenges initiative was developed to increase collaboration between the two institutions in the hopes of bringing together approaches from engineering and basic science with clinical medicine. To do this, the program sought to focus the research agenda on the rapid translation from bedside to bench and back to bedside.

- *Grand Challenge 1: Diagnostics* - This challenge was launched with the goal of developing cost-effective and accurate diagnostics to guide individual clinical decisions based on real-time monitoring and massive patient data sets. Through this challenge, we have given $750,000 to eight teams of investigators through two cycles of grants.

- *Grand Challenge 3: Neurosciences* - This challenge was launched with the goal of developing joint ventures which link basic and clinical research to accelerate progress towards more effective diagnostic approaches and therapies in clinical neuroscience. Through this challenge, we have given $500,000 to six teams of investigators.

MGH Research Scholars
In January 2011, ECOR launched the MGH Research Scholars Program, a major initiative to award research funding to outstanding faculty in our community in support of innovative, cutting-edge research. As of 2016, 42 Scholars have been appointed, each receiving research funding of $100,000 a year for five years.

Other ECOR Awards
The **Howard M. Goodman Fellowship** honors Howard M. Goodman, PhD, founder of the MGH Department of Molecular Biology in 1982 and Chief of that Department until 2004. Dr. Goodman's guiding principle was that great science should not be encumbered by the continual need to convince the world concerning the merit of an individual scientific vision. He believed in choosing scientists of demonstrated excellence and giving them the resources to pursue their goals with vigor, a model that was resoundingly successful. Each year a Goodman Fellow is chosen from the MGH community to honor that legacy and to support the pursuit of excellence by young scientists of uncommon passion and ability. The award is for two years at $150,000.

The **Martin Research Prizes** are awarded annually in honor of Harvard Medical School (HMS) Dean Emeritus Joseph Martin, MD, PhD. Dr. Martin served as Dean of Harvard Medical School from July 1997 to July 2007. Each year, ECOR awards two $100,000 Martin Research Prizes to recognize outstanding research papers published by MGH investigators in Fundamental research and Clinical research.

Awards and Honors
The summer of 2014 saw the creation of the MGH Committee on Awards and Honors, chaired by Dr. Samuel Thier, president of MGH from 1994-1997. The committee ensures that there is an MGH nominee for over 40 major national and international scientific awards and prizes, and for providing hospital endorsements for faculty member admission to distinguished honorific societies. The committee is comprised of 15 esteemed leaders from throughout our institution who meet regularly. In 2016, the committee championed the nominations of more than 35 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 2016 include the following:

Academia Ophthalmologica Internationalis (AOI)
Janey L. Wiggs, MD, PhD, FARVO (Ophthalmology)

Academy of Radiology Research Board of Directors
Miriam K. Bredella, MD (Radiology)

Alan Meyers Award from the Disability Section of the American Public Health Association
Lisa I. Iezzoni, MD (Medicine/Mongan Institute Health Policy Center)

Alzheimer's Drug and Discovery Foundation Grant
Neil Vasdev, PhD (Radiology)

American Academy of Arts and Sciences
Bruce R. Rosen, MD, PhD (Radiology & Martinos Center for Biomedical Imaging)
Ralph Weissleder, MD, PhD (Radiology & Center for Systems Biology)

American Heart Association Center Awards
Anthony Rosenzweig, MD (Medicine/Cardiology)
Saumya Das, MD, PhD (Medicine/Cardiology)
Ravi V. Shah, MD (Medicine/Cardiology)
Marc J. Semigran, MD (Medicine/Cardiology)

American Nurses Foundation Nursing Research Grant
Kim Francis, RN, PhD, PHCNS-BC (Obstetrics & Gynecology)

American Society for Radiation Oncology (ASTRO) Gold Medal
Anthony L. Zietman, MD, FASTRO (Radiation Oncology)

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

American Society for Bone and Mineral Research Rising Star Award
Deborah M. Mitchell, MD (Pediatrics)

American Society of Hematology E. Donnall Thomas Prize
David T. Scadden, MD (Cancer Center & Center for Regenerative Medicine)

American Society for Microbiology (ASM) Antimicrobial Research Award
David C. Hooper, MD (Medicine/Infectious Diseases)

Bill and Melinda Gates Foundation, Grand Challenges Explorations Award
Patricia K. Donahoe, MD (Surgery)
David Pepin, PhD (Surgery)

Boston Business Journal's 2016 Women to Watch in Science and Technology
Susan A. Slaugenhaupt, PhD (Neurology & Center for Genomic Medicine)

Doris Duke Charitable Foundation Clinical Scientist Development Award
Lynn T. Matthews, MD, MPH (Medicine/Infectious Diseases & Center for Global Health)
Elaine W. Yu, MD, MS (Medicine/Endocrine)

Endre A. Balazs Prize
Reza Dana, MD, MSc, MPH, FARVO (Ophthalmology)

Get Konnected 100: Boston's 100 Most Influential People of Color in the Health & Human Service, Life Sciences
Joseph R. Betancourt, MD, MPH (Medicine/Mongan Institute Health Policy Center)
Rakesh K. Jain, PhD (Radiation Oncology)

Harrington Scholar - Innovator Award
David J. Milan, MD (Medicine/Cardiology)

Harvard Medical School (HMS) Office for Diversity Inclusion and Community Partnership (DICP) Faculty Fellowship
Richelle C. Charles, MD (Medicine/Infectious Disease)

Howard Hughes Medical Institute (HHMI), the Simons Foundation and the Bill & Melinda Gates Foundation Faculty Scholar
Jay Rajagopal, MD (Medicine/Pulmonary and Critical Care Medicine & Center for Regenerative Medicine)

Institute of Mathematical Statistics
Emery N. Brown, MD, PhD (Anesthesia, Critical Care & Pain Medicine)

King Faisal International Prize in Biology
Vamsi K. Mootha, MD (Molecular Biology & Center for Genomic Medicine)

Lurie Prize in Biomedical Sciences
Jeannie T. Lee, PhD (Molecular Biology & Pathology)

Michael J. Fox Foundation (MJFF) for Parkinson's Research Bachmann-Strauss Prize for Excellence in Dystonia Research
Laurie Ozelius, PhD (Neurology)

National Academy of Inventors
Denise Faustman, MD, PhD (Medicine/Endocrine/Diabetes)
Mehmet Toner, PhD (Surgery & Center for Engineering in Medicine)
Ralph Weissleder, MD, PhD (Radiology & Center for Systems Biology)
Warren M. Zapol, MD (Anesthesia, Critical Care & Pain Medicine)

National Academy of Medicine
James A. Perrin, MD, FAAP (Pediatrics)

National Academy of Science
Robert E. Kingston, PhD (Molecular Biology)

National Institute on Drug Abuse (NIDA) Avenir Award
Daniel Lingwood, PhD (Ragon Institute)

National Institutes of Health (NIH) Advisory Committee to the Director
Jose C. Florez, MD, PhD (Medicine/Endocrine/Diabetes & Center for Genomic Medicine)

National Institutes of Health (NIH) Pioneer Award
Bradley E. Bernstein, MD, PhD (Pathology)
Seok-Hyun "Andy" Yun, PhD (Dermatology & Wellman Center for Photomedicine)

National Institutes of Health (NIH) Transformative Research Award
Cammie F. Lesser, MD, PhD (Medicine/Infectious Diseases)

National Medal of Science
Rakesh K. Jain, PhD (Radiation Oncology)

Pew Scholars Program in the Biomedical Sciences Award
Radhika Subramanian, PhD (Molecular Biology)

President of the American Physiological Society (APS)
Dennis Brown, PhD (Medicine/Nephrology/Program in Membrane Biology & Center for Systems Biology)

Radiology Alliance for Health Services Research Achievement Award
G. Scott Gazelle, MD, PhD, MPH (Radiology)

Robert Wenner Award
Mikael J. Pittet, PhD (Radiology & Center for Systems Biology)

Victor Levin Award for Neuro-Oncology Research
David N. Louis, MD (Pathology)

William Allan Award from the American Society of Human Genetics (ASHG)
James F. Gusella, PhD (Neurology & Center for Genomic Medicine)

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PROMOTE

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

The Office of the Scientific Director is primarily charged with promoting science at Mass General through three main initiatives. Our marketing efforts are focused on increasing awareness of research at MGH both to our own community and to external audiences. We work with the Development Office to increase philanthropic giving for research through programs such as the MGH Research Scholars and Research Institute chairs. Finally, we are building new relationships with industry through our Strategic Alliance initiative and a close partnership with the Partners Innovation Office. We were also tasked this year with performing a scientific review of all MGH Research Cores, which yielded some interesting data and action items to improve the services we provide to our research community. Below, I expand on each of these and give a few highlights from the past year.

Marketing

In 2016, we launched a variety of new initiatives to help promote the remarkable work of our research community. *From the Lab Bench* is a monthly newsletter that features an update from the Scientific Director and two or three accompanying articles or videos about the Mass General research community. Since its launch in April 2016, we have featured over 30 researchers in the newsletter. Research Roundup is a monthly column that appears in MGH Hotline, a campus-wide newsletter. The goal of this column is to translate recent research news into a very accessible format that will appeal to patients, the general public and the entire Mass General community. We also created 15 short videos over the past year to promote research and our scientists. This includes features on new research studies for press releases and Facebook posts, descriptions of new Research Institute initiatives, and videos to support crowdfunding campaigns and funding applications.

We launched several programs designed to help our investigators better communicate their science to the general public. In September 2016, we hosted "The Art of Talking Science" in conjunction with HUBweek. This event gave researchers from the Boston/Cambridge area an opportunity to give a four-minute presentation on their science to a panel of celebrity judges, who provided feedback and advice for improvement. In November, we invited the Alan Alda Center for Communicating Science to campus for "How to Communicate Science and Influence People," an interactive plenary session designed to help researchers understand the difficulties inherent in communicating science to lay audiences, and to brainstorm strategies to close the communication gap.

In conjunction with the MGH Development Office, we launched a new platform for crowdfunding research projects in reaction to a request that we frequently heard from investigators when meeting with groups on campus. We also initiated a communications internship program designed to give aspiring science writers from local colleges—and from within our own postdoctoral community—an opportunity to write stories and social media posts about research at MGH. Finally, we are working 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, the main Mass General site and Facebook page). Initially a challenge, the sharing of content and ideas across these departments has improved significantly over the past year and the result is better awareness of the depth and breadth of the research enterprise at MGH – which is our ultimate goal.

Advancement

We continue to work closely with our colleagues in the Development Office to educate philanthropists and potential donors about the important role research plays in driving new discoveries in medicine. Fundraising this past year has been very successful, and our ability to raise unrestricted support for research continues to grow. In 2016, we awarded six new MGH Research Scholars, bringing the total number of Scholars awarded over the past six years to 42. This remarkable donor-supported program has had a substantial impact on research at MGH. Due to a truly generous gift from The Kayden Foundation, we established the first endowed Research Institute chair to foster and accelerate cutting-edge research in perpetuity. The Bernard and Mildred Kayden Endowed MGH Research Institute Chair was awarded to Bradley Bernstein, MD, PhD this past spring. We continue to work towards our goal of supporting more members of our research community with MGH Research Scholar Awards and Research Institute Chairs.

We also received a pivotal gift from Fred and Donna Seigel, who have donated funds specifically to support our Communicating Science initiative that is highlighted in the marketing section of this report. Our research community has directly benefited from their gift through our HUBweek competition, the Art of Talking Science, and through a presentation made by the Alan Alda Center for Communicating Science. Drs. Slaugenhaupt, Orf and other research leadership have promoted Mass General research at numerous donor events and meetings and members of the Research Institute Steering Committee meet regularly with individual donors to discuss the initiatives of the Institute. At the annual Research Institute Advisory Council (RIAC), the Advancement Committee agreed on new strategies to identify

potential donors and the Committee will meet this year in a special session to advance those strategies. Overall the success of our collaboration with the Development Office can be seen in their willingness to make research a philanthropic priority and in the growing portfolio of support for our investigators.

Strategic Alliances
In 2015 we developed and launched the Strategic Alliance Initiative with the objective of helping our investigators establish productive collaborations with industry, biotech, and venture communities at all stages of their work; from fundamental research and proof of concept (early translation), to development and transfer to market and patient care (late translation). With the incredible support of the Strategic Alliance (SA) Committee of the Research Institute Advisory Council (RIAC), composed of key leaders in the field of biomedical research from industry and venture capital, we have been able to push many of our programs forward in 2016. The Strategic Alliance Initiative has been focused on three key areas.

MGH Research Portfolio
We initiated the research portfolio as a key mechanism to:

(i) Build common understanding of the research at Mass General which will serve as a comprehensive scientific foundation for promoting our research
(ii) Enable programmatic efforts across departments and centers
(iii) Establish a sound mechanism to define well-informed strategies and tactics for engaging with industry across different themes

In 2016 we were able to gather research projects outlines from scientists representing 15 departments and centers, and we are working to extract the essence in a one-paragraph pitch format. These pitches will be used for press inquiries, donor proposals, and in our work on creating cross-departmental programs. We also leveraged the research outlines to invite researchers to present their work to MGH Development and Partners Healthcare Innovation colleagues at our monthly Research Portfolio Wrap Sessions. In addition, researchers who engaged with the Research Institute by submitting research outlines were often selected to have their work highlighted by our marketing team.

RIAC Strategic Alliance Programs
The RIAC-SA programs come from research "themes" that have been collected from departments, centers and institutes across campus. In 2016, we were able to structure four SA programs around Epigenetics, Cancer Immunotherapy, Neuroinflammation in Neurodegeneration, and Microbiome, which brought together 61 investigators from many departments and thematic centers. These groups presented their problem-driven programs to external industry and venture partners and we are currently working towards introducing these programs to hand-selected companies in the next few months. In 2017, we plan to launch three new programs in Cardiovascular, Rare, and Infectious Diseases.

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

(i) Why and how to think about the potential applications of their research early in the discovery process,
(ii) How to develop a translational plan that includes research, intellectual property, and business perspectives,
(iii) How to build and manage a translation team, and
(iv) How to interact with industry.

The program involves a 20-week teaching course and, for one team per year, a problem-driven research project opportunity. We are currently working on funding the program through submission of an NIH training grant and industry support and plan to launch in 2017.

Supporting the MGH Research Community
Briefly, we also support our research community by meeting regularly with Partners Healthcare Innovation to ensure that our goals are aligned, we host meetings with companies interested in working with MGH investigators and streamline introductions where needed, we work on proposals with MGH investigators to companies and/or other academic institutions, and we support and coordinate the Partners Healthcare Innovation programs at MGH including the Sanofi iAwards, Pfizer Centers for Therapeutic Innovation, and Industry Fellowships.

Scientific Review of MGH Research Cores
The Research Institute is tasked with enabling more formal and thoughtful planning of shared resources, such as research space, internal funding and research cores. To begin the work of improving the effectiveness of our core facilities, we surveyed all MGH research core directors, visited each core and met with the directors, and we conducted a survey of the entire MGH research community. We contacted 41 core directors and were able to meet the directors and support staff associated with 36 of these cores. From our conversations with the Core staff and the survey they completed for us we can summarize the key 'needs' as 1) more visibility; 2) better nurturing and engagement of the core community; 3) institutional funding to help support cores; and 4) help with budgeting and compliance.

The survey we sent to the MGH research community had a good response rate, with 45% of respondents being research faculty. One of the most interesting but concerning findings was that a significant number of our faculty and staff, approximately 30%, do not know about the research core infrastructure either in general or as it relates to specific services provided by existing Cores. The good news is that among the respondents who had used MGH Cores, the overall level of satisfaction was very high. As a result of the in-person meetings and surveys we were able to create a list of recommendations to research leadership on how best to grow and sustain the MGH Research Cores in the coming years. Our full report and recommendations can be found here: https://mghresearch.partners.org/ResearchMgmt/ResearchCores.aspx

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

Founded in 1996, the Division of Clinical Research (DCR), formerly known as the MGH Clinical Research Program (CRP), is now entering its 21st 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.

DCR Centers

- Biostatistics Center
- Clinical Research Center (CRC)
- Translational Research Center (TRC)
- The Yvonne L. Munn Center for Nursing Research
- Partners Biobank at MGH
- Pediatric Translational Research Center (PTRC)
- Think Tanks
- Bioinformatics Consortium

DCR Units

- Clinical Research Support
- Comparative Effectiveness
- Drug Discovery Rounds
- Education
- Electronic Health Records Research
- Imaging Biomarkers
- Information Technology
- Omics
- Patient-Centered Outcomes Research
- Qualitative Analysis
- Survey Research

Following DCR's Mission, as well as MGH Strategic Plan recommendations, the following progress has been made in 2016 through its centers and units:

Drug Discovery Rounds are face-to-face advisory sessions with Key Advisors:

- Mark Fishman (former president of Novartis Institutes for Biomedical Research)
- Edward Scolnick (former president of Merck Research Laboratories)
- Steve Paul (former president of the Lilly Research Laboratories)
- Henri Termeer (former CEO of Genzyme)

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

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

- Think Tank on Rare Diseases (chaired by Florian Eichler)
- Think Tank on Neuroinflammation (chaired by Rudy Tanzi and Chris McDougle)
- Think Tank on Microbiome (chaired by Alessio Fasano and Ashwin Ananthakrishnan)

Bioinformatics Consortium, lead by Ruslan Sadreyev. The goal 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.

Harvard Catalyst: DCR continues to build close partnerships with Harvard Catalyst.

Translational Research and Clinical Research Centers (TCRC): 18-bed unit on White 12.
The TRC's overall goal is to facilitate moving basic scientific discoveries and new technologies, discovered both at the MGH and in the local biopharma community, toward the clinic to improve diagnostic capabilities and therapeutic interventions. The co-location of the TRC with the CRC was realized with the opening of the new Translational and Clinical Research Centers (TCRC) in the fall of 2016. The TRC can now evaluate the utility of new technologies in early stage, patient-based clinical trials. The TRC spent most of 2016 preparing for the opening of the new TCRC. This effort was a continuation of the groundwork laid in 2015, focusing on three key elements: 1) working with the construction crew to ensure the new TCRC was ready to open by the end of the year; 2) continuing to work with Partners to improve administrative processes that are required to conduct clinical trials at the MGH; 3) hiring key individuals that can provide the administrative infrastructure that can support clinical investigators engaged in clinical trials, particularly those partnered with industry partners.

Simches 2 clinical exam/evaluation space: provides space on Simches a one-stop shop for clinical investigators by:

- Continuing to provide CRC and PM support for MGH investigators
- Creating a CRC satellite
- Moving/consolidating bioinformatics
- Establishing CTO, IRB and PHS Innovation office hours

To view a complete version of DCR 2017 Progress Report, please visit: http://www.massgeneral.org/research/DCR/Assets/Files/DCR-progressreport-2016.pdf

The Partners Biobank at MGH — Susan A. Slaugenhaupt, PhD & Jordan W. Smoller, MD; Co-Directors

The Partners Biobank at MGH was devised to be a collaborative effort among patients, clinicians, and scientists to better understand disease, identify targets for therapy, and enable personalized medicine, by collecting and storing fully consented blood, serum, and plasma samples, linked to electronic medical records, from patients across the institution. Through the Research Institute, resources were committed to add personnel, space, and equipment to jumpstart the consent and collection program at MGH. In its first five years of operation, the Biobank collected only 8,500 samples across all of Partners. With the additional resources contributed over the past three years, we have seen a dramatic increase in patient recruitment to over 55,000. Through the dedicated efforts of the MGH team, including Biobank manager Nicole Allen, the MGH program has enjoyed great success since the implementation of the strategic plan. From a recruitment standpoint, the MGH program reached record consent and collection metrics in 2016 thanks to the growth of our team and successful partnerships with high volume clinical departments and research teams including the Center for Perioperative Care, Radiology, Dermatology, the Cancer Center, Pathology, Neurology, Chelsea Community Health Center, the Emergency Department research team, the Cardiovascular Biorepository, the Biorepository for Neurological Injury research team, and the Acute Psychiatric Service research team. Notably, the MGH co-directors and team expanded recruitment operations to Spaulding Rehabilitation Hospital's inpatient facility, and supported Dr. Kerry Ressler in setting up Biobank recruitment at McLean Hospital. Most recently, the Biobank partnered with the MGH Department of Medicine on an innovative recruitment protocol that will integrate Biobank enrollment into the largest clinical and educational service at the MGH. The Partners Institutional Review Board just approved a pilot to have resident volunteers train to obtain informed consent from inpatients on the Bigelow Service, which is a major step forward and hopefully a vision into the future for research recruitment at MGH.

The addition of two dedicated Biobank consent/collection rooms on Wang 2 and Yawkey 3 have made the link between research and clinical care seamless, as patients who come to the Biobank labs are able to contribute both research and clinical samples at the same time. Increasing awareness of the Biobank to both patients and our investigators is a priority of the Research Institute. Design is complete and acquisition is underway for electronic Biobank "kiosks" that will be placed in the in the Wang and Yawkey lobbies. The Institute hired a marketing and education specialist to help in promoting the Biobank to patients and the MGH community, and efforts to increase active on-line recruitment via Patient Gateway are ongoing. The Community Advisory Panel that launched in 2015 continues to be a tremendous

success with members contributing much-needed advice for patient engagement techniques. The Biobank has also expanded its services to investigators and enhanced the profile of research activities at Partners sites both at an institutional and national level. Partners provided funding to genotype the first 50,000 Biobank samples, 10,000 of which were genotyped this year with data freely available to investigators via the Biobank Portal. Because of the success of the Biobank, our co-directors have successfully competed for national grants that brought tremendous resources to the Institution. Biobank investigators are part of the eMERGE network, a national network funded by the National Human Genome Research Institute that combines genetic data with electronic medical record systems for large scale, high-throughput genetic research. Most recently, Partners Healthcare, in collaboration with Boston Medical Center has been named one of the Precision Medicine Initiative's (PMI) health provider organizations to help enroll a diverse cohort of over 1 million people into the NIH-run PMI Cohort Program (the All of Us Research Program). These new resources, together with the extraordinary efforts of the Biobank staff, have resulted in a major increase in subjects recruited. Goals for this coming year include installation of the kiosks, expansion of Biobank operations into the Department of Medicine inpatient service, recruitment in other community health centers, outreach to new employees, continued improvement to the online consent and web-based content, implementation of a more formal marketing campaign both to our patients and to our physicians within the hospital, launching enrollment for the PMI Cohort Program, and full integration of sample consent and collection within the clinical phlebotomy operations of the hospital.

SUPPORT

By the Number$ - Another All-Time High — Gary J. Smith, MPA, Senior Administrative Director, MGH Research Management

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

Research revenues for FY16 reached an all-time high of $850M ($655M direct costs and $195M indirect), a $50M increase from FY15. Our awarded dollars from the National Institutes of Health (NIH) in FY16 increased from $353M to $363M, with the percentage of funding awarded to MGH from the entire NIH extramural grant pool (market share) remaining at 1.5%. This is a testament to the perseverance and resilience of the MGH research faculty amid challenging budget times at NIH. With a proposed increase to the NIH budget planned for this coming year, we are hopeful that our NIH funding will continue to increase and provide much-needed growth to our federal funding base.

We saw significant increases compared to the previous fiscal year in the volume of proposals submitted to DHHS (6%), Industry/Corporate (30%), Foundations (6%) and Non-Profit (6%). Overall, MGH submitted 4,706 research proposals to all sponsors in FY16, up 8% from the prior fiscal year. DHHS success rates for MGH proposals are approximately 22%, four points higher than the NIH national average of 18%.

Research expenditures from direct DHHS funding (which consists mostly of NIH funding), now accounts for 42% of MGH research, down 1% from last year's 43%. Although the percentage of our DHHS research funding base went down, our DHHS-sponsored research expenditures increased from $343M in FY15 to $353M in FY16. Again in 2016, MGH remains the largest recipient of NIH funding among independent hospitals and 15th nationally for all institutions.

Research expenditures for all of our other sponsor types continue to remain strong in FY16. Industry/Corporate expenditures increased 3% to $63M. The remaining sponsors, which include non-profit organizations, subcontracts, foundations, internal, and gifts/endowments totaled $404M in FY16. Investigators continue to turn to these sources of funding to buffer the constraints on NIH support. The cumulative annual growth rate for FY12-FY16 across all sponsor types was 9%.

In aggregate, research activity (direct + indirect dollars) continues to comprise slightly under one quarter (23%) of the total MGH annual operating budget and is distributed across more than 40 departments and centers.

A New Minimum Indirect Cost Rate for Research Grants

Academic medical centers, research universities, and all other institutions that engage in federal research have a federally-negotiated rate at which the indirect costs associated with research are reimbursed. While most federal grants include reimbursement for the full negotiated overhead rate (as a percentage of the grant direct costs), most foundations and non-profit organizations that sponsor research pay for the direct costs of research but provide little or no funding to cover the indirect costs associated with the study. Sadly, foundations do not realize (or do not believe) that their failure to cover the indirect costs requires the hospital to actually pay in real operating dollars those indirect costs in order for the hospital to accept the grant.

Each year, MGH loses tens of millions of dollars of indirect cost (IDC) recovery from sponsors who pay less than our government-negotiated indirect rates. A number of these sponsors (mostly foundations, public charity, or non-profit organizations) pay no indirect costs or pay an amount below the hospital gift/sundry IDC minimum of 15%. These unrecovered costs are real and substantial, and must be covered from general hospital operating margins that are increasingly being squeezed by the dramatic shifts in healthcare reimbursement. In FY15 (the most recent year that we have complete data), indirect costs at MGH totaled $275.3M and the hospital recovered $184.5M, leaving an investment (loss) of $90.8M.

Labs that are funded primarily or exclusively with these no- or low-overhead awards are being subsidized both by the clinical operations of the hospital and by those research labs funded by awards that do pay full overhead. Accordingly, effective December 1, 2016, MGH (and all Partners institutions) instituted a new policy regarding acceptance of research awards that pay an IDC level below the hospital minimum of 15%. Specifically, all research grant applications submitted to foundations, public charity, or non-profit institutions on or after December 1st must have an IDC rate of not less than 15%. If the award does not include funds sufficient to meet this requirement (because of a sponsor limitation to indirect cost reimbursement), then the PI and/or their department will be financially responsible for covering the shortfall with sundry funds that will be escrowed at the time the award is made. Investigators who wish to apply for grants paying below the 15% IDC minimum, who do not have sundry resources to cover the shortfall, must consult with their supervisors/mentors and/or units/departments before applying to ensure there is a fund identified to cover the IDC delta. Training fellowships from foundations, public

charity, and non-profit organizations are excluded from this minimum IDC requirement, while industrial training fellowships are subject to the 15% minimum IDC recovery.

Research leadership is aware that foundation awards are important to junior faculty and it set the policy specifics to minimize the impact on them. Research fellowships, an important funding vehicle for young PI's and their postdocs and graduate students, are excluded from the 15% minimum requirement. Also, in FY15, a total of 55 junior PI's were impacted, with a median cost of only $2,200 per PI. Hopefully, this amount will be manageable for most junior faculty but, if not, then the policy affords that junior faculty member an opportunity to discuss the foundation grant opportunity with their departmental mentor and/or chief. These discussions will increase the visibility of the faculty member's research program within the department and provide a basis for the department to consider funding the IDC shortfall.

Finally, we do not expect that most foundations paying less than 15% IDC will simply increase to our minimum. But the new policy should create opportunity for dialogue with these foundations to help them realize that these indirect costs are very real and extremely costly to the hospital in terms of real dollars it must spend to accept foundation grants. Even at 15% (the minimum the hospital assesses on all gifts it receives), the hospital, at the current federally-negotiated IDC rate of 71%, is contributing 56% IDC toward every 15% IDC project they accept. Thus, when the hospital accepts a $1M foundation grant paying 15% IDC, the hospital is spending an additional $560,000 from its general operating funds in order to allow that work to be done here.

MGH Makes the New NIH Postdoctoral Pay Scale Mandatory
When President Obama issued an executive order this past summer raising the salary minimum for exempt workers from $23,660 to $47,476, NIH increased its postdoctoral salary scale to comply, increasing the starting postdoc salary several thousand dollars to $47,484. Subsequently in November, the U.S. District Court for the Eastern District of Texas granted a nationwide injunction, halting the new federal minimum from taking effect, although NIH did not retract the announcement of its new pay scale.

The hospital's policy regarding postdoc salaries has always been to adopt the prior year's NIH scale as a recommended rate in order to allow investigators time to adjust their grant budgets to the new pay scale. Even then, investigators could pay less than the recommended scale by applying for an exception based on financial hardship. This policy led to an inequitable distribution of postdoc salaries based on what departments and investigators felt they could/should pay.

The issuance of President Obama's executive order, even though it was subsequently halted from taking effect, prompted research and HR leadership at the hospital to look carefully at our postdoc pay scale and policy. With the cost of living in Boston being one of the highest in the country and seeing the inequities created by a recommended pay scale, the hospital adopted a new policy requiring all postdoc salaries to meet at least the new NIH minimum pay rate. Post docs whose salary does not meet the NIH level must have their pay increased to meet it prior to February 1, 2017. Departments and PIs were asked to review all available funding sources to ensure that they have money available to pay all postdocs to comply with the new pay minimum.

Recognizing that some Departments/PIs may not have this additional funding available on such short notice, the hospital agreed to provide supplemental funding for a period of one year to accommodate the mandated salary increases. PI's were afforded an opportunity to apply for one-year supplemental funding to cover any budget shortfall relating to postdoc salaries by submitting a form endorsed by their chief of service. A committee consisting of the ECOR Chair, SVP for Research, and selected departmental chiefs reviewed the PI's request and funding status (as well as the overall fiscal status of his/her department) to determine what amount of funding, if any, would be provided.

Space – The Final Frontier! — Michael L. Fisher, LPD, Director, Research Space Management Group

The Research Space Management Group (RSMG), working under the organizational sponsorship of the Research Institute and responsible to the Executive Committee of Research (ECOR) and the Research Space Advisory Committee (RSAC), is responsible for all aspects of research space allocations, utilization, and physical space reconfigurations ranging from minor site renovations to major building/floor construction projects. Partnering closely with RSAC and MGH leadership, RSMG assists in developing space strategies, fulfilling research space needs, optimizing space use, and supporting the overall institutional research objectives.

MGH currently owns or leases approximately 1.25M net assignable square feet (nasf) of space. The percent allocations amongst the campuses are similar to last year with 42% in the Charlestown Navy Yard (CNY), 23% on the main campus, 21% in Charles River Park, and the remainder in various metro Boston and Cambridge locations. Several research groups located at various leased sites relocated to 125 Nashua Street in FY16, allowing a decrease in the overall number of research leases. The 20,500 nasf of efficiently configured replacement research space at Nashua Street has effectively fulfilled the dry space needs for a number of researchers and administrative staff.

Indirect cost (IDC) density overall rose from $160 per square foot to $178 per square foot this past year. The funding of several large grants, improvement in sponsor mix, and an increase in space efficiencies contributed to the increase in IDC. Through a combination of more efficient space utilization, inter-departmental space transfers, and several renovation projects, RSMG in conjunction with RSAC was able to satisfy a large number of space requests during FY16. At the beginning of the fiscal year, requests for new or additional space equaled 90,512 nasf. Currently, requests for space total 51,760 nasf, a 43% reduction from the prior fiscal year. Of these outstanding requests, 71% is for wet research space and 29% is for dry research space.

Part of RSMG's initiative to assist departments with better space utilization was fulfilled by sponsoring several "Lab Spring Clean-Up Days" on the Charlestown, Cambridge, and Main Campuses. On these days, departments were encouraged to discard broken or unused pieces of equipment ranging from small desktop items to -80 freezers. Old computers were collected and returned to Partners Information Services for proper disposal, expired or unused chemicals were properly contained and disposed of, and unused supplies were collected and, when feasible, were recycled to other departments. These events afforded many departments enough space to purchase new, more energy- and space-efficient pieces of equipment, or to rearrange their work space to utilize their areas more efficiently

A number of medium and large renovation projects totaling $7.7M were completed during fiscal year 2016. Among these were the complete renovation of Warren 6 for the Department of Psychiatry, Phase 1 of the Simches 3 Cardiology Project, and the renovation of White 12 for the Translational and Clinical Research Centers. In addition, several large projects with an estimated cost of $28.4M are at various stages of completion, ranging from programming, design development, permitting, construction, final approvals and punch list item resolution. Programming for the building 149 (B149) 10th and 2nd Floor Project is in progress, Phases 2 & 3 of the Simches 3 Cardiology Project are in the permitting stage, and construction is underway for a Cardiology Project on the first and third floors in the Edwards Building. The B149-08 Infrastructure Project to improve temperature and humidity control in the vivarium is at the punch list stage, and is quickly moving toward completion. Several smaller projects, too numerous to list here, are also in construction. In FY17, Research has several projects proposed for an estimated $11.9M. This estimate represents a 45% reduction in the initial FY17 Capital Requests from Research, and is the result of a detailed examination of and a scaling back of the scope of several projects as well as a reprioritization of the original list to comply with the parameters outlined by the institution for the FY17 capital budget process.

Survey and Analytical Activity
RSMG, working with the Partners' Research Space Management System (RSMS) development team, improved the overall functionality of the RSMS database application in 2016, eliminating technical application issues as well as inefficiencies in the reporting module. In conjunction with BWH, RSMG also worked with the development team to streamline and standardize key reports used in the survey process, helping to ensure data consistency and enabling trend analyses. In the continuing effort to improve space metrics, we are also working with the programmers to implement new people metrics which will better capture both seat and space utilization. These metrics, in conjunction with the existing financial metrics, will provide a transparent and quantifiable measure of space utilization and provide detail, down to the PI site level, which is often necessary for senior management to respond to space requests, new program initiatives, and institutional expansion needs. As part of the annual IDC negotiation process, RSMG continues to work closely with Partners Research Reimbursement to verify room utilization, staff occupancy, and funding support in on-site research space.

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

On any given day, approximately 105,000 mice, rats, guinea pigs, rabbits, sheep, pigs, non-human primates, and amphibians plus more than 35,000 zebrafish are housed and used within 95,000 square feet dedicated for such purposes on both hospital campuses. In addition, the hospital operates two off-site facilities including the MGH Center for Transplantation Services (CTS) swine production facility located in Grafton, MA, which manages a breeding herd of 200 uniquely inbred miniature swine for allogeneic and xenogeneic organ transplant protocols, and BL-2/BL-3 rodent facilities that support the Ragon Institute in Cambridge, MA.

The Center for Comparative Medicine (CCM) is the central laboratory animal care service for MGH investigators and is led by Donna Matthews Jarrell, DVM, DACLAM, who also serves as the MGH Attending Veterinarian. CCM facilities are located on the Cambridge Street campus, the Charlestown Navy Yard Campus and the Cambridge Campus. Its activities include husbandry, animal procurement, importing and exporting mouse lines from other academic institutions, interinstitutional transportation, preventive and clinical veterinary care, training in animal manipulative techniques, surgery and post-operative support, mouse breeding and colony preservation, and consultation in animal modeling and protocol design. Over 130 employees, including seven staff veterinarians (five of whom are board-certified in laboratory animal medicine) and a leadership team of 18 mid- and director-level managers, provide these services throughout MGH.

Specific efforts were taken in 2016 to:

- Improve animal welfare in partnership with the MGH IACUC. Innovative educational materials, including video demonstrations and visual or pictorial-based descriptions were developed for laboratory leadership to utilize in laboratory-based procedural areas to assure best practices and protocol compliance related to rodent experimental surgery and anesthesia monitoring. In addition to these educational materials, CCM also led the social housing initiative which significantly increased the number of animals socially housed with a conspecific partner for all species.
- Initiate key capital projects on both the Cambridge Street campus as well as the Charlestown Navy Yard to increase rodent caging capacity by 15-20% with no increase in overall animal facility square footage as well as address on-going HVAC environmental deficiencies.
- Control operational costs through continued elimination of non-valued added activities and process improvements resulting in a positive operating margin (OM) for FY16 while maintaining FY14-15 per diem rates for the research community.
- Increase regulatory compliance as demonstrated by the most recent 2016 fall IACUC semi-annual facility inspection results where CCM was documented for the first time to have zero (0) significant or major deficiencies.
- Expand research support services (beyond husbandry) by 25% compared to previous years utilizing current front-line technical personnel.

Lastly, CCM continued to host more than 40 site visits in 2016 from manufacturing, healthcare, research and laboratory animal leaders who have expressed interest in adopting a lean operations model in their facilities and programs. Partnerships now expand to the Greater Boston Manufacturing Partnership, Lean Enterprise Institute, Franklin Park Zoo as well as the Association for Manufacturing Excellence (AME) which has selected the Center for Comparative Medicine as a local tour site during their national conference planned for the summer of 2017. Seminars and webinars on this subject were presented at annual conferences of the American College of Laboratory Animal Medicine, the American Association of Laboratory Animal Science, the Public Responsibility in Medicine and Research and through our on-going affiliation with the Vivarium Operations Excellence Network (http://www.voenetwork.com). In 2016 the VOEN grew by 50% to 34 members representing six countries all with a focus on improving the quality of care provided to research animals while minimizing problems that directly impact MGH research with a focus on fiscal control and responsibility.

The Institutional Animal Care and Use Committee (IACUC) governs the use of research animals at MGH. The Committee is fully constituted in accordance with regulatory requirements and is comprised of 30 members including veterinary staff, IACUC administrators, research investigators from many departments and research centers throughout the MGH Research Institute, and two community representatives. The IACUC Chair is Dr. Warren Zapol, Reginald Jenney Professor of Anesthesia and (HMS) Chief Emeritus, Department of Anesthesiology and Critical Care Medicine (MGH). Dr. Zapol is supported by Dr. James Allan, Assistant Professor of Surgery and Associate Vice Chair-IACUC and Mark Randolph, Director, Plastic Surgery Research Laboratory, and Assistant Vice Chair-IACUC. The IACUC staff office supporting the IACUC is led by Anne Clancy, PhD.

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

Approximately 2,800 transactions were processed by the MGH IACUC in the past year, including almost 150 new IACUC protocols. A continued focus for process improvement, under the joint leadership of Drs. Clancy and Jarrell and with the full participation of their respective departmental leadership teams, has been turn-around-time for protocol review, as well as other initiatives to provide support to the animal research community while maintaining the highest ethical standards in the program. Complete metrics data for the MGH IACUC are available on the Partners Research Navigator website Research-Analytics-Reporting.

Highlights of the animal care and use program in the past year:

- USDA conducted an annual inspection of the MGH animal research facility; no deficiencies were identified in the program.
- The City of Cambridge conducted its annual inspection of the MGH animal research facilities; no deficiencies were identified in the program.
- The IACUC and CCM continued to collaborate with RSMG, Safety and MGH investigators to implement and maintain the satellite animal housing program to ensure the requirements of the Guide for environment, housing, and management of research animals in laboratory housing areas are met. There are currently 19 approved PI-managed satellite housing locations at MGH.

- The IACUC, in collaboration with the PhD Steering Committee, ECOR representatives and others, redesigned the IACUC Form set. The forms were revised to remove redundancy, extraneous narrative and to provide more "check-box"-type options to streamline the protocol submission and review process. These forms are expected to be rolled out with Insight 4.0 in 2017.
- In response to suggestions from the research community the IACUC collaborated with CCM and developed a number of procedure templates that can be used when submitting an IACUC protocol for review.
- In collaboration with the Isuggest animal working group, the IACUC and CCM made a number of improvements to the program including streamlining the Facility Access Request Process and establishing a mouse strain data base that can be used to query PIs for mouse strains bred in the facilities.

Research Support IS Committee — Carl Blesius, MD & Deverie Bongard, MBA; Co-Chairs

The Research Support IS Committee (RSIS) was created to serve as a more formal interface for project teams across Partners to help coordinate technical efforts within the MGH research community. The committee works regularly on numerous tactical projects (e.g., web support, software selection, software development, policy/procedural issues, etc.) but is also involved in major strategic initiatives. The overarching focus is to help identify and implement solutions and infrastructure to best support the cutting edge and dynamic technical needs of the research community.

Accomplishments

Some highlights from 2016 include:

- Using the Researcher Profiles software to help identify who belongs to the MGH research community, increasing the total number of known research-associated staff from 6,000 to over 11,000
- Rolling out the Learn Research Training System, https://learn.partners.org, for in-person Research Institute training, and now supporting over 500 researchers and 120 courses in the last 3 months of the year
- Releasing the other planned technical components of Learn in December in preparation for providing the research community a consolidated advanced training dashboard in 2017
- Jointly releasing, with the Partners Technical Services Office, a successful proof-of-concept internal cloud to cut provisioning time for research systems from weeks to minutes
- Creating an electronic data capture system to support research registry needs
- Significantly improving clinical trial discovery and search through the upgrade of https://clinicaltrials.partners.org and its integration into the patient research portal
- Cataloging and starting the unification of Research Institute-related branding and communication across groups, departments, and divisions for internal communications

Strategic Priorities in 2017

In 2017, we will continue to leverage local expertise to solve problems and identify areas where consolidation and streamlining of resources, services, and procedures can help leverage limited research resources to better meet the technical needs of the research community. The Researcher Profiles System and its integration with the Partners Identity Management System will continue to be a major focus, further unifying researcher staff information that can be programmatically acted upon. We will specifically apply this information to create dynamic cohorts for targeted research communications (i.e. emails), help automate research processes/procedures, and feed other research systems and reports. Additional concentrated focus will be placed on refining the training system's advanced Learner dashboard and other RITE Committee research training priorities. Finally, in collaboration with Partners IS, we will be targeting some specific infrastructure and support issues we have identified (e.g. Wi-Fi coverage in research areas, research server provisioning, and improving response time on research-related help desk items).

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

The Research Institute Training and Education Committee (RITE), in collaboration with the Laboratory of Computer Science and the Clinical Research Education Unit of the Division of Clinical Research, is continuing to develop the LEARN platform (https://learn.partners.org/) to streamline and organize required compliance trainings as well as optional courses for professional development.

The LEARN platform will provide:

- Identity management
- Advanced Learner Dashboard to allow participants and managers to quickly see what courses have been taken and what needs to be taken in the future
- Course catalogue to allow learners to search for courses

- Course management for administrators who organize courses (participants can sign up, go on waiting lists, be contacted by email, receive acknowledgments about attendance)
- Easy sign up using Partners login or eCommons login
- Tailored compliance trainings based on a survey to determine the specific courses to meet an individual's regulatory and compliance requirements (depending on their responsibilities)
- Reports to managers who need to know if their staff is up to date on compliance trainings
- Outlook Invites to integrate course schedules into a participant's outlook calendar

The RITE committee has been particularly concerned about redundant training requests and realized that at least four sources of trainings exist throughout Partners. All too frequently, these efforts are not coordinated. The RITE committee will be working with Partners to reduce and possibly eliminate redundant trainings and increase coordination across MGH and Partners.

Isuggest - The Expanded Program Takes Off

As described in my report last year, Isuggest was rolled out in March, 2016 as a Partners-wide expanded version of the Continuous Research Operations Improvement (CROI) Program launched in 2012 at MGH. This program provides straightforward ways for members of our research community to offer ideas that will help us improve our support of the research enterprise. Major improvements that Isuggest offers over CROI include: 1) Active involvement in decision making at the highest levels of hospital and Partners Research Management, with business owners who control resources necessary to implement suggestions becoming actively involved in their prioritization; 2) A new web-based, iPad/ iPhone-friendly interface that allows suggestions to be submitted easily and commented upon using a Facebook-like (thumbs up/thumbs down) feature; 3) A new, more intuitive infrastructure program that serves as the primary vehicle for the tracking and reporting of ideas; 4) Greater publicity for the program through "Suggestion of the Month" announcements complete with a photo of the suggestor, presented at every regularly-scheduled research meeting in the hospital.

Regarding the suggestions themselves, some are simple "tactical" suggestions to correct or simplify a process, while others have called for more "strategic" in-depth reviews of programs, processes, and/or policies that have taken many months to implement (e.g., an IRB protocol status dashboard). All, however, have resulted in some form of improved service to the research community. This past year alone, over 200 suggestions were received and over 100 were implemented through Isuggest. Notable successes include elimination of the annual re-credentialing process for all non-MD professional staff (saving thousands of hours of administrative busywork and over $30,000 in background check fees annually), and providing full access to all research buildings for our faculty members by remotely reprogramming faculty ID badges and simplifying the access authorization process.

Research Safety - Greater Visibility and a Spring Cleaning

The end of 2016 marked the fourth year of operation of the Research Safety Committee (RSC). 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, such as safety documentation, creation of a safety website, safety training, and the tracking of hazardous materials. 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.

This past year was marked by a number of significant accomplishments. 1) A monthly safety newsletter was started and distributed to all research personnel electronically and posted in all labs through the departmental safety coordinators. Each single-page edition features a variety of important safety tips and policies. 2) The lab safety rounds program, during which each lab space on campus is walked through and surveyed for safety compliance annually, was transformed by putting it into a web-based format. Lab checklists and inspection points are accessed through an online program that allows the surveyors to use iPads and/or iPhones to record findings and schedule work orders to correct deficiencies. The program also notifies principal investigators of the findings and sends reminders when problems are not corrected in a timely fashion. 3) A major lab "spring cleaning week" project was undertaken during which additional waste management and safety personnel were engaged to work with lab groups to clean out old chemicals and equipment that had been accumulated over the years. Every building on campus participated and over $85,000 in expired waste chemicals and materials were safely disposed. 4) Significant progress was made on the development of a safety training survey and database, to be used to document training and warn researchers of upcoming expiration dates. Eventually, a personalized training dashboard will be made available containing this information as well as synopses of all training courses offered through the hospital.

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

Andrew Chase, Vice President of Research Management and Research Finance, who reports to Peter Markell, Executive Vice President of Administration and Finance, CFO, and Treasurer of Partners HealthCare, leads the Partners Research Management team. They work in close collaboration with Harry Orf, PhD, Senior Vice President of Research, at MGH and Paul Anderson, MD, Chief Academic Officer and Senior Vice President of Research at BWH, as well as Anne Klibanski, MD, Chief Academic Officer of Partners HealthCare, and Chris Coburn, Chief Innovation Officer.

Research Management remains focused on providing the highest level of support to the MGH research community. In the past year, Research Management supported the submission of 4,708 proposals. MGH finished the year up 8% in proposal volume from last year and every sponsor type – federal, foundation, industry – saw an increase from FY15. Also, the quality of proposals at the MGH remains strong with a success rate of 22% of applications being funded.

With its strong success rate, the MGH continues to expand its research activity. FY16 saw research activity grow to $831M of expenses. A key theme within the MGH research activity remains collaborative research, across different disciplines within the hospital, and with other institutions. As these collaborations increase, Research Management continues to adapt its service model to focus on contracting activities and the downstream billing and invoicing associated with these contracts. Contracting has been a major focus area over the past year. Turnaround times for most contracting activities have been maintained despite the increase in volume. Also, the time waiting on payments to the MGH from other institutions for our work in these collaborations decreased significantly in FY16. Contracting remains a priority area for Research Management and new approaches will be tested over the next year to reduce overall turnaround time.

There have been many other process improvements and changes in Research Management over the past year that have benefited the investigators and MGH administrators. Most notably, we helped the NIH design and test their new online grant application system and were early adopters to submit proposals using the new system. This new system, named ASSIST, is a dramatic improvement in ease of use and functionality from the Adobe Form Sets that were previously required. ASSIST has now been rolled out across the MGH research areas with 100% adoption expected by March of 2017.

We also continue to explore the best administrative support models for investigators and have successfully piloted new Post Award roles that include both departmental and central responsibilities. These roles eliminate traditional handoffs in the key transactional areas and allow for a more efficient model. Because of the success in these pilots, Research Management is looking to pilot similar integrated responsibilities with proposal submissions.

2017 will no doubt provide its share of challenges and opportunities for improvement and Research Management is well positioned to support the Investigators and the MGH research community to continue its success.

Partners Innovation — Chris Coburn, Chief Innovation Officer

Partners Innovation is MGH's commercialization arm with a global business development mandate. It creates commercial outcomes worldwide from MGH's unique capabilities. It's core units are venture investing, business development, international consulting, innovation management and market sectors -- nine clinical vertical units that are designed to strategically engage industry, enable internal priority setting and drive larger and more frequent industrial outcomes.

Partners Innovation had a number of significant outcomes - all in support of MGH investigators and leadership. They include the launch of a series of spin offs with Boston Nanotech, the launch of Center for Clinical Data Sciences, AI diagnostics center with $5-10M in annual revenue and new companies, a major liquid biopsy newco in partnership with one of the largest companies in health care, also two major joint ventures, and the acquisition of a MGH Parkinson therapy spin-off and Innovation Fund portfolio company.

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

Through a commitment from MGH, Innovation grew to $100 million under management expanding the ability to bring game-changing breakthroughs to patients. It is complemented by the Wellman Center Fund which is focused on photomedicine.

The World Medical Innovation Forum will be held May 1-3, 2017 in Boston. It will feature the newest technologies to diagnose, treat and manage cardiovascular and cardio metabolic disease.

In addition, an international pilot – the World Neuroscience Innovation Forum – will be held on March 27, 2017 in London at the Crick Institute with a focus on neurodegeneration and neuroinflammation. Partners HealthCare International was combined with Partners Innovation to increase the global opportunities to monetize the unique assets and know-how of the MGH faculty. The total team now exceeds 110 with a breadth of high value capabilities.

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

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

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

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

OII staffs the above three committees. In order to fulfill its responsibility, OII organizes its work into four areas:

- The Research Activities section review investigators' financial interests in connection with hospital research activities for potential conflicts of interest. This group is responsible, among other things, for ensuring compliance with Public Health Service regulations on PHS-funded research.
- The Outside Activities section reviews the outside activities (personal consulting arrangements and the like) of physicians and staff to ensure they are consistent with Partners policy, and is responsible for obtaining COA review of outside activities of senior institutional officials.
- The Educational Grants section oversees the receipt of industry funding in support of Partners educational activities to ensure compliance with Partners policy. This section also handles conflicts arising in purchasing and similar types of transactions.
- The Systems and Education section works with Partners Research Applications Group to design the online conflict of interest disclosure system; administers the Annual Disclosure process to physicians and staff; provides online and in-person training to the Partners community; maintains the OII web site; and coordinates the distribution of educational materials to the Partners community.

Significant accomplishments in each of the OII sections during FY16 included the following:

1. Research Activities – in addition to handling, as part of the normal workflow, the processing of over 20,000 financial interest disclosures needed for compliance with PHS regulations and HMS and Partners COI policies:
   - Worked extensively with the Partners Committee on Outside Activities (COA) and staff of HMS and affiliated hospitals on making a fundamental change in the HMS I(a) and I(b) rules (and comparable Partners Policy), shifting the rules' orientation from an absolute prohibition to one based on a rebuttable presumption approach with a process for evaluating and granting requests for exceptions.

- Developed a process for the intake, preparation, and consideration by COA and the HMS Standing Committee of petitions under the revised HMS and Partners rules and worked with investigators to present the first six petitions to COA and the HMS committees.

2. Outside Activities – in addition to handling, as part of the normal workflow, over 1800 consulting and related agreements:
   - Developed guidelines for when Partners individuals may participate in company videos, consistent with Partners policies, particularly the policies prohibiting company promotional activity and inappropriate use of the institutions' names.
   - Worked with COA and CMOs to finalize standard procedures to manage conflicts arising when part-time Partners clinicians and researchers have concurrent primary appointments with industry.
   - Worked with COA to finalize a framework for analyzing and managing conflicts arising when individuals having financial interests in a company supervise others who work on institutional service agreements with that company.

3. Educational Grants – in addition to handling, as part of the normal workflow, over 300 grants bringing in over $4M in funding:
   - In response to feedback that the current Trainee Travel Policy was more restrictive than policies of peer institutions, worked with the ERB to re-evaluate the Policy in light of those of other institutions, determined that the Partners policy was more permissive than that of other institutions, and accordingly reaffirmed the current policy.
   - Worked with the ERB and the Partners Academic Education Committee to assess the legal and policy implications of exhibit space at Partners educational activities taking place in a hospital building, and adopted policy addressing such situations

4. Systems and Education – in addition to handling, as part of the normal workflow, the distribution and completion of disclosure forms to nearly 11,000 Partners staff:
   - Worked with Partners Research Applications Group to achieve and implement major usability upgrades to Insight Disclosure system.
   - Per federal regulations, retrained Public Health Services funded investigators on Conflicts of Interest in research.
   - Conducted office-wide assessment of OII needs, and management training for OII managers.

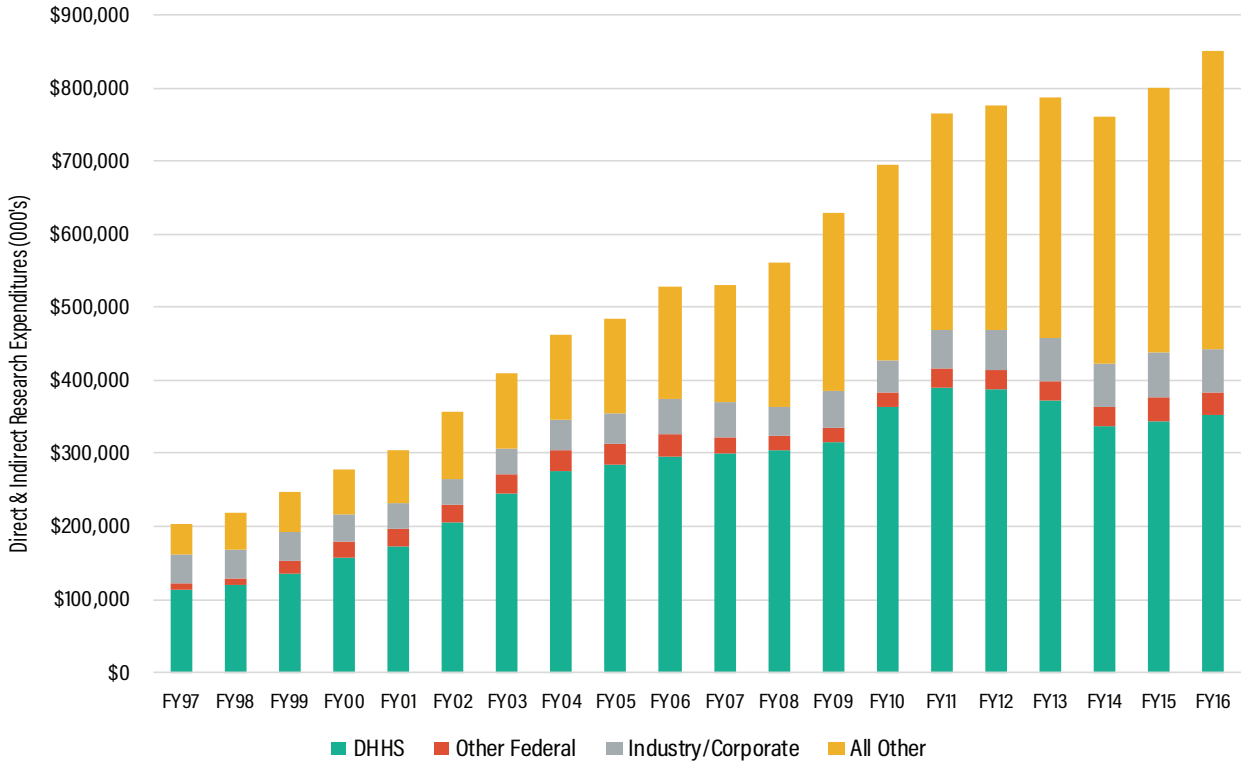
Overall, significant progress has been made in 2016 implementing the strategic plan for research and improving the services that support the Research Institute. I am grateful to the many MGH and Partners research staff who have affected these changes and appreciate the continued dedication and initiative they offer to constantly improve and strengthen our research enterprise.

Respectfully submitted,

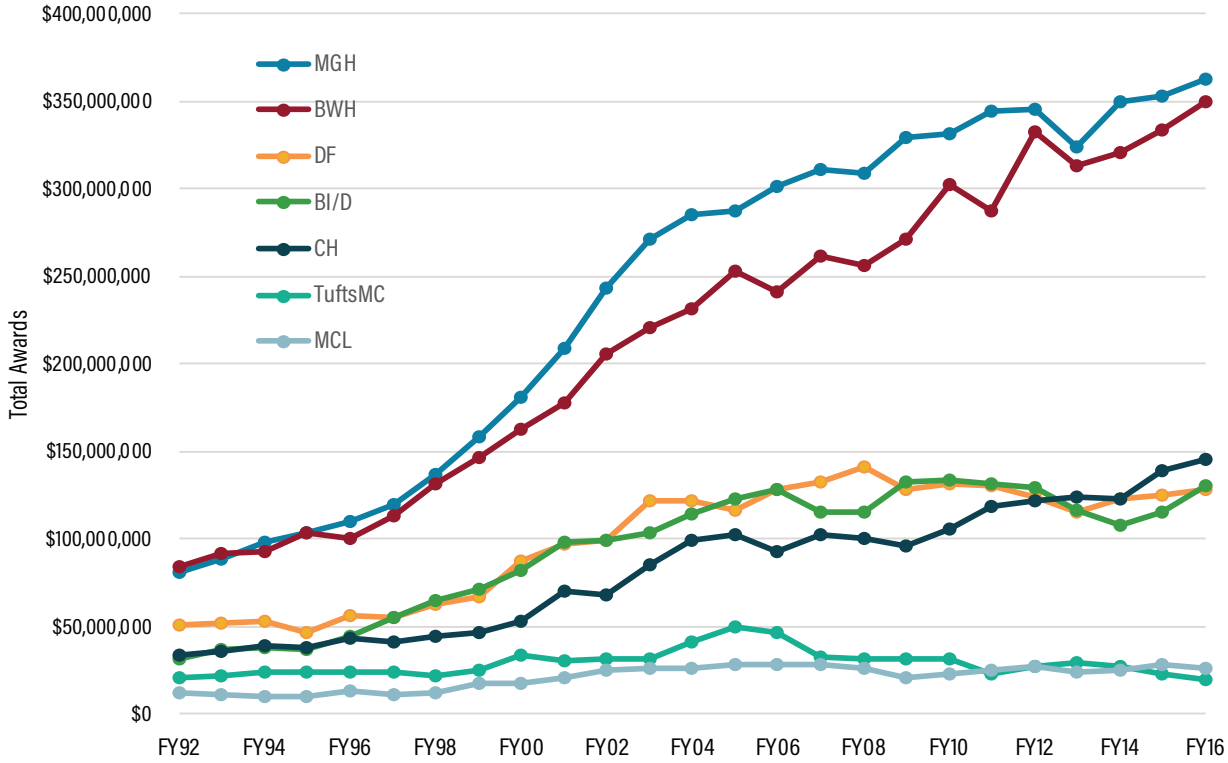
Harry W. Orf, PhD
Senior Vice President for Research
Massachusetts General Hospital

MGH Research has grown 352% over 20 years to $850M

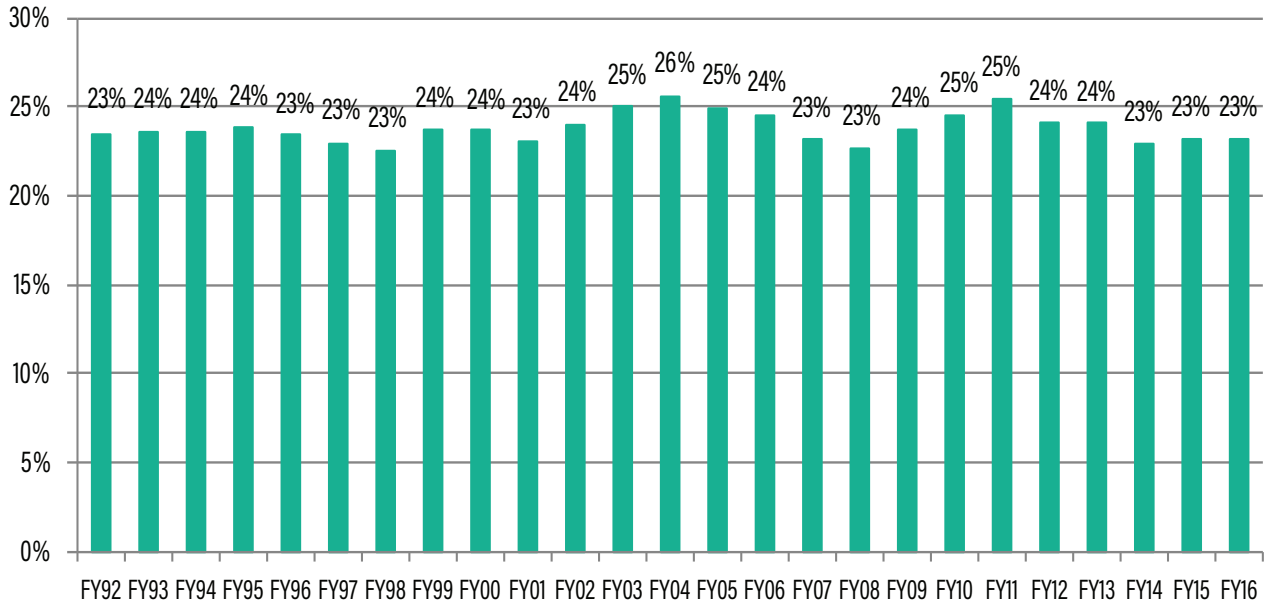
MGH combined research has grown at a compounded annual growth rate of 7.3% between FY2000 and FY16. The 5-year moving average annual growth has decreased from 7.1% in FY10 to 3.5% in FY16; the FY15-FY16 growth was 6.2%, with increases across every sponsor category.



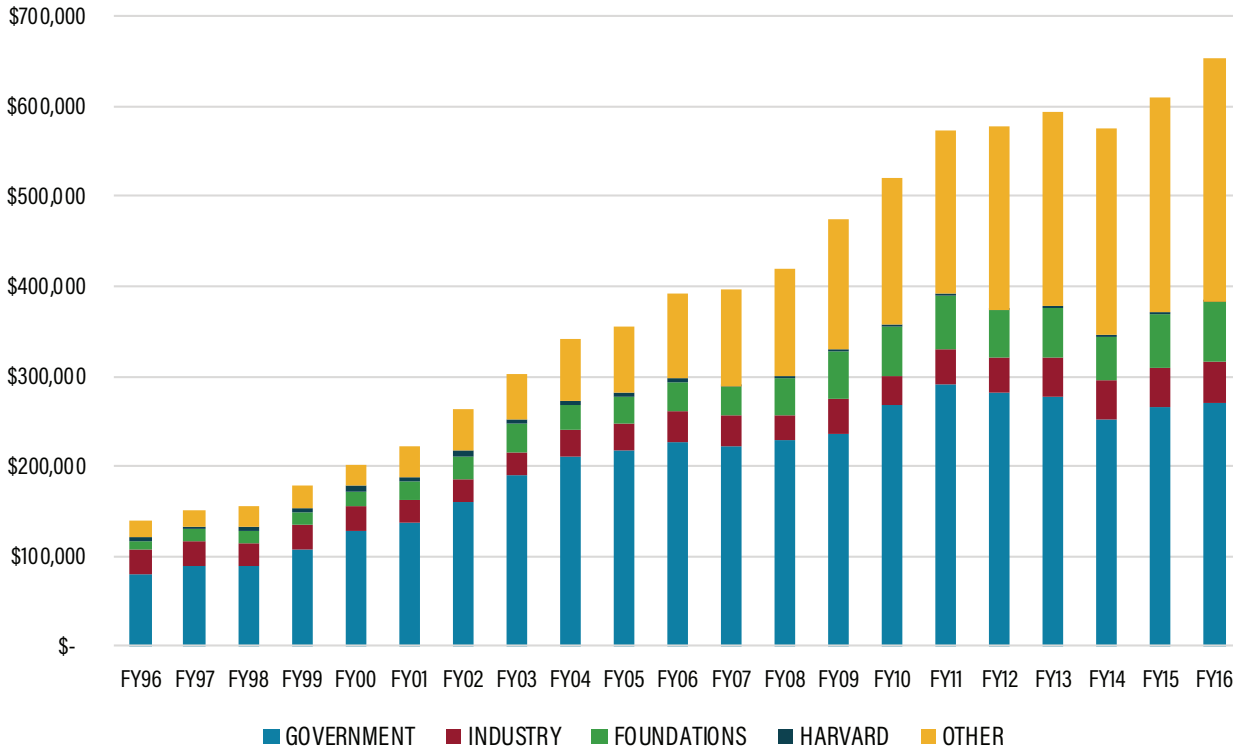
NIH Extramural Awards - Top Local Hospitals FY1992 - FY2016



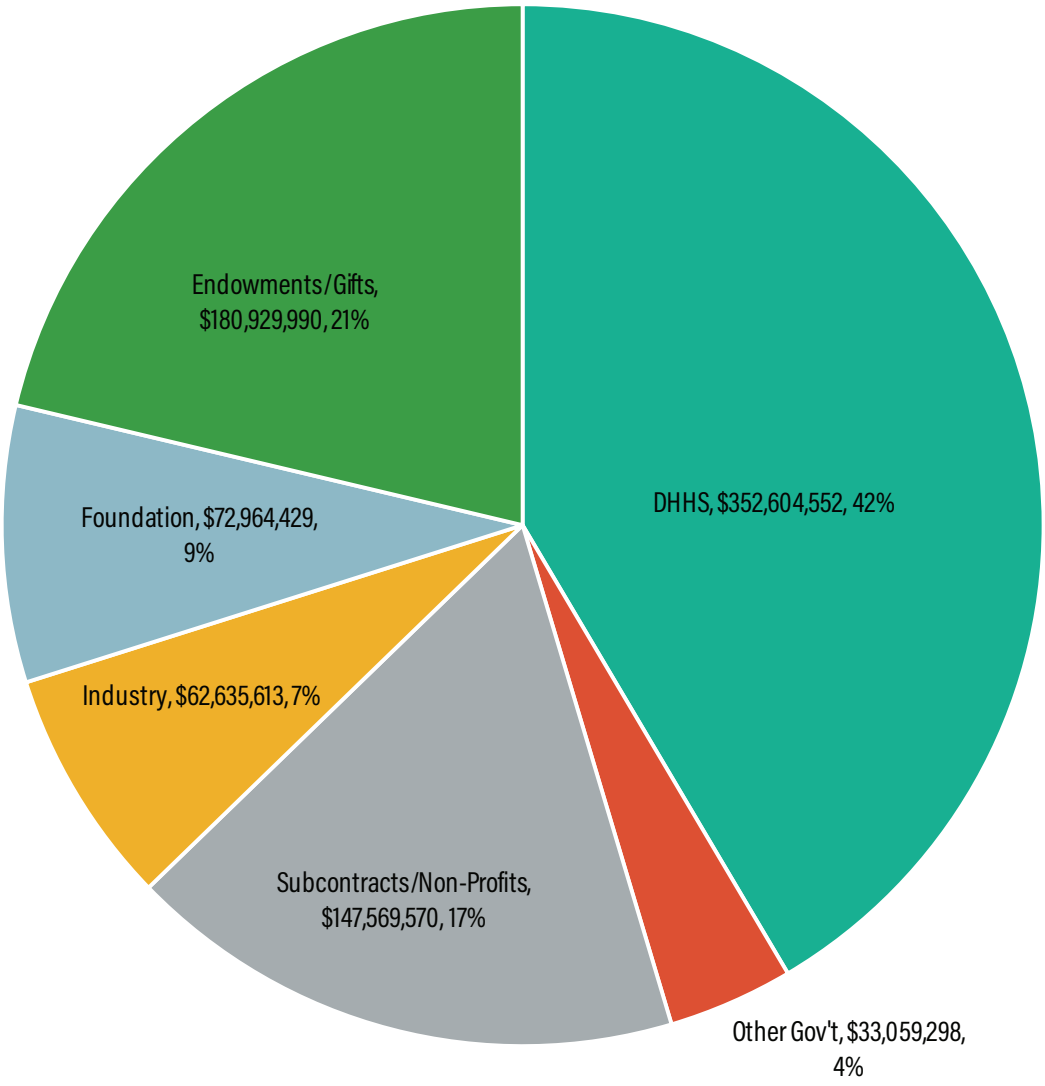
MGH Research Revenue as a Percentage of Total MGH Operating Revenue FY92 - FY16



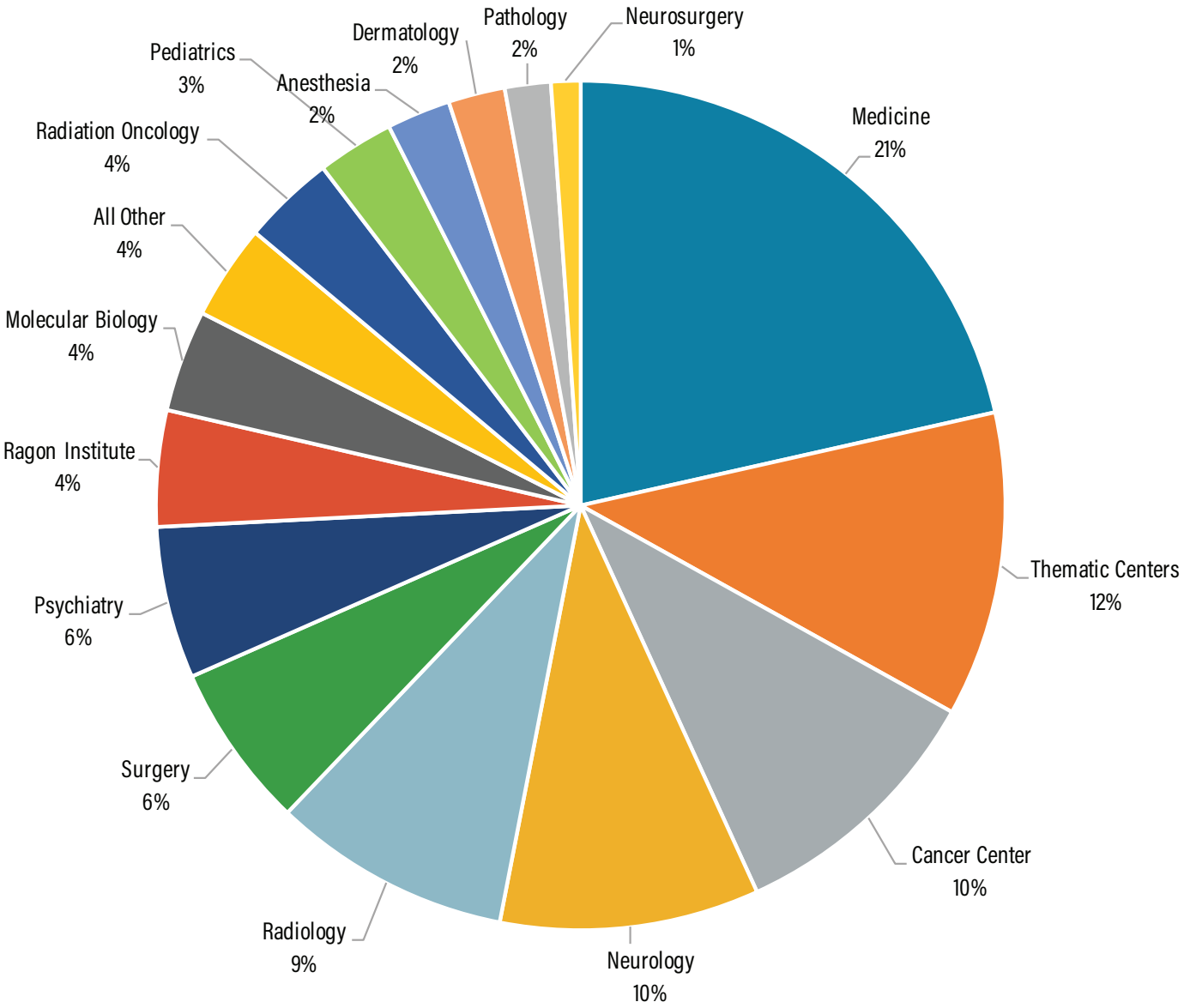
MGH Direct Research Expenditures by Sponsor FY96 - FY16 (in $Millions)



MGH Total Research Expenditures by Funding Type



MGH Total Research Expenditures by Department



MGH Science Activity by Sponsor
FY16: 10/1/15 - 9/30/16

Type of Activity	Direct	Indirect	Total
Federal & State	$270,550,663	$115,121,006	$385,671,669
Non-Federal	$382,922,856	$79,168,928	$462,091,784
Total Expenses FY 16	**$653,473,519**	**$194,289,934**	**$847,763,453**
Federal Activity by Sponsor			
DHHS	$247,509,397	$105,102,973	$352,612,370
DOD	$17,607,334	$8,840,499	$26,447,833
DOE	$434,604	$43,689	$478,293
USAID	$1,158,314	$135,798	$1,294,112
NSF	$845,007	$479,671	$1,324,678
Other Federal	$749,993	$142,209	$892,202
Total Other Federal Activity	$20,795,252	$9,641,866	$30,437,118
Subtotal Federal	$268,304,649	$114,744,839	$383,049,488
State	$2,246,014	$376,167	$2,622,181
Total State Activity	$2,246,014	$376,167	$2,622,181
Total Federal and State	**$270,550,663**	**$115,121,006**	**$385,671,669**
Non-Federal Activity by Sponsor			
Industry	$45,570,262	$16,060,708	$61,630,970
Foundations	$65,551,977	$7,412,452	$72,964,429
Subcontracts/Other Nonprofit	$117,138,807	$35,321,164	$152,459,971
MGH Endowment & Gifts	$153,800,068	$20,374,604	$174,174,672
Total Non-Federal Activity	$382,061,114	$79,168,928	$461,230,042
Total Expenses	$652,611,777	$194,289,934	$846,901,711
Harvard Medical School	$861,742	$-	$861,742
Grand Total	**$653,473,519**	**$194,289,934**	**$847,763,453**

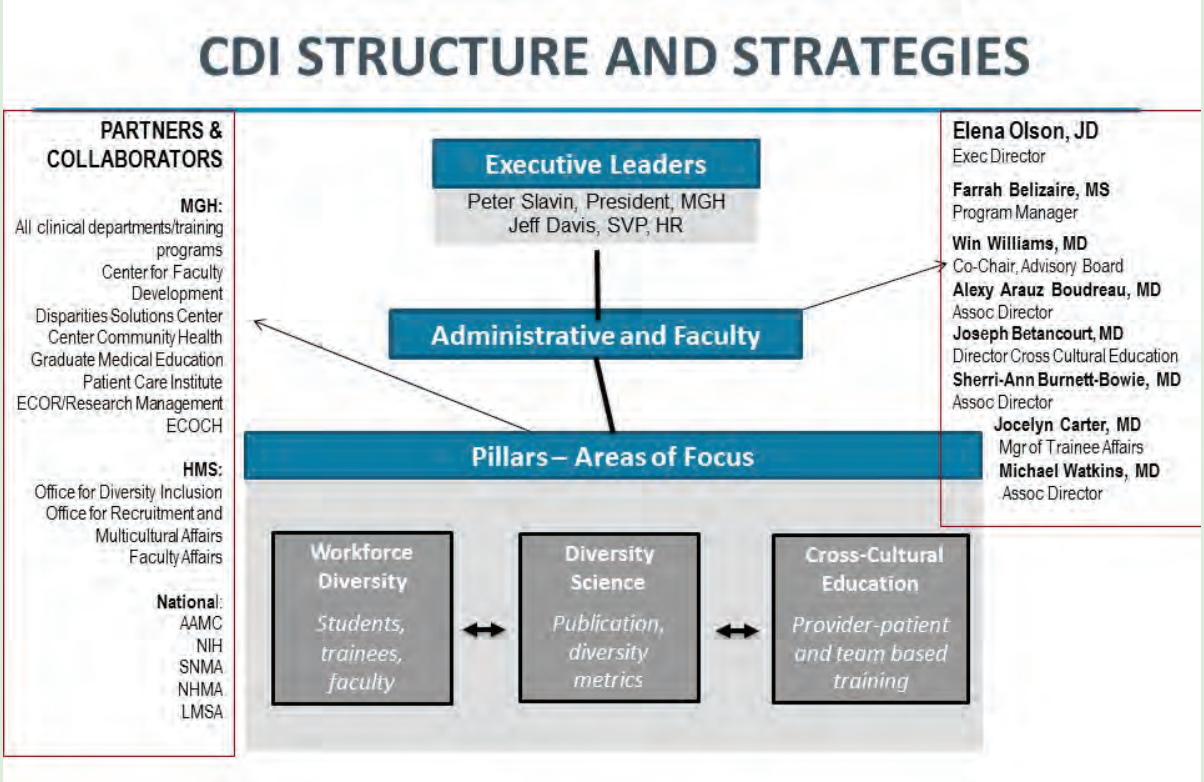
Center for Diversity and Inclusion (CDI)

Programmatic Report

Elena B. Olson, JD, Executive Director

Mission

CDI's mission is to facilitate and promote the advancement of students, physicians and researchers who are underrepresented in medicine (URM), as well as to help develop culturally competent physicians at MGH. CDI reflects Mass General's longstanding and nationally recognized commitment to building an inclusive community where trainees and faculty thrive and where patients receive exceptional, compassionate and equitable healthcare.



Focus

CDI accomplishes its mission by focusing on three areas:

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

Strategic Priorities

- Integrating above focus areas into all MGH mission areas and the fabric of the institution
- Continued collaboration with ECOR and Partners Research Management in advancing the research workforce initiative (detailed below)
- Educating workforce on cross-cultural teamwork and communication, race/racism and social determinants of health
- Developing outcome measurement for all CDI programs
- Disseminating knowledge and innovation through publications and national presence

Achievements

Overall
Center for Diversity and Inclusion: CDI was a key contributor to developing strategic priorities for the MGH Executive Diversity Committee. We have enhanced communication/marketing, including online videos of testimonials from trainees, clinicians and physician/scientists on the value of CDI and working at MGH.

Professional Leadership and Workforce Diversity
Developing the Student Pipeline: CDI expanded its signature Summer Research Trainee Program (SRTP), which brings in URM college and medical students to conduct novel research at MGH, to 20 students (10 college and 10 medical students). We conducted a comprehensive online survey of past participants (~250) to determine SRTP's career impact on alumni. A manuscript undergoing final edits describes our data and program and soon will be ready for submission to a peer-reviewed journal. This work is in collaboration with colleagues at the Mongan Institute for Health Policy.

Recruiting Trainee Talent: At the core of our goals is the ability to attract talented physicians who will provide the very best care for the increasingly diverse patients that MGH serves. The CDI has helped make great strides in enhancing the representation of URM trainees. We have worked collaboratively with every MGH-affiliated residency training program to provide unconscious bias training for selection committees, implement strategies and tactics specific to the department, and bring together a community of trainees to help attract this talent. In 2016, we matched overall 13% URMs into our residency programs, with several programs exceeding 25%, which is well above the percentage of national graduates. What is most significant are the reasons cited by those who selected MGH: as part of an excellent clinical program and training, applicants stated their interaction with faculty and residents demonstrated a welcoming community that values diversity and inclusion, and a place where they can see opportunities for their future careers growing and flourishing. This feedback tells us we are making a difference.

MGH Trainee Mentoring: The Career Development Liaison Program (CDLP) matches URM interns and residents in each residency training program at MGH with a URM faculty, with the aim to provide mentoring, counseling and networking across disciplines.

CDI Resident and Fellow Committee (RFC): The RFC is an interdisciplinary committee of the CDI, and they have been at the forefront of recent race discussions, recruitment, career development and community outreach. The RFC Board is an invaluable resource for all URM residents and fellows. Additionally, they are actively involved in mentoring youth through the Center for Community Health Improvement as well as HMS URM students.

Advancing the Diversity of the MGH Research Workforce: The low percentage of NIH funded investigators who are Black and Latino remains a challenge both nationally and at MGH. CDI developed a marketing campaign to educate both potential mentors and mentees about funding opportunities through NIH Diversity Supplements. Several surveys were conducted to garner interest from MGH PIs identified as being eligible to have a diversity supplement; from current faculty looking to become successful independent investigators; and from SRTP alumni interested in research.

Promoting Clinical and Research Faculty through the CDI Faculty Development Award Program (FDA): To date, CDI has awarded a total of 43 Physician/Scientist (PSDA) and Clinician-Teacher (CTDA) awards. These awards, which provide mentorship and funding for clinical, education and research projects, have had enormous impact on advancing the careers of URM faculty and the innovation at MGH. On average, recipients bring in eight times the Award investment to Mass General in the form of external grants. Recipients are also more likely to stay at MGH (88%) than those individuals who do not receive funding (60%). As a direct outcome of CDI's efforts in faculty development, ECOR funded three Physician/Scientist Development Awards this year, and one of the PSDA recipients became the first African American in the past 4 years to receive NIH R01 funding.

Cross-cultural Education/Social Determinants of Health
Education and training are at the core of our inclusion efforts. CDI has been at the forefront of designing and implementing educational initiatives that focus on enhancing the quality of patient care and the experience of our diverse workforce. We have advanced four critical initiatives: 1) The cross-cultural Quality Interactions e-learning curriculum designed by Joe Betancourt, MD, MPH, the CDI's program director for multicultural education, and the Disparities Solutions Center team, which focuses on provider and patient interactions and communications through an interactive, case-based online program. 2) A cross-cultural approach to teamwork and communication curriculum, which focuses on team-based interactions and has been rolled out to residents and nurses in the MGHfC (Department of Pediatrics) and at the unit level in 2015. This program is spearheaded by CDI Associate Director Alexy Arauz Boudreau, MD, MPH, and Executive Director

Elena Olson, in partnership with the Institute for Patient Care and Nursing. 3) Unconscious bias training for selection committees and departmental leadership spearheaded by CDI Associate Director Sherri-Ann Burnett-Bowie, MD, MPH and Ms. Olson. 4) Social Determinants of Health video was disseminated to the entire MGH workforce through mandatory yearly training.

Science of Diversity and Inclusion
Along with the Summer Research Trainee Program outcomes survey manuscript described above, the CDI is in the processes of updating and submitting several ongoing studies. Current manuscripts in development include the CDI as a best practice model in the nation, as well as outcomes and qualitative studies showing the positive impact of CDI programs, i.e., the MFDA.

CDI is also working closely with the Mongan Institute for Health Policy and the MGH Diversity Committee to develop metrics of diversity and inclusion for the institution and each clinical and research department.

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

Mission
The Center for Faculty Development (CFD) facilitates the career advancement and job satisfaction of faculty, research fellows and graduate students at the MGH. Our strategies are to:

- Develop and implement programs for faculty/trainees at all stages in their careers - from early careers to senior leadership - that promote academic and career development.
- Provide information, education and resources to increase faculty effectiveness.
- Provide support and education regarding academic advancement and promotion processes.
- Provide counseling, advice and support.

Focus
The CFD is an umbrella organization geared broadly for all faculty and includes three distinct branches: the Office for Clinical Careers (OCC), the Office for Research Career Development (ORCD) and the Office for Women's Careers (OWC), which address specific concerns for each respective constituency. In addition, a Graduate Student Division and Post Doctoral Division are housed within the ORCD branch to address the needs of the graduate student and post doctoral communities.

Achievements
In 2016 the CFD and its offices again saw continuing success in the integrated approach to providing services and resources to our faculty and trainees. Many of our programs were collaborations between different CFD offices, and where appropriate we opened programs to fellows and residents. This year, the CFD and its associated offices sponsored 96 professional development programs with 3,158 faculty, fellows, students and other professional staff in attendance at these programs. The program themes spanned career development, academic advancement, management, communications, negotiation, Responsible Conduct of Research, leadership, networking and work-life balance. This year, the CFD also facilitated the completion of the CFD faculty mentoring program with the Hospital Medicine Unit.

In addition, 317 individuals visited the CFD and/or one of its offices this past year for a total of 373 office consultations. 252 of these visits were with a CFD staff member (69% faculty, 31% fellows, graduate students, residents and other staff) and 121 met with an external advisor (50% faculty, 50% fellows, graduate students, residents, and other staff). The vast majority of the visits were for career advice, grant funding and promotion.

In response to a SAC recommendation, the CFD established a dedicated Post Doctoral Division (PDD) within the CFD and named Dr. Marcia Goldberg as inaugural director.

Strategic Priorities
- Meet with all new Chiefs to review departmental faculty data and CFD resources.
- Provide professional development programs, workshops that meet the needs of our faculty and trainees, as well as networking opportunities for the faculty and trainees.
- Facilitate the annual New Faculty Orientation to familiarize new faculty with MGH/MGPO senior leadership and available resources to enhance their MGH experience.
- Recognize and celebrate outstanding mentorship by sponsoring the annual John T. Potts, Jr., MD, Faculty Mentoring Award.
- Sponsor and administer the Caring for Dependent(s) (CFD) Awards to help defray additional dependent care costs that go above and beyond care needs while a faculty member is traveling to an academic/society meeting.
- Offer individual consultations to help faculty and research fellows with advice and guidance.
- Facilitate consultation services to understand the usage of the Community of Science (COS) PIVOT database.
- Monitor and report on the Annual Career Conference (ACC) statistics.
- Develop and facilitate the implementation of an online system for the ACC process in departments.
- Develop and facilitate the implementation of an online system to track the internal status of HMS faculty promotions.
- Collaborate with the Mass General Physician's Organization on gender parity issues.

Center for Faculty Development (CFD)

Programmatic Report

Office for Research Career Development - Dennis Brown, PhD, Director

Mission

The Office for Research Career Development (ORCD) addresses the specific needs of the MGH research faculty and trainees. Areas of emphasis for this office are to:

- Develop programs to advance the career pathways of research faculty in an academic medical center environment.
- Strengthen the career guidance and mentoring offered to trainees at the pre- and post-doctoral level.
- Enhance communication within the research community.
- Provide individual counseling, advice and support.

Focus

The ORCD serves the hospital's large community of faculty investigators as well as its graduate students and post doctoral research fellows, including administering the MGH Guidelines for Research Fellows and advising the Mass General Post Doctoral Association (MGPA). In 2016, the ORCD continued to offer individual career counseling, to organize professional development seminars, to provide networking opportunities, and to advocate on behalf of the research community.

Achievements

- Counseled 78 faculty, fellows and research staff in individual meetings aimed at career advice.
- Collaborated with the MGH Development Office to offer 89 individual consultations on identifying research funding opportunities.
- Offered a six session Responsible Conduct of Research (RCR) series designed for NIH trainees and open to all MGH researchers.
- Provided English as a Second Language (ESL) classes specifically designed for researchers. Two 12-week semesters of ESL each served 80-90 students, who were divided into classes based on English skill level.
- Sponsored the 10th annual Research Fellows Poster Celebration to recognize the excellent research conducted by MGH post doctoral fellows. Approximately 70 posters on display highlighted post docs' research accomplishments.
- Organized multiple seminar series including Communication Skills, Grant Writing Workshops and an Orientation Program for research fellows.
- Advised the MGPA, which continues to be very active, with eight subcommittees devoted to the career and networking needs of post doctoral fellows.
- Supported the MGPA in an initiative to organize site visits at local biotech companies for post docs with interests in this career path.
- Offered the Career Explorations Series, with seminars and panels on careers in academia (both faculty and non-faculty tracks), publishing, and industry research.
- With the MGPA, offered educational programs to internationally trained MD researchers who wish to do US medical residencies.
- Refined the process for granting extensions on the 5-year term limit on the research fellow position by requiring career advice meetings for all post docs who wish to remain on the research fellow track for more than 6 years.
- Piloted the first and second phases of the Career Pathways for Post Docs Internship program, which gives post docs hands-on experience for future career moves.

Strategic Priorities

- In 2017 the opening of the Post Doctoral Division (PDD), a division of the ORCD, will enhance the existing programming and career support for MGH research fellows, much as the Graduate Student Division has done for pre-doctoral trainees, and market itself to the post doctoral fellow community as well as the larger MGH research community.
- The six session New Investigator Advancement Initiative (NIAI) for MGH faculty who hold their 1st NIH R-level grant or equivalent (including institutional startup packages) will continue.
- Provide programming and advocacy for MGH research faculty geared toward career development, guidance and career satisfaction, especially in light of the complex and difficult funding climate.
- Contribute to efforts to assist researchers in transition due to funding issues or the shrinking faculty job market, including:
- Supporting the use of the non-faculty track Research Scientist position in order to retain highly trained individuals.
- Increasing awareness of/programs for alternative career opportunities (e.g., industry, scientific publishing, college teaching, lab management or administration).
- Educating faculty on the availability of and application process for MGH interim funding.
- Offer programming for research trainees, in particular career exploration programs, and seminars to prepare them for future

success in the changing research environment, including exploring research careers in academia outside the faculty track.
- Facilitate collaborations between the Graduate Student Division and the Post Doctoral Division to help form mentoring relationships between post doc mentors and graduate student mentees.
- Continue to grow the Career Pathways for Postdocs Internship Program with expanded opportunities and internship sites.

Graduate Student Division - Thilo Deckersbach, PhD, Director

Mission

The Graduate Student Division (GSD) is designed and intended to serve the practical needs of graduate students from all academic institutions that are associated with clinical and research faculty at MGH and foster a graduate student community at MGH. The GSD areas of emphasis are:

- Serve basic and academic needs of graduate students.
- Provide programs, services, and resources.
- Create a sense of community.
- Enhance the overall experience of students affiliated with MGH.
- Establish relationships with area graduate schools.

Focus

The GSD supports the hospital's graduate student community - more than 500 non-employee PhD students performing their research at MGH. It also provides assistance to the faculty working with graduate students. The focus of the GSD this past year was to offer targeted educational seminars designed to help graduate students build professional, communication, and networking skills; highlight student publications; pilot student travel awards and enhance GSD visibility by increasing communications with PIs of PhD graduate students.

Achievements

In the past year the GSD provided 16 educational programs to help graduate students in the following areas: negotiation and conflict management, job search strategy, resume building, interview skills, fellowship applications, and funding opportunities. The GSD expanded efforts to provide individual career counseling and networking opportunities for graduate students here at MGH by counseling 23 graduate students and connecting approximately 16 individuals with an external career consultant to offer a total of 39 office consultations.

In collaboration with PHS Media the GSD scripted and recorded a MGH Graduate Student Division video to help market and promote opportunities for the graduate students in research offered at MGH. The GSD developed and delivered the international student "Buddy" System to help connect new international graduate students with those who have been at MGH for a longer period of time. In 2016 the GSD offered and piloted the GSD T-Pass Savings to help graduate students not eligible for the MGH employee discount to defray their T-Pass transportation costs, sponsored and administered the GSD Graduate Student Travel Awards to help graduate students when traveling to an academic/society meeting directly related to their academic advancement and instituted "Paper of the Month" culminating in a "Paper of the Year." With the help of the GSD Committee members MGH students have a networking community and active presence on social media. The GSD collaborated with the Northeastern Section Younger Chemist Committee (NSYCC) to organize the Fall Career Symposium for graduate students and post docs. Similar to last year, the GSD maintained its close relationships with local school administrations and participated in the Harvard-MIT HST Faculty Poster session. In addition, the GSD continued oversight of the MGH Graduate Student registration process with good results.

Strategic Priorities

- Programming: sponsor and administer a GSD Mentoring Award to recognize a PI who has demonstrated outstanding contribution in helping graduate students to advance their skills and provide support with academic work.
- Communication: support GSD Communication efforts by offering GSD Select, a collection of original research papers published by graduate students with their MGH mentor, and selecting the best paper as "paper of the year."
- Community building: collaborate with PDD and ORCD to connect graduate students with MGH post docs and develop graduate student and post docs mentoring relationships.
- Networking and Education: work with the GSD and PDD advisory group to identify areas for improvements and to enhance networking.
- Knowledge: facilitate in-person orientation for new graduate students.

In addition, the GSD will continue to:

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

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

Mission

The Office for Women's Careers (OWC) facilitates the career advancement of women faculty at MGH. Areas of emphasis for this office are to:

- Increase the number of women faculty in leadership positions.
- Increase the number of women faculty promoted by academic criteria.
- Increase retention and job satisfaction of women faculty.
- Develop and implement programs to promote career development and work life balance.
- Provide individual counseling, advice and support.

Focus

The OWC at MGH is a branch of the Center for Faculty Development (CFD) and was created to foster a gender equitable environment to assure that women and men faculty will be given the same opportunity to succeed in research and clinical careers at MGH. Through many programs and collaborations, the OWC provides career development resources for women and endeavors to build a sense of community among women faculty across the institution. The office focuses on reducing barriers to career advancement and by request advises women faculty on various career matters. It also develops programs on topics such as leadership skills, negotiation, promotion, mentoring, presentation skills, finance, and academic writing. The OWC also offers opportunities for women faculty to network with peers and female role models in academic leadership positions.

Achievements

- Partnered with individual departments, including Anesthesia, Medicine (DOM) and Surgery, to promote internal efforts towards the advancement of female faculty. For example, collaborated with the DOM's new committee on Women in Medicine and Anesthesia faculty who started a group of faculty parents.
- Organized the highly successful annual Women in Medicine celebration, which recognizes achievements by female faculty and includes a lecture from a distinguished female leader. This year's speaker was Dr. Juanita Merchant of the University of Michigan.
- Contributed to MGH's Diversity Committee, on which Dr. Rigotti is an invited member.
- Facilitated "A Study of Gender Differences in Physician Compensation at the MGPO" presentations by the Mass General Physicians Organization (MGPO), and began the process of identifying strategies and initiatives to mitigate differences.
- Fostered networking with female leader role models with the "Meet and Greet Networking Series."
- Supported the growing community of Claflin Distinguished Scholars with a panel discussion for prospective applicants and the Claflin Consultation Initiative (CCI) to provide individual coaching to applicants by alumnae, and the annual Claflin Luncheon to welcome the newest Scholars.
- Sponsored the annual program focused on leadership skills, this year with a focus on "Building Leadership Skills." Also sponsored a program for women faculty on "Effective Mentoring Relationships."
- Offered community-building programs such as the Faculty Parents Group and the Managing Parenthood and Your Career series, with discussions aimed at providing information and peer support to faculty and trainees with childrearing responsibilities.
- Facilitated the annual Business of Life workshop to help faculty develop strategic plans to advance their career and personal life. In concert with this workshop, offered individual coaching with attendees to support their personal goals identified during the workshop.
- Developed a closed Facebook group for women faculty, providing them with an informal means of networking on their own schedule.
- Included trainees in OWC programs. Sponsored the second annual mentored lunch for women postdocs, in which trainees met in small groups with women faculty to hear advice on trainee-to-faculty transitions.
- Counseled 27 women faculty aimed at career advice and supporting gender equity and 7 women faculty sought guidance from an external career consultant. These individuals visited the office for a total of 36 consultations.

Strategic Priorities

- Collaborate with the MGPO to continue the process of identifying and developing initiatives and providing resources to ensure gender equity; these may include negotiation skill building, publishing programs, as well as academic advancement programs.
- Expand professional development programs and workshops that meet the needs of women faculty, addressing in particular the challenges of career and parenting, as well as leadership issues and negotiating strategies for women. Continue to support departmental programs in these areas and others, as identified.
- Advocate for women faculty – especially women seeking flexibility in the work environment and female physician-scientists seeking support in developing their research careers.
- Offer the Claflin Consultation Initiative and annual panel discussion to support Claflin Distinguished Scholar Award applicants.
- Collaborate with MGH Center for Diversity and Inclusion, DOM Women in Medicine Committee and the HMS Joint Committee on the Status of Women.
- Offer the successful Leadership Workshop for women faculty covering topics relevant to women faculty interested in leadership growth.
- Provide networking opportunities for all women faculty, especially junior and mid-career faculty who are seeking mentoring and networking opportunities to develop into leaders. Expand these networking opportunities to include more trainees.
- Develop new ways for women faculty to network and support each other with Facebook and other forms of social media.
- Participate in the planning for the annual Celia White Tabor Women in Medicine lecture and associated events.

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

Mission

The Office for Clinical Careers (OCC) facilitates the career advancement and promotion of clinical faculty at the MGH. Areas of emphasis for this office are to:

- Develop and implement programs to promote career development.
- Provide support and education regarding the promotion process.
- Enhance clinical practice/practice management.
- Encourage work life balance.
- Provide individual counseling, advice and support.

Focus

The Office for Clinical Careers (OCC) at MGH, a branch of the Center for Faculty Development (CFD), was created to facilitate career advancement/promotion for staff with clinical appointments, to provide career advice to clinical investigators, to enhance clinical practice/practice management, and to encourage/enhance work-life balance.

Achievements

- Advised 105 faculty and fellows from a cross section of departments in 113 consultation sessions regarding: career advice, CV/cover letter critique, and promotion.
- Worked with the Advisory Council on what skills clinicians need (leadership training, teaching skills, "Speaking Up," and time management were the top discussion items).
- Sponsored 8 educational programs: Can I Really Write A Book?, Can I/Should I Be Promoted?, CV Narrative, Drafting Your Chief's Letter, Effective Teaching Techniques, Speaking Up and Giving Feedback, Scholarly Writing Seminar Series, and Writer's Block to promote academic advancement and help to "demystify" the HMS promotions' process.
- Participated in departmental outreach by visiting departmental meetings to present on the Center for Faculty Development and facilitate career advancement seminars.
- Presented faculty development seminar to visiting Chinese scholars.

Strategic Priorities

- Expand professional development programs and workshops to meet the needs of clinical faculty, stressing academic and career advancement.
- Collaborate with the Post Doctoral Division within the Center for Faculty Development to address clinical fellow needs.
- Advocate for clinical faculty and their career and work life balance needs.
- Promote awareness of/celebrate clinical faculty promotions and academic achievements.
- Advise individual clinical faculty on career and academic advancement.

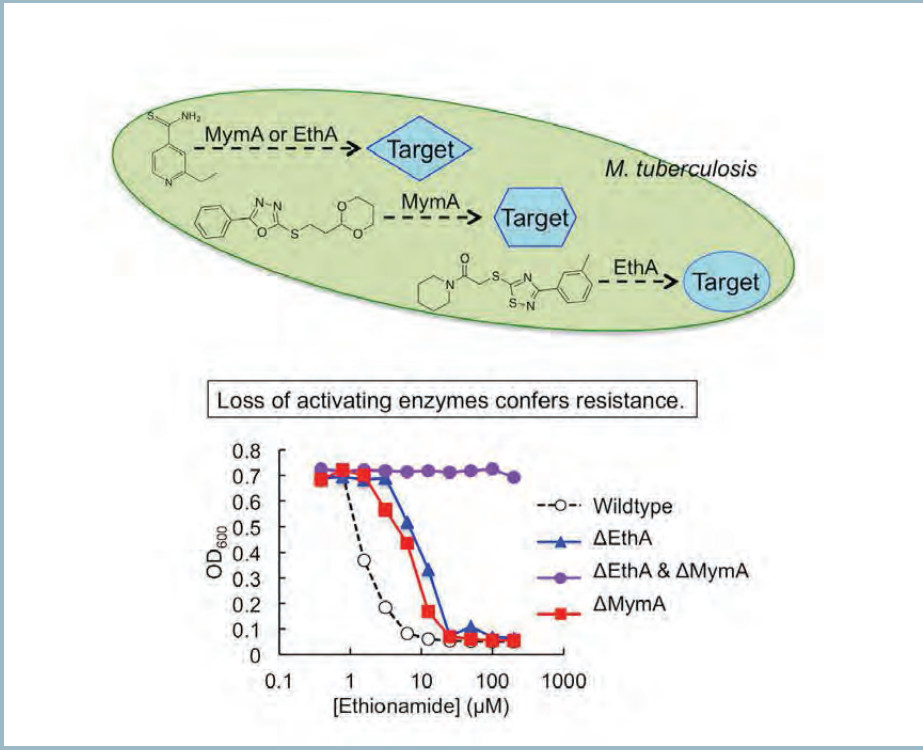
- Collaborate with departmental initiatives and do outreach to departments.
- Implement new strategies to market programs to clinical faculty.
- Conduct Exit Interviews with departing clinical staff to understand reasons for leaving MGH.
- Collaborate with the MGPO on work life balance issues for clinicians.
- Contribute to ECOTE and its working committees to enhance the community of clinician educators.

Brian Seed, PhD, Director

The Center for Computational and Integrative Biology (CCIB) supports inquiries into prebiotic chemistry, astrobiology, genome editing, plant biology, translational medicine, chemical genomics, novel therapeutic mechanisms, and mid- to late-stage clinical development. The mission of the Center is to support its investigators and to foster an environment that supports interdisciplinary or unconventional research programs that may fall outside the scope of conventional NIH-funded single investigator awards. In addition the Center supports IND-enabling and post-IND clinical research activities that require project management resources and/or experience conducting studies that must be carried out in a regulated environment.

Translational Medicine Group

New approaches to the treatment of human diseases and the clinical evaluation of candidate therapies are the focus of the Translational Medicine Group at MGH, led by Mason Freeman, MD, Professor of Medicine. The Translational Medicine Group has experience interacting with and conducting studies under the regulatory purview of the major competent authorities of the ICH signatory countries (FDA, EMA and PMDA) and has managed clinical operations in North and South America, Asia and Europe. The Translational Medicine Group also provides support and leadership for the hospital Translational Research Center, which is intended to provide facilities and staffing to expedite clinical studies proposed by investigators based at the hospital or within the biopharmaceutical community. An 18-bed clinical trial facility has been designed and dedicated to support this mission. The longest-standing and largest program supervised by the Translational Medicine Group supports the clinical development of an inhibitor of the sodium glucose linked transporter 2 that has potential for the treatment of type 2 diabetes. The Translational Medicine Group has supported this program from late pre-clinical development.



Baeyer-Villiger Monooxygenases EthA and MymA Are Required for Activation of Replicating and Non-replicating *Mycobacterium tuberculosis* Inhibitors

Sarah Schmidt Grant,[1,2,3,4,5] Samantha Wellington,[1,4,5] Tomohiko Kawate,[1,3,4] Christopher A. Desjardins,[1] Melanie R. Silvis,[1] Carl Wivagg,[1] Matthew Thompson,[1] Katherine Gordon,[1] Edward Kazyanskaya,[1] Raymond Nietupski,[1] Nathan Haseley,[1] Noriaki Iwase,[1] Ashlee M. Earl,[1] Michael Fitzgerald,[1] and Deborah T. Hung [1,3,4]

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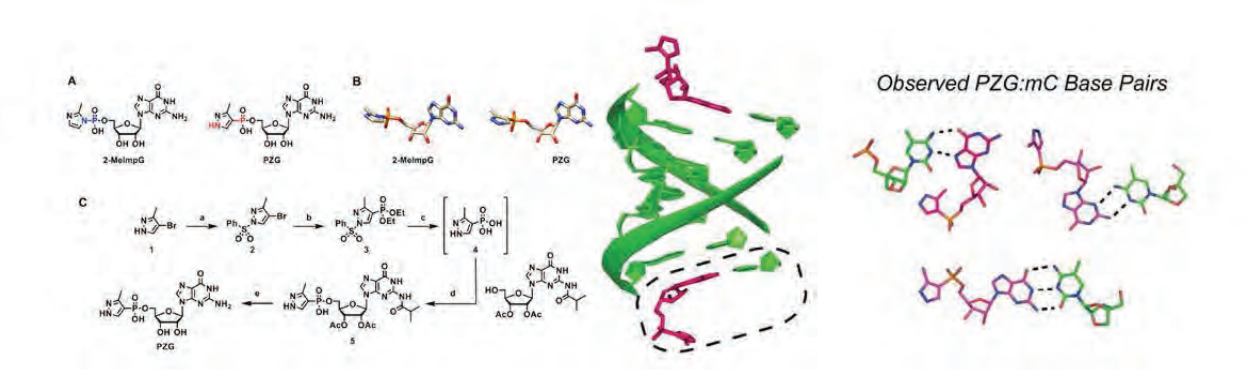
Tuberculosis, the disease induced by Mycobacterium tuberculosis, is one of the oldest recognized and most tenacious of human infectious diseases. Despite many years of study, the biology of M. tuberculosis is still poorly understood, and new discoveries continue to be made on the pathways that sustain the bacterium in its intracellular host, the macrophage, as well as the targets of historically effective, but often poorly understood anti-tubercular agents. The Hung lab has been applying new technologies and approaches from chemical genomics to bring modern chemical methodologies to bear on this ancient adversary. One of the idiosyncrasies of anti-tubercular agents is that many are prodrugs that must be activated in vivo to be effective. The anti-tubercular drugs ethionamide, thiacetazone and isoxyl are activated by flavin monooxygenases that catalyze Baeyer-Villiger oxidation, an unusual reaction that converts ketones to esters. M. tuberculosis has as many as six of these unusual oxidases and the Hung lab has found that several compounds previously identified by them to be active against the most resistant, non-replicative form, of the bacteria are activated by the same monooxygenases that mediate the activation of other anti-tubercular agents.



Unusual Base-Pairing Interactions in Monomer-Template Complexes

Wen Zhang [1,2] Chun Pong Tam, [1,2,3] Jiawei Wang[4] and Jack W. Szostak [1,2,3]

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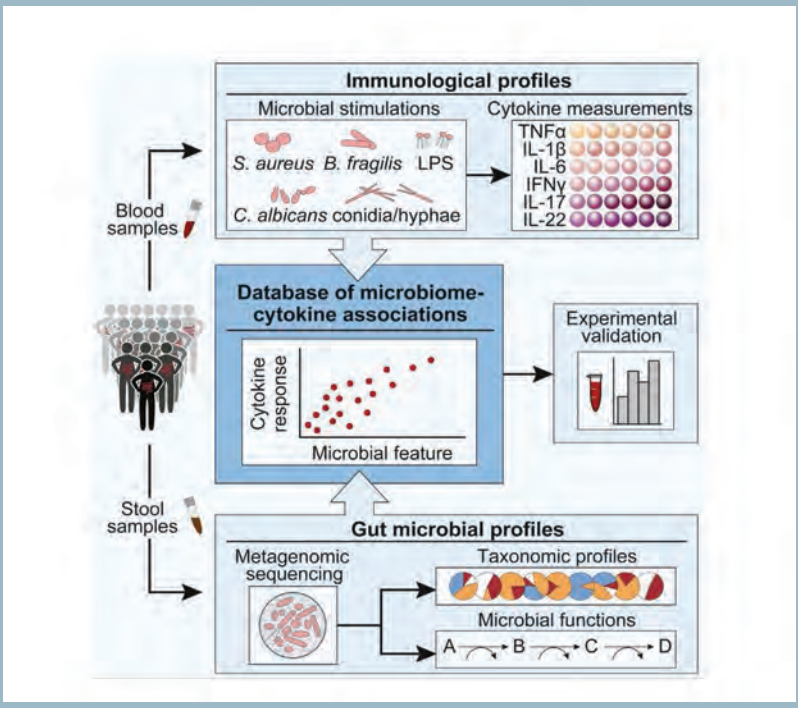
To capture enzymes in the act of catalysis, scientists often turn to X-ray crystallography of mutant enzymes that cannot complete the catalytic cycle, or of enzymes bound to transition state inhibitors, molecules that mimic the putative activated intermediate that the enzyme energetically favors. Much less is known about the mechanisms of action of ribozymes, biocatalysts similar to enzymes that are posited to have been important in the inception of life. Identifying ribozyme mutants is not straightforward, and capturing the act of catalysis is challenging, in part because ribozymes are more flexible and more thermolabile than enzymes. To identify structural relationships between precursor mononucleotides and templates of a model polymerase ribozyme, scientists in the Szostak group have synthesized an unreactive phosphonate-linked pyrazole analogue of an imidazole actvated nucleotide that has been previously used to study nonenzymatic primer extension. High-resolution X-ray crystallographic data were collected from the analogue co-crystallized with structurally rigidified RNA primer–template complexes bearing single or multiple monomer binding sites. Both Watson–Crick and noncanonical guanine:cytidine base pairs were observed. In most structures, the phosphate and leaving group moieties of the monomers had low electron densities, indicating a variety of conformations were present, whereas in some structures the distance from 03′ of the primer to the phosphorus of the incoming monomer was too great to allow for reaction. These effects may influence the rate and fidelity of nonenzymatic RNA replication, raising the possibility that ribozyme polymerases could enhance RNA replication by enforcing Watson–Crick base pairing between monomers and primer–template complexes, and by bringing the reactive functional groups into closer proximity.



Linking the Human Gut Microbiome to Inflammatory Cytokine Production Capacity

Melanie Schirmer,[1,2] Sanne P. Smeekens,[3] Hera Vlamakis,[1] Martin Jaeger[3] Marije Oosting,[3] Eric A. Franzosa,[1,2] Robter Horst,[3] Trees Jansen,[3] Liesbeth Jacobs,[3] Marc Jan Bonder,[4] Alexander Kurilshikov,[4,5,6] Jingyuan Fu,[4,7] Leo A.B. Joosten,[3] Alexandra Zhernakova,[4] Curtis Huttenhower,[1,2] Cisca Wijmenga,[4] Mihai G. Netea,[3] and Ramnik J. Xavier[8,9,10,11]

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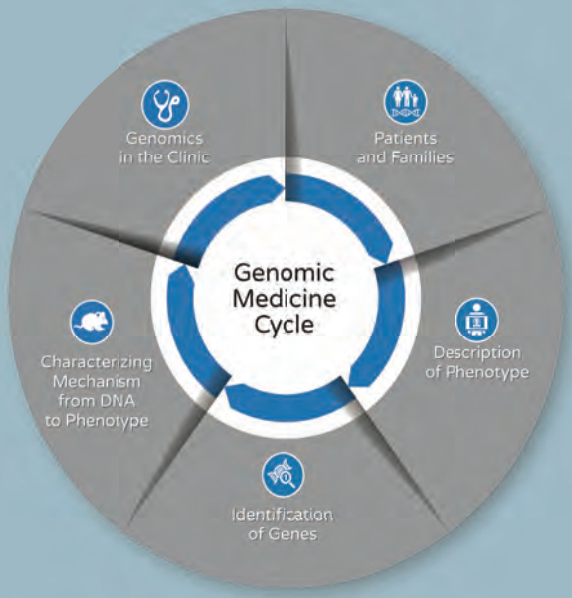
Maladaptive host-commensal relationships have been linked to aberrant immune responses, often heralded by the production inflammatory cytokines. As part of the Human Functional Genomics Project (HFGP), the Xavier lab has begun to investigate how gut microbial communities may affect cytokine responses in humans. Microbiome-cytokine interaction patterns that are stimulus specific, cytokine specific, and cytokine and stimulus specific have been observed. TNFα and IFNγ production are associated with specific microbial metabolic pathways, palmitoleic acid metabolism and tryptophan degradation to tryptophol, respectively. Palmitoleic acid decreased TNFα production but had no effect on IFNγ. Similarly, excess tryptophan had little effect on immune status, whereas tryptophol acted as an immunosuppressant, decreasing IFNγ production. These findings point to specific metabolites and pathways that sustain microbial-host communication that has the potential to affect adaptive and pathological host-commensal relationships.

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

Thematic Center Report

Sekar Kathiresan, MD, Director

The MGH Center for Genomic Medicine (CGM; formerly Center for Human Genetic Research) is a thematic center whose mission is to promote the application of the powerful tool set that genomics provides to investigate fundamental mechanisms in all areas of human disease and leverage these mechanistic insights to develop new diagnostics, therapies, and/or management strategies. Sekar Kathiresan, MD, assumed leadership of CGM in April 2016. Over the past year, CGM has collectively gone through a strategic planning process that addressed two questions: where does the Center want to go and how will the Center get there?



The goal of the Massachusetts General Hospital Center for Genomic Medicine (CGM) is the promulgation of the Genomic Medicine Cycle.

Over the next five years, CGM will build on its considerable strengths in gene discovery and mechanistic research and will seek to lead a new effort to bring genomics to medicine. CGM will look to 'complete the genomic medicine cycle' - from genetic discoveries to mechanism to the clinic - by assessing where genomic medicine will have the greatest impact on human health, and by driving efforts to implement genomic medicine in those areas, at MGH and beyond. We are planning strategic initiatives in four domains: 1) building scientific community; 2) taking steps to complete the cycle; 3) training future leaders in genomic medicine; and 4) fostering strong partnerships to ensure sustainability. Several of the strategic initiatives are being implemented in 2017 including new faculty recruitment and three genomic medicine demonstration projects (sequencing to identify those at risk for sudden cardiac death, whole genome sequencing as a diagnostic test, and a precision medicine research unit).

CGM would like to highlight key achievements in four domains:

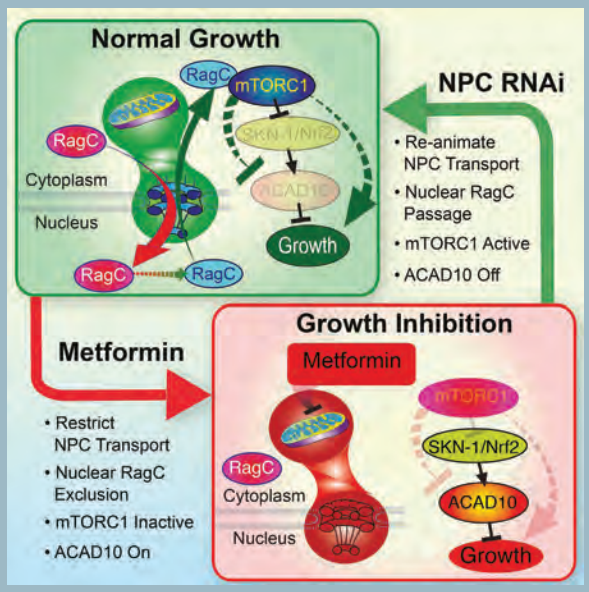
1. **Science.** CGM faculty made a number of important scientific observations this past year including:
   - An ancient, unified mechanism for metformin growth inhibition in C. elegans and cancer, Cell 2016 Dec; 167(7), p1705–1718. e13. Here, Alex Soukas, MD, PhD revealed a pathway by which a commonly used anti-diabetes drug – metformin – affects cell growth.
   - Genome-wide association analyses of sleep disturbance traits identify new loci and highlight shared genetics with neuropsychiatric and metabolic traits, Nat Genet. 2016 Dec 19. doi: 10.1038/ng.3749. Richa Saxena, PhD, identified numerous gene regions that contribute to sleep disturbance traits and showed genetic correlation between sleep disturbance traits and measures of adiposity.
   - Genetic risk, adherence to a healthy lifestyle, and coronary disease, N Engl J Med November 13, 2016. DOI: 10.1056/NEJMoa1605086. Sekar Kathiresan, MD and his team showed that high inherited risk for myocardial infarction can be counter-balanced by adherence to a favorable lifestyle.
   - Analysis of protein-coding genetic variation in 60,706 humans, Nature. 2016 Aug 18;536(7616):285-91. doi: 10.1038/nature19057. Daniel MacArthur, PhD, and his team have developed a DNA variant database that is now the gold-standard for the clinical interpretation of genome sequence data.
   - The genomic landscape of balanced cytogenetic abnormalities associated with human congenital anomalies, Nat Genet. 2017 Jan;49(1):36-45. doi: 10.1038/ng.3720. Epub 2016 Nov 14. Michael Talkowski, PhD, and his team performed whole genome sequencing to understand the spectrum of balanced rearrangements that contribute to congenital anomalies.

2. **Honors.** Alex Soukas, MD, PhD, and Daniel MacArthur, PhD, garnered the Massachusetts General Hospital Martin Research Prizes for fundamental and clinical research, respectively. James Gusella, PhD, was the recipient of the 2016 William Allan Award from the American Society of Human Genetics. The Allan Award recognizes a scientist for substantial and far-reaching scientific contributions to human genetics and is the highest scientific honor awarded by the American Society of Human Genetics. Jordan Smoller, MD, DSc,

organized the New England Precision Medicine Consortium and this team was selected by the National Institutes of Health to serve as an enrollment center for the All of Us Research Program, a national cohort study of 1 million or more persons. Recruitment of more than 100,000 All of Us participants is planned to occur locally including at CGM research space in the Simches Research Building.

3. **Administration.** CGM has restructured its administrative team to better support the 41 faculty members. New support has included the hiring of dedicated information technology support, renovations of space for bioinformatics seating capability of 20 new individuals, and the creation of a new website.

4. **Community.** CGM has taken steps to build community and collaboration among the 400+ employees in the center. Community-building steps have included town hall events, a team to participate in the MGH Be Fit competition, development of a regular newsletter, a travel awards program, and the creation of regular service/volunteer opportunities.



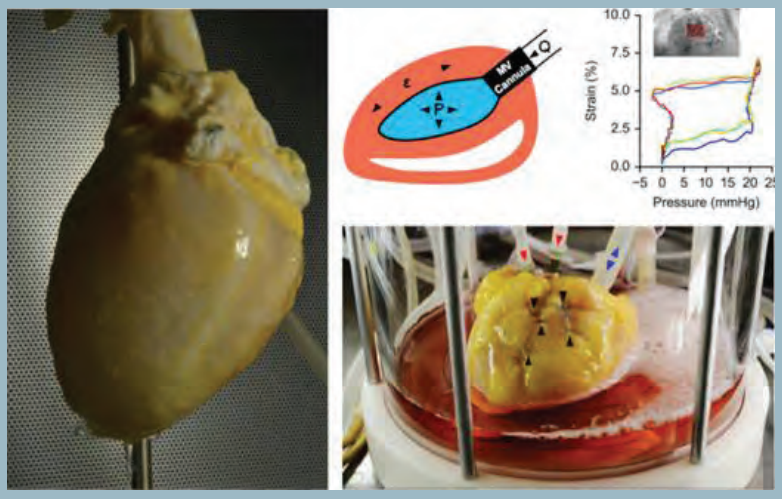
Metformin both suppresses cancer cell growth and promotes organismal longevity through a key transcriptional target that is induced through inhibition of mitochondrial respiration and modulation of mTOR signaling.

David Scadden, MD, Director

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

Ott Lab

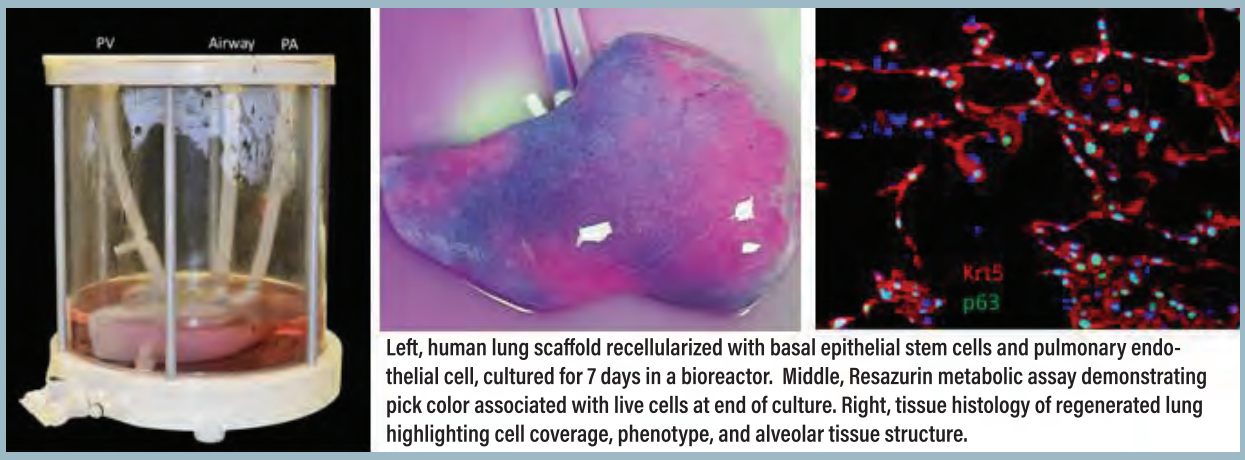
In 2016, the Ott lab created functional, electrically active human myocardium from clinically relevant matrix and cell sources. This is the first report of human myocardium of clinically relevant scale regenerated from pluripotent stem cells within a human heart matrix in ex vivo whole organ culture. Through this work, they also constructed and validated a fully automated, biomimetic bioreactor system for long-term culture of whole human hearts (under perfusion and mechanical stimulation), which is not possible using currently available technologies. These advancements signify substantial steps forward from a tissue and organ engineering perspective, but also provide novel and unique test beds for cardiac regenerative strategies such as cardiac cell therapy and ex vivo organ repair.



A perfused native decellularized human heart (left panel). Functional schematic and validation data for our human heart bioreactor (top right). A reseeded human heart being cultured in our biomimetic bioreactor system (bottom right; cell injections – black arrows, perfusion – red arrows, LV pump – blue arrows).

In addition, the lab has made significant progress toward engineering a patient-specific graft for transplantation. A recent manuscript published in Biomaterials described the approach to recellularization and ex vivo regeneration of rodent and human lungs, using donor tissue-isolated basal epithelial stem cells. Through a collaboration with the New England Organ Bank, donated human lungs serve as both the source of lung scaffold and endogenous cell populations capable of rapid expansion in vitro. Fundamental tissue and organ function was demonstrated following recellularization, including cell proliferation and metabolism and gas exchange during organ culture. The lab is now progressing to test these constructs in a porcine lung transplantation model.

Gilpin SE, Charest JM, Ren X, Tapias LF, Wu T, Evangelista-Leite D, Mathisen DJ, Ott HC. Regenerative potential of human airway stem cells in lung epithelial engineering. Biomaterials. 2016 Nov; 108:111-9



Left, human lung scaffold recellularized with basal epithelial stem cells and pulmonary endothelial cell, cultured for 7 days in a bioreactor. Middle, Resazurin metabolic assay demonstrating pick color associated with live cells at end of culture. Right, tissue histology of regenerated lung highlighting cell coverage, phenotype, and alveolar tissue structure.

The Ott lab has made progress in better understanding the acellular lung scaffold and the influence of the extracellular matrix in lung tissue regeneration. In a collaborative report published this year, novel in-depth methods to analyze the ECM after decellularization were described.

Proteomic analysis of naturally-sourced biological scaffolds. Li Q, Uygun BE, Geerts S, Ozer S, Scalf M, Gilpin SE, Ott HC, Yarmush ML, Smith LM, Welham NV, Frey BL. Biomaterials. 2016. Jan;75:37-46

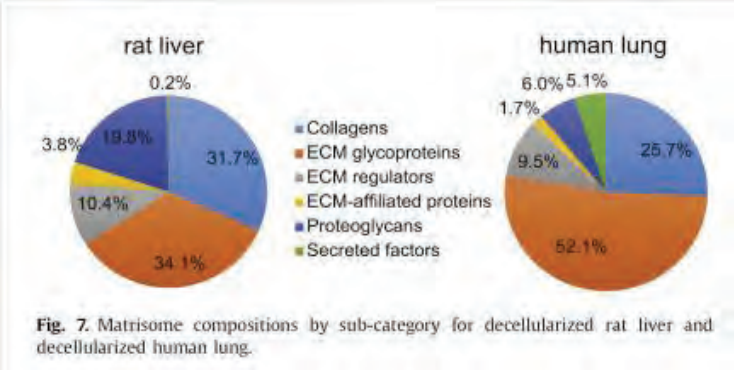


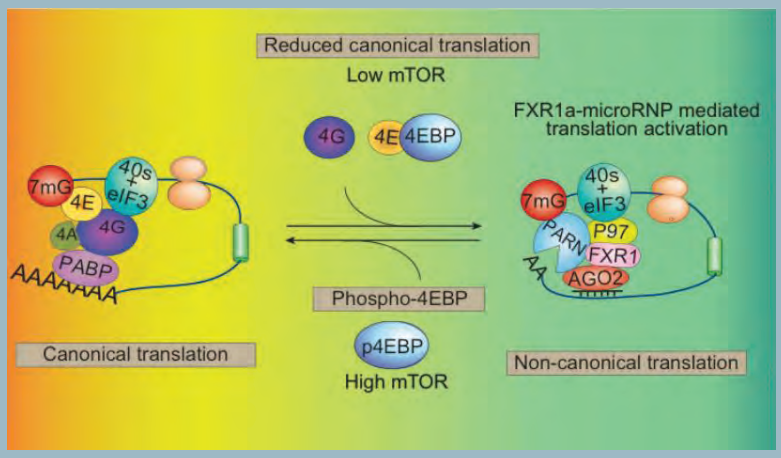
Fig. 7. Matrisome compositions by sub-category for decellularized rat liver and decellularized human lung.

This work has continued to further investigate the differences in ECM derived from neonatal lung in the process of post-natal alveolar development, and older lungs from more traditional donors. These studies have identified novel protein components that are enriched in younger scaffolds, which can be used to recondition older lung scaffolds and enhance epithelial regeneration. This work is being prepared for publication, and will be presented at the 2017 American Thoracic Society meeting.

Vasudevan Lab

A specialized mechanism of translation mediated by FXR1a-associated microRNP in cellular quiescence. Bukhari SI, Truesdell, SS, J, Lee, S, Kollu, S, Classon, A, Boukhali, M, Jain, E, Mortensen, RD, Yanagiya, A, Sadreyev, RI, Haas, W, and Vasudevan, S. (2016). Molecular Cell. 61(5):760-773.

Quiescent (G0) cells, including dormant cancer stem cells, are a critical, assorted subpopulation in cancers that survive clinical therapy. G0 cells are transiently non-proliferative—and therefore, withstand chemotherapy that targets cycling cells; G0 cells subsequently re-enter proliferation and cause recurrence. Such cells switch to a distinct gene expression profile, which could enable their survival. G0 regulators and their gene expression remain to be characterized. Canonical translation is decreased in G0 cells with specific mRNAs translated by unknown mechanisms. The translation mechanisms and profiles in G0 cells will provide important insights against cancer persistence.



Our data revealed that canonical translation is decreased in dormant cancer cells, and alternative gene expression occurs to enable survival. Canonical translation mechanisms are impaired in G0 due to low mTOR activity and 4EBP activation due to dephosphorylation, which blocks conventional cap and poly(A) dependent translation via inhibition of the canonical cap binding protein, eIF4E. Our studies reveal that in quiescent leukemic cells, where canonical translation is impaired by low mTOR activity, an alternative microRNA-protein complex (microRNP)—that lacks the conventional microRNP repressor and contains a key translation activator and cancer regulator, FXR1a—selectively recruits target mRNAs, and associates with specialized cap binding and ribosome recruitment translation factors that promote non-canonical, poly(A) independent translation of selectively-recruited mRNAs.

While activation by microRNAs is also observed by multiple groups in other distinct conditions, and with specific mRNAs and microRNAs, how distinct mRNAs are selected for activation and the mechanism of translation activation were unclear. Our data reveal that microRNA-mediated translation activation requires target mRNAs with unadenylated/shortened poly(A) tails. In G0, we identified Poly(A) ribonuclease (PARN) as an alternate cap binding protein, and eIF4G2/p97, as an alternate ribosome recruitment factor. PARN, a cap binding deadenylase, is able to bind the cap increasingly of specific mRNAs as the competition with eIF4E is reduced due to active 4EBP. PARN binding on mRNA caps leads to increased poly(A) tail shortening on mRNAs. Shortened poly(A) tails enable mRNAs to avoid Poly(A) binding protein (PABP) and thereby, the canonical translation mechanism that is inhibited in G0. These alternate cap binding and ribosome recruitment factors, PARN and p97, are associated with the 3'-UTR bound FXR1a-microRNP that enables their recruitment to specific mRNAs. P97, like eIF4G, enables 40S ribosome subunit recruitment to initiate translation, but lacks canonical cap complex- and PABP-interacting domains of eIF4G—which are not required as translation is non-canonical here. These data reveal a specialized translation mechanism that is important for G0, where FXR1a-microRNP connects specific, poly(A) shortened mRNAs to the ribosome through alternative factors,

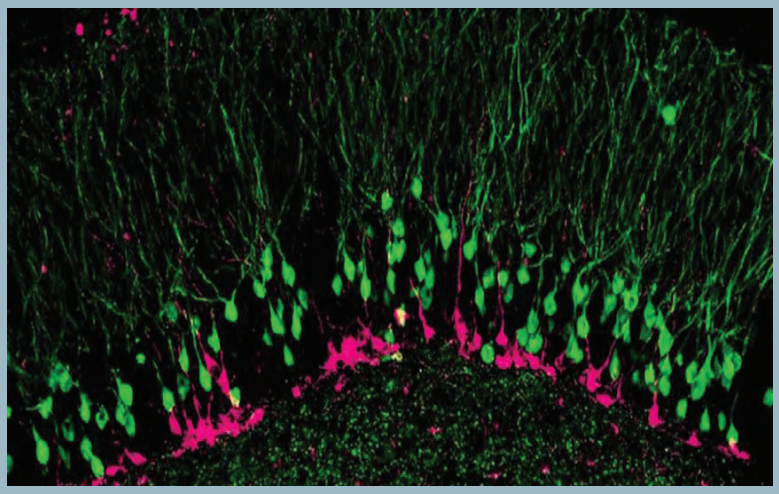
PARN and p97, in these conditions of reduced canonical translation. Our findings reveal that this specialized mechanism regulates specific gene expression in dormant subpopulations in cancer, with distinct immune gene mRNAs translated, which could enable cell survival.

Sahay Lab

Modulating Neuronal Competition Dynamics in the Dentate Gyrus to Rejuvenate Aging Memory Circuits. McAvoy KM, Scobie KN, Berger S, Russo C, Guo N, Decharatanachart P, Vega-Ramirez H, Miake-Lye S, Whalen M, Nelson M, Bergami M, Bartsch D, Hen R, Berninger B, Sahay A. Neuron. 2016 Sep 21;91(6):1356-73.

New stem cells in the dentate gyrus section of the hippocampus—the brain structure responsible for memory and learning—grow and integrate with existing cells to make memories stronger and more precise. The new cells compete for space among the intertwined connections of the older neurons; as the brain ages, fewer new cells survive. Sahay lab has shown they can manipulate two of the mechanisms involved in this process, boosting the survival of the new neurons in the brains of mice.

The researchers engineered the increase of a protein, Klf9, in older neurons in mice. This increase cleared one-fifth of the spines found on dendrites, a neuron cell structure, and doubled the number of new neurons added to the brain circuitry. When the researchers reversed the process, the old dendritic spines reformed, restoring competition with the new cells in the dentate gyrus. Although the previously integrated neurons remained, no new neurons were added. Similar results occurred when the researchers deleted Rac1, a protein important for dendritic spine growth, in older neurons. In this case, the survival of new neurons increased.



Young neurons (pink), responsible for encoding new memories, must compete with mature neurons (green) to survive and integrate into the hippocampal circuit. Photo courtesy of Kathleen McAvoy, PhD, Sahay Lab.

The findings suggest that manipulating these two proteins may enhance hippocampal cell generation in middle-aged and older mice and may result in stronger and more precise memories. More research is needed, but the Klf9 and Rac1 proteins may present promising targets for therapies to prevent cognitive impairment or age-related memory decline.

Scadden Lab

We focus on blood. This year we developed an in vivo tracking system that allowed us to define an unexpected feature of hematopoietic stem cells (HSC). Specifically, and contrary to accepted principles, HSC are not highly plastic with the ability to acquire differentiation fate as needed by physiologic cues. Rather, stem cells are hard-wired at a clonal level and able to make only a limited spectrum of cells (*Cell* 2016; Nov 17;167;1310.). These functional limitations are epigenetically scripted and preserved even under conditions of extreme organismal stress. This finding suggests that HSC are like chess pieces with fixed functional attributes and that as we age, our ability to be resilient to challenges in our 'end game' may be dictated by the pieces we have left.

We developed a non-genotoxic method of enabling hematopoietic stem cell transplantation that is of particular interest for advancing the application of gene editing and gene therapy strategies. The method uses an immunotoxin and resulted in high efficiencies of engraftment (93%) while sparing the bone marrow niche and thymus (*Nat Biotechnology* 2016; Jul;34;738). Practical application was shown by curing a mouse model of sickle cell anemia. The technology was licensed and is part of a biotechnology company to transform stem cell transplantation for non-malignant disease, Magenta Therapeutics, launched with $49.5M of venture capital funding.

We also used a stem cell driven approach to myeloid leukemias to develop a novel therapy capable of inducing AML differentiation and depletion of leukemic stem cells (*Cell* 2016; Sep 22;167;171). Based on a phenotypic screen, we defined lead compounds and a common molecular target, DHODH, that when inhibited had the unexpected effect of overcoming the differentiation blockade imposed by the spectrum of genotypic changes seen in AML. It is the basis for clinical development with Bayer Pharmaceuticals of DHODH inhibitors.

Ralph Weissleder, MD, PhD, Director

The mission of CSB is to analyze at a systems level how biological molecules, proteins and cells interact in both healthy and diseased states. Through a multidisciplinary approach that combines clinical insight with powerful analytical technologies, faculty pursue systems-level research that is both fundamental to our understanding of biology as well as directly applicable to the diagnosis and treatment of human disease. While these approaches can be generalizable to a variety of diseases, the Center has particular strengths in complex human conditions such as cancer, cardiovascular disease, diabetes, autoimmune disease, renal disease and reproductive biology. The CSB's mission is enabled by faculty with particular expertise in advanced bioimaging (at all scales), bioengineering, biology, chemistry, genomics, and mathematical modeling. The Center is a major node within the Harvard-wide Systems Biology Program, and its faculty maintain joint appointments or affiliations with the HMS Department of Systems Biology, the Broad Institute, various clinical departments at MGH, as well as with the other MGH Thematic Centers. The CSB is structured into 12 PI laboratories (Bernstein, Brown, Breton, Higgins, Lee, C. Lin, H. Lin, Nahrendorf, Pittet, Shaw, Swirski and Weissleder), Core Platforms (Bioimaging, Chemical Biology, Biocomputing) and several thematic research programs. The CSB is located within the Simches Research building and occupies approximately 33,000 square foot of space. There are currently 200 full time employees, including 41 faculty.

Achievements

An immune cell that protects against cancer (Science. 2016; 352(6282):242-246)

Macrophages are mostly viewed as tumor-promoting cells. They can infiltrate solid tumors in high numbers, and their presence at the tumor site is often associated with decreased patient survival. However, much less is known about macrophages located outside the tumor stroma. Pittet and colleagues show that a population of lymph node macrophages, called subcapsular sinus (SCS) macrophages, unexpectedly protects against melanoma. They also unravel the mechanism pointing to exosomes released from tumor cells.

- Pucci F, Garris C, Lai CP, Newton A, Pfirschke C, Engblom C, Alvarez D, Sprachman M, Evavold C, Magnuson A, von Andrian UH, Glatz K, Breakefield XO, Mempel TR, Weissleder R, Pittet MJ. SCS macrophages suppress melanoma by restricting tumor-derived vesicle–B cell interactions. Science. 2016;352(6282):242-246 - PMID: 26989197 - PMCID: PMC4960636

Single molecule analysis of nucleosomes (Science. 2016; 352(6286):717-21)

Different combinations of histone modifications have been proposed to signal distinct gene regulatory functions, but this area is poorly addressed by existing technologies. The Bernstein group applied high-throughput single-molecule imaging to decode combinatorial modifications on millions of individual nucleosomes from pluripotent stem cells and lineage-committed cells. They identified definitively bivalent nucleosomes with concomitant repressive and activating marks, as well as other combinatorial modification states whose prevalence varies with developmental potency. They showed that genetic and chemical perturbations of chromatin enzymes preferentially affect nucleosomes harboring specific modification states. Last, they combined this proteomic platform with single-molecule DNA sequencing technology to simultaneously determine the modification states and genomic positions of individual nucleosomes. This single-molecule technology has the potential to address fundamental questions in chromatin biology and epigenetic regulation.

- Shema E, Jones D, Shoresh N, Donohue L, Ram O, Bernstein BE. Single-molecule decoding of combinatorially modified nucleosomes.. Science. 2016;352(6286):717-21 - PMID: 27151869 - PMCID: PMC4904710

Ingest, Digest, Recycle: Where red blood cells and the iron they contain are recycled (Nature Med. 2016;22(8):945-951)

Iron gives blood its red color. The metal is essential to life, but it can be toxic because of its oxidative properties. Remarkably, we receive relatively little of our daily iron needs through diet. By far the majority of the iron we need is recycled. According to current thinking, as red blood cells age, large phagocytes residing in the spleen capture them, digest the cell structures, and recycle iron. A new paper from the Swirski and Lin groups shows that most red blood cell disposal actually occurs in the liver, especially when demands for disposal increase (as they do in many physiologic and pathophysiologic situations). Moreover, specialized white blood cells consume old red blood cells in the circulation before migrating to the liver to shuttle iron for storage and new red blood cell production. The process buffers against dangerous fluctuations in iron availability, keeping the body in balance.

- Theurl I, Hilgendorf I, Nairz M, Tymoszuk P, Haschka D, Asshoff M, He S, Gerhardt LM, Holderried TA, Seifert M, Sopper S, Fenn AM, Anzai A, Rattik S, McAlpine C, Theurl M, Wieghofer P, Iwamoto Y, Weber GF, Harder NK, Chousterman BG, Arvedson TL, McKee M, Wang F, Lutz OM, Rezoagli E, Babitt JL, Berra L, Prinz M, Nahrendorf M, Weiss G, Weissleder R, Lin HY, Swirski FK. On-demand erythrocyte disposal and iron recycling requires transient macrophages in the liver. Nature Med. 2016;22(8):945-951 - PMID: 27428900 - PMCID: PMC4957133

Improved HbA1c measurements in diabetes (Sci Transl Med. 2016;8:359ra130)

The amount of glycated hemoglobin (HbA1c) in diabetic patients' blood provides the best estimate of the average blood glucose concentration over the preceding 2 to 3 months. It is therefore essential for disease management and is the best predictor of disease complica-

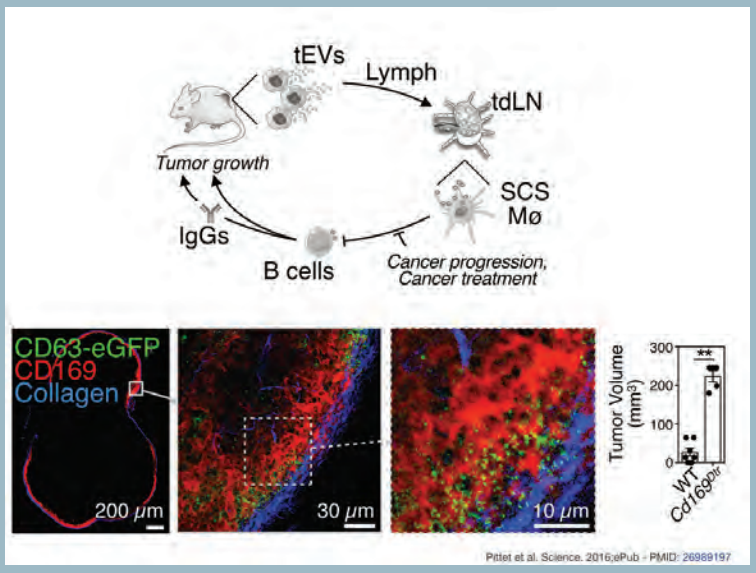
tions. Nevertheless, substantial unexplained glucose-independent variation in HbA1c makes its reflection of average glucose inaccurate and limits the precision of medical care for diabetics. The true average glucose concentration of a nondiabetic and a poorly controlled diabetic may differ by less than 15 mg/dl, but patients with identical HbA1c values may have true average glucose concentrations that differ by more than 60 mg/dl. The Higgins group combined a mechanistic mathematical model of hemoglobin glycation and red blood cell kinetics with large sets of within-patient glucose measurements to derive patient-specific estimates of nonglycemic determinants of HbA1c, including mean red blood cell age. They found that between-patient variation in derived mean red blood cell age explains all glucose-independent variation in HbA1c. They then used their model to personalize prospective estimates of average glucose and reduced errors by more than 50% in four independent groups of greater than 200 patients. The current standard of care provided average glucose estimates with errors >15 mg/dl for one in three patients. The patient-specific method reduced this error rate to 1 in 10. The personalized approach should improve medical care for diabetes using existing clinical measurements.

- Malka R, Nathan DM, Higgins JM. Mechanistic modeling of hemoglobin glycation and red blood cell kinetics enables personalized diabetes monitoring. Sci Transl Med. 2016;8:359ra130 - PMID: 27708063

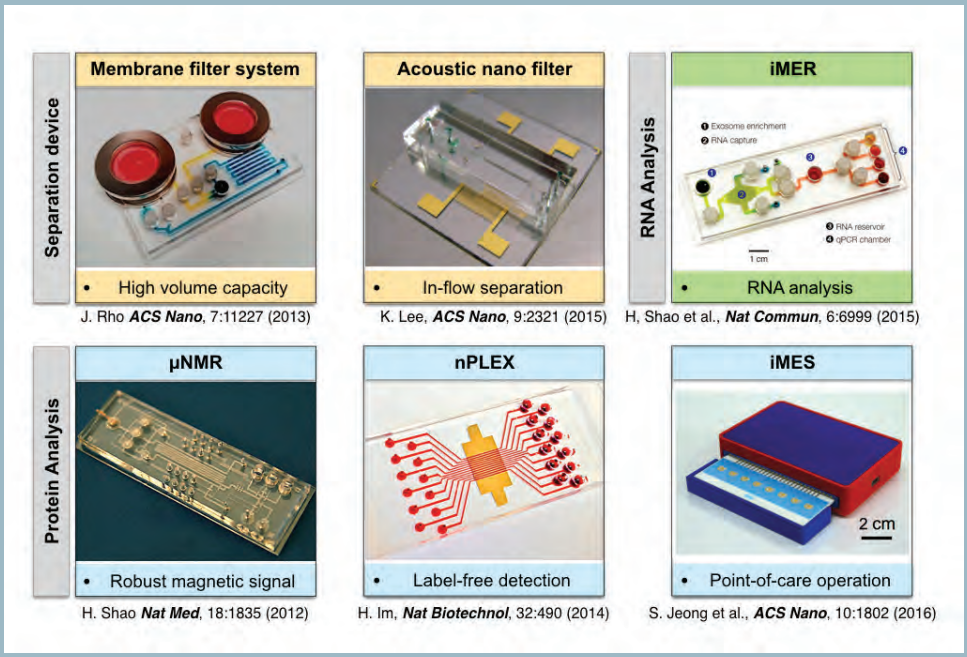
A recipe to improve cancer immunotherapy (Immunity. 2016;44:1-12)
Novel immune checkpoint blockade therapies can be extraordinarily effective but may benefit only the minority of patients whose tumors are pre-infiltrated by antitumor immune cells called CD8+ T cells. In a study published in Immunity, the Pittet lab reports that rationally selected immunogenic chemotherapy can convert tumor microenvironments lacking T cells into ones displaying antitumor T cell immunity. This process makes unresponsive tumors sensitive to immune checkpoint blockade therapies and consequently raises hope to feasibly expand the proportion of human cancers responding to these therapies.

- Pfirschke C, Engblom C, Rickelt S, Cortez-Retamozo V, Garris C, Pucci F, Yamasaki T, Poirier-Colame V, Newton A, Redouane Y, Lin YJ, Wojtkiewicz G, Iwamoto Y, Mino-Kenudson M, Huynh TG, Hynes RO, Freeman GJ Kroemer G, Zitvogel L, Weissleder R, Pittet MJ. Immunogenic Chemotherapy Sensitizes Tumors to Checkpoint Blockade Therapy. Immunity. 2016;44:1-12 - PMID: 26872698 - PMCID: PMC4758865

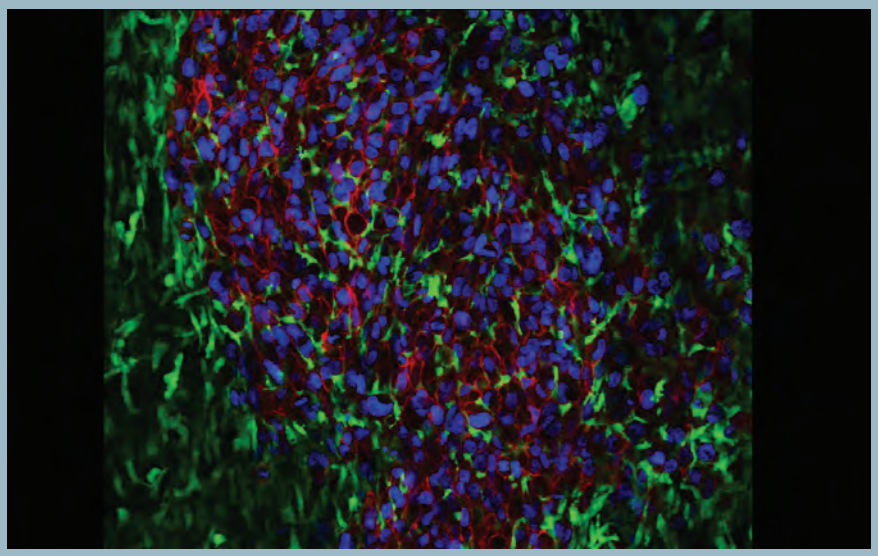
For a complete list of > 130 publications from CSB in 2016, please see here: https://csb.mgh.harvard.edu/publications?year=2016



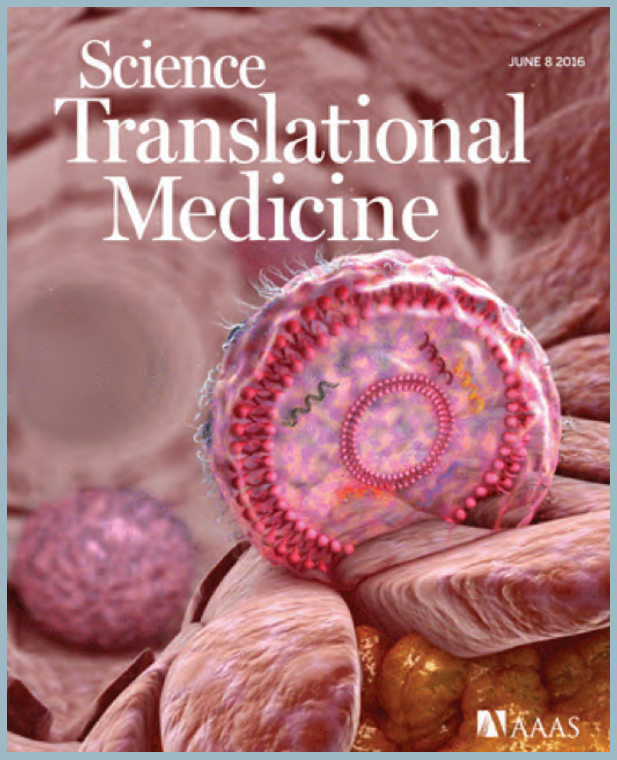
Tumor derived exosomes emerge a s a major mediator of tumor growth via an immune axis. Tumor derived extracellular vesicles (tEV) are shed by melanomas and are drained by regional lymph nodes. There, they are removed by sub capsular macrophages (SCS), a process which keeps the tumor in check. If SCS are exhausted or depleted, escaping tEV will stimulate tumor growth via an IgG axis. Bottom: Representative multiphoton micrographs of an explanted lymph node from a mouse carrying CD63-eGFP+ B16F10 melanoma on week 2 after tumor challenge. The green vesicles can be seen in SCS. Bottom right: B16F1 melanoma tumor volume in wild-type or SCS depleted mice (Cd169Dtr/Wt treated with DT i.p. (n = 5-7)). Note the massive increase in tumor volume when SCS are exhausted. (Science. 2016;352(6282):242-246)



Liquid biopsy of cancer exosomes. Different analytical devices built by the Lee group for isolation and analysis of circulating, tumor derived extracellular vesicles ("exosomes"). The nPLEX device has been used to study > 150 patients with pancreatic neoplasm. The latest device (iMES) allows point-of-care operation (ACS Nano 2016;10:1802).



New mouse model to study innate immune cells in tumor microenvironment. MerTk-GFP mice were created with CRISPR-CAS technology to visualize tumor associated macrophages (TAM, green) in tumors (HT1080 Membrane-apple in red and H2B-iRFP in blue). Note the extensive TAM infiltration (green cells).



Quintuple-target RNAi: hitting five targets at once
Vascular endothelial cells express five adhesion molecules to recruit leukocytes from the blood stream: E- and P-selectin, ICAM-1 and -2, and VCAM-1. In atherosclerosis, activated endothelial cells express high levels of these signals, thus expanding the number of neutrophils and monocytes that migrate from blood into a growing plaque. After myocardial infarction, the adhesion molecule expression increases even further due to higher autonomic nervous activity. In collaboration with MIT investigators, the Nahrendorf team used a new class of nanoparticles with high avidity to endothelial cells to decrease endothelial cell adhesion molecule expression. The polymeric nanoparticles made of low-molecular-weight polyamines and lipids were loaded with 5 distinct siRNAs silencing the expression of all adhesion molecules. Multiple gene silencing was enabled by exquisite silencing efficiency after nanoparticle delivery. Hitting five targets at once, the therapy reduced recruitment of leukocytes to atherosclerotic plaques in mice, dampening vascular wall inflammation and making plaques smaller. Furthermore, RNAi decreased migration of leukocytes into infarcted myocardium, improving the recovery after ischemia. Such a strategy may help to prevent reinfarction and heart failure in high-risk patients with acute MI. Sci Transl Med 2016;8:342.

Macrophages (MΦ) and dendritic cells (DCs) play major roles in the epididymis. Unraveling immune cell functions in the male reproductive tract is an essential prerequisite for the design of innovative strategies aimed at controlling male fertility and treating infertility.

R. Rox Anderson, MD, Director

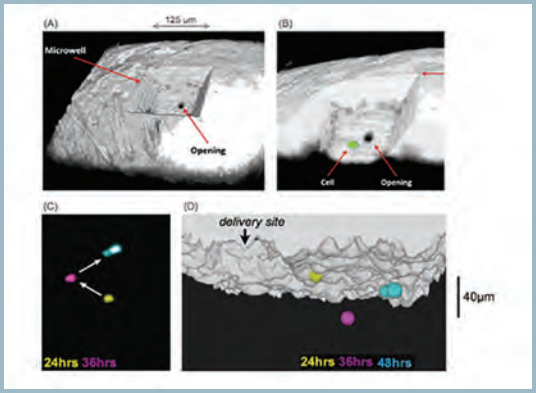
Photomedicine encompasses all of light's beneficial, harmful, diagnostic, therapeutic, surgical, medical and technological aspects in biology and medicine. We are the world's largest research center in this field, with ~250 people, and still growing.

- The faculty includes 6 full, 7 associate, and 6 assistant professors.
- Prevalent research topics include: point-of-care optical diagnostics, novel immunization strategies, cancer treatments, coronary artery imaging, esophageal cancer screening, diagnosis and treatment of infections, trauma interventions, wound care, human melanoma genetics, tissue-selective therapies, pain, light-activated drugs, rapid diagnosis and treatment of coagulopathies, advanced microscopy, mammalian photobiology, and bio-inspired optical technologies.
- This year, we were the leading source of MGH and Partners royalty income.
- 40 inventions were disclosed, 60 patents were filed, 57 patents were issued and over 200 articles published in peer-reviewed publications.
- In collaboration with Partners Innovations, Lynn Drake spearheaded a novel ~$50M investment fund, to foster tech transfer from the Center, and early research.
- Research fellowships were initiated honoring Tom Deutsch and Franz Hillenkamp, physicists who played key roles at Wellman.

Research Highlights in 2016

Imaging and Microscopy

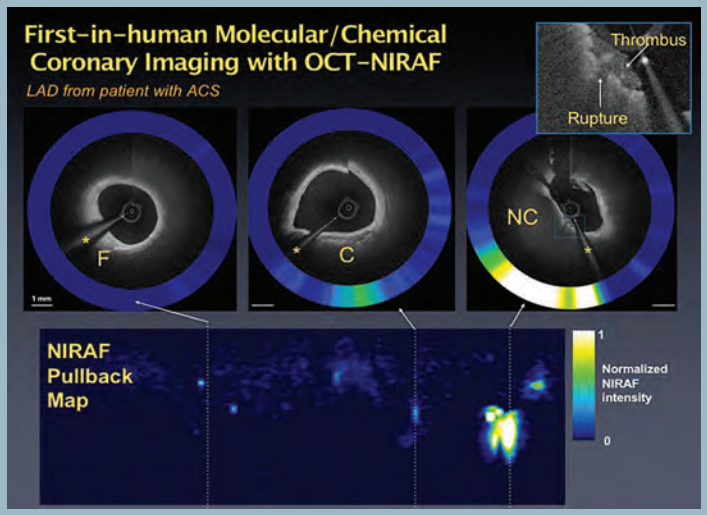
Understanding the bone marrow micro-environment. A series of fundamental discoveries about hematopoesis, stem and cancer cell are coming from Charles Lin's laboratory. In a Nature paper, the functional roles of sinusoidal vessels for cell trafficking were defined. [Itkin T, et al. Distinct bone marrow blood vessels differentially regulate haematopoiesis. Nature 2016;532(7599):323-328 - PMID: 27074509



Other work revealed mechanisms for a single stem cell to fully reconstitute bone marrow, opening a way to new therapies. Laser micro-dissection was used to create a well in bone (A), with a small passageway to the underlying marrow. A laser optical trap was then used to implant a single stem cell (B), which rapidly migrated into the marrow and began dividing (C, D) within 48 hours. [Ito K, et al. Self-renewal of a purified Tie2+ hematopoietic stem cell population relies on mitochondrial clearance. Science. 2016;354(6316):1156-1160]

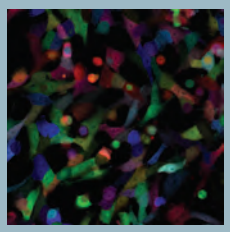
Live imaging of pheomelanin, a pigment commonly associated with melanoma. The red-hair pigment pheomelanin is strongly associated with cutaneous melanoma, and probably plays a causative role. Conor Evans designed and built a coherent anti-stokes Raman (CARS) microscope that for the first time can image pheomelanin in situ, in vivo, without any stains or genetic manipulation. In collaboration the MGH Cutaneous Biology Research Center, CARS was used to study pheomelanin content and its intracellular distribution in red haired mice, human skin, and human melanomas. This unprecedented capability is promising for future research on pheomelanin induction, signaling, melanomagenesis, and potential protection against melanoma. [Wang H, et al. In vivo coherent Raman imaging of the melanomagenesis-associated pigment pheomelanin. Nature Scientific Reports 2016; 6:37986 doi:10.1038/srep37986]

Coronary artery imaging. Three teams at Wellman Center are engaged in coronary artery imaging for diagnosis and guided treatment. Brett Bouma leads an international collaboration using optical coherence tomography (OCT), including new imaging technologies. Separately, Gary Tearney this year reported that a near-infrared autofluorescence (NIRAF) signal is seen only at the highest risk sites for coronary artery plaque rupture, as in the human coronary artery image to the right.

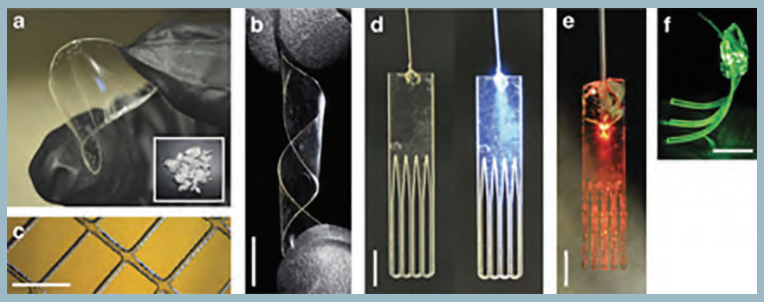


NIRAF combined with the structural images provided by OCT is highly promising to guide proper treatment of unstable atherosclerotic plaques. [Ughi GJ et al. Clinical Characterization of Coronary Atherosclerosis With Dual-Modality OCT and Near-Infrared Autofluorescence Imaging. JACC Cardiovasc Imaging. 2016;9(11):1304-14].

Seeing lymphatics without disturbing them. Ben Vakoc's laboratory has figured out how to non-destructively microscopically image lymphatics and lymph flow in tissue. No dyes or genetic modifications are needed. [Blatter C, et al. In vivo label-free measurement of lymph flow velocity and volumetric flow rates using Doppler optical coherence tomography. Sci. Reports. 2016; 6:29035]



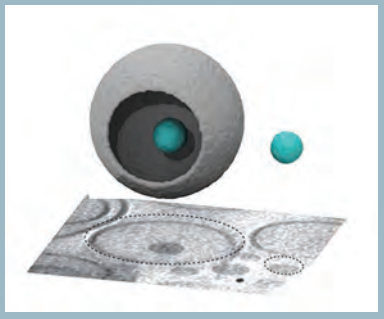
Can millions of diverse cancer cells be individually tracked?
Yes. Hensin Tsao and Charles Lin created a spectrally diverse melanoma line (termed "melachroma" cells), allowing them to study clonal selection, dynamics and therapeutic selection. Wu JW, et al. Defining Clonal Color in Fluorescent Multi-Clonal Tracking. Sci Rep. 2016 Apr 13;6:24303



Potential New Therapies
Making light go deep. Light is versatile – it can sterilize, activate drugs, bond, stimulate, and heal – but only for tissues that can be reached by light. Andy Yun's laboratory has made biocompatible, implantable, bioabsorbable optical waveguides capable of delivering light into deep body tissues. The waveguides can assume many different shapes, as shown. Nizamoglu S, et al. Bioabsorbable polymer optical waveguides for deep-tissue photomedicine. Nature Communications 2016;7:10374

Stabilizing and "passivating" live tissues. Irene Kochevar and colleagues have discovered that green light activation of rose bengal (RB), a stain commonly applied to cornea, can harmlessly strengthen tissue by crosslinking collagens. Treatment stiffened rabbit corneas in vivo, without necrosis or damage, for months. These results further support a potential new treatment for keratoconus. [Zhu H, et al. Cornea crosslinking with Rose Bengal and green light: Efficacy and safety evaluation. Cornea 2016;35(9):1234-41.] In related work, Robert Redmond and MGH surgical collaborators found that treatment with RB activated briefly by green light, strengthens vein-to-artery grafts and shunts, preventing restenosis, thrombosis and failure. This treatment may prevent the high shunt-failure rate in renal dialysis patients. [Goldstone RN, et al. Photochemical tissue passivation attenuates AV fistula intimal hyperplasia. Ann Surg 2016; Oct 17 epub ahead of print]

Light activated nano-cocktails for cancer. Essential challenges for new molecular pathway-targeted cancer treatment include avoiding systemic toxicity, and tumor escape. Tayyaba Hasan and colleagues created stable nanoparticles that release multiple agents upon activation by near-infrared light. A photodynamic therapy drug was used to destabilize the nanoparticles, causing local release, with promising results in realistic models of pancreatic cancer. [Spring BQ, et al. A photoactivable multi-inhibitor nanoliposome for tumor control and simultaneous inhibition of treatment escape pathways. Nature Nanotech 2016;11,378–387]



3D render of a photoactivable nanoliposome shell, encapsulating an anticancer drug-containing nanoparticle. A free particle is seen on the right, and a 2D image projection is shown at bottom.

Reconstituting human skin in a wound, without donor site morbidity. Wounds from burns and other major trauma often require skin grafting, but the grafting process itself causes another painful, scarring wound at the donor site. Rox Anderson and colleagues have shown that skin "copying" is possible, by harvesting and transferring many tiny, full-thickness columns of skin. The donor sites heal rapidly without a scar, and the transferred skin columns re-organize to produce functional skin at the wound site. The technology was licensed, developed, commercialized and is expected to become clinically available in 2017. [Tam J, et al. Reconstitution of full-thickness skin by microcolumn grafting. J Tissue Regen Med 2016;Jun 14 doi:10.1002/term.2174 epub ahead of print]

Contact our faculty and explore other Wellman discoveries at www.massgeneral.org/wellman

Jeanine Wiener-Kronish, MD, Chief

Research activities at the Department of Anesthesia, Critical Care and Pain Medicine (DACCPM) are an integral aspect of the departmental overall mission focusing on patient care, education, research innovation, and community service. DACCPM research activities have an international reputation and encompass a broad range of disciplines with active research units focused in the areas of cardiac and pulmonary pathophysiology, molecular and system neuroscience, pharmacology, pain neurobiology, neuroimaging, stem cell research, genetics, comparative outcome research, biomedical engineering, and new drug and medical device development. DACCPM has over 200 research staff including M.D. and/or Ph.D. investigators, post-doctoral fellows, and graduate students. The laboratories and clinical research units are located on the main MGH campus and at the MGH-East research facility at the Charlestown Navy Yard. Research activities at DACCPM are supported by about 80 grants per year, including 41 NIH grants in 2016. The DACCPM faculty publishes annually over 200 journal articles and numerous books/book chapters.

Strategic Priorities

Retaining and expanding a premier research team: We have a long-term plan to foster the growth of three tiers of investigators, including a) T32 and K08 trainees, b) junior and mid-level investigators, and c) well-established senior investigators. Over years, we have provided 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.

Establishing a research platform that promotes integration between basic science and clinical research: We have been implementing several initiatives to support clinical and comparative outcome research including competitive intra-departmental clinical research funds and establishment of a clinical research core with a first-tier statistical faculty. We also have internal clinical research funding mechanisms that provide financial support for conducting clinical research.

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

Achievements

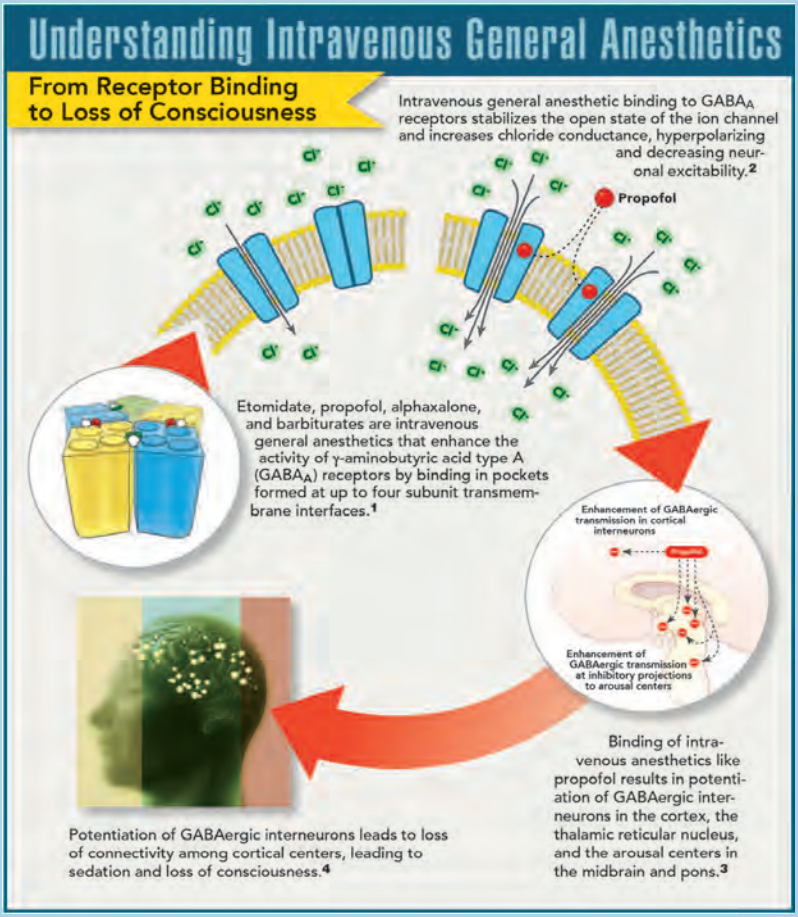
Hypoxia as a treatment for Leigh's Syndrome: In collaboration with Vamsi Mootha M.D., Ph.D. and Isha Jain, A.B., the Zapol lab studied the effects of ambient hypoxia on a mouse model of Leigh's Syndrome. This error in ATP metabolism of the NDUFS4 mouse produces neurological dysfunction and death in about 55 days. Surprisingly, we learned that reducing inhaled O2 levels to 11% prevented brain disease and allowed the mice to live for over 250 days (Jain IH, et al SCIENCE 2016; 352:54-61). The effects of reducing the oxygen levels remain to be explored in healthy adults and in adults and children with mitochondrial diseases. Dr. Lorenzo Berra is commencing a healthy adult study at MGH with metabolomic measurements by Rohit Sharma of the Mootha lab.

A new role of brain dopaminergic function in regaining consciousness after general anesthesia: In a study published in the Proceedings of the National Academy of Sciences (2016), Dr. Norman Taylor and colleagues discovered that activation of dopamine neurons in the ventral tegmental area (VTA) restores conscious behaviors in anesthetized mice. Using optogenetics, a recently developed technique that allows for activation of specific brain cells with pulses of light, the investigators showed that mice anesthetized with isoflurane would get on their feet and begin walking when dopamine cells in the VTA were activated with blue lasers. Although VTA dopamine neurons are well known to be involved in reward, motivation and cognition, Taylor and colleagues demonstrated that these cells are also critically involved in promoting wakefulness. The ability to reverse the state of general anesthesia by stimulating arousal centers in the brain may also lead to new treatments for conditions such as coma or opioid overdose.

New cellular mechanisms of general anesthetic agents: Dr. Stuart Forman and colleagues published a major research paper in Anesthesiology (2016) that summarizes a large number of their experiments probing the interactions of four intravenous general anesthetics (alphaxalone, etomidate, propofol, and a barbiturate) with all five intra-subunit transmembrane sites in synaptic hetero-pentameric GABA-A receptors that mediate the major effects of these drugs. This article was accompanied by an editorial and a cover image. The experiments used receptor mutations, biochemistry, and electrophysiology to test for evidence of contact between drugs and selected amino acids. The major findings are that 1) substituted cysteine modification-protection (SCAMP) results are fully concordant with the gold-standard photolabeling in identifying anesthetic interactions with a subset of the tested amino acids, while another approach using tryptophan mutations is not; 2) SCAMP identifies new anesthetic contact residues and shows that etomidate binds in two inter-subunit sites, a barbi-

turate binds in a distinct pair of homologous sites, and propofol binds all four sites, overlapping with those where both etomidate and the barbiturate bind; 3) alphaxalone does not bind to any of these sites; and 4) none of the four anesthetics we tested interacts with the fifth (alpha+/gamma-) subunit interface.

General anesthesia-induced neurotoxicity and cognitive impairment. Recently, clinical and experimental observations have suggested that anesthetic can induce long-term morphological and functional alterations in the brain. Dr. Zhongcong Xie and colleagues have conducted extensive research to understand the cellular mechanisms of anesthetic-induced neurotoxicity and cognitive impairment including delirium. He and colleague recently published an article in Nature Neuroscience Review (2016), summarizing the available mechanistic data regarding anesthesia and impaired cognitive performance in both young and mature nervous systems. Critical appraisal of the translational value of animal models and potential future research works in the field of anesthesia neurotoxicity are also discussed in the article.



Daniel A. Haber, MD, PhD, Director

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

Our strategic priorities include building technologies to enable early blood-based detection of cancer, establishing paradigms for precision oncology using genetically-informed small molecule inhibitor therapies, and creating a leading cancer immunology program, including checkpoint inhibitors and engineered T cell therapies, integrated within our translational research enterprise. In addition to these major thematic areas of emphasis, we will continue to support fundamental, investigator initiated discovery, which we believe to be the centerpiece of our successful research enterprise.

For the purposes of this review, research highlights are presented for the Center for Cancer Research (CCR) and the Division of Hematology Oncology (Department of Medicine), which are jointly administered through the Cancer Center. Dr. Nick Dyson serves as Scientific Director (CCR) and Dr. David Ryan is Chief of Hematology/Oncology and Clinical Director of the Cancer Center. Total annual research funding for CCR and Hematology/Oncology is $70M (including industry clinical trials contracts).

Achievements

Highlighted 2016 accomplishments for the Cancer Center are grouped into three thematic areas:

Cancer Epigenetics

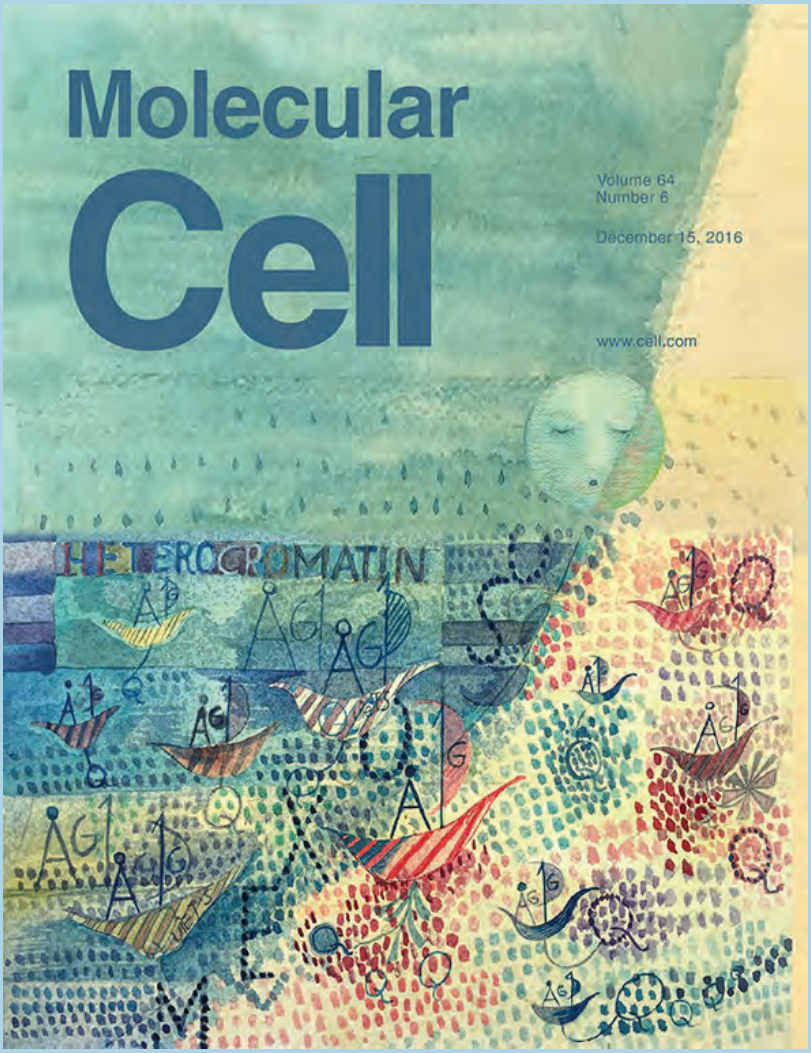
Dr. Raul Mostoslavsky and his team discovered a new pathway regulating tumor aggressiveness in patients with pancreatic ductal adenocarcinoma (PDAC), involving inhibition of a chromatin deacetylase (SIRT6) and de-repression of an oncofetal protein called Lin28b. This pathway appears to enhance "dedifferentiation" of the tumor cells, thereby driving increased aggressiveness and metastasis and it offers a unique opportunity for novel therapies (Kugel et al Cell. 2016 Jun 2;165(6):1401-15). Quiescence (G0) is a ubiquitous stress response through which cells enter reversible dormancy and involves dramatic changes to chromatin and transcription of cells. Dr. Motamedi and his colleagues revealed a unique function for constitutive heterochromatin proteins (the establishment of the global G0 transcriptional program) indicating that stress-induced alterations in Argonaute-associated sRNAs can target the deployment of transcriptional regulatory proteins to specific sequences (Joh et al, Mol Cell. 2016 Dec 15;64(6):1088-1101). Also, a novel network linking metabolic and epigenetic alterations was identified by Dr. Bardeesy's lab. The network was shown to be central to oncogenic transformation downstream of the liver kinase B1 (LKB1, also known as STK11) tumor suppressor, an integrator of nutrient availability, metabolism and growth. The study defined a hypermetabolic state that incites changes in the epigenetic landscape to support tumorigenic growth of LKB1-mutant cells, while resulting in potential therapeutic vulnerabilities (Kottakis et al, Nature. 2016 Nov 17;539(7629):390-395).

Targeted Therapies and Drug Resistance

Genetic alterations in the fibroblast growth factor receptor (FGFR) pathway are promising therapeutic targets in many cancers, including intrahepatic cholangiocarcinoma (ICC). Drs. Lipika Goyal, Andrew Zhu and colleagues reported the molecular basis for acquired resistance to FGFR inhibitor BGJ398 in patients via integrative genomic characterization of cell-free circulating tumor DNA (ctDNA), primary tumors, and metastases. Serial analysis of patient-derived samples revealed marked inter- and intra-lesional heterogeneity, with different FGFR2 mutations in individual resistant clones. Molecular modeling and in vitro studies indicate that different mutations leading to BGJ398 resistance may be surmountable by structurally distinct FGFR inhibitors (Goyal et al, Cancer Discov. 2016 Dec 29. pii: CD-16-1000). In lung cancer, Dr. Alice Shaw and her colleagues showed that serial biopsies of tumors can inform effective therapy for patients with EML4-ALK mutant cancers responding to first-line crizotinib, by the next generation inhibitor lorlatinib (Shaw et al. N Engl J Med. 2016 Jan 7;374(1):54-61). In breast cancer, Dr. Goss and colleagues reported that postmenopausal women with early breast cancer benefit from extending aromatase inhibitor therapy with letrozole from 5 to 10 years, with a significant reduction in breast cancer recurrence (Goss et al, N Engl J Med 2016; 375:209-219July 21, 2016). Finally, in a multidisciplinary collaboration between Drs. Mehmet Toner, Shyamala Maheswaran, Aditya Bardia and Daniel Haber, Cancer Center investigators used cultured circulating tumor cells (CTCs) from patients with drug resistant ER+ breast cancer to show a high degree of cell fate plasticity, with interconversion between high-proliferative/drug sensitive (HER2+) and low-proliferative/drug resistant (Notch1+) phenotypes, suggesting that simultaneous suppression of both phenotypes may be critical to eradicate advanced breast cancer (Jordan et al. Nature. 2016 Sep 1;537(7618):102-106).

Quality of care and palliative therapy

In a significant advance relating to the quality of oncologic care, Dr. Areej El-Jawahri and her colleagues reported the results of a randomized controlled trial of an inpatient palliative care intervention for patients hospitalized for hematopoietic stem cell transplantation (HCT). Involvement of palliative care for patients with hematologic malignancies during hospitalization for HCT led to a significant and sustained improvement in their quality of life (QOL) metrics, depression, anxiety, and symptom burden related to standard transplant care alone. These findings demonstrated that palliative care can ameliorate the substantial quality of life deterioration and complex symptoms experienced by patients during hospitalization for HCT, which has long been perceived as a natural and unmodifiable aspect of the transplant process (El-Jawahri et al, JAMA. 2016 Nov 22;316(20):2094-2103).



Argonaute (Ago1) guides histone H3 lysine 9 methylation (H3K9me) to euchromatic regions in quiescence. In this issue of Molecular Cell, Joh et al. (pp. 1088–1101) show that as cells enter quiescence (moon), they load Ago1 (ships) with euchromatic small RNAs to mediateQuiescent-induced TranscriptionalRepression (Q) of a set of euchromatic genes. Exosome activity separates heterochromatic (dark blue) from euchromatic (yellow) regions. When entering quiescence, the exosome barrier opens, permitting euchromatic transcripts (differently colored dots) to become substrates for RNAi degradation. Ago1, acquiring new color (sRNAs) as it crosses the exosome barrier, targets Q to the corresponding color in euchromatin. Cover design by Mo Motamedi and Katya Popova; artwork by Katya Popova.

John A. Parrish, MD, CEO

The Consortia for Improving Medicine through Innovation and Technology (CIMIT; www.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 Projects Deliver. 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 career impact on one or more team members.

CoLab®: CIMIT in a Cloud to Encourage, Manage, and Measure Innovation. Effectively traversing the healthcare innovation cycle involves numerous interrelated processes with people and groups operating behind numerous institutional firewalls throughout the CIMIT consortium and beyond. In response to the resulting logistical challenges, CIMIT developed a suite of cloud-based software tools—CIMIT CoLab®—to manage those processes efficiently and to facilitate communications and collaborations across disciplines, functions, and institutions. CoLab is being used by CIMIT and its collaborators in greater Boston and increasingly with collaborators around the world, like the NHS in England, to enable effective collaborations in managing processes, such as proposal and "challenge" calls; working together in secure, virtual workspaces; capturing metrics; and providing the real-time status of a portfolio of projects, ideas, or initiatives.

CIMIT Accelerator Team: Fast Track to Patient Impact. The CIMIT Accelerator Team was formed to more efficiently and consistently drive projects to commercialization. Under the direction of Mike Dempsey, the Accelerator Team comprises former founders and CEOs of MedTech companies who fully understand the medical device and diagnostic markets and clinical implementation (http://cimit.org/accelerator). Members systematically screen the pool of active CIMIT projects for candidates to accelerate. If a project is chosen, an Accelerator Team member works closely with the investigator team to research, create, and, to the extent practical, implement an Impact Plan – a business plan designed to convey the broad clinical and commercial potential of a specific technology and the steps needed to achieve that potential over 12 to 18 months.

CIMIT Provides Numerous Funding Opportunities for MGH Investigators. In 2016, CIMIT was the recipient of large awards from federal agencies that have provided significant funding to MGH investigators. The NIBIB award supports innovations that transform the delivery of primary care through point-of-care technology-based solutions (http://cimit.org/web/cimit-poctrc/home). The NHLBI award seeks to expand the universe of commercializable technologies for heart, lung, blood, and sleep disorders (www.b-bic.org). The Joint Warfighter Program of the DoD moves CIMIT-funded projects with relevance to military medicine closer to commercialization and use in the care of wounded warriors and civilians.

Achievements

Joint Warfighter Program new funding to CIMIT provided $5M of direct costs towards the research of MGH investigators in cutting-edge, commercializable projects: Robert Redmond, Julian Goldman, Rajiv Gupta, and Mark Ottensmeyer.

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

Under the leadership of MGH investigator James Gordon, CIMIT is at the forefront of developing simulation systems, including the widely-used COMET system that was licensed several years ago. Continuing this work, Dr. Gordon worked with Paul Tessier (CIMIT Accelerator Team) to develop, prototype, and patent a family of innovative, low cost, modular simulators that provides similar functionality to solutions costing 20 times as much. This work has garnered the attention of the DoD and resulted in a first-phase, $1.6M contract to further develop the concept. The outcome of this first phase of work was presented to the Department of Defense in February 2016.

Consortia for Improving Medicine Through Innovation and Technology (CIMIT)

Department Report

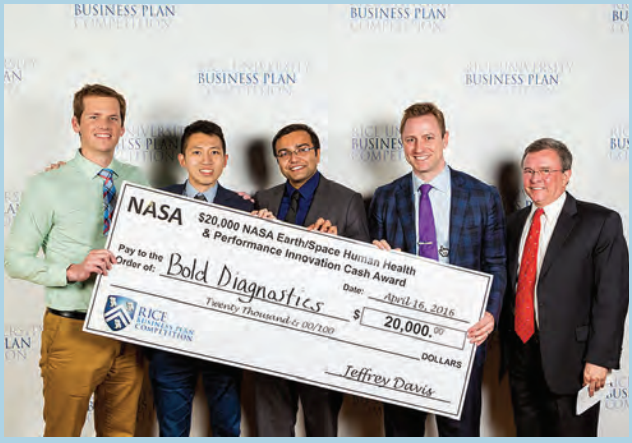
CIMIT's contribution to the influential National Academies of Science report on trauma

John Parrish, CIMIT CEO, served on the committee for the National Academies of Sciences, Engineering and Medicine report "A National Trauma Care System: Integrating Military and Civilian Trauma Systems to Achieve Zero Preventable Deaths After Injury" (www.nationalacademies.org/TraumaCare), released in June 2016, which focused on deaths after injury and minimizing disability among survivors. To lead this effort, CIMIT has launched a program in Warfighter Health to develop and commercialize solutions for trauma care that have applications to both military and civilian populations.

CIMIT's CRAASH Course

In 2016, CIMIT continued to hold healthcare commercialization boot camps. With funding from the National Science Foundation, CIMIT customized the traditional I-Corps program to focus on healthcare. The 10-week program facilitates the acceleration of healthcare innovations from the academic lab through commercialization. It is taught by industry veterans and is based on decades of experience from the Coulter Foundation, MIT, Yale, and CIMIT. The program formalizes development of a tested business model through the process of validating business hypotheses. Emphasis is placed on understanding economic buyers and their problems to be solved. Teams from around the country collect evidence to support the assumptions around the entire business (not just the science) through interviews and market testing. Each week teams present and defend findings to a panel of experts, attend lectures, and complete readings. Teams develop a commercialization roadmap based on data from actual customers and other stakeholders. Teams also receive 1:1 mentoring from successful healthcare entrepreneurs and group coaching from commercialization experts and investors.

To date, of the entire cohort of 23 teams, 10 (43%) have successfully obtained funding from a commercially motivated funder.



Bold Diagnostics, a CRAASH participant and part of CIMIT's Point of Care Technologies in Primary Care program went on to obtain 8 additional awards for over $128K.

A 2016 Spring CRAASH graduate, Cerillo has been awarded with CIMIT's Excellence in Innovation Award for $5,000. They have also moved on to win a $225,000 Small Business Innovation Research (SBIR) Phase 1 award. (L-R John Collins, PhD, MGH CRAASH Executive, Kevin Seitter and Jason Papin from Cerillo, and Paul Tessier, MGH CRAASH Executive)

David E. Fisher, MD, PhD, Chief

MGH Dermatology has played a unique role in the history of modern dermatology, as well as in the current delivery of exceptional care, research, community outreach, and education in cutaneous medicine. The core mission of the department is to provide patients from our community and from around the globe, with outstanding medical care that is tightly linked to our commitment to move our understanding of skin diseases into new frontiers of understanding and innovation. Our department houses an extremely busy dermatology clinic that cares for >1000 patients per week. In additional to general dermatology care, our department offers specialized clinics in numerous areas including Pediatric Dermatology, Cosmetic Dermatology, High-Risk Non-melanoma Skin Cancer, Rheumatologic Dermatology, Hair-loss, Urgent-care, Dermatologic Surgery, Dermatology Clinical Trials Unit, and Inpatient Consult Team. Our Multi-disciplinary Pigmented Lesions/Melanoma Clinic is tightly coordinated with MGH Cancer Center. It was the first of its kind in the US and just celebrated its 50th anniversary with an International Symposium. A laboratory research arm of our department is the Cutaneous Biology Research Center, which houses laboratories of 14 Principal Investigators who are faculty members of the department and conduct independent research programs. The topics covered by their investigations include stem cells, inflammation, drug discovery, skin signaling, ultraviolet radiation, itch, pain, pigmentation, epigenetics, hair biology, cancer immunotherapy, targeted therapy, metabolomics, cryobiology, lasers, and cell death mechanisms. This unit houses an unusually rich collection of cutting edge investigations ranging from basic biology to applied cutaneous medicine, and harbors numerous academic-industry collaborative initiatives. Additional research faculty whose academic home is in Dermatology include researchers in the Wellman Center for Photomedicine, an MGH Thematic Center that has made seminal contributions to the current practice of dermatology.

In the year 2016, research and scholarly activities undertaken by faculty in the Department of Dermatology gave rise to 194 publications, as well as 253 speaking engagements. $18.5M research funding was spent from a cross section of funding sources which include NIH, Department of Defense, multiple Foundations, Industry partners, royalties, and philanthropy. The Department holds the leadership role and is home to a National Cancer Institute sponsored multi-million-dollar Program Project Grant in Melanoma which is shared with researchers across Harvard Medical School. A research program in Cancer Immunotherapy was recently initiated as a partnership with MGH Cancer Center. Renovated laboratory space has been generated, and 4 outstanding investigators, who include physician-scientists and world class experts in immunology, will occupy this space. Our Dermatologic Epidemiology Program was also recently started, and includes an active partnership with Harvard Medical School's Population Medicine Department. The MGH Department of Dermatology is very proud of its Community Service and Educational missions, which represent core priorities of the department. Free skin cancer screenings, dermatologic care to the homeless, and teaching of trainees from diverse constituencies, including high school, undergraduate college, medical school, and postgraduate clinical or research stages, comprise these valuable activities. Trainees travel to MGH Dermatology from overseas, and share the teachings at their home institutions. Finally, MGH Dermatology is proud of the numerous collaborations which exist across departments at MGH, including extensive interactions with the Cancer Center, Pathology, Anesthesia, Plastic Surgery, Radiation Oncology, Psychiatry, Infectious Diseases, Rheumatology, and many others.

Achievements

Loss of cohesin complex components Stag2 or Stag3 confers resistance to BRAF inhibition in melanoma. Che-Hung Shen, Sun Hye Kim, Sebastian Trousil, Dennie T. Frederick, Adriano Piris, Ping Yuan, Li Cai, Lei Gu, Man Li, Jung Hyun Lee, Devarati Mitra, David E. Fisher, Ryan J. Sullivan, Keith T. Flaherty, Bin Zheng. Nature Medicine. 2016. 22:1056–1061

BRAF(V600E) is a frequent driver oncogene mutation in melanoma, and has been successfully targeted by small molecule kinase inhibition. However, resistance almost invariably develops, resulting in tumor progression. This study identifies a mechanism of BRAF-inhibitor resistance: loss of function mutations in the Stag2 or Stag3 genes within specimens derived from patients experiencing acquired resistance to BRAF inhibitor therapy. The mechanism through which these factors induce treatment resistance involves diminished expression of the DUSP6 phosphatase, a negative regulator of ERK signaling.

***In vivo* Coherent Raman Imaging of the Melanomagenesis-associated Pigment Pheomelanin. Wang H, Osseiran S, Igras V, Nichols AJ, Roider EM, Pruessner J, Tsao H, Fisher DE, Evans CL. Scientific Reports 6, Article number 37986; 2016.**

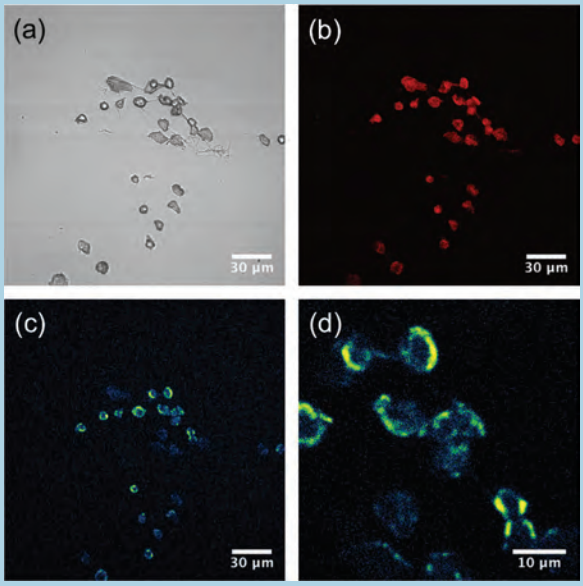
Recent observations have suggested that red pigment (pheomelanin) may function as a pro-carcinogenic contributor to melanoma formation. However, within skin, as opposed to hair, pheomelanin is difficult to visualize with the naked eye, likely leading to delays in early detection of pheomelanotic melanomas. This study reports the development of a novel coherent Raman spectroscopy method for the non-invasive detection of pheomelanin-containing melanocytic neoplasms—an approach which could significantly aid early detection of cutaneous skin lesions.

Autopalmitoylation of TEAD Proteins Regulates Transcriptional Output of the Hippo Pathway. PuiYee Chan, Xiao Han, Baohui Zheng, Michael DeRan, Jianzhong Yu, Gopala K. Jarugumilli, Hua Deng, Duojia Pan, Xuelian Luo and Xu Wu . Nature Chemical Biology, 2016,12(4):282-9.

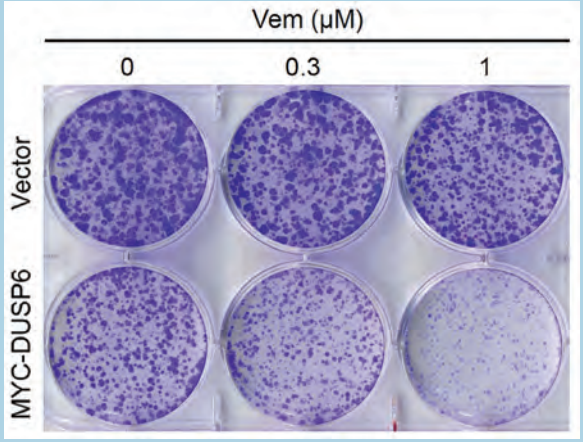
TEAD transcription factors bind the coactivators YAP and TAZ and regulate output of the Hippo pathway, thereby controlling organ size and tumorigenesis. Protein S-palmitoylation attaches the fatty acid, palmitate, to cysteine residues to regulate protein trafficking, membrane localization and various signaling activities. This study showed that human TEADs possess intrinsic palmitoylating enzyme–like activity, undergoing autopalmitoylation at conserved cysteines under physiological conditions. In addition to solving the crystal structures of lipid-bound TEAD, the authors found that palmitoylation was required for TEAD binding to YAP and TAZ, thus linking autopalmitoylation to transcriptional regulation of the Hippo pathway.

Cellulitis: A Review. Adam B Raff and Daniela Kroshinsky. JAMA 316(3):325 (2016)

Cellulitis is a common medical condition, estimated to occur in 14.5 million cases annually and costing $3.7 billion in ambulatory care costs. Because the majority of cases are associated with unknown causative organisms, management presents significant challenges. Recent studies have suggested that a high fraction of presumed cases (including admitted patients) are not truly attributable to cellulitis, raising prospects that improved diagnostic tools and criteria could significantly impact clinical management and outcomes.



Images of melanocytes from "redhair/fairskinned" mice, harboring loss-of-function in the Mc1r gene that is also responsible for human red/pheomelanotic pigmentation. Panel A shows trans-illumination of the melanocytes. Panel B shows fluorescence imaging of tdTomato, a fluorescence tag genetically engineered to be expressed within the murine melanocytes seen here after isolation from skin, Panels C and D show low and high power images of pheomelanin pigment within melanocytes, visualized using Coherence Anti-Stoke Raman Spectroscopy. (from In vivo Coherent Raman Imaging of the Melanomagenesis-associated Pigment Pheomelanin. Wang H, Osseiran S, Igras V, Nichols AJ, Roider EM, Pruessner J, Tsao H, Fisher DE, Evans CL. Scientific Reports 6, 37986; 2016)



Clonogenic growth assays of melanoma cells in which Stag2 has been silenced, which stimulates colony growth. Simultaneous overexpression of the ERK phosphatase DUSP6 results in growth suppression, demonstrating its ability to rescue tumor suppression downstream of Stag2 (from Loss of cohesin complex components Stag2 or Stag3 confers resistance to BRAF inhibition in melanoma. Che-Hung Shen, Sun Hye Kim, Sebastian Trousil, Dennie T. Frederick, Adriano Piris, Ping Yuan, Li Cai, Lei Gu, Man Li, Jung Hyun Lee, Devarati Mitra, David E. Fisher, Ryan J. Sullivan, Keith T. Flaherty, Bin Zheng. Nature Medicine. 2016. 22:1056–1061

David F. M. Brown, MD, Chief

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

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

Over the past year we have broadened our research portfolio to include more studies on pediatrics, geriatrics, vascular emergencies, and critical care. We continue to increase our research support from federal sponsors, and to grow our research faculty, fellows and clinical research coordinator team.

Goals for 2017
1. Effectively transition the physician research leadership and explore ways to improve the overall structure of the department's research administration, including insuring that day-to-day research activities align with a strategic plan.
2. Improve research operation tracking and team-based approaches to enrollment to maximize efficient use of our research coordinators.
3. Continue to develop collaborations with inpatient research entities through shared protocols.

Achievements
Dumas O, Mansbach JM, **Hasegawa K, Sullivan AF**, Piedra PA, **Camargo CA**. A clustering approach to identify severe bronchiolitis profiles in children. *Thorax* 2016; 71: 712-718. PMID: 27339060

Although bronchiolitis is generally considered a single disease, recent studies suggest heterogeneity. Dumas and colleagues studied infants in two multicenter severe bronchiolitis studies. The investigators identified several distinct clinical profiles (phenotypes) by a clustering approach. The observed heterogeneity has important implications for future research on the etiology, management and long-term outcomes of bronchiolitis (e.g., risk of developing childhood asthma).

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

Hasegawa K, Linnemann RW, Mansbach JM, Ajami NJ, Espinola JA, Petrosino JF, Piedra PA, Stevenson MD, **Sullivan AF**, Thompson AD, **Camargo CA Jr.** The fecal microbiota profile and bronchiolitis in infants. *Pediatrics* 2016; 138: pii: e20160218. PMID: 27354456

Little is known about the association between the gut microbiota and infant bronchiolitis. Hasegawa and colleagues compared fecal microbiome profiles from infants hospitalized with bronchiolitis (cases) and age-matched healthy controls. The Bacteroides-dominant profile in fecal samples was associated with a higher likelihood of bronchiolitis. These findings support further research on the health effects of the human microbiome, along with the development of novel, microbiome-related interventions to decrease risk of bronchiolitis and other common diseases.

Boulouis G, Morotti A, Brouwers HB, Charidimo A, Jessel MJ, Auriel E, Pontes-Neto O, Ayres A, Vashkevich A, Schwab KM, Rosan J, Viswanathan A, Gurol ME, Greenberg SM, **Goldstein JN.** Association between hypodensities detected by computed tomography and hematoma expansion in patients with intracerebral hemorrhage. JAMA Neurology.2016; 73: UU961-968. PMID: 27323314

This study highlighted a novel finding on noncontrast CT that can predict which patients with intracerebral hemorrhage will develop hematoma expansion. Hypodensities within an acute ICH detected on an NCCT scan may predict hematoma expansion, independent of other clinical and imaging predictors. This novel marker may serve as a useful addition to clinical algorithms for determining the risk of and treatment stratification for hematoma expansion helping to guide intensive care and anti-expansion therapies to the highest risk patients.

Pursnani A, Celen C; Schlett CL, Mayrhofer T; Zakroysky P; Lee H; Ferencik M; Fleg JL, Bamberg F; Wiviott SD, Truong QA, Udelson JE, **Nagurney JT**, Hoffmann U. Coronary artery disease: Use of coronary computed tomographic angiography findings to modify statin and aspirin prescription in patients with acute chest pain. Am J Cardiol. 2016; 117:319-324. PMID: 26762723

This study addressed the research question of how does the discovery of CAD on cardiac CTA in ED patients affect discharge prescriptions. It demonstrated that physician knowledge of CCTA results leads to improved alignment of aspirin and statin therapy with the presence and severity of CAD but that many patients with CCTA-detected CAD are not discharged on aspirin or statin. These findings suggest opportunity for practice improvement when CCTA is performed in the emergency department.

Dr. Tommy Heyne, Emergency Ultrasound Fellow, teaching point-of-care ultrasound to a group of novice learners in Ljubljana. Dr. Heyne and others from Center for Ultrasound Research and Education (CURE) at MGH travelled to the WINFOCUS conference in Slovenia in 2016 to engage in collaborative research. CURE members are regularly involved in presenting, moderating, and judging research at this and other conferences.

Dr. Carlos Camargo (left) was recipient of the American College of Emergency Physicians (ACEP) Outstanding Contribution to Research Award. This award is given annually by ACEP to the Emergency Medicine researcher who has made the largest contribution to research over a career. It was presented by Dr. Rebecca Parker (right), the current President of ACEP.

Collaborating closely with Dr. Jaques Reifman (center) and the US Army Biotechnology HPC Software Applications Institute, MGH faculty member Dr. Andrew Reisner (right) was a recipient of the 2016 Heyman Service to America Medal (Science and Environment category) for developing and validating the APPRAISE system. which provides automated decision-support during traumatic injuries. The medal was presented by Michèle Flournoy (left), former US Under Secretary of Defense for Policy.

Kohei Hasegawa, MD, MPH (center) received the 2016 Society of Academic Emergency Medicine (SAEM) Young investigator Award. Pictured (from left): Ali Raja, MD, MBA, MPH (SAEM program committee chair and Vice Chair of Emergency Medicine at MGH); the three awardees; and Deborah Diercks, MD (SAEM President). Dr. Hasegawa was honored for his research on severe bronchiolitis, asthma exacerbations, and emergency airway management.

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

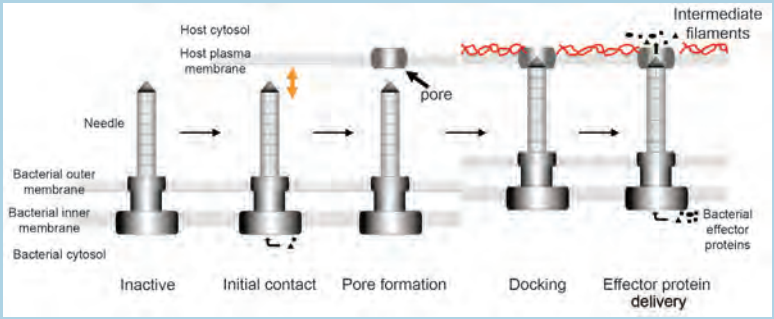
As the largest of the MGH Departments, the Department of Medicine is integral to the MGH mission statement: *"Guided by the needs of our patients and their families, we aim to deliver the very best health care in a safe, compassionate environment; to advance that care through innovative research and education; and to improve the health and well-being of the diverse communities we serve."* The Department plays a key role in the MGH and MGPO strategic and operational priorities, including the ongoing commitment to high quality care, population health, and workforce diversity. In addition, the Department and faculty leaders are central to the implementation of the recent MGH/MGPO strategic plan recommendations including the establishment of an MGH Research Institute, optimization of inpatient flow, and development of a specialized services center to grow international and other business.

The Department of Medicine Roadmap for the next decade was designed to synergize with the MGH/MGPO priorities by identifying cross-cutting Departmental goals that link to the four missions of clinical care, research, education, and community health. Each goal supports the overall priorities of the MGH and MGPO and enables the development of Departmental activities that span one, two, three or even all four missions. Having cross-cutting goals serves to create connections and collaboration across the Department, to increase the efficiency of Departmental support, and to assist with resource prioritization. Accomplishments within the Department of Medicine and its ten clinical divisions and ten research units in 2016 spread across the following themes: genomic science, innate immunology and immune tolerance, therapeutic interventions, and population health.

Achievements

Genomic Science

A common mechanism by a major group of bacterial pathogens to promote disease is a specialized apparatus known as a type 3 secretion system (injectisome). **Marcia Goldberg, MD** and colleagues performed a genome-wide screen designed to identify human proteins required for infection by the type 3 secretion-dependent human pathogen Shigella flexneri. They found that host cell intermediate filaments are required for efficient type 3 secretion mediated translocation of effectors by S. flexneri and other pathogens that use type 3 secretion, including Salmonella Typhimurium and Yersinia pseudotuberculosis. These findings establish that stable docking of these bacteria onto human cells specifically requires intermediate filaments, is a process distinct from translocon pore formation, and is a prerequisite for bacterial secretion of effector proteins. By experimentally separating translocon pore formation from bacterial docking to the cell and from effector secretion, this work separates steps in pathogenesis that were not previously known to be separable, enabling mechanistic analyses of individual steps in the process of cellular infection. (1) Arhinia, or absence of the nose, is a rare malformation of unknown etiology that is often accompanied by ocular and reproductive defects. **Natalie Shaw, MD** and colleagues sequenced 40 people with arhinia (38 independent families), revealing that 84% of unrelated subjects harbor a missense mutation localized to a constrained region of SMCHD1 encompassing the ATPase domain. SMCHD1 mutations cause facioscapulohumeral muscular dystrophy type 2 (FSHD2) via a trans-acting loss-of-function epigenetic mechanism. Shared mutations and comparable DNA hypomethylation patterning was discovered between these distinct disorders. CRISPR/Cas9-mediated alteration of smchd1 in zebrafish yielded arhinia-relevant phenotypes. Transcriptome and protein analyses in arhinia probands and controls showed no differences in mRNA or protein abundance but revealed regulatory changes in genes and pathways associated with craniofacial patterning. Mutations in SMCHD1 thus contribute to distinct phenotypic spectra, from craniofacial malformation and reproductive disorders to muscular dystrophy, which the group speculates to be consistent with oligogenic mechanisms resulting in pleiotropic outcomes. (2)



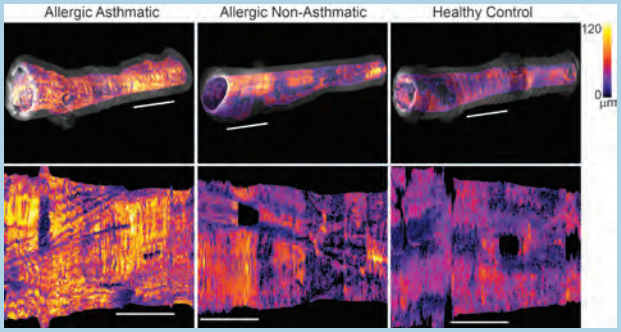
Model of intermediate filament contribution to docking and bacterial effector translocation by the S. flexneri type 3 secretion system. (a) The type 3 secretion system is synthesized in S. flexneri. (b) S. flexneri makes contact with host cell plasma membrane. (c) The translocon pore proteins are secreted through the type 3 secretion system and insert into the plasma membrane to form the translocon pore. (d) In the presence of (but not in the absence of) intermediate filaments, the type 3 secretion needle docks on the extracellular face of the translocon pore. (e) In the presence of (but not in the absence of) intermediate filaments, there is efficient translocation of bacterial effector proteins into the cytosol of the host cell. A Russo BC, Stamm LM, Raaben M, Kim CM, Kahoud E, Robinson LR, Bose S, Queiroz AL, Herrera BB, Baxt LA, Mor-Vaknin N, Fu Y, Molina G, Markovitz DM, Whelan SP, Goldberg MB. Intermediate filaments enable pathogen docking to trigger type 3 effector translocation. Nat Microbiol. 2016. 1:16025. PMCID PMC5006386.

Jose Florez, MD PhD and **Jason Flannick, PhD** collaborated with international colleagues to perform whole-exome sequencing in 12,940 individuals with and without type 2 diabetes from five ancestry groups (European, African, Latino, East Asian and South Asian), and whole-genome sequencing in an additional 2,657 European individuals. They found a number of novel signals, but more critically established that there is no evidence in support of the hypothesis that postulates that rare variants of strong effects have a large contribution to genetic risk. Instead, the data are most consistent with a model in which type 2 diabetes is caused by a large collection of common variants, which will require larger sample sizes for conclusive detection. This project constitutes a tour de force, not only for scientific discovery but for clarification of a long-standing debate in human genetics. (3) **Amit Majithia, MD** conceived and deployed an approach to assign a functional score to every possible mutation that can occur in the gene PPARG, implicated in type 2 diabetes and congenital lipodystrophy. In essence, he thought to fast-track evolution and bypass the constraints of natural selection by generating every possible mutation in a gene of interest, and assessing its functional impact in a high-throughput assay. He established a pipeline for the creation of comprehensive substitution libraries via Mutagenesis by Integrated Tiles or "MITE-seq", developed by collaborator Tarjei Mikkelsen, PhD at the Broad Institute. He created every potential mutation of each amino acid in the PPARG sequence to every other possible amino acid, and produced a catalog that describes the functional impact of each possible mutation before it is discovered in nature. He characterized all amino acid changes and correlated them with mutations discovered in patients phenotyped in subspecialty clinics, calibrating the functional impact of each and corroborating what is and is not pathogenic. The resulting database was made available to clinicians via an internet-based app (MITER). This approach is scalable and translatable to many other genes of interest, and may greatly facilitate and accelerate the clinical interpretation of incidental findings in exome sequences. (4)

Innate Immunity and Immune Intolerance

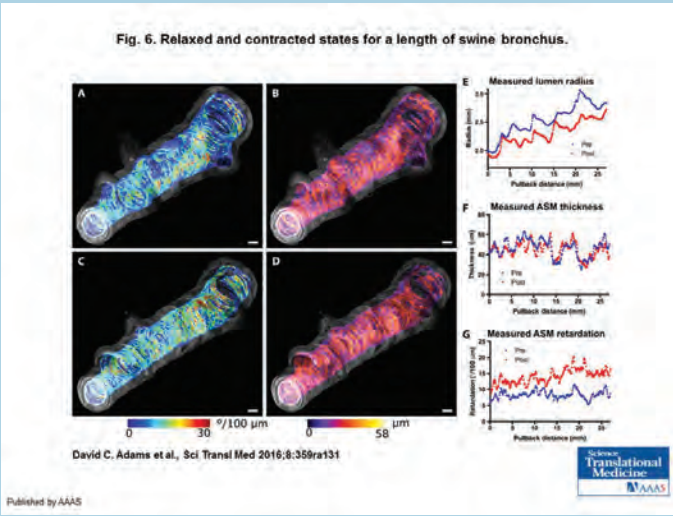
HIV-infected individuals receiving combined antiretroviral therapy (ART) face an increased risk of myocardial infarction, thought to be fueled in part by systemic immune activation and arterial inflammation. The degree to which initiation of ART can reduce arterial inflammation has not been tested, and is a key focus for the field. **Steven Grinspoon, MD** and colleagues show that ART resulted in favorable changes in immune parameters – suppressing viremia, markedly reducing activated CD4+ and CD8+ T cells, increasing classical CD14+CD16- monocytes, reducing systemic inflammatory markers like CXCL10, and reducing inflammation in the axillary lymph nodes. In contrast, arterial inflammation as measured by FDG-PET continued to increase over the course of ART. The finding that newly initiated combined ART in treatment-naive HIV patients had discordant effects to restore immune function without reducing arterial inflammation strongly suggests complementary strategies to reduce arterial inflammation among ART-treated HIV-infected individuals may be needed. (5) **Ramnik Xavier, MD PhD** and his group followed gut microbiome development from birth until age three in 222 infants in Northern Europe, where early-onset autoimmune diseases are common in Finland and Estonia but are less prevalent in Russia. They found that Bacteroides species are of low abundance in Russians but dominate in Finnish and Estonian infants. Therefore, their lipopolysaccharide (LPS) exposures arose primarily from Bacteroides rather than from Escherichia coli, which is a potent innate immune activator. They went on to show that Bacteroides LPS is structurally distinct from E. coli LPS and inhibits innate immune signaling and endotoxin tolerance; furthermore, unlike LPS from E. coli, B. dorei LPS does not decrease incidence of autoimmune diabetes in non-obese diabetic mice. Early colonization by immunologically silencing microbiota may thus preclude aspects of immune education and promote development of autoimmunity. These findings have major implications for the pathogenesis of autoimmunity and suggest approaches to preempt autoimmunity in predisposed persons. (6)

Dematiaceous or "pigmented" molds are found ubiquitously in the environment and cause a wide-spectrum of human disease. **Jennifer Reedy, MD, PhD** and colleagues focused their study on Exserohilum rostratum, a dematiaceous mold that cause 753 infections and 64 deaths during a multistate outbreak due to injection of contaminated methylprednisolone. During the fungal meningitis outbreak, voriconazole was selected as the treatment agent of choice due to its in vitro efficacy, ability to penetrate the central nervous system, and better tolerability. Despite the in vitro efficacy of voriconazole, relapse of infection occurred after 4.5 months of therapy, highlighting that antifungal therapy alone may not be sufficient for treatment and that an effective host immune response is critical for cure of infection. The group shows that macrophages are incapable of phagocytosing Exserohilum. Despite a lack of phagocytosis, macrophages production of pro-inflammatory cytokines including TNFα, MIP-1α, and MIP-2 is triggered by hyphae but not spores and depends upon Dectin-1, a cell surface C-type lectin receptor that recognizes the carbohydrate β-1,3 glucan. Dectin-1 is specifically recruited to the macrophage-hyphal interface but not the macrophage-spore interface due to differences in carbohydrate antigen expression between these two fungal forms. Corticosteroid and antifungal therapy perturb this response, resulting in decreased cytokine production. In vivo soft tissue infection in wild-type mice demonstrated that Exserohilum provokes robust neutrophilic and granulomatous inflammation capable of thwarting fungal growth. However, co-administration of methylprednisolone acetate results in robust hyphal tissue invasion and a significant reduction in immune cell recruitment. Their results indicate that Dectin-1 is crucial for macrophage recognition and pro-inflammatory cytokine response to Exserohilum and that corticosteroids potently attenuate the immune response to this pathogen. (7)



A novel method of imaging airway smooth muscle (ASM) in vivo – orientation-resolved optical coherence tomography (OR-OCT) – was used to demonstrate that allergic asthmatics have increased ASM mass compared to allergic non-asthmatic and healthy control subjects. Top panels are volumetric reconstructions of ASM thickness (color) overlaid on airway structure (grayscale). Bottom panels are flattened images used for quantification. Scale bar 6 mm. J. L. Cho, M. F. Ling, D. C. Adams, L. Faustino, S. A. Islam, R. Afshar, J. W. Griffith, R. S. Harris, A. Ng, G. Radicioni, A. A. Ford, A. K. Han, R. Xavier, W. W. Kwok, R. Boucher, J. J. Moon, D. L. Hamilos, M. Kesimer, M. J. Suter, B. D. Medoff, A. D. Luster, Allergic asthma is distinguished by sensitivity of allergen-specific CD4+ T cells and airway structural cells to type 2 inflammation. Science Translational Medicine 8, 359ra132 (2016).

A multidisciplinary team lead by **Andrew Luster, MD, PhD** has used novel imaging and immunological tools to reveal key differences in the sensitivity of airway cells to inflammation between allergic individuals with and without asthma. Luster's team asked why some individuals allergic to airborne allergens develop asthma while many others do not. The team included colleagues in pulmonary and critical care medicine led by **Benjamin Medoff, MD** that sampled the airway response to allergens via bronchoscopy for 36 participants with allergic asthma, 48 with similar allergies but no history of asthma, and 5 healthy control participants. They found that both allergic patients with and those without asthma responded to the allergen challenge with type 2 inflammation in the airways while healthy controls had no response. However, asthmatic participants had larger amounts of mucous and increased levels of a mucous protein that makes mucus more gelatinous and increases airway hyper-reactivity. Both allergic groups were found to have similar increases in the levels of T cells in the airways, including allergen-specific $CD4^+$ T cells that were identified in the airway for the first time using novel immunologic reagents developed for this study. However, allergen-specific T cells in participants with asthma had higher levels of type 2 innate immune receptors making them more sensitive to signals released from allergen-activated epithelium and innate immune cells. By discovering that the response of airway structural cells to type 2 inflammation induced by aero-allergens appears to be a critical determinant for the development of allergic asthma, it may be possible to identify novel targets to treat or reverse asthma. (8) Assessing the structure and function of airway smooth muscle, and how it is altered in asthma, is critical to advancing our understanding of the disease and in improving clinical outcomes through personalized therapy. However, until now, it has not been possible to see the complex network of airway smooth muscle in living patients. **Melissa Suter, PhD** and her team have developed a new imaging tool that reveals the volumetric rope-like banding structure of smooth muscle as it wraps around the airway. This imaging platform can not only see the amount and organization of smooth muscle, it can also measure how intensely these smooth muscle bands are contracting, revealing how the activated muscle fibers work to constrict and close the airway in asthmatic patients. Suter and colleagues conducted preclinical studies to validate the accuracy of the imaging platform, and subsequently translated the technology into the clinical setting. They imaged healthy volunteers and subjects with mild asthma and demonstrated for the first time that even mild asthmatics showed a significant increase (2x) in the amount of airway smooth muscle. This unprecedented ability to measure airway smooth muscle structure and function is likely to be a game changer in asthma and other constrictive lung diseases, as is evident by the excitement in the field to obtain access to this new technology. (9) Deposition of antibody-antigen immune complexes (ICs) in tissues underlies the pathogenesis of a wide variety of autoimmune diseases. In these diseases, collectively referred to as "type III hypersensitivity", IC-deposition leads to a local inflammatory response characterized by immune cell infiltration and activation. The neutrophil is the first immune cell recruited into tissue, however, the mechanism by which deposited ICs initiate and propagate neutrophil infiltration into tissue is not known and is of considerable therapeutic importance. The prevailing paradigm of "type III hypersensitivity" is that tissue-resident cells sense ICs through Fcγ Receptors and complement receptors and elaborate secondary mediators, such as TNF and IL-1, which activate endothelial cells to promote neutrophil recruitment. The Luster Lab adopted the technique of intravital multiphoton microscopy to image the development



Birefringence microscopy platform for assessing airway smooth muscle structure and function in vivo. Adams DC, Hariri LP, Miller AJ, Wang Y, Cho JL, Villiger M, Holz JA, Szabari MV, Hamilos DL, Scott Harris R, Griffith JW, Bouma BE, Luster AD, Medoff BD, Suter MJ. Sci Transl Med. 2016 Oct 5;8(359):359ra131. PMID: 27708064

of IC-induced arthritis in live mice. They found that the complement C5a receptor (C5aR) was the key initiator of neutrophil adhesion on joint endothelium. C5a presented on joint endothelium induced β2 integrin-dependent neutrophil arrest, facilitating neutrophil spreading and transition to crawling, and subsequent leukotriene B4 receptor (BLT1)-mediated extravasation of the first neutrophils. The chemokine receptor CCR1 promoted neutrophil crawling on the joint endothelium while a different chemokine receptor CXCR2 amplified late neutrophil recruitment and survival once in the joint. Thus, imaging arthritis has defined a new paradigm for type III hypersensitivity where C5a directly initiates neutrophil adhesion on the joint endothelium igniting inflammation. (10)

Iron is an essential component of the erythrocyte protein hemoglobin and is crucial to oxygen transport in vertebrates. In the steady state, erythrocyte production is in equilibrium with erythrocyte removal. In various pathophysiological conditions, however, erythrocyte life span is compromised severely, which threatens the organism with anemia and iron toxicity. **Herbert Lin, MD** and colleagues identified an on-demand mechanism that clears erythrocytes and recycles iron. They show that monocytes that express high levels of lymphocyte antigen 6 complex, locus C1 (LY6C1, also known as Ly-6C) ingest stressed and senescent erythrocytes, accumulate in the liver via coordinated chemotactic cues, and differentiate into ferroportin 1 (FPN1, encoded by SLC40A1)-expressing macrophages that can deliver iron to hepatocytes. Monocyte-derived FPN1(+)Tim-4(neg) macrophages are transient, reside alongside embryonically derived T cell immunoglobulin and mucin domain containing 4 (Timd4, also known as Tim-4)(high) Kupffer cells (KCs), and depend on the growth factor Csf1 and the transcription factor Nrf2 (encoded by Nfe2l2). The spleen, likewise, recruits iron-loaded Ly-6C(high) monocytes, but these do not differentiate into iron-recycling macrophages, owing to the suppressive action of Csf2. The accumulation of a transient macrophage population in the liver also occurs in mouse models of hemolytic anemia, anemia of inflammation, and sickle cell disease. Inhibition of monocyte recruitment to the liver during stressed erythrocyte delivery leads to kidney and liver damage. These observations identify the liver as the primary organ that supports rapid erythrocyte removal and iron recycling, and uncover a mechanism by which the body adapts to fluctuations in erythrocyte integrity. (11)

In type 1 diabetes (T1D), the effectiveness of current insulin therapy is limited in addressing hypoglycemic unawareness, while islet transplantation requires lifelong immune suppression and donor organs are relatively scarce. The **Vaccine & Immunotherapy Center (VIC)** has made seminal publications regarding the use of the chemokine CXCL12 to enable transplanted tissue to evade immune rejection. VIC has now established a collaboration with the Harvard Stem Cell Institute to conduct preclinical evaluation of the use of CXCL12 with human stem cell-derived insulin-producing beta cells for treatment of T1D. The unlimited availability of these insulin-producing beta cells along with the ability to eliminate the need for systemic immune suppression through CXCL12-mediated local immune modulation could potentially provide a curative treatment for T1D. Preclinical studies of this combination treatment in murine models of T1D are already under way. VIC has also recently established a collaborative relationship with the company Aperisys that would facilitate the development of novel immunotherapies for ovarian cancer and mesothelioma. VIC will execute defined preclinical studies in established murine models to examine the hypothesis that the efficacy of established immunotherapies, including tumor-targeted immune-activating fusion protein VIC-008 as well as immune checkpoint inhibitors, can be significantly increased through the addition of the CXCR4 antagonist AMD3100. In 2016 initial studies in murine models of ovarian cancer and mesothelioma showed that VIC-008/AMD3100 or PD-1/AMD3100 combination treatments significantly delayed tumor growth and prolonged mouse survival. The emerging preclinical dataset on tumor remission, mouse survival, and changes in immune cell composition within the tumor microenvironment in response to therapy will support the identification of effective combination immunotherapies for ovarian cancer and mesothelioma that can be translated in the near term into treatments for patients with these diseases. (12)

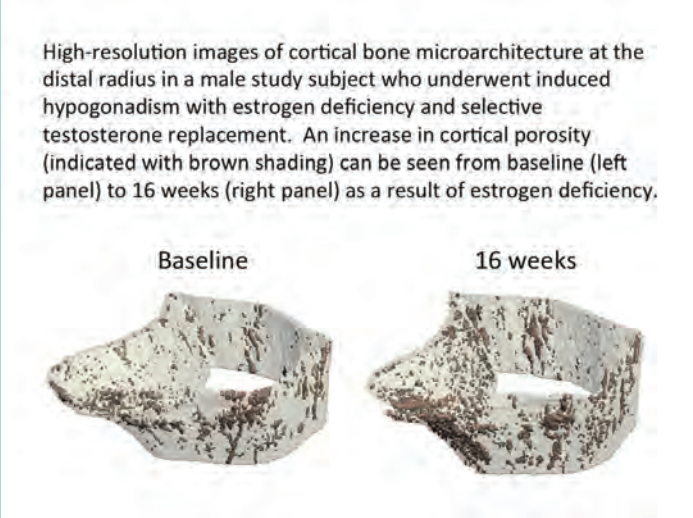
Therapeutic Interventions

Influenza A virus (IAV) is one of the best-characterized human RNA viral pathogens. However, a physiologically relevant role for the RNA interference (RNAi) suppressor activity of the IAV non-structural protein 1 (NS1) remains unknown. Plant and insect viruses have evolved diverse virulence proteins to suppress RNAi as their hosts produce virus-derived small interfering RNAs (siRNAs) that direct specific antiviral defense by an RNAi mechanism dependent on the slicing activity of Argonaute proteins (AGOs). Recent studies have documented induction and suppression of antiviral RNAi in mouse embryonic stem cells and suckling mice. However, it is still under debate whether infection by IAV or any other RNA virus that infects humans induces and/or suppresses antiviral RNAi in mature mammalian somatic cells. In important work led by **Kate Jeffrey, PhD**, in collaboration with **Christian Reinecker, MD**, her lab demonstrated that mature human somatic cells produce abundant virus-derived siRNAs. They showed that the biogenesis of viral siRNAs from IAV double-stranded RNA (dsRNA) precursors in infected cells is mediated by wild-type human Dicer and potently suppressed by both NS1 of IAV as well as virion protein 35 (VP35) of Ebola and Marburg filoviruses. This work collectively demonstrates that influenza A infection induces and suppresses antiviral RNAi in differentiated mammalian somatic cells. (13) Exhausted or dysfunctional T cells in cancer and chronic viral infection express distinctive patterns of genes, including sustained expression of programmed cell death protein 1 (PD-1). However, the regulation of gene expression in exhausted T cells is poorly understood. In a study conducted by the lab of **Nicholas Haining, MD**, with **Georg Lauer, MD, PhD** and **Raymond Chung, MD**, for the first time the accessible chromatin landscape is defined in exhausted $CD8^+$ T cells and shown

to be distinct from functional memory CD8⁺ T cells. Exhausted CD8⁺ T cells in humans with HCV infection and a mouse model of chronic viral infection acquire a state-specific epigenetic landscape organized into functional modules of enhancers. Genome editing showed that PD-1 expression is regulated in part by an exhaustion-specific enhancer that contains essential RAR, T-bet, and Sox3 motifs. Functional enhancer maps may now offer targets for genome editing that alter gene expression preferentially in exhausted CD8⁺ T cells. (14)

Giant cell arteritis (GCA, a.k.a. temporal arteritis) afflicts over 200,000 Americans. The disease has multiple potential severe complications, including vision loss in 15-20% of patients and long-term morbidities that include complications of aortitis (e.g., aneurysm) and other manifestations of large-vessel vasculitis. Since the invention of cortisone in 1949, no treatment other than glucocorticoids has been shown to be effective for GCA. Based on his experience with a single critically ill patient treated at MGH, **John Stone, MD** organized and led the GiACTA trial, an international, 76-center clinical trial of an interleukin-6 receptor blocker (tocilizumab) in GCA. This trial became the largest conducted to date in this disease and achieved both its primary endpoint (sustained remission off steroids) and all its secondary endpoints, demonstrating superiority of both tocilizumab regimens to a 52-week prednisone regimen at one year. The trial marks the first time in the history of this disease that a medication has been shown to be an effective steroid-sparing agent. Tocilizumab was recently given a Breakthrough Designation for the treatment of GCA, and regulatory approval is anticipated soon throughout the world. (15)

Osteoporosis is a major public health problem in our aging population, with tremendous morbidity and mortality associated with fragility fractures. The only current approved osteoporosis medication that builds new bone is parathyroid hormone amino acids 1-34. While safe and effective, its use is significantly limited by need for daily injections. An important unmet need in osteoporosis therapeutics is the development of an orally-available "anabolic" treatment agent. **Marc Wein, MD, PhD** and colleagues recently reported a major advance towards this goal by describing the skeletal effects of YKL-05-099, a small molecule inhibitor of the kinase SIK2. This project began as a basic investigation into the intracellular signaling mechanisms responsible for PTH effects in bone. Walking down the pathway downstream of the PTH receptor in osteocytes, it was observed that a crucial step involved inhibiting the kinase SIK2. Teaming with **Nathanael Gray, PhD** and **Ramnik Xavier, MD, PhD,** they asked if SIK2 inhibitors might mimic effects of PTH. Compounds like YKL-05-099 regulated gene expression in cultured bone cells in a manner quite similar to PTH. Once daily treatment of mice with YKL-05-099 for 2 weeks led to significant increases in bone mass, osteoblast numbers and bone formation rates. Studies are now ongoing to better understand its safety profile, and to establish efficacy of YKL-05-099 in preclinical disease models. Therefore, inhibiting SIK2 with orally-available small molecule kinase inhibitors may be a promising novel treatment strategy to boost bone formation and bone strength in osteoporosis. (16) Severe hypogonadism induces bone loss in adult men; however the relative contributions and thresholds levels of androgen and estrogen deficiency in hypogonadal bone loss have been unclear. **Elaine Yu, MD** and colleagues have reported the results of their large randomized controlled physiologic study of induced hypogonadism with selective testosterone and/or estrogen replacement. They found that decreases in bone density and disruptions in cortical bone microarchitecture occurred with estrogen deficiency, and that this decline was independent of testosterone levels. Thus, they provide definitive evidence that estrogens primarily regulate bone homeostasis in adult men, and that both testosterone and estrogen levels must decline substantially to impact bone. These data have direct clinical implications by detailing therapeutic intervention thresholds for skeletal health in hypogonadal men, and suggest an unintended skeletal consequence of non-aromatizable androgens. (17)



High-resolution images of cortical bone microarchitecture at the distal radius in a male study subject who underwent induced hypogonadism with estrogen deficiency and selective testosterone replacement. An increase in cortical porosity (indicated with brown shading) can be seen from baseline (left panel) to 16 weeks (right panel) as a result of estrogen deficiency.

Elaine Yu and colleagues, JCI 2016;126:114-1125

Preeclampsia is a devastating complication of pregnancy. Soluble Fms-like tyrosine kinase-1 (sFlt-1) is an antiangiogenic protein believed to mediate the signs and symptoms of preeclampsia. **Ravi Thadhani, MD** and colleagues conducted an open pilot study to evaluate the safety and potential efficacy of therapeutic apheresis with a plasma-specific dextran sulfate column to remove circulating sFlt-1 in 11 pregnant women (20-38 years of age) with very preterm preeclampsia (23-32 weeks of gestation, systolic BP ≥140 mmHg or diastolic BP ≥90 mmHg, new onset protein/creatinine ratio >0.30 g/g, and sFlt-1/placental growth factor ratio >85). They evaluated the extent of sFlt-1 removal, proteinuria reduction, pregnancy continuation, and neonatal and fetal safety of apheresis after one (n=6), two (n=4), or three (n=1) apheresis treatments. Mean sFlt-1 levels were reduced by 18% (range 7%-28%) with concomitant reductions of 44% in protein/creatinine ratios. Pregnancy continued for 8 days (range 2-11) and 15 days (range 11-21) in women treated once and multiple times, respectively,

compared with 3 days (range 0-14) in untreated contemporaneous preeclampsia controls (n=22). Transient maternal BP reduction during apheresis was managed by withholding pre-apheresis antihypertensive therapy, saline prehydration, and reducing blood flow through the apheresis column. Compared with infants born prematurely to untreated women with and without preeclampsia (n=22 per group), no adverse effects of apheresis were observed. In conclusion, therapeutic apheresis reduced circulating sFlt-1 and proteinuria in women with very preterm preeclampsia and appeared to prolong pregnancy without major adverse maternal or fetal consequences. A controlled trial is warranted to confirm these findings. (18)

Alexander Soukas, MD, PhD, and colleagues advanced the understanding of the molecular mechanism of action of the type 2 diabetes drug metformin, and expanded its applicability to cancer therapy. They made the observation that metformin slows growth in C. elegans, suggesting that this organism could serve as a model for investigating the drug's effects on cancer. In a series of experiments, they found that metformin's action against cancer relies on two elements of a single genetic pathway – the nuclear pore complex, which allows the passage of molecules into and out of the nucleus, and the enzyme ACAD10. Metformin's suppression of mitochondrial activity reduces cellular energy, restricting the traffic of molecules through the nuclear pore. This inhibits mTORC1, resulting in activation of ACAD10, which both slows the growth and extends the lifespan of C. elegans. To take this observation into mammalian systems, the investigators confirmed that application of drugs in the metformin family induced ACAD10 expression in human melanoma and pancreatic cancer cells, an effect that depends on the function of the nuclear pore complex. Without the complete signaling pathway – from mitochondrial suppression, through nuclear pore restriction to ACAD10 expression – cancer cells were no longer sensitive to the effects of metformin-like drugs. (19) **Steven Russell, MD,PhD,** and colleagues continued the development and validation of the bionic pancreas, a device which uses a novel algorithm to integrate a glucose sensor with a bihormonal pump that infuses both insulin and glucagon to manage type 1 diabetes. In their most recent study, they compared the bionic pancreas with conventional insulin pump therapy. The bionic pancreas achieved superior glycemic regulation, with lower mean glucose levels but less hypoglycemia. This represents one additional step toward the highly-anticipated FDA approval of this device. (20)

Population Health

Sanja Percac-Lima, MD and colleagues evaluated the impact of a community-based intervention to improve cancer screening, specifically in vulnerable populations. In a randomized controlled trial, the team demonstrated that patient navigation for comprehensive cancer screening using a population-based health information technology system can significantly increase breast, cervical and colorectal screening rates in patients at high–risk for non-adherence with care. This paper prompted an invited commentary in the same issue and was highly cited for supporting a rapidly emerging approach towards improving access to care and minimizing disparities in care delivery. (21) **Daniel Singer, MD** and colleagues have led efforts to define the risks and benefits of anticoagulation in patients with atrial fibrillation (AF) and evaluate tools to identify the optimal patients for treatment. The CHA2DS2-VASc stroke risk score is recommended by leading guidelines to guide use of anticoagulants for patients with AF. It has notable flaws. The team helped develop a novel risk prediction tool, the ATRIA stroke risk score, and demonstrated superiority over CHA2DS2-VASc in this paper, applying the algorithms to a Swedish national database. (22)

In 2012, the Boston Housing Authority (BHA) in Massachusetts implemented a smoke-free policy prohibiting smoking within its residences. **Douglas Levy, PhD** and colleagues performed a range of analyses, including assessing BHA residents' experiences before and after the smoke-free policy implementation and comparing them to that of nearby residents of the Cambridge Housing Authority, which had no such policy. The research team found that resident support for smoke-free policies is high. However, lack of enforcement of smoke-free policies may cause frustration and resentment among residents, potentially leading to a decrease in housing satisfaction. (23) There is an ongoing move toward payment models that hold providers accountable for the care of their patients. The success of these new models depends in part on the stability of patient populations. **John Hsu, MD, Christine Vogeli, PhD** and colleagues investigated the amount of population turnover in a large Medicare Pioneer accountable care organization (ACO) in 2012-14. They found that substantial numbers of beneficiaries joined or left the ACO population during that period. Beneficiaries who were active in a care management program were less likely to leave the ACO than similar beneficiaries who had not yet started such a program. The research team recommended policy changes to increase the stability of ACO beneficiary populations, such as permitting lower cost sharing for care received within an ACO and requiring all beneficiaries to identify their primary care physician before being linked to an ACO. (24)

Rochelle Walensky, MD, MPH, and colleagues sought to project the clinical and economic effects of reaching the UNAIDS 90-90-90 treatment goals by 2020 in South Africa. They found that achieving UNAIDS targets would avert 2,051,000 HIV transmissions, 2,478,000 deaths, and 1,689,000 maternal orphans while saving 13,340,000 life-years over 10 years. While they projected a required additional $15.979 billion over 10 years, the intervention was very cost-effective at $1,260 per year of life saved. This analysis was presented at the UNAIDS High Level Meeting on Ending HIV/AIDS in June 2016, and was featured on the NIH Director's blog. (25) Over 40% of people living with HIV in the US smoke cigarettes, but smoking cessation interventions have not been widely integrated into HIV care. **Krishna Reddy, MD** and

Rochelle Walensky, MD MPH attends UNAIDS High Level Meeting on Ending HIV/AIDS at the UN in New York City in June 2016. The anticipated clinical and economic effects of 90-90-90 in South Africa (Walensky RP et al., Ann Intern Med 2016; 165:325-33).

colleagues used a mathematical simulation model to project the life expectancy of people with HIV according to smoking status. They found that a person with HIV who adheres to antiretroviral therapy loses over 8 years of life from smoking, which is about double the loss from HIV itself. Smoking cessation by one-quarter of HIV-infected smokers in the US could save over a quarter million years of life. Smoking is now the primary killer of people with HIV who are on treatment, and this study provides evidence to make smoking cessation a priority in HIV care programs. (26)

A controversial *Science* paper published last year concluded that only a third of the variation in cancer risk among tissues is attributable to environmental factors or inherited predispositions, while most is due to random mutations arising during stem cell divisions. That study challenged the substantial body of knowledge for the importance of environmental factors in cancer development and created considerable confusion for the public regarding the preventability of cancer. To clarify the message and provide an updated overview of the contributions of common lifestyle factors to cancer burden in the US, **Mingyang Song, MD** led a study that demonstrated that between 40% and 60% of cancer cases among white Americans could be prevented if each person adopted a healthy lifestyle, which encompasses no smoking, limited alcohol consumption, maintenance of a healthy weight, and regular physical activity. The study provides strong evidence against the "bad luck" hypothesis and reinforces the critical importance of primary prevention for cancer control. The study has been widely covered by the press and highlighted in numerous reports to support the enormous potential of lifestyle modification for cancer prevention. (27) In 2016, the US Preventive Services Task Force (USPSTF) included colorectal cancer prevention into their rationale for routine low-dose aspirin use among certain subgroups of adults with specific cardiovascular risk profiles. However, the USPSTF have emphasized the need for additional research into the effect of long-term aspirin use, not only on the incidence of colorectal cancer but on that of overall cancer, according to a range of doses and by subgroups. To address these challenges, among the 88?084 women and 47?881 men who underwent follow-up for as long as 32 years in the Nurses' Health Study and Health Professionals Follow-up Study, **Yin Cao, MPH, ScD** and colleagues examined the potential benefits of aspirin use for overall and subtype-specific cancer prevention at a range of doses and durations of use and estimated the absolute benefit of aspirin in the context of screening. The team found that, compared with nonregular use, regular aspirin use was associated with a lower risk for overall cancer (RR, 0.97; 95% CI, 0.94-0.99), which was primarily owing to a lower incidence of gastrointestinal tract cancers (RR, 0.85; 95% CI, 0.80-0.91), especially colorectal cancers (RR, 0.81; 95% CI, 0.75-0.88). The benefit of aspirin on gastrointestinal tract cancers appeared evident with the use of at least 0.5 to 1.5 standard aspirin tablets per week; the minimum duration of regular use associated with a lower risk was 6 years. Among individuals older than 50 years, regular aspirin use could prevent 33 colorectal cancers per 100?000 person-years (population-attributable risk [PAR], 17.0%) among those who had not undergone a lower endoscopy and 18 colorectal cancers per 100?000 person-years (PAR, 8.5%) among those who had, suggesting that aspirin use may complement CRC screening and may have an absolute benefit regardless of endoscopy status. (28)

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Robert E. Kingston, PhD, Chief

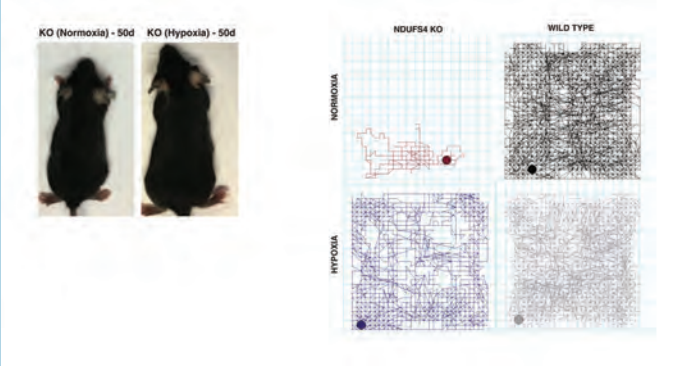
The Department of Molecular Biology at Massachusetts General Hospital is a part of both the research community of the hospital and the Division of Medical Sciences of the Harvard Graduate School of Arts and Sciences. We also have a strong connection with the Department of Genetics at HMS, where most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

At present, approximately 180 people, including 15 faculty, over 120 postdoctoral fellows and graduate students, and about 40 staff members, comprise the Department of Molecular Biology. Our areas of excellence include:

- Chromatin remodeling, long noncoding RNAs, X-chromosome inactivation (Kingston, Lee), epigenetics, (Hochedlinger, Kingston, Lee), reprogramming & pluripotency (Hochedlinger).
- Human genetics, mitochondrial physiology and disease (Mootha), and mitochondrial membrane proteins (Mootha, Chao).
- Plant biology, signaling, and pathogen defense. Innate immune signaling pathways (Ausubel, Sheen).
- Bacterial pathogenesis (Ausubel, Hung) and fungal pathogenesis (Ausubel).
- Cytoskeletal assembly, dynamics, and transport (Blower, Subramanian), macromolecular assembly dynamics (Chao).
- Chemical biology (Hung, Szostak). Synthetic biology, chemical evolution, and protocells (Szostak).
- Insulin signaling (Avruch, Ruvkun). Kinase/GTPase mediation of mitogen and stress signaling (Avruch).
- V(D)J recombination (Oettinger).
- Synapse formation, transmission, and trafficking (Kaplan).
- miRNA and RNAi pathways. Aging in C. elegans. Search for extraterrestrial life (Ruvkun).

Achievements

In the spring of 2016, after having completed a high-profile Ph.D. in the laboratory of John Kuriyan and successful postdoctoral training with Stephen Harrison, Luke Chao was recruited by the MGH Department of Molecular Biology to be an Assistant Molecular Biologist, with an appointment as an Assistant Professor of Genetics at Harvard Medical School. Dr. Chao works on macromolecular assemblies that affect the dynamics, structure, and fusion of cell membranes. In Steve Harrison's lab, he worked on flavivirus membrane fusion and developed techniques to measure the kinetics of single fusion events in the absence and presence of fusion inhibitors. In his own lab, Luke will work on the structure of mitochondrial membranes and the proteins that associate with those membranes. This a field that offers promise for advancing our understanding mitochondrial diseases, and Dr. Chao is one of the few scientists working in this domain. We welcome Dr. Chao to the vibrant research community at MGH.



A breakthrough in study from the Mootha lab in 2016. In a mouse model of Leigh syndrome, a mitochondrial disorder, knocking out Ndufs4 (a repressor of the hypoxia response) and exposure to hypoxia alleviates disease symptoms. Animals exposed to hypoxia show an improvement in body weight (left), core temperature maintenance, locomotor activity (right), and neurologic behavior.

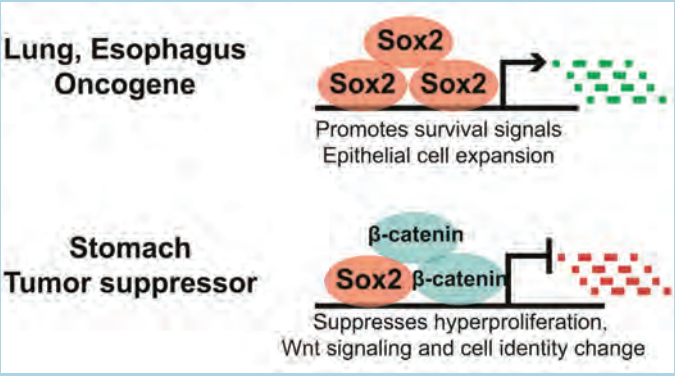
Congratulations to Bob Kingston, Chief of the Department of Molecular Biology, who is one of 84 scientists elected to the National Academy of Sciences in 2016. Dr. Kingston was recognized for his research on chromatin remodeling, a fundamental mechanism by which eukaryotes regulate gene expression. Advances from the Kingston Lab have significant implications for our understanding of basic biology, such as development and epigenetics, and for the advancement of therapeutics that target chromatin regulation. Dr. Kingston is the sixth member of our Department to be elected to the National Academy.

Congratulations as well to Jeannie Lee, who was selected by the Foundation for the National Institutes of Health as the recipient of the 2016 Lurie Prize in Biomedical Sciences. Dr. Lee was recognized for her leadership in the field of X chromosome inactivation and epigenetic regulation by long noncoding RNAs. This honor is the latest in a series of awards and recognitions for Dr. Lee, including the Pew Scholar Award, the Molecular Biology Award of the National Academy of Sciences, and election to the National Academy in 2015.

Molecular Biology

Department Report

Over the course of the past year, our faculty have published several highly regarded publications in important fields. For example, Gary Ruvkun's lab identified key elements of cellular response to proteasome dysfunction, which has the potential to lead to new therapeutics (doi: 10.7554/eLife.17721); using a genome-wide CRISPR screen, Vamsi Mootha's lab discovered that regulation of the hypoxia response could be used as a therapy for devastating mitochondrial diseases (Figure 1; doi: 10.1126/science.aad9642); Konrad Hochedlinger's group found that the stem cell factor Sox2, which has been reported to be an oncogene in epithelium tissues, functions as a tumor suppressor in the stomach of mice (Figure 2; doi: 10.1016/j.celrep.2016.07.034); Jack Szostak's lab discovered a catalytic process that brings us a step closer to understanding how RNA functioned as the first biopolymer (doi: 10.7554/eLife.17756); and Mike Blower's lab showed that transcription of centromeres produces a stable noncoding RNA that is important for ensuring equal segregation of chromosomes, a discovery with potential implications for cancer therapy (doi: 10.1016/j.celrep.2016.04.054).



New insights on the role of the stem cell factor Sox2 and tumorigenesis. Konrad Hochedlinger's lab found, unexpectedly, that Sox2, which has been reported to be an oncogene in epithelium tissues, functions as a tumor suppressor in the stomach of mice. They showed that Sox2 loss contributes to tumorigenesis by derepressing WNT signaling and facilitating a partial gastric-to-intestinal fate switch.

Merit Cudkowicz, MD, MSc, Chief

Guided by the needs of our patients, the mission of the Department of Neurology is to be the preeminent academic neurology department in the US by providing outstanding clinical care while rapidly discovering new treatments to reduce and eliminate the devastating impact of neurological disorders; training the very best neurologists and scientists of the future; and improving the health and well being of the diverse communities we serve. Our core values are excellence in service, innovation, education and neuroscience research in the field of neurology.

Mass General hosts the nation's largest hospital-based neuroscience research program (ranked #1 in NIH funding for hospital-based neurology programs). Our greatest asset in achieving our research goals is our faculty, whose numbers continue to grow. We have several faculty members serving on NIH councils and who sit as leaders of major disease consortiums (e.g. ALS, HD, Parkinsons, adrenoleukodystrophy). Despite a challenging federal funding environment, the Department of Neurology research revenue increased 17% over the prior year, bringing in $98.5M in total research revenue.

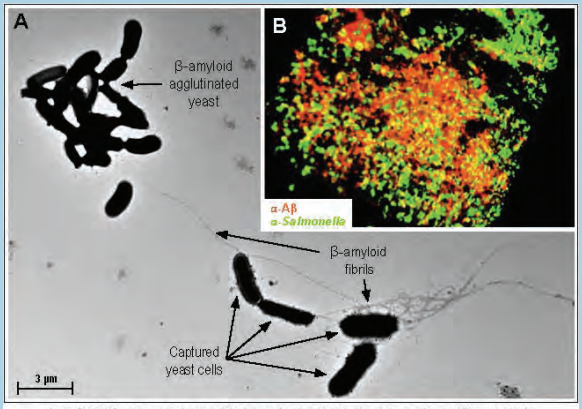
Strategic Research Priorities

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

Achievements

Alzheimer's Disease: β-amyloid generation is an innate immune pathway

The hallmark pathology in Alzheimer's disease (AD) is cerebral deposition of amyloid-β peptide (Ab) as insoluble β-amyloid plaques. Aβ has been the chief target for therapeutic intervention in AD for over three decades. Aβ is typically characterized as a functionless catabolic byproduct and β-amyloid generation intrinsically abnormal. In prevailing amyloidosis models polymorphic soluble oligomer intermediates generated in the β-amyloid pathway are neurotoxic agents mediating neurodegeneration in AD. In 2010 Dr Moir's research group proposed Aβ may actually play a physiological role in innate immunity as an antimicrobial peptide (AMP). AMPs are critically important for combating infections in the immunoprivileged brain were adaptive immunity is highly constrained. In their most recent 2016 study, Dr. Robert Moir's research group confirmed expression of human Aβ protects against bacterial and fungal pathogens, dramatically increasing host survival in transformed cell culture and transgenic C. elegans and mouse acute infection models. Most significantly, protective antimicrobial Aβ pathways led to β-amyloid seeding and entrapment of invading pathogens within amyloid plaques. Findings suggest polymorphic oligomers are key for Aβ's in vivo protective antimicrobial actions, broadening the peptides antimicrobial activity spectrum and mediating targeting and binding of microbial cell wall carbohydrates. Once bound to microbial surfaces, oligomers and rapidly assembling protofibrils sterically inhibit host cell adhesion and provide a nidus and anchor for Aβ fibril propagation. Growing Aβ fibrils then capture, agglutinate, and finally entrap the unattached microbes in protease-resistant insoluble β-amyloid networks. Independent researchers recently confirmed Aβ oligomerization and β-amyloid generation mediate protective antimicrobial activities. An innate immune role for β-amyloid stands in stark contrast to prevailing views of Aβ oligomerization that characterize the self-association and aggregation of the peptide as strictly abnormal and exclusively pathological events. Moreover, identification of a physiological role for Aβ oligomerization is likely to help advance our understanding of the etiology and pathogenesis of AD and inform current and future therapeutic strategies aimed at preventing pathological β-amyloid accumulation. The studies findings are also highly germane to the emerging infection hypothesis of AD. Microbial-seeding of β-amyloid suggest a plausible mechanism by which viral, bacterial, or fungal pathogens may lead directly to brain amyloidosis. The study received extensive coverage from over 50 media outlets worldwide, including the front pages of the New York Times and USA Today, and was recently cited as among the top five Neurology advances for 2016 in MedPage Today.

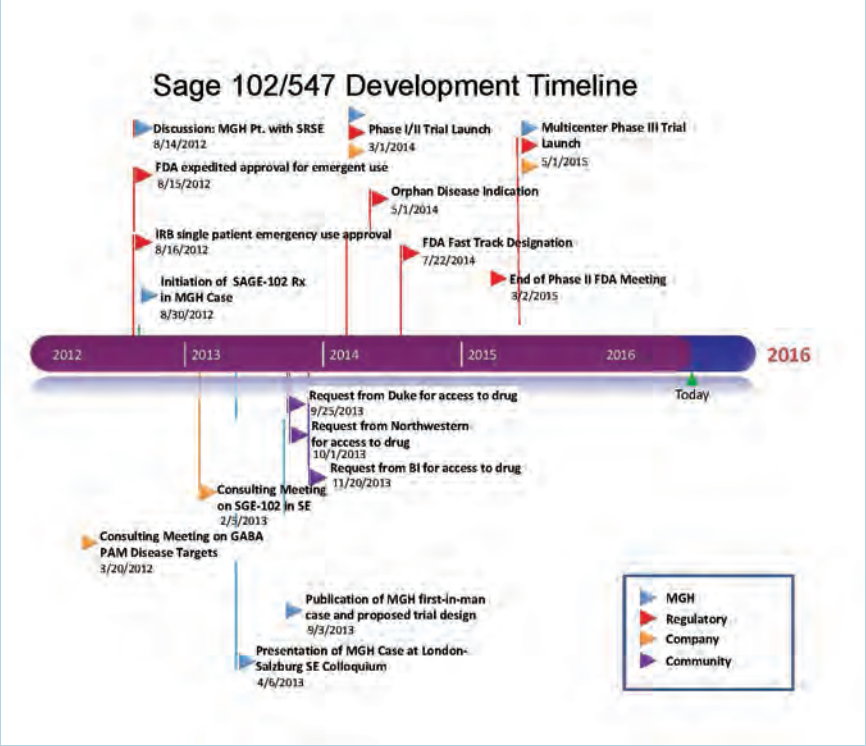


β-amyloid fibrils capture and entrap infecting pathogens in (**A**) cell culture media and (**B**) mouse brain.

Kumar DK, Choi,SH, Washicosky KJ, Eimer, WA, Tucker S, Ghofrani J, Lefkowitz A, McColl G, Goldstein LE, Tanzi RE, and Moir RD. Amyloid-β peptide protects against microbial infection in mouse and worm models of Alzheimer's disease. Sci Transl Med. 2016 May 8;340ra372.

Neurotherapeutic Blueprints: Taking Research from Bench to Bedside

Through partnerships with patient communities, clinical insights, and collaborations between bench and clinical scientists, the Department of Neurology is uniquely positioned to convert basic science discoveries into experimental therapeutics. This year, several of our ongoing efforts to develop new therapies for our patients were marked by key milestones.



Development of a Novel Drug for Status Epilepticus

Sage-547 (formerly SGE-102) is a novel positive allosteric modulator of GABAA receptors that is active at both γ-subunit containing synaptic receptors and δ-subunit containing extra-synaptic receptors. Experimental evidence indicates that synaptic receptors are rapidly internalized early in status epilepticus, leading to a loss of efficacy of benzodiazepines that bind only receptors containing the –subunit. The development of Sage-547 is based, in part, on the hypothesis that it will retain efficacy in ongoing status because γ-subunit containing recpetors are preserved on the extrasynaptic membrane. In late 2012 in the course of caring for a patient with super-refractory status of unknown etiology Neurology's Epilepsy Team recognized the opportunity to try the Sage compound after 9 failed attempts to take the patient off general anesthetic drugs. the Sage compound was administered using an infusion algorithm designed to achieve the maximal serum level as then permitted by the FDA of 150 nM over a 5 day period . Remarkably, under treatment with the experimental compound the patient was weaned off the anesthetic drugs and t made an excellent recovery, albeit with some of the longterm complications of a long ICU stay. This experience, reported by Dr. Andrew Cole at the Status Epilepticus Colloquium in Salzberg in April 2013, led quickly to multiple requests for access to the drug that were fulfilled by Sage and its collaborators under a compassionate use protocol. A formal Phase II trial was launched in March 2014, and the FDA gave approval for a pivotal Phase III double blind randomized placebo controlled trial in April 2015. That trial, the first randomized blinded trial of a novel agent for status ever, led by Dr. Eric Rosenthal as the global PI, is now in the late stages of recruitment and is scheduled to read out later this year. Importantly, the development of this potential paradigm shifting treatment for a serious neurological disease has been accomplished in record time because of the cooperative partnership between MGH Neurology faculty members, particularly Drs. Cole and Rosenthal, and Sage Therapeutics, based in Cambridge.

Therapy Development in Amyotrophic Lateral Sclerosis and Frontotemporal Dementia

Expanded GGGGCC repeats in a non-coding region of the C9ORF72 gene are the most common genetic cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). Several pathogenic mechanisms have been proposed including loss of function from reduced expression of C9ORF72 and/or toxicity derived from the expansion-containing RNAs. Dr. Clotilde Lagier-Tourenne's lab built several mouse models and used cultured neurons derived from patients to develop new therapeutic approaches including RNA-targeting antisense oligonucleotides (ASOs) and immunotherapies for patients with ALS/FTD.

In collaboration with IONIS Pharmaceuticals Dr. Tourenne's lab identified ASOs which reduce GGGGCC-containing nuclear foci without altering overall C9ORF72 RNA levels in patient cells (Lagier-Tourenne et al. PNAS 2013). They subsequently demonstrated that treatment with ASOs alleviated pathological and behavioral abnormalities in mice expressing expanded C9ORF72 (Jiang et al. Neuron 2016).

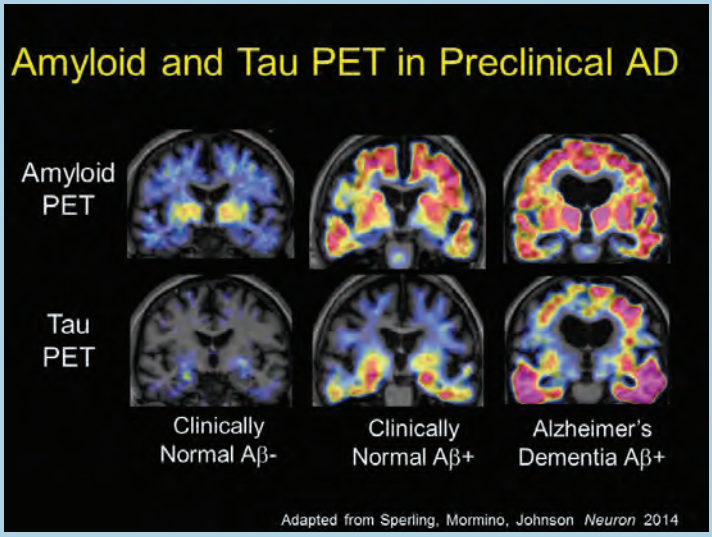
These findings established ASO-mediated degradation of repeat-containing RNAs as a significant therapeutic approach for ALS/FTD and represented a crucial step in the development of lead compounds for a clinical trial being prepared by IONIS Pharmaceuticals and Biogen. Notably, a similar ASO-mediated lowering approach is currently tested in ALS patients with SOD1 mutations and was shown to be safe in an initial clinical trial led by Dr. Cudkowicz (Miller et al. Lancet Neurology 2013).

A Novel Therapy for Familial dysautonomia

Familial dysautonomia (FD), or Riley-Day syndrome, is a rare, fatal, congenital sensory and autonomic neuropathy caused by a "leaky" mRNA splicing defect that results in reduced levels of IKAP protein. Patients have a complex neurological phenotype primarily due to defective primary sensory neurons in the dorsal root ganglia. In 2001, Dr. Sue Slaugenhaupt and her group discovered discovered that FD is caused by a single-base change in the 5' splice site of intron 20 in the IKBKAP gene that leads to variable exon skipping and reduced protein expression. The goal of Dr. Slaugenhaupt's work for nearly the past decade has been to develop therapies that directly target mRNA splicing in order to increase the amount of functional IKAP protein. Through an NINDS sponsored drug screening consortium Dr. Slaugenhaupt's lab discovered that kinetin, a plant cytokinin, can rescue IKBKAP splicing. Armed with this promising lead compound and relevant cell and animal models, the FD project was chosen to be part of the NIH Blueprint Neurotherapeutics Network. The program was conceived to assist investigators through the "valley of death" in the drug development pipeline. Acting as a collaborative framework, Blueprint gives academic labs access to NIH-funded CROs and to consultants with expertise in drug discovery. Through the Blueprint program, Dr. Slaugenhaupt's group synthesized and tested more than 500 new splice modulating small molecules, many of which show dramatic improvement in efficacy and potency over kinetin. This program was licensed to PTC Therapeutics, Inc. in late 2015 and together we are working to bring a new treatment that directly targets the molecular mechanism of FD to the clinic.

Detection of Preclinical Alzheimer's disease: Implications for Prevention Trials

Converging data from PET amyloid imaging, cerebrospinal fluid studies and large autopsy series suggest that one-third of clinically normal older individuals harbor a substantial burden of cerebral amyloid-beta (Aß). It remains unknown whether these individuals are indeed in the preclinical stages of Alzheimer's disease (AD) and what proportion will progress to dementia over time. Accumulating evidence from these "Aß-positive normals" in Dr. Reisa Sperling's Harvard Aging Brain Study show aberrant network function, cortical thinning, increased neocortical tau on Tau PET imaging, and other "AD-like" abnormalities on multi-modality imaging, as well as increased risk of cognitive decline.



One of the continued dilemmas in the field is how best to identify individuals who are clearly on the AD trajectory but at an earlier enough stage of pathology to be maximally responsive to therapeutic intervention. Dr. Reisa Sperling's Anti-Amyloid Treatment in Asymptomatic AD (A4) Study will enroll over 1150 older individuals with evidence of amyloid accumulation on screening PET scans to determine if treatment with an anti-amyloid antibody, initiated prior to cognitive impairment, will slow neuro-degeneration and the progression of memory decline towards AD dementia. The A4 Study is a 3-year Phase 3 registration trial with a primary cognitive endpoint as well as multiple biomarker outcomes, including Tau PET imaging. The A4 Study is being conducted at 67 sites in US, Canada, Australia and Japan, and will complete enrollment in 2017. The A4 Study has now added Tau PET imaging as a secondary outcome (see Figure below) which will allow us to test the hypothesis that decreasing amyloid burden can slow the spreading of tau pathology into the neocortex, and prevent cognitive decline strongly associated with neurodegeneration. The recently launched EARLY ("A5") Study is utilizing a similar trial design with a BACE inhibitor in an asymptomatic population age 60-85. Dr. Reisa Sperling and her collaborators are now working on the "A3" Study, Ante-Amyloid Prevention of AD, a new trial that aims to prevent amyloid accumulation prior to amyloid positivity, moving closer to primary prevention of AD.

Dietary Change Found to Help Patients with Rare Familial Neuropathy

Hereditary Sensory and Autonomic Neuropathy Type 1 (HSAN1) is a rare autosomal dominant disorder caused by mutations in the enzyme serine palmitoyl-CoA transferase. Dr. Florian Eichler and his lab discovered that the mutations induce a permanent shift in the substrate

preference from serine to alanine thereby forming a class of neurotoxic deoxysphingolipids. After providing proof of concept experiments in cell culture and animal models, he now reports on a two-year, delayed-start placebo-controlled clinical trial to evaluate safety and efficacy of oral L-serine in humans with HSAN1. Eighteen HSAN1 patients with prominent sensory loss, foot ulcers or shooting pains were enrolled. Subjects were equally randomized to L-serine or placebo for 1 year. At 48-weeks, the placebo group crossed-over to L-serine for one additional year.

Sixteen subjects completed their 96-week visit. No serious adverse events related to L-serine were reported. Over the first year participants on L-serine experienced significant improvement on the neuropathy scale CMTNS compared to placebo (-1.8 units, 95% CI -3.3 to -0.3, $p = 0.02$). Both groups improved in the second year of the study, with a diminished difference in CMTNS at 96 weeks (-1.45 units, 95% CI -3.7 to 0.81, $p=0.20$). Overall patients on treatment experienced less sharp pain compared to the placebo group (-0.69 points on the neuropathic pain scale, CI -3.14 to 3.43, $p=0.92$). Importantly, after one year of treatment the neurotoxic lipids declined significantly among subjects on L-serine compared to those on placebo (41% decrease in deoxysphingosine vs. 9.2% increase on placebo ($p=0.001$); 59% decrease in deoxysphinganine vs. 11% increase on placebo, ($p < 0.001$). The studies suggest that L-serine is a safe and potentially efficacious long-term treatment option for patients with HSAN1.

Robert L. Martuza, MD, FACS, Chief

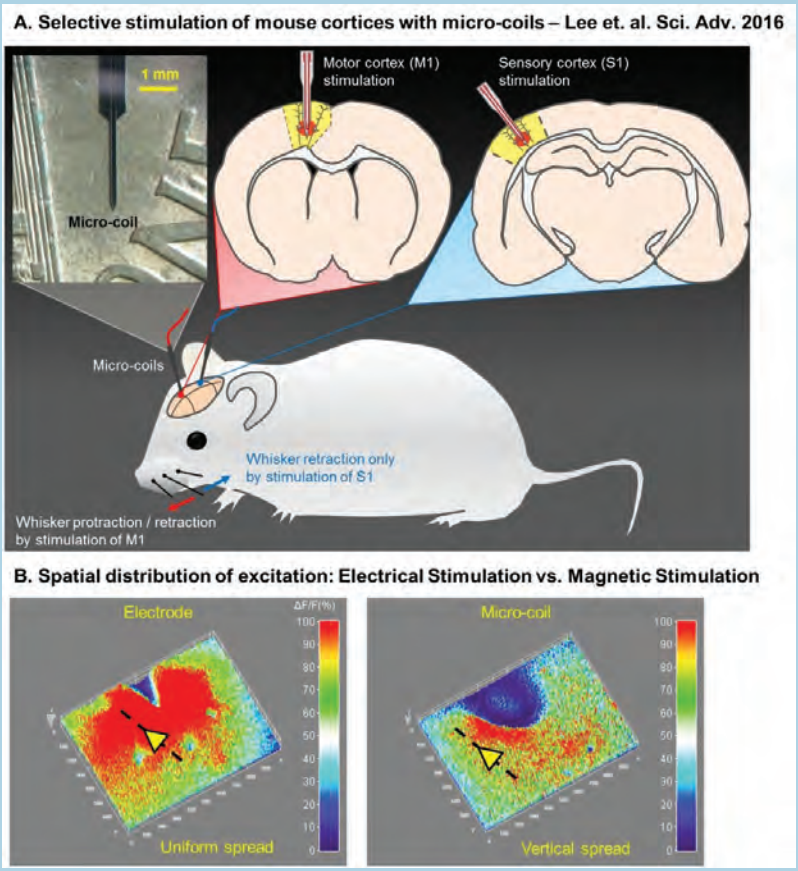
The mission of the Department of Neurosurgery is to advance an understanding of the nervous system and to use this to advance therapy. The Department focuses on clinical care, basic research and translational studies taking research from the bench to the bedside. Herein are two examples aimed at developments to allow a re-wiring or reprogramming of the nervous system.

Achievements

John Pezaris and colleagues in an article in Scientific Reports examined the mechanisms of learning to recognize objects in a simulation of artificial vision. This modeling of the device to restore sight to the blind under development in the Visual Prosthesis Laboratory has implications for post-implant rehabilitation for eventual implant recipients.

Pezaris has received a prestigious Fulbright Scholar Award and will be pursuing a collaborative research project at the University of Athens, Greece for four months to study longitudinal improvements in reading ability with artificial vision. Pezaris has received an award from the Medical Technology Enterprise Consortium, a public-private foundation that supports research of interest to the US Department of Defense. Under the award, the Visual Prosthesis Laboratory will develop a prototype device for sight restoration that will be ready for initial testing in blind human volunteers in three years.

Shelley Fried and colleagues developed an microcoil, small enough to be safely implanted into cortex and demonstrated its effectiveness for magnetically activating cortical neurons as well as driving cortical circuits. Such an approach has considerable benefits over conventional electrode implants. For example, coils produce electric fields that are spatially asymmetric and therefore, can be harnessed to selectively activate specific types of neurons, e.g. vertically-oriented pyramidal neurons, without simultaneous activating other types, e. g horizontally-oriented passing axons. As a result, the effects of stimulation can be more focally confined with coils than they can with electrodes. Micro-coils are also attractive because the magnetic fields they induce are highly permeable through all biological materials and thus, the foreign body responses and gliosis that plague conventional cortical electrode implants do not similarly diminish the effectiveness of coils. The increased safety and better selectivity with micro-coils suggests they will be a more attractive approach for applications such as Brain-Computer Interfaces and cortical prostheses than existing electrode-based devices.

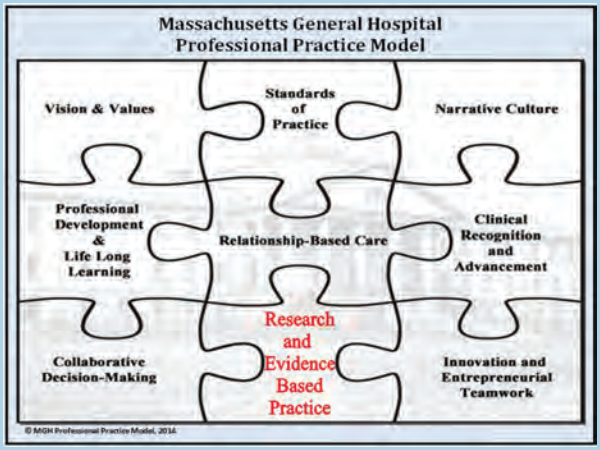


Nursing

Department Report

Gaurdia E. Banister, RN, PhD, FAAN, Executive Director

At the Massachusetts General Hospital, the advancement of nursing science through research and utilization of evidence-based practice (EBP) is designed to promote an environment that generates and extends knowledge, optimizes patient care delivery, and improves the work environment. Within Patient Care Services (PCS), the commitment to research and EBP is clearly articulated within the Professional Practice Model (PPM, Figure 1) that provides structural support for clinicians to guide the delivery of knowledge-driven, safe, relationship-based, cost-effective, high-quality patient care. Science is embedded within each element of the PPM, showcasing MGH's commitment to produce and use science to create a healing, caring and creative environment for clinicians, patients, and families.



Nursing and Patient Care Services Professional Practice Model

The **Yvonne L. Munn Center for Nursing Research (Munn Center)** at MGH is one of four centers in the Institute for Patient Care (IPC). The IPC serves as an integral arm of PCS that supports activities that inform care delivery, promote professional development, stimulate innovation and help to create an environment of inquiry and discovery among staff. The Munn Center was implemented in 2008 and has developed an infrastructure to advance a research agenda that:

- promotes innovation
- provides mentorship to staff
- fosters a research agenda that compliments the scholar's goals as well as the goals of PCS
- mobilizes internal and external grant funding
- informs other scholars of research outcomes through publications and national/international scholarly forums
- facilitates a culture of inquiry by supporting research and evidence-based practice initiatives that advance clinical practice and optimize quality patient-centered outcomes

The Munn Center seeks to collaborate with other researchers across the MGH enterprise and beyond to support and advance the Munn Center's research agenda. Opportunities for multi-site investigations help to inform and expand new knowledge and to build programs of research that increase funding opportunities and research across disciplines. The Munn Center has created links to a growing cadre of external faculty nurse scientists from local, national and international schools of nursing who contribute to the mission of the center. By conducting and disseminating research, mentoring staff and participating in research activities sponsored by the Munn Center, these scholars increase the visibility of nursing research at MGH and beyond.

Research Priorities

The Munn Center's research priorities are designed to improve the health of the communities we serve by identifying and managing patients' response to illness, understanding the meaning of the illness experience for patients and families, addressing strategies to manage care transitions and promote the health and well-being for patients and their caregivers. In addition, researchers within PCS are concerned with the impact of the care environment on clinicians' overall satisfaction with the workplace. Examples of current programs of research within the Munn Center that support these priorities include:

- care of the older adult
- ethics in clinical practice
- symptom management (e.g. pain management, pressure ulcer prevention)
- health services research and workforce evaluation
- complementary interventions to enhance healing and promote recovery
- transition care and the community

Achievements

Connell Nursing Research Scholars Program

The MGH has a growing number of nurses prepared at the doctoral level (N=60+). The generous support of the William F. Connell family allowed the establishment of the Connell Nursing Research Scholars Program (CNRS) in 2012 to provide nurses working in clinical practice an opportunity to engage in a mentored, post-doctoral learning experience with a goal of advancing their program of research by apply-

ing for external funding and engaging in scholarly activities. To date, ten nurses have been named Connell Nursing Research Scholars. Their areas of research include workforce evaluation and the development and testing of a leadership influence tool, expanding interventions in pain management (especially in the older adult), development and testing of an infant feeding tool, and optimization of health in vulnerable populations (e.g. women and HIV). These areas of research have led to interdisciplinary research investigations, additional funding, and extensive scholarship. In 2016, four of the CRNS received extension awards to complete data analysis, extend data collection or instrument development, publish, and test new methodologies to understand phenomena of concern to patient care. Other outcomes included acquisition of external grant funding through the Health Resources and Services Administration (HRSA), the American Nurses Foundation and the National Institutes of Health.

Nursing Research Studies and Awards

The ultimate goal of the Munn Center is to stimulate inquiry and translate data uncovered through research to continually improve our patient and family outcomes and the nursing workforce environment. Key Munn Center achievements for 2016 are presented below.

Continuity of Care: Kevin Mary Callans, RN, BSN, Carolyn A. Bleiler, RN, MSN, Jane Flanagan, PhD, ANP-BC and Diane L. Carroll, PhD, RN, FAAN conducted a study designed to improve continuity of care for pediatric patients discharged with tracheostomies. She engaged family members in focus groups and yielded several notable findings: family members want to be pushed to learn, rather than having nurses hold back until they appear ready to learn; family members are very aware of and respond to a perception that the nurses performing the training are confident; they trust caregivers that listen and adjust their care in response; and there is a realization of fulfillment by being able to give back and help other families that are beginning the same journey. Callans presented findings of her study in a podium presentation at the International Conference on Nursing Science in Singapore in November 2016.

Health Services Research and Workforce Evaluation: Jeanette Ives Erickson, RN, DNP, NEA-BC, FAAN, Marianne Ditomassi, RN, DNP, MBA, NEA-BC and Dorothy Jones, RN, EdD, FAAN, FNI have developed, refined, and utilized a nursing workforce survey since 1996. This program of research is designed to evaluate staff satisfaction with the MGH Professional Practice Environment. The most recent iteration is the Professional Practice Work Environment Inventory (PPWEI) and it is comprised of 72 items with an eight or nine factor component structure; the survey is administered every 12-18 months. With each round, psychometric properties are evaluated to ensure consistency and reliability. Their manuscript entitled Psychometric Properties of the Professional Practice Work Environment Inventory (PPWEI) will be published in the Journal of Nursing Administration in Spring, 2017.

Impact of Uncertainty on Patient Outcomes: Andrea Hansen, RN, PhD(c), CNS-BC, OCN was awarded the 2016 Yvonne L.Munn Doctoral Fellowship in Nursing Research to support her dissertation study, Living with Uncertainty: Perspectives of Those Living with Metastatic Non-Small Cell Lung Cancer (NSCLC). The study aims to describe the experience and impact of uncertainty in patients diagnosed with metastatic NSCLC. Hansen will also explore coping strategies used by patients and triggers of uncertainty to inform clinicians regarding new ways to provide support to patients throughout their illness trajectory.

Moral Distress: Ellen Robinson, RN, PhD, nurse ethicist and Connell Nursing Research Scholar, is conducting a study, Understanding Difficult Decision-Making for Families and serves as the site PI for the UCLA study, CO-ADVOCATE: A Program to Prevent Ethical Conflicts and Moral Distress in Intensive Care Units. These studies will be exploring the concept of moral distress and decision-making in order to develop strategies that decrease moral distress in caregivers

Pain Assessment: Kim Francis, PhD, RN, PHCNS-BC, Connell Nursing Research Scholar, has worked with her external research mentor, Jacqueline McGrath PhD, RN, FNAP, FAAN, from the University of Connecticut and the Munn Center's Dorothy Jones, RN, EdD, FAAN, FNI. Dr. Francis received a Society of Pediatric Nurses grant to fund her continuing program of research focused on neonatal pain assessment entitled Testing the Feasibility of Utilizing Infrared Thermography for Pain Assessment with ELGA Infants: A Pilot Study. The study will evaluate the feasibility of infrared thermography for the identification of extremely low gestational age (ELGA) infant pain. This technology will be used to assess facial temperature to detect changes in facial expression along with changes in temperatures in the affected extremities during painful procedures. The goal is to determine if using this novel technology provides clinicians with useful information for the assessment of pain in this population.

Patient Discharge Decision-making: Gaurdia Banister, RN, PhD, NEA-BC, FAAN is the MGH Principal Investigator (PI) for the multi-site study Readiness Evaluation and Discharge Interventions: Implementation as a Standard Nursing Practice for Hospital Discharge (READI). Dr. Banister hosted the study PIs, Marianne Weiss, DNSc, RN from Marquette University and Linda Costa, PhD, RN, NEA-BC from the University of Maryland. Three protocols that added a component to discharge readiness assessment were used including the discharge readiness assessment by the discharging nurse; discharge readiness assessment by the discharging nurse informed by patient self-re-

port of discharge readiness; and the patient-informed nurse assessment, with the addition of an instruction to the discharging nurse to initiate and document nursing actions for patients with low readiness scores.

Restraint Utilization and Care Outcomes: Jeanne Dolan, RN, MSN, clinical nurse on the Surgical Intensive Care Unit (SICU), received a Munn Research Award to conduct the study Understanding Determinates of Physical Restraint Use among Critical Care Patients: An Exploratory Study of Nurses. Dolan found that patient safety and behavior are the primary nursing determinates of restraint use in the SICU. SICU patients experience complex diagnoses and life-sustaining interventions including intubation/ventilation and multiple invasive lines which pose unique challenges to patient safety. Nurses engage in a critical thought process to determine restraint use. Her work has been accepted for publication in the American Journal of Critical Care.

Recovery from Surgery and Impact on Caregivers: Ann Malley, APRN-NP, PhD completed a postdoctoral fellowship at the University of Pennsylvania to further her study The Patient and Family Caregiver Experience During the Transition of Care into the Preoperative Environment for Hip and Knee Joint Replacement. Study findings suggest that older adults often considered joint replacement a quality of life intervention and that perioperative care was often standardized to achieve organizational efficiency rather than to effectively engage older patients and their family caregivers. Family caregivers often found themselves functioning as care coordinators. Malley and Meg Bourbonniere, RN, PhD, Munn Center Nurse Scientist, will present the study findings at the Eastern Nursing Research Society meeting in 2017.

Vulnerable Populations: Sara Looby, ANP-BC, FAAN, Connell Nursing Research Scholar, received a Claflin Distinguished Scholar Award from the MGH Executive Committee on Research (ECOR). Dr. Looby is a co-investigator with Markella Zanni, MD on this study and is the first nurse scientist to be recognized for this prestigious MGH award. The Claflin Award supports the 2016 NIH-funded research study, Cardiovascular Risk in HIV-Infected Women: Sex-Specific Mechanisms of Risk and Risk Reduction among REPRIEVE Trial Participants. This interdisciplinary study examines sex-specific mechanisms of cardiovascular disease risk and risk reduction in HIV in women enrolled in the REPRIEVE trial, an international, randomized control study that investigates whether treatment with a statin medication will reduce risk of heart disease in patients living with HIV. Within this larger, multidisciplinary study the team will evaluate the effects of an evidence-based research education and recruitment campaign designed to engage women with HIV into this clinical research as this group has been underrepresented in past research.

Publication Highlights

Callans, K. M., Bleiler, C., Flanagan, J., & Carroll, D. L. (2016). The transitional experience of family caring for their child with a tracheostomy. Journal of Pediatric Nursing, 31, 397-403.

Erickson, J. I., Ditomassi, M. & Jones, D. (2015). Fostering a Research Intensive Organization: An Interdisciplinary Approach for Nurses from Massachusetts General Hospital. Indianapolis, IN: Sigma Theta Tau International Honor Society of Nursing.

Flanagan, J., Winters, L., Habin, K. Post, K. and Wigler, D. (2016). The experience of initiating oral adjuvant treatment for the treatment of estrogen positive breast cancer. Oncology Nursing Forum. 43(4). E143-E152 doi: 10.1188/16.onf.e143-e152.

Looby, S. E., Fitch, K. V., Srinivasa, S., Lo, J., Raferty, D., et al. (2016). Reduced ovarian reserve relates to monocyte activation and subclinical coronary atherosclerotic plaque in women with HIV AIDS. 30(3), 383-93.
Rosa, K.C. (2016). Integrative review on the use of Newman praxis relationship in chronic illness. Nursing Science Quarterly. 29(3), 211-218.

Lipkis-Orlando, R., Carroll, D.L., Duffy, M., Weiss A., & Jones, D.A. (2016). Psychometric evaluation of the staff perception of the disruptive patient behavior scale. Journal of Nursing Administration, 46, 250-256.

Nursing Research Day

The Munn Center hosted its annual Nursing Research Day in May 2016. The interactive poster session featured more than 40 presenters of original research, evidence-based practice initiatives, and quality improvement projects. The keynote speaker, Bea Kalisch, PhD, RN, FAAN, Professor Emerita of the University of Michigan, School of Nursing, delivered a fascinating presentation on her groundbreaking research into missed nursing care and its effect on patients and nurses. The program culminated with an announcement of new grants to support nursing research from Susan Slaugenhaupt, PhD, Scientific Director of the MGH Research Institute. This type of celebration sets the stage for recognizing on an annual basis the accomplishments of nurse researchers within MGH and also provides an opportunity to identify key areas or programs of research that could expand inquiry and collaboration with other disciplines.

Jeffrey L. Ecker, MD, Chief

Our department-based research complements our clinical goals 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 infrastructures.

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

Achievements

Dingens A, Carlson T, Reed S, Mitchell C. Bacterial Vaginosis and Adverse Outcomes Among Full-Term Infants: A Cohort Study. BMC Pregnancy Childbirth. 2016 Sep 22;16(1):278

In this retrospective cohort study of 12,340 mother-infant pairs, Dr. Mitchell and colleagues showed that a diagnosis of bacterial vaginosis (BV) during pregnancy is associated with higher rates of respiratory distress, NICU admission and neonatal sepsis among full term infants. While BV has previously been associated with adverse outcomes in preterm birth, it has not been thought to have an impact on babies born at term. These findings may lead to changes in clinical care of women with BV in pregnancy to reduce adverse neonatal outcomes.

Styer AK, Luke B, Christianson MS, Vitek W, Baker V, Armstrong A, Polotsky AJ. Factors associated with the use of elective single embryo transfer and pregnancy outcomes in the United States 2004-2012. Fertil Steril 2016; 106(1):80-89.

This study evaluated factors associated with elective single-embryo transfer (eSET) utilization and its effect on assisted reproductive technology outcomes in the United States. Fresh IVF cycles of women ages 18-37 using autologous oocytes with either one (SET) or two (double-embryo transfer [DET]) embryos transferred and reported to the Society for Assisted Reproductive Technology Clinic Outcome Reporting System between 2004 and 2012 were analyzed. Cycles were categorized into four groups with ([+]) or without ([–]) supernumerary embryos cryopreserved. The SET group with embryos cryopreserved was designated as eSET. Outcomes are measured by the likelihood of eSET utilization, live birth, and singleton non–low birth weight term live birth, modeling using logistic regression. Measures are presented as adjusted odds ratios (aORs) and 95% confidence intervals (CIs). It concludes expanding insurance coverage for IVF would facilitate the broader use of eSET and may reduce the morbidity and healthcare costs associated with multiple pregnancies.

Hernandez SF, Chisholm S, Borger D, Foster R, Rueda BR, Growdon WB. Ridaforolimus improves the anti-tumor activity of dual HER2 blockade in uterine serous carcinoma in vivo models with HER2 gene amplification and PIK3CA mutation. Gynecol Oncol. 2016 Jun;141(3):570-9.

We observed dose dependent in vitro abrogation of downstream target proteins including phospho-AKT and phospho-S6. In both in vivo models, single agent ridaforolimus impaired xenograft tumor growth. Combination ridaforolimus and L/T, however, further improved the observed anti-tumor activity only in the ARK1 model with the PIK3CA gene mutation (E542K). The addition of mTOR inhibition to dual HER2 blockade added no additional anti-tumor effects in the ARK2 xenografts. Western blot and immunohistochemical analysis of downstream pathway alterations following in vivo treatment revealed dual HER2 blockade with ridaforolimus was necessary to induce apoptosis, decrease proliferation and abrogate phospho-S6 protein expression in the PIK3CA mutated model. These pilot data suggest that PIK3CA gene mutation may be an effective biomarker for selecting those HER2 over-expressing USC tumors most likely to benefit from mTOR inhibition.

Ophthalmology

Department Report

Joan W. Miller, MD, FARVO, Chief

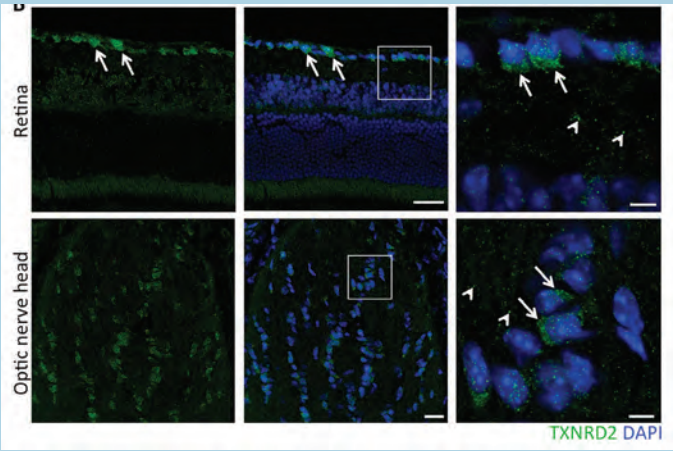
The research mission of the Mass. Eye and Ear/MGH Department of Ophthalmology is focused on eliminating blinding diseases and disorders of the eye and visual system. With the incorporation of Schepens Eye Research Institute in 2011, the Department is now one of the largest vision research groups in the world. Today, we are well-positioned to bring focused efforts toward accelerating prevention, management and rehabilitation of vision-threatening disorders.

Tackling blinding diseases using a multifaceted, multidisciplinary approach has been the mainstay of the Department's past success in translational medicine. This approach has led to advancements such as proton beam irradiation, photodynamic therapy, anti-VEGF therapies, and the Boston Keratoprosthesis, which have saved sight or improved vision for millions of people worldwide. The Department pursues a programmatic research strategy focused on areas of greatest unmet medical need, including inherited retinal degenerations and Age-related Macular Degeneration (AMD), diabetic eye disease, and optic neuropathies, particularly glaucoma. Our largest investment has been directed toward developing our genetics and genomics programs?with significant emphasis and support in the areas of retina and glaucoma; we believe that leveraging genetic information will accelerate our understanding of diseases and help identify therapeutic targets. At the same time, we are maintaining our commitment to other programs, including, cornea and ocular surface, oncology, immunology, infectious disease, vision rehabilitation and perception.

Achievements

Three new genes identified that contribute to primary open-angle glaucoma

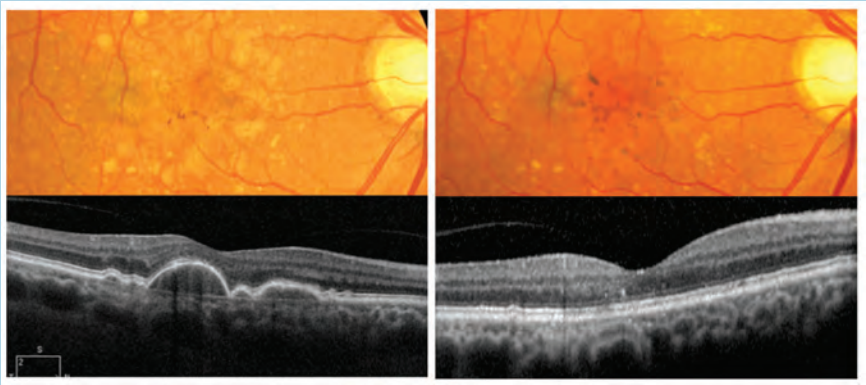
In the largest genome-wide study of its kind, Janey Wiggs, MD, PhD and collaborators from HMS Ophthalmology and Case Western Reserve University School of Medicine, identified three genes that contribute to the primary open-angle glaucoma (POAG), which is the most common type of glaucoma. Researchers conducted a meta-analysis of genome-wide association study (GWAS) results from 3,853 people with POAG and compared them to a control group of 33,480 people of European descent using human genomes collected through the NEIGHBORHOOD consortium, a National Eye Institute collaborative. After replicating the analysis using data from an Australian study, and comparing the analysis to three more data sets (Australia, Europe, China), three susceptibility loci were identified: TXNRD2, ATXN2, and FOXC1. The findings, published in the February 2016 issue of Nature Genetics, provide key insight that ultimately may be used to develop gene-based testing and treatment strategies for glaucoma.



TXNRD2 is expressed in the retina and optic nerve head. Representative images of immunofluorescence using an anti-TXNRD2 antibody shows TXNRD2 (green) present in cells in the ganglion cell layer (arrows) as well as significant punctate staining in the inner plexiform layer (arrowheads, I). Significant staining was also observed in cells in the optic nerve head indicative of astrocytes that form pial columns (arrowhead, F). For each antibody, at least 3 sections from 6 eyes were assessed. No staining, not even punctate staining, was observed in the no primary control tissue (data not shown). Blue=DAPI. Scale bars: A, B, G, H=20um; C, F, I, L=5um; D, E=15um; J, K=25um.

Patients with high-risk macular degeneration show improvement with intensive statin treatment

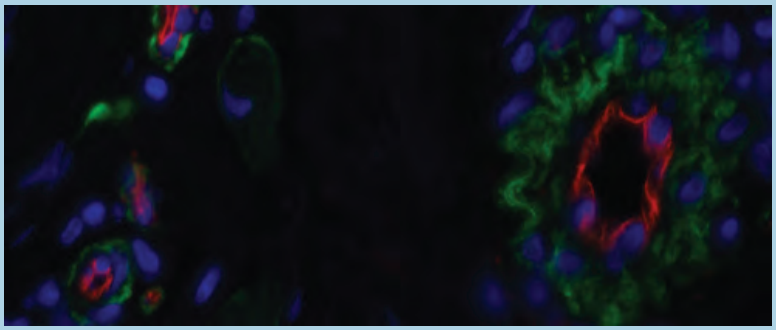
In a Phase I/II clinical trial, researchers from Mass. Eye and Ear/Harvard Medical School and the University of Crete found that high dose statin treatment led to clearing of lipid deposits under the retina that is a feature of eyes with high-risk macular degeneration. Led by Demetrios Vavvas, MD, PhD and Joan W. Miller, MD, the study results were published in EBioMedicine—a new online journal led by editors of the journals Cell and The Lancet. Twenty-three patients with dry AMD marked by soft lipid deposits in the outer retina were prescribed a high dose (80 mg) of atorvastatin (Lipitor R). Of the 23 patients included in the study, 10 experienced an elimination of the deposits under the retina and mild improvement in visual acuity. Although these findings are preliminary, they support the connection between lipids, AMD, and atherosclerosis, and also suggest a potential therapy for patients with dry AMD, for whom treatments are currently lacking. FDA-approved, atorvastatin is readily available, and taken by millions of patients for high cholesterol and heart disease. As a next step, investigators are planning a larger, prospective multicenter trial to further investigate the efficacy of the treatment in a larger sample of patients with dry AMD.



Left: before statin treatment; Right: same patient, one year after statin treatment

Researchers shed light on the anti-adhesive molecule in vascular endothelium suggesting new direction for anti-inflammatory therapy

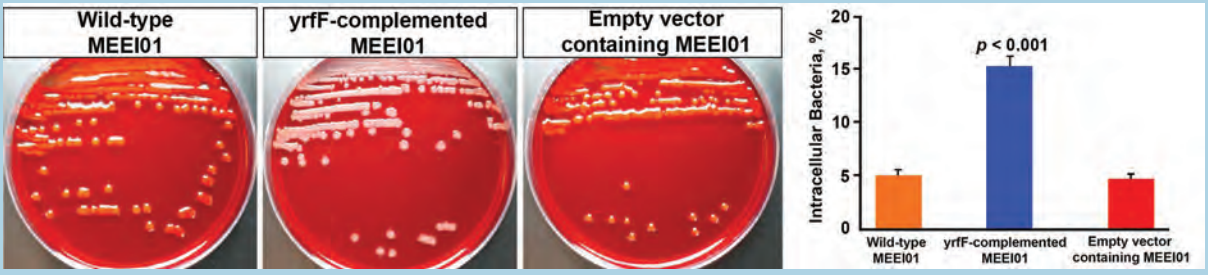
Mass. Eye and Ear researchers have gained new insight into how a non-inflammatory state is maintained in the body. In a paper published in Nature Communications, the researchers describe the role of endomucin, a molecule on the surface of the vascular endothelium that under healthy circumstances resists the adhesion of white blood cells as they move through the circulatory system. Their findings suggest that promoting the expression of endomucin (displayed in red in image) may prevent the recruitment of white blood cells that is the hallmark of inflammation.The research, led by Patricia D'Amore, PhD, MBA and Pablo Argüeso, PhD, shows that in healthy, non-inflamed tissue, endomucin plays a critical role in preventing neutrophils from sticking to the endothelium. During inflammatory conditions, however, the endomucin on the endothelial cell surface is dramatically reduced and the levels of pro-adhesives molecules on the endothelium increase, resulting in neutrophil accumulation. The researchers showed both adherence and infiltration of inflammatory cells could be blocked by experimentally expressing excess endomucin in the vascular endothelium. Most current treatments for inflammation involve targeting the activities of cytokines and inflammatory mediators, which have risks and limitations. This new knowledge may be used to develop treatments for inflammation by promoting the expression of endomucin to prevent the movement of inflammatory cells from the capillaries into inflamed tissues.



Endomucin (red) expression in normal, non-injured tissue. Endomucin plays a key role maintaining a non-inflammatory endothelial cell surface by preventing adhesion of white blood cells to the vascular surface.

Mass. Eye and Ear researchers identify and successfully treat a new antibiotic-resistant superbug

Mass. Eye and Ear clinicians and scientists recently discovered a new mutation in a highly antibiotic-resistant strain of E. coli that resists clearance by the body's own immune system by inhibiting white blood cells that ordinarily kill and remove bacteria. In a paper published in JAMA Ophthalmology, the researchers describe a case in which a patient was diagnosed with severe infection of the cornea, and the underlying bacterium was determined to be a multidrug resistant "ESBL E. coli," a microbe that has the ability to resist the action of a wide range of antibiotics. Two antibiotics were identified to which the microbe was still sensitive and, following the application of these in eye drops, the infection resolved. Recognizing the unusually high antibiotic resistance of this microbe and its atypical link to cornea infection, the research team led by Michael Gilmore, PhD, used state-of-the-art genomics capabilities of the Harvard Ophthalmology Ocular Genomics Institute to analyze the microbe's DNA. They found the new mutation in this already aggressive type of ESBL E. coli, termed ST131—the bacterium now produced a layer of slime that blocked the ability of white blood cells to trap and kill it. The development of resistance to attack by white blood cells, coupled with resistance to most antibiotics, is cause for concern. In their paper, the research team shares a test to help physicians recognize and address this particular microbe.



Graph indicates phagocytosis of each strain by RAW264.7 murine macrophages. Error bars indicate standard error of the mean. These data show that phagocytosis-resistant variants of E coli ST131 arise in vivo effected by a novel yrƒF mutation.

Oral and Maxillofacial Surgery

Department Report

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

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

Bench to Bedside ⇄ Bedside to Bench

Bone Biology (SBRC)

CRANIOFACIAL - ZIKA, GAPO, FD
3-D Treatment Planning--- 4D incl growth
Benign Tumors
Odontogenic Tumors (COCA, others)
Regenerative Medicine/ Tissue Engineering
Immediate implantation, banked cells, scaffold, co-constructs
Minimally Invasive Surgery- Midface- orbit
Navigation--- OsteoMark
LASER (cutting, welding, pain control)
TMJ -- OA, JIA
Drug Effects on Bone: MRONJ, NSAID, INF, Marijuana etc
Dental-research----MGH Dental/HSDM (perio/pulp)
----Orthodontics/HSDM (tooth/bone)

Applied Investigation (CACI)

Dental-research----MGH Dental/HSDM
----Orthodontics/HSDM
OroFacial Pain
Obstructive Sleep Apnea
TMJ ----
OMFS– OUTCOME STUDIES

QS/QI Research
Education/Simulation

Skeletal Biology Research Center (SBRC) is located in the Thier 5 Laboratory (approx.1500sq ft.). The translational science performed focuses on bone biology and rare tumor biology (giant cell tumor and clear cell odontogenic carcinoma). Another area of study is metabolic/inflammatory bone disorders (GAPO, MRONJ, microbiology-sterile osteomyelitis/necrosis, synovial chondromatosis). In addition, there is also an emphasis on in-vivo tissue engineering (distraction osteogenesis) and ex-vivo tissue engineering (bone, cartilage and joint). We have developed a standard minipig model for the study of the biology of bone. We have started work on osteoarthritis, with newly recruited Dr. Somi Kim. Other components of the program include distracter device design, 3-D imaging/treatment planning, navigation and minimally invasive technologies.

Center for Applied Clinical Investigation (CACI) plays a significant role in evidence based studies related to the diagnosis, management and outcomes of common problems within our specialty, such as wisdom teeth extraction, dental implantology and medication related osteonecrosis of the jaws (MRONJ), maxillofacial pathology, orofacial pain and temporomandibular joint surgery outcomes. The center serves to study outcomes (retrospective and prospective) on treatment protocols developed in the department. We have initiated QI/Safety and Education /Simulation research.

Achievements

This year was used to plan, oragnaize and create new collaborations. Dr. Merri August was named director of the Center for Advanced Clinical Investigation (CACI), and Dr. Zach Peacock as the director of the Skeletal Biology Research Center (SBRC). We recruited a full-time biochemist/biophysicist, who studies bone biology, Dr. Tanya Besschetnova. We have hired two student-researchers; Josh Kwolek to conduct QI/QS research and Alyssa Cappetta to conduct Education/Simulation research. We have attracted four international fellows; Baboucarr Lowe (scaffold design, nano technology), Garance Diallo (bone and gingiva bioengineering), Dr. Jose Dasilva (MRONJ), and Dr. Halissa Simplicio (drug effects of tooth movement), to carry our these interesting studies.

New collaborations include the department of Pathology, Drs. Iafrate, Faquin and Rivera, (Genetics of Clear Cell Odontogenic Carcinoma), Infectious Disease , Dr. Fuscho (effects of ZIKA of Craniofacial Bone Sutures), and Oncology, Dr. Raje, (genetics of bone metabolism and MRONJ).

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

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

The Department of Otolaryngology at Massachusetts Eye and Ear/Harvard Medical School is home to one of the largest and most productive communities of otolaryngology researchers anywhere in the world. Our investigators are supported by more than $10 million in annual research funding from the National Institutes of Health, working alongside clinical fellows, research fellows, otolaryngology residents, doctoral students, and research staff to probe the basic biology of and to develop leading-edge treatments for disorders of the ear, nose, throat, head, and neck.

Together, our faculty and staff led Mass. Eye and Ear to have a remarkably productive year in 2016, as demonstrated by our more than 300 peer-reviewed publications, including publications in many high impact journals. From new FDA-approved clinical trials for vestibular schwannoma and meningioma treatment to pioneering discoveries in gene therapy, our faculty work diligently year after year to improve outcomes and find new treatments for our patients.

In recognition of our strong commitment to advancing the field, U.S. News & World Report ranked Mass. Eye and Ear as the #1 hospital in the nation for the otolaryngology specialty in their 2016–2017 hospital survey for the second consecutive year.

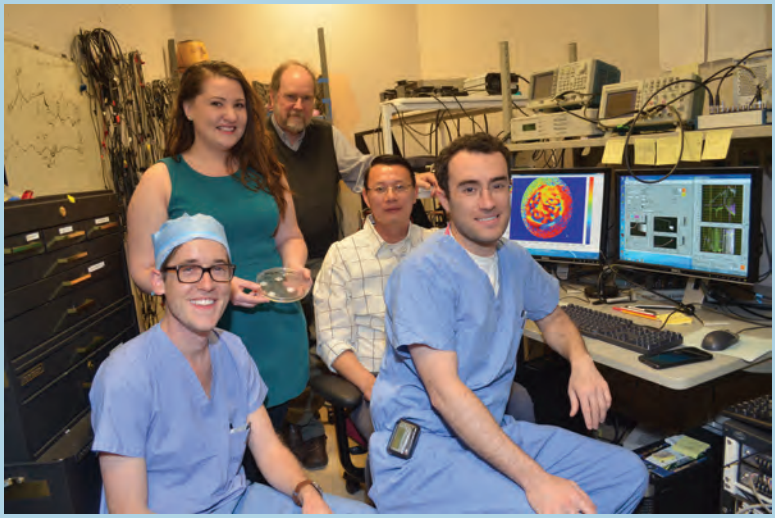
For more information, please visit www.MassEyeAndEar.org/research/otolaryngology.

Achievements

Researchers develop 3-D printed implantable materials to repair the ear

In collaboration with the Wyss Institute at Harvard, Mass. Eye and Ear's Aaron K. Remenschneider, MD, MPH, and Elliott D. Kozin, MD, have led efforts to design and manufacture 3-D printed tympanic membrane (TM) grafts for patients with perforated eardrums that need to be repaired. Their research shows the feasibility of creating TM grafts with acoustic properties that reflect sound induced motion patterns of the human TM. Furthermore, the 3-D printed grafts have mechanical properties that demonstrate increased resistance to deformation compared to temporalis fascia. Experiments using the 3-D printed grafts in an animal model are currently underway.

Kozin ED, Black NL, Cheng JT, Cotler MJ, McKenna MJ, Lee DJ, Lewis JA, Rosowski JJ, Remenschneider AK. Design, fabrication, and in vitro testing of novel three-dimensionally printed tympanic membrane grafts. Hearing Research. 2016 Oct; 340:191–203.



(L-R) Aaron K. Remenschneider, MD, MPH, Nicole Black, MS, John J. Rosowski, PhD, Jeffrey Tao Cheng, PhD, and Elliott D. Kozin, MD, are working together to develop 3-D printed implantable materials to repair the ear. Photo by Garyfallia Pagonis.

Researchers find evidence of "hidden hearing loss" in college-age subjects

A team of researchers from the Eaton-Peabody Laboratories (EPL) at Mass. Eye and Ear, led by Stéphane F. Maison, PhD, MS, has, for the first time, linked in young people with normal hearing sensitivity, symptoms of difficulty understanding speech in noisy environments with evidence of cochlear synaptopathy, a condition known as "hidden hearing loss." While audiometric thresholds and the ability to understand speech in quiet environments were the same across all subjects, researchers recorded reduced responses from the auditory nerve in participants exposed to noise on a regular basis. That loss was matched with difficulties understanding speech in noisy and reverberating environments.

Liberman MC, Epstein MJ, Cleveland SS, Wang H, Maison SF. Toward a differential diagnosis of hidden hearing loss in humans. PLOS ONE. 2016; 11(9):e0162726.

Eaton-Peabody Laboratory scientist Daniel B. Polley, PhD, has helped explain a common auditory complaint in which patients can detect sound normally but report difficulty understanding speech. Photo by Garyfallia Pagonis.

Brain's 'amplifier' compensates for lost inner ear function
Researchers from Mass. Eye and Ear, including Daniel B. Polley, PhD, have described, for the first time, the adult brain's ability to compensate for a near-complete loss of auditory nerve fibers that link the ear to the brain. The findings suggest that the brain's natural plasticity can compensate for inner ear damage to bring sound detection abilities back within normal limits; however, it does not recover speech intelligibility. This imperfect hearing recovery may explain a common auditory complaint in which some patients report difficulties understanding speech despite having normal hearing thresholds.

Chambers AR, Resnik J, Yuan Y, Whitton JP, Edge AS, Liberman MC, Polley DB. Central gain restores auditory processing following near-complete cochlear denervation. Neuron. 2016 Feb; 89(4):867–79.

Acute exacerbations mediate quality of life impairment in chronic rhinosinusitis
The classic paradigm for the pathophysiology of chronic rhinosinusitis (CRS) is that chronic sinonasal symptomatology, driven by inflammatory mechanisms, leads directly to decreased quality of life. However, CRS has other disease-defining characteristics, including acute exacerbations during which patients experience spikes in symptomatology that are sometimes associated with acute sinus infections. Whereas the chronic sinonasal symptomatology of CRS is treated with topical medications, acute exacerbations are often treated with systemic therapies, such as antibiotics and corticosteroids, which may have significant side effects and are thus, a source of significant morbidity in CRS. In a prospective study, researchers from Mass. Eye and Ear, led by Ahmad R. Sedaghat, MD, PhD, showed, for the first time, that the frequency of acute exacerbations of CRS experienced by patients is a significant mechanism for decreased quality of life that is on par with the quality of life detriment caused by chronic sinonasal symptomatology.

Phillips KM, Hoehle LP, Bergmark RW, Caradonna DS, Gray ST, Sedaghat AR. Acute exacerbations mediate quality of life impairment in chronic rhinosinusitis. J Allergy Clin Immunol Pract. 2016 Nov 2.

Successful intraoperative electrophysiologic monitoring of the recurrent laryngeal nerve
A multidisciplinary team of researchers from Mass. Eye and Ear, including Gregory Randolph, MD, FACS, FACE, developed a protocol for intraoperative nerve monitoring (IONM) of the recurrent laryngeal nerve (RLN) based on published evidence and their experience with 3,000 patients over a 16-year period. The team presented an up-to-date clinical algorithm, including setup and troubleshooting of an IONM system, endotracheal tube placement, and anesthetic parameters. They reported that no complications related to monitoring or endotracheal tube placement were noted when the IONM protocol was implemented at Mass. Eye and Ear. This protocol has proven to be vital in standardizing care and in avoiding intraoperative errors. This work is believed to be the first interdisciplinary collaborative protocol for monitored neck surgery based on their clinical and published experience.

Macias AA, Eappen S, Malikin I, Goldfarb J, Kujawa S, Konowitz PM, Kamani D, Randolph GW. Successful intraoperative electrophysiologic monitoring of the recurrent laryngeal nerve, a multidisciplinary approach: The Massachusetts Eye and Ear Infirmary monitoring collaborative protocol with experience in over 3000 cases. Head and Neck. 2016 Apr 9.

David N. Louis, MD, Chief

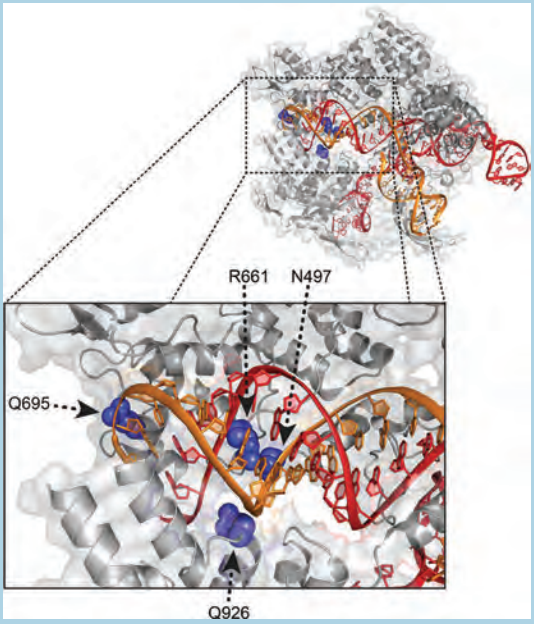
Pathology plays a major and substantial role in academic medicine, as a natural bridge between the diagnosis of human disease and experimental biological investigation. Major advances in molecular pathology and in pathology informatics are accelerating the pace of diagnostic and translational research. In turn, the rapidity and frequency of interactions between clinical and scientific areas makes this a very exciting time in the field of pathology. Laboratory-based scientific research is a major component of MGH Pathology, and is complemented by productive clinical research activities. As a result, MGH Pathology provides an exciting stage for basic and translational research.

MGH Pathology Research has robustly grown over the past 15 years, building an exceptional and well-funded group of basic science and translational investigators with particular strengths and expertise in cancer biology, genomics, epigenomics, and genome editing technology. We are currently implementing initiatives identified from our departmental strategic planning process: leveraging our 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 with our Center for Integrated Diagnostics. We believe that these efforts will 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

Kleinstiver BP, Pattanayak V, Prew MS, Tsai SQ, Nguyen NT, Zheng Z, **Joung JK.** High-fidelity CRISPR-Cas9 nucleases with no detectable genome-wide off-target effects. ***Nature***. 2016 Jan 28; 529(7587): 490-5.

CRISPR-Cas nucleases have greatly simplified the practice of targeted genome editing, a broadly applicable technology for biomedical research that also holds tremendous promise for the development of novel therapeutics. However, these nucleases can also induce unwanted mutations at "off-target" sites, a major concern for therapeutic applications. This paper describes the engineering of a "high-fidelity" version of the widely used Streptococcus pyogenes Cas9 (SpCas9) nuclease that shows no detectable off-target cleavage in human cells as judged by one of the most sensitive existing methods for detecting these events at a genome-wide scale. These high-fidelity SpCas9 nucleases substantially decrease the risk of off-target mutations for research and therapeutic applications.



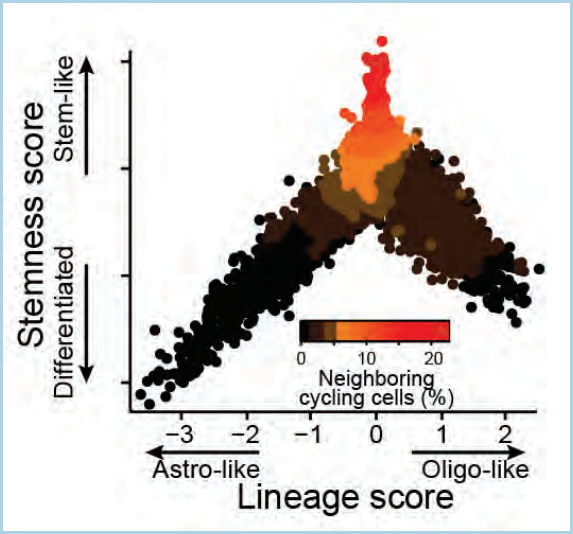
Structure-guided engineering of high-fidelity CRISPR-Cas nuclease variants. Structural representation of a Cas9 nuclease/guide RNA complex bound to its target DNA, from PDB: 4UN3. The four residues that form hydrogen bond contacts to the target-strand DNA backbone are and that were mutated to create the high-fidelity variant are highlighted in blue; note that the HNH domain of the Cas9 nuclease is hidden for visualization purposes.

Tirosh I, Venteicher AS, Hebert C, Escalante LE, Patel AP, Yizhak K, Fisher JM, Rodman C, Mount C, Filbin MG, Neftel C, Desai N, Nyman J, Izar B, Luo CC, Francis JM, Patel AA, Onozato ML, Riggi N, Livak KJ, Gennert D, Satija R, Nahed BV, Curry WT, Martuza RL, Mylvaganam R, **Iafrate AJ, Frosch MP**, Golub TR, **Rivera MN, Getz G**, Rozenblatt-Rosen O, Cahill DP, Monje M, **Bernstein BE, Louis DN**, Regev A, **Suvà ML**. Single-cell RNA-seq supports a developmental hierarchy in human oligodendroglioma. ***Nature.*** 2016 Nov 2.

This study represents the largest effort ever undertaken to characterize brain tumors at the single-cell level, directly in patient samples and the first to deploy single-cell RNA-seq in low-grade gliomas. It is the first study that (i) identifies cancer stem cell and their differentiated progeny in a human tumor in a completely unbiased way, based on a genome-wide expression signature, in situ; (ii) relates developmental programs to genetic evolution, demonstrating that a similar hierarchy is identifiable in distinct genetic clones; (iii) shows that neural stem cells are the main source of proliferating cells in gliomas in patients, early in their pathogenesis; and (iv) refines the candidate cell-of-origin of these tumors. Collectively, this work redefines many key aspects of the pathogenesis of brain tumors and provides clear insight into their cellular architecture, with critical implications for clinical management.

Liau BB, Sievers C, Donohue LK, Gillespie SM, Flavahan WA, Miller TE, Venteicher AS, Hebert CH, Carey CD, Rodig SJ, Shareef SJ, Najm FJ, van Galen P, Wakimoto H, Cahill DP, Rich JN, Aster JC, **Suvà ML**, Patel AP, **Bernstein BE**. Adaptive Chromatin Remodeling Drives Glioblastoma Stem Cell Plasticity and Drug Tolerance. ***Cell Stem Cell.*** 2016 Dec 2. pii: S1934-5909(16)30399-X. doi: 10.1016/j.stem.2016.11.003. [Epub ahead of print]

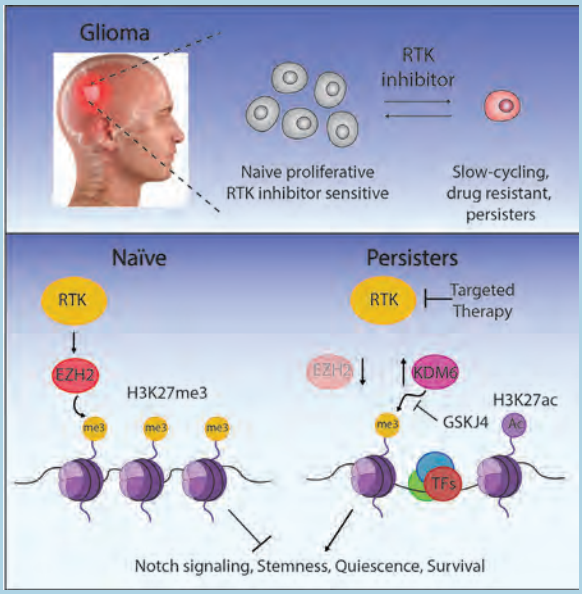
This paper demonstrates that glioblastoma stem cells (GSCs) reversibly transition to a slow-cycling, persister-like state following RTK inhibitor treatment. The persister state is marked by redistribution of repressive chromatin, upregulation of primitive neurodevelopmental programs, and dependency on histone demethylase KDM6. Persister-like cells pre-exist in primary human glioblastoma tumors, and thus may account for treatment failure. The study exemplifies how cancer cells may hijack primitive developmental programs and invoke chromatin reorganization for proliferation, adaptation, and tolerance.



Inferred developmental hierarchy in oligodendroglioma cells (n=4,044). Lineage and stemness scores of malignant cells from six patient tumors, with color-coded density for cycling cells (fraction of cycling cells within a Euclidean distance of 0.3) from each tumor across the backbone of the hierarchy.

Malka R, Nathan DM, **Higgins JM**. "Mechanistic modeling of hemoglobin glycation and red blood cell kinetics enables personalized diabetes monitoring." ***Science Translational Medicine***. 2016 Oct 5; 8(359): 359ra130.

This paper combined an understanding of the chemistry of glucose and the biology of blood cells in a mathematical model. The resulting model revealed that differences in blood cell age from one patient to the next are responsible for all of the error in the widely used HbA1c test and enabled determination of a personalized glucose level for each patient. This new method reduces errors by more than 50% using existing routine medical tests and will make it much easier for patients and their physicians to keep diabetes under control. More generally, this work shows how mathematical modeling of existing clinical laboratory data can generate novel insights into mechanisms of human disease with immediate translation to personalized medicine.



Intratumoral heterogeneity and alternate chromatin states underlie drug resistance in glioblastoma. RTK-amplification in GSCs drives rapid proliferation. Following RTK-targeted therapy, some cells reversibly transition to a slow cycling, drug-resistant state, characterized by KDM6-dependent chromatin remodeling, and activation of alternative signaling pathways. Liau et al. Cell Stem Cell, 2016 (DOI: http://dx.doi.org/10.1016/j.stem.2016.11.003)

Ronald E. Kleinman, MD, Chief

The research mission of the Department of Pediatrics is to advance translational basic, clinical and population science related to the health and development of infants, children, and adolescents. Research at MGHfC recognizes the challenges and opportunities for child health research dictated by the changing social, economic and health care policy landscape in the US, including the shift toward Precision Medicine. Across the Department, our research integrates multidisciplinary clinical and scientific expertise with local, regional, national and international collaborations.

With the appreciation that biological events beginning during gestation and continuing into childhood can strongly influence disease onset during childhood and beyond, we intend to expand our integrated models focused on pre-clinical/early and translational clinical studies to provide the rationale for possible therapeutic and/or preventive interventions. Our overarching goal is to improve the lives of children and families through science. A current strategic priority is to develop new effective personalized and preventive strategies for disorders starting in childhood by integrating multi-level, multisystem data ranging from the molecular to the whole child in order to prevent or reverse development of disease. 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 locally to advance new therapeutic, preventative and educational interventions for the millions of children affecting by the spectrum of allergic disease including both IgE- and non IgE-mediated forms of food allergy and asthma. A major research focus within the Division is on the mechanisms of immune-mediated food hypersensitivities including IgE-mediated food allergy, chronic gastrointestinal inflammatory diseases related to food allergy such as eosinophilic esophagitis and allergic proctocolitis. To advance this research effort, The Food Allergy Center at Massachusetts General Hospital (FAC@MGH) was established in 2010 as a multi-disciplinary research and clinical care virtual center with the recruitment of Dr. Shreffler to provide leadership, and the core participation of clinicians and investigators from Allergy / Immunology, Rheumatology, Gastroenterology, Dermatology, Pathology, Psychology, Nutrition, Child Life and the Harvard CTSA-supported, MGH Clinical Research Center (CRC). At the time of its inception, there were no clinical trials, interventional or otherwise, focused on food allergy at MGH. To date, the FAC@MGH has initiated than 30 IRB-approved studies on food allergy. These studies represent almost 3,000 research participants in total, more than 2,000 of whom have undergone oral food provocation tests (food challenges). These include randomized interventional trials for food allergy, including two studies funded by NIAID – (NCT01750879, NCT02698033), enrolling 100s of patients and conducting 1000s of study visits, demonstrating the capacity to carry out randomized interventional trials for the food allergic population, including the necessary regulatory compliance (cGCP and ICH), pediatric and adult patient recruitment, data management and all other necessary requirements. We have in these last six years carried out more clinical studies, involving more study participants, than any other center in Boston. Two studies, Gastrointestinal Microbiome and Allergic Proctocolitis (GMAP) and the Resolution of Allergy to Milk Protein (RAMP), have demonstrated our capacity to also carry out larger population cohort / low risk interventional trials: GMAP is an observational healthy newborn cohort study that has enrolled >950 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 and 2 years of age). RAMP is a randomized double blind trial (n=230) to assess the impact of probiotic and hydrolyzed milk formula to hasten tolerance to milk protein. In addition to a research concentration in Food Allergy, Dr. Perdita Permaul leads a project focused on the interaction between childhood obesity and allergic inflammation. The Division enjoys strong collaborations with academic and industry groups at BWH (The Channing Laboratory), BCH, MIT, The Broad Institute, Sanofi and others.

Cardiology

The Pediatric/Congenital Cardiology division is involved in research in basic science and health services research to understand the causes of congenital heart disease and to study clinical interventions to improve the provision of pediatric cardiovascular care and foster a patient centered environment. We are fortunate to have a robust clinical and academic environment to promote these research endeavors. Members of our service are engaged in basic science research understanding the genetic etiologies of vascular pathology such as aortopathies (for example, Marfan syndrome and Loeys Dietz syndrome). We are also involved in health services research specifically in the area of patient safety and quality as it pertains to pediatric cardiology. We have ongoing investigations evaluating diagnostic accuracy of cardiac imaging, investigations evaluating of parental health literacy among congenital heart disease families, and studies of resource use among patients undergoing congenital heart surgery. Our preventative cardiology service has collaborated with the Harvard T.H. Chan School of Public Health on projects to examine outpatient and wireless means to track physical activity and caloric intake.

Critical Care Medicine

The Division of Pediatric Critical Care Medicine focuses on two areas in which we have achieved national and international recognition:

innovative technology (led by Drs. Natan Noviski and Phoebe Yager) and global health (led by Dr. Ryan Carroll) in the clinical research arena; and neuroscience basic science research in the field of traumatic brain injury and protective mechanisms against oxidative injuries to the brain, led by Drs. Michael Whalen and Josephine Lok, respectively. Dr. Whalen was recently chosen to lead the animal studies group of Harvard affiliated investigators by the leadership of the NFLPA Grant to Harvard University. The mission of that study group is to use mouse models of human concussion, developed in Dr. Whalen's lab, to elucidate disease mechanisms of concussion and chronic traumatic encephalopathy. In addition, in the area of neuroscience clinical research, Dr. Sarah Murphy leads our efforts in several national multi-center studies including the ADAPT (site PI) and TRACK II TBI (co-investigator) studies.

Endocrinology

The focus of research in the Division of Endocrinology is to enhance the understanding of endocrine systems and endocrine disease during the childhood, adolescent and transition years. Areas of particular interest include investigations into the biology of conditions that span the nutritional spectrum from obesity to the female athlete triad to anorexia nervosa, utilizing state-of-the-art neuroimaging techniques coupled with investigations of circulating hormones important in appetite regulation, and carbohydrate, fat and bone metabolism, studies of the immunology of diabetes, and molecular approaches to beta cell regeneration. We will continue to foster an environment of inquiry and investigation among our faculty and fellows, work on optimizing funding opportunities to maintain a strong research base within the division. This includes intra- and extra-mural collaborations with other laboratories actively engaged in these areas to create a rich and interactive reinforcing environment that will lead to changes in medical care paradigms for children with endocrine disorders

Gastroenterology, Hepatology & Nutrition

Mucosal Immunology and Biology Research Center

Our mission is to expand clinical, basic and translational research in pediatric gastroenterology and nutrition to provide better outcomes for pediatric patients. Using a multidisciplinary approach, our major basic research mission is to characterize the role of the enteric mucosa and its mucosal barrier function at the interface between microbial luminal stimuli and lymphoid effector responses. We focus on the enterocyte and its involvement in microbial "crosstalk," lymphoid-nerve-epithelial interactions and inappropriate developmental responses secondary to epigenetic pressure by the gut microbiota during the first 1000 days of life. We also look at host-pathogen interactions during infection as well as how the enterocyte functions both as a barrier to antigen trafficking and as a site for the beneficial effects of probiotics in chronic inflammation. Finally, we are interested in the gut-brain axis, particularly as concern small intestinal and blood brain barriers in the contest of neuroinflammatory diseases. Our researchers examine strategies used by gut microbiota to affect the host and how these interactions lead to both local and systemic chronic inflammation and autoimmunity in the Mucosal Immunology and Biology Research Center. In addition, active clinical and translational research to implement personalized and primary preventive medicine is carried out in our Airway, Voice and Swallowing Center for Children; the Center for Celiac Research and Treatment; the Center for Diagnostic, Therapeutic and Interventional Endoscopy; the Center for Inflammatory Bowel Disease; the Center for Nutrition; the Center for Pediatric Hepatobiliary and Pancreatic Disease; the Food Allergy Program; the Liver Transplantation Program; the Lurie Center for Autism Pediatric Gastroenterology Program; the Neurogastroenterology Program and the Pediatric Weight Center.

General Academic Pediatrics

Our internationally-known academic research division continues to be dedicated to improving the health of children and adolescents through research on prevention and reduction of the burden of chronic disease among children; reduction and elimination of disparities in children's health and healthcare; and improving the health of populations across the lifecourse through innovations in research, patient care, education, and community advocacy. We also conduct research to prepare and support primary care pediatricians in the delivery of health care innovations. This research leverages clinical and community partnerships.

Genetics and Metabolism

Our Division is dedicated to understanding the genetic underpinnings of developmental and congenital disorders affecting the entire life course. We are actively engaged in basic science at the cellular and sub-cellular level at the bench and as well in translational and clinical studies to inform counseling, diagnostic and management services to help patients and physicians better understand the genetic contributions to their health and disease and to diagnose and treat a wide variety of genetic/ metabolic conditions. We have established specialty clinics in Metabolism, Lysosomal Storage Diseases, Mitochondrial disease, Turner Syndrome, William syndrome, 22q Deletion Syndrome, Hereditary Hemorrhagic Telangiectasia, CHARGE syndrome, a multidisciplinary Sensorineural Hearing Loss Clinic at the MEEI, an Autism Genetics Clinic at the Lurie Center, Pitt Hopkins Syndrome Clinic and Pediatric Cancer Predisposition Clinic. Our multidisciplinary Down Syndrome Clinic is world renown leading the way in care and research. This clinic enrolled patients in three new groundbreaking therapeutic trials of agents to improve cognitive function in people with Down syndrome. The MGH Genetics Division has been at the forefront of applying clinical whole exomic sequencing for diagnosis and new gene discovery in selected patients. Our services impact every field of pediatric and adult medicine.

Hematology/Oncology
The Hematology Oncology service will continue to focus on building excellence in multi-disciplinary clinics for our oncology and hematology patients and enhancing our clinical and lab based research efforts. The Brain tumor and head and neck sarcoma clinics are prime examples of this effort. These two multidisciplinary programs show increased growth with respect to new patient accruals and enrollment on clinical trials. In addition to our therapeutic studies, we continue to have important companion studies examining quality of life and neurocognitive sequelae after completion of treatment. Our Long-Term Survivor Clinic, a member of the New England childhood cancer survivor consortium, is reaching out to more of our adult survivors of childhood cancer and collaborating with the MGH Cancer Center in new initiatives including Sexual health and fertility. This consortium presents an opportunity for additional collaborative research in our growing population of long term survivors. We are collaborating across disciplines and departments at MGH and MGHfC with respect to our lab based research initiatives. Our joint research effort with Dr. Rivera in the Department of Pathology has focused on the epigenetics of Ewing's sarcoma and medulloblastoma. We have a new and exciting project with Dr. Jain in Radiation oncology examining the influence of the microenvironment in various pediatric solid tumors and novel approaches to treating medulloblastoma. We continue to collaborate with our colleagues at the Broad Institute at MIT in performing both germ line and tumor whole exome sequencing to identify new germ line mutations that predispose to malignancy in our youngest patients.

Infectious Disease
The Pediatric Infectious Disease Unit has been active in both basic science and in translational/clinical research. Dr. Harris's externally funded cholera research efforts encompass investigation of the immune response to Vibrio cholerae infection with an emphasis on vaccine response and development, and exploration of the molecular epidemiology and ecology of V. cholerae. Dr. Warren's pivotal discovery over the past several years of the differential genomic responses between humans and mice to sepsis and inflammation has led to the establishment of a large multicenter project to investigate mechanisms responsible for species-specific sensitivity to inflammation and to develop novel therapies to treat human sepsis. Dr. El Saleeby has continued to pursue host-respiratory syncytial virus (RSV) interactions, and is beginning to establish a program in antibiotic/antiviral pharmacology. Dr. Pasternack has been part of a clinical and research consortium focused on the study of children with PANDAS (pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection). Dr. Pierce is engaged in the development of novel molecular diagnostic tools for the clinical microbiology laboratory.

Lurie Center
At the Lurie Center for Autism, the primary focus is to partner with individuals and families to incorporate groundbreaking research into the practice of clinical medicine. The integration of clinical care and clinical research through the initiation of clinical treatment trials continues to be a focus. In July 2016, we welcomed the first Director of Research Dr. Staci Bilbo. Her primary goal will be to conduct and oversee preclinical and translational research projects, including those involving neuroimaging, genetics, and animal models of autism and neuroimmunology, with the aim of accelerating their translation into novel treatment approaches that will ultimately be paired with individual patients. A second goal is to initiate and strengthen collaborations with research groups across Boston, the nation and the world, capitalizing on modern informatics approaches and attracting new researchers into the field of autism.

Neonatology and Newborn Medicine
The research efforts in the Neonatology and Newborn Medicine Unit are multifaceted and range from basic science to epidemiology. All research projects share a common mission, which is to advance scientific knowledge aimed at improving the care and treatment of our very vulnerable patients and their families. Reflective of the broad spectrum of issues we face clinically: from extremely low birth-weight infants and the myriad medical issues they face, to full-term infants with various congenital anomalies or those born with physiologic dependence to opioids due to in-utero exposure, we have the following main research foci: 1. Developmental biology including the use of human pluripotent stem cells to better understand how genetic disorders and prematurity affect human development and efforts to create new strategies and treatment to mitigate their negative impact; 2. Neuroprotection strategies, including an examination of those factors that affect neurodevelopmental outcomes following hypoxic post-natal insults; 3. interventions to mitigate the effects of substance abuse disorders pre and post natally.

Nephrology
The Nephrology Division has a major focus on the molecular biology of rare genetic disorders affecting the regulation of mineral ion homeostasis, with a particular emphasis on the different forms of pseudohypoparathyroidism type Ib (PHP1B) and hypoparathyroidism. A novel, maternally inherited GNAS deletion was identified as a cause of autosomal dominant PHP1B and a novel GNA11 mutation was identified as another cause of autosomal dominant hypoparathyroidism; interestingly, this latter mutation is associated not only with hypocalcemia, but also with short stature implying that the mutation in this signaling protein accelerates growth plate maturation.

Pulmonary

The research focus of the Pulmonary Division encompasses 4 areas. The first area of research, led by Dr. Bernard Kinane, is the genetic basis of lung disease, including interstitial lung disease and non-cystic fibrosis bronchiectasis. In collaboration with the Partners Center for Personalized Medicine, we have developed novel whole exome and genetic panel approaches, which allow for rapid and multiple gene analysis. This year we defined the spectrum mutations in a protein called ABCA3 that cause interstitial lung disease. The second area, led by Dr. Lael Yonker, is an effort to develop new approaches to the treatment of Pseudomonas infections in the airway of patients with Cystic Fibrosis by defining the mechanisms that induce airway inflammation. A particular direction was the identification of the mechanisms by which neutrophil migration is regulated by Pseudomonas infections. The third area, led by Drs Yonker and Fracchia, is clinical research looking at the use of correctors and potentiators of CFTR to treat cystic fibrosis. The fourth area, led by Drs. Kinane and Scirica, examines the use of social media to educate teenagers about the impact of obesity on severity of asthma and to use these media to implement effective lifestyle changes for the treatment of obesity.

Achievements

Academic Pediatrics

The Impact of the First 1,000 Days on Childhood Obesity

Obesity is seen in all age groups in the United States, with one-third of U.S. children and adolescents ages 2 to 19 estimated to be overweight or obese. The first 1,000 days, or the period from conception until a child turns 2, is increasingly recognized as a critical period for the development of childhood obesity and its adverse consequences. Dr. Elsie Taveras and her research team published two review papers that examined evidence on risk factors in the first 1,000 days for developing childhood obesity later in life and evidence on interventions in the first 1,000 days that could prevent childhood obesity later in life. Despite mounting evidence that the first 1,000 days is an important period in the development and prevention of childhood obesity, no previous systematic review focused on the factors that contribute to childhood obesity during this period. The systematic review of nearly 300 studies finds several risk factors during the first 1,000 days that were consistently associated with later childhood overweight, including higher maternal pre-pregnancy BMI; maternal excess weight gain during pregnancy; prenatal tobacco exposure; high infant birth weight; and high infant weight gain. Targeting these factors holds promise for childhood obesity prevention efforts. The systematic review of interventions occurring in the first 1,000 days showed that most interventions demonstrated an effect by focusing on individual- or family-level behavior changes through home visits; individual counseling or group sessions in clinical settings; or using a combination of home and group visits. Taken together, the two papers suggest that programs and efforts focusing on multiple risk factors and delivered at multiple levels (individual, family, and community) through various sectors (healthcare, industry, and policy) may help reduce childhood obesity risk. The challenge now is to be innovative in the creation of population-level obesity prevention interventions that are cost-effective and sustainable.

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Impact of the Tobacco 21 Project in Massachusetts

For the past 5 years Dr. Winickoff and his team have been leading the research and advocacy effort to change the tobacco sales age to 21 years old. Dr. Winickoff and his team began volunteering time and setting up local meetings with boards of health to convince them to raise the tobacco sales age to 21. Data from this effort demonstrated a 47% reduction in smoking among high school students after the minimum age for purchasing tobacco was raised to 21 in Needham, MA. Dr. Winickoff's article: Tobacco 21 an Idea Whose Time has Come published in the New England Journal of Medicine (2014) gave wide attention to this novel tobacco control strategy in the medical community. The follow-up paper: Have Tobacco 21 Laws Come of Age? NEJM (2016), demonstrate high levels of support nationally for this approach regardless of political party affiliation. This team's ongoing research and dissemination efforts have directly led to 140 cities and towns in Massachusetts adopting tobacco 21 sales laws. Dr. Winickoff has also presented this research to the Institute of Medicine (IOM) in Washington D.C., which, in a separate report, concluded that raising the tobacco sales age to 21 will save hundreds of thousands lives.

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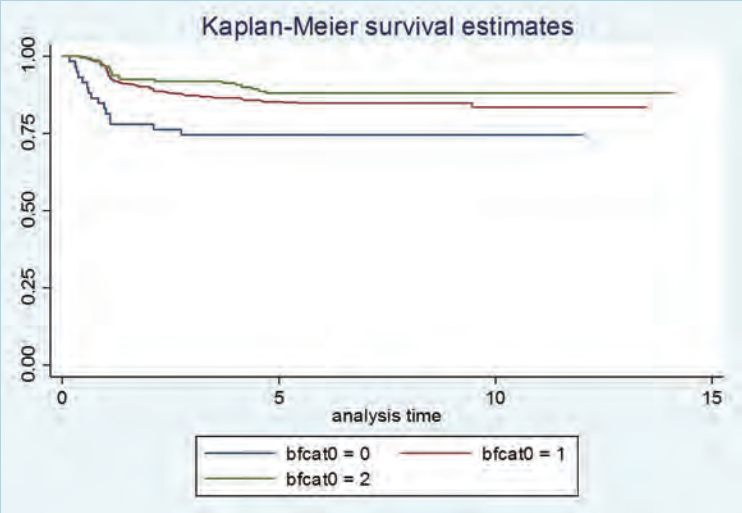
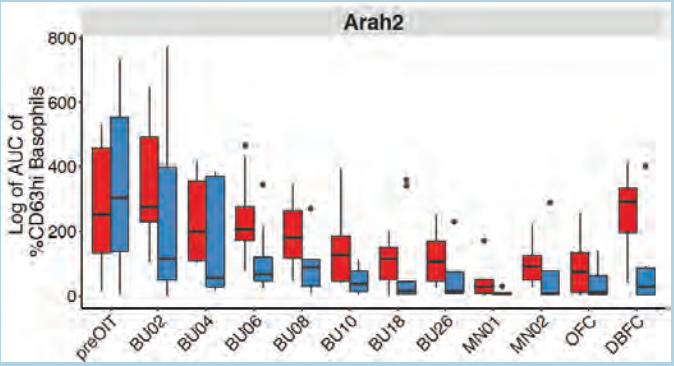


Lack of breast feeding in the first 2 months (blue line) is a risk factor for allergic proctocolitis in comparison to either exclusive breast feeding (red) or breast feeding with milk formula supplementation. Martin, Virkud, Keet, Shreffler, Yuan, et al. GMAP Study (manuscript in preparation).

Allergy and Immunology Risk Factors for the Development of Allergic Proctitis

From the Gastrointestinal Microbiome and Allergic Proctocolitis (GMAP) cohort, we have for the first time prospectively defined the cumulative incidence of allergic proctitis (AP) in a U.S. suburban cohort and evaluated risk factors for the development of this early form of food allergy, predominantly triggered by cow's milk allergen. Breast-feeding was associated with lower rates of AP, particularly when combined with milk formula supplementation. Mode of delivery, perinatal antibiotic exposure, and presence of siblings were not associated with AP.



Patil, Ruiter, Shreffler, et al. (manuscript in preparation).

Mechanism of Immune Tolerance during Oral Allergen Immunotherapy

Basophil suppression during oral allergen immunotherapy for peanut allergy is transient in patients who fail to achieve a sustained clinical benefit (red boxes) versus those who do (blue boxes) as seen by divergence in response to stimulation with the peanut allergen, Arah2, at the DBFC time point. These findings suggest that the mechanisms of transient suppression are distinct from those resulting in sustained clinical protection.

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Endocrinology

Studies from the Division of Pediatric Endocrinology have demonstrated that estrogen sufficient (eumenorrheic) adolescent and young adult athletes 14-25 years old engaged in aerobic activities perform better for measures of verbal memory and executive function than estrogen deficient (amenorrheic) athletes (AA) and non-athletes respectively. They have better organizational strategies that are known to be beneficial for learning and memory, an effect probably mediated by estrogen, and have better executive control, which could represent the combined positive influence of exercise and estrogen status. Following six months of estrogen replacement, AA randomized to the transdermal 17-beta estradiol estrogen patch, but not those randomized to oral ethinyl estradiol pills, show significant improvements in both verbal memory and executive control compared to those randomized to no estrogen.

Effects of Exercise and Estrogen Status on Cognitive Function (Verbal Memory and Executive Control) in Adolescent and Young Adult Athletes 14-25 years old

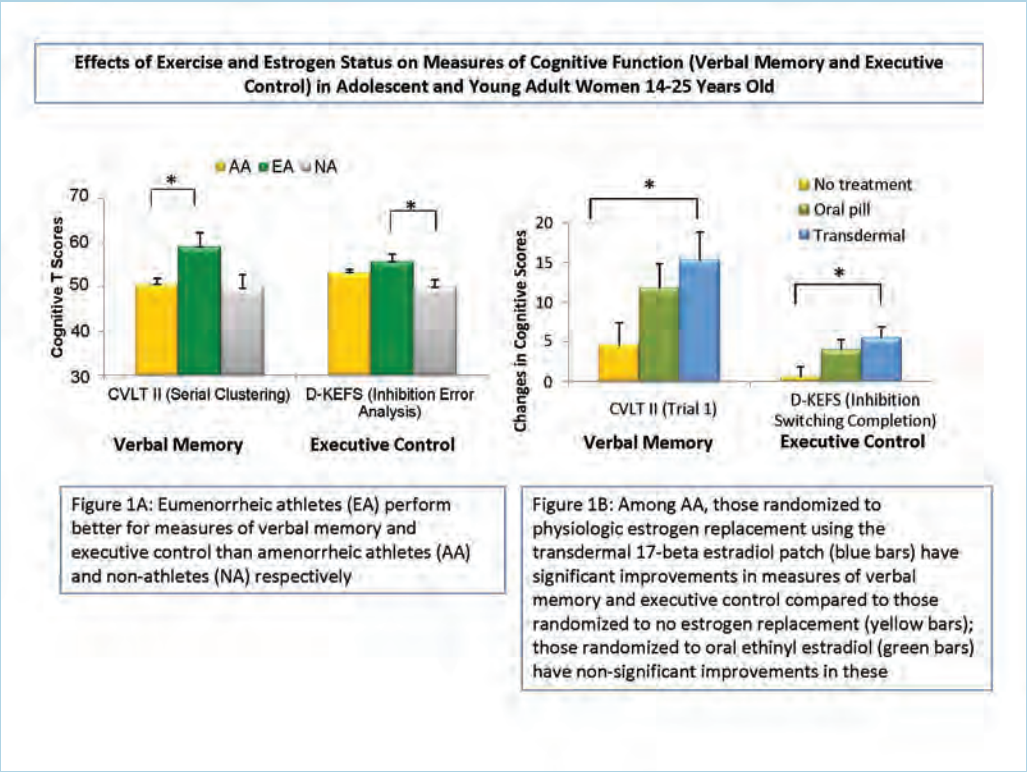

Figure 1A: Eumenorrheic athletes (EA) perform better for measures of verbal memory and executive control than amenorrheic athletes (AA) and non-athletes (NA) respectively

Figure 1B: Among AA, those randomized to physiologic estrogen replacement using the transdermal 17-beta estradiol patch (blue bars) have significant improvements in measures of verbal memory and executive control compared to those randomized to no estrogen replacement (yellow bars); those randomized to oral ethinyl estradiol (green bars) have non-significant improvements in these

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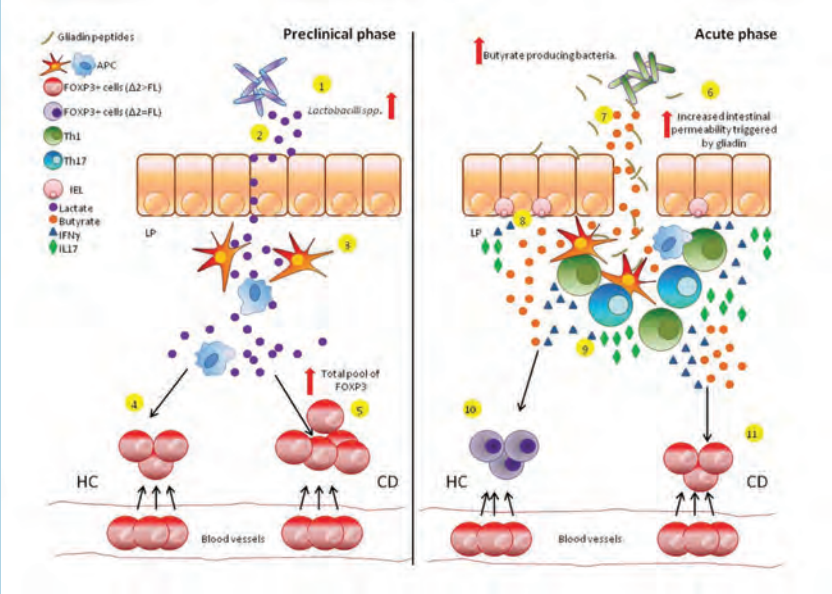
Mucosal Immunology and Biology Research Center - Pediatric Gastroenterology, Hepatology & Nutrition

Researchers at MIBRC have been successful in securing NIH, industry, and foundation funding to continue supporting our basic, translational, and clinical research portfolio, The Center for Celiac Research and treatment at MGHfC, a key component of the Harvard Program of Celiac Research, celebrated its 20th anniversary this year, consolidating its international visibility for its cutting edge education, research, and clinical care. A major focus of our laboratory has been to examine the role of the gut microbiome in causing epigenetic changes of key host functions that can be mechanistically linked to disease pathogenesis. Our recent work has shown, for the first time, that changes in the intestinal microbiome cause epigenetic modifications that are mechanistically associated with immune surveillance. That is, we have shown how factors in the environment of the intestinal microbiome activate the adaptive immune response that can be linked to the onset of celiac disease. This work involved a study of two isoforms of FOXP3, a transcription factor fundamental for the suppressive function and differentiation of Treg cells, which are critical in protecting against autoimmunity. The findings from this work show that innate defects in

the Treg cell population can lead to a different metabolic response to the same microenvironment. This is the first report of an epigenetic effect of microbiota-derived metabolites and inflammatory cytokines playing a key role in a key immune component of an autoimmune disease such as celiac disease.

Proposed Sequence of Events Contributing to the Development of Celiac Disease



Increased production of lactate associated with enrichment in Lactobacilli spp. has been shown to characterize the preclinical phase of individuals predisposed genetically to CD .The interaction between this microbial-derived metabolite and antigen-presenting cells (APC) triggers a regulatory phenotype on the cells . CD patients seem to be more responsive to lactate than healthy controls (HC). During the active state of the disease the small intestine of CD patients is characterized by a drop in lactate levels, an increased intestinal permeability due to the interaction between gliadin and epithelial cells, high production of butyrate from the microbial flora, and production of a high amount of proinflammatory cytokines. In HC subjects the local micro-milieu characterized by this proinflammatory environment and microbiome-derived excess butyrate causes the FoxP3 epigenetic switch toward the more functional (and, therefore, more protective) FL isoform restoring the equilibrium between FoxP3 isoforms. Conversely, in CD patients Treg cells are not capable of undergoing this epigenetic modification and persistently over-express FoxP3 D2 (less functional) over FL, leading to chronic inflammation and, eventually, autoimmune enteropathy.

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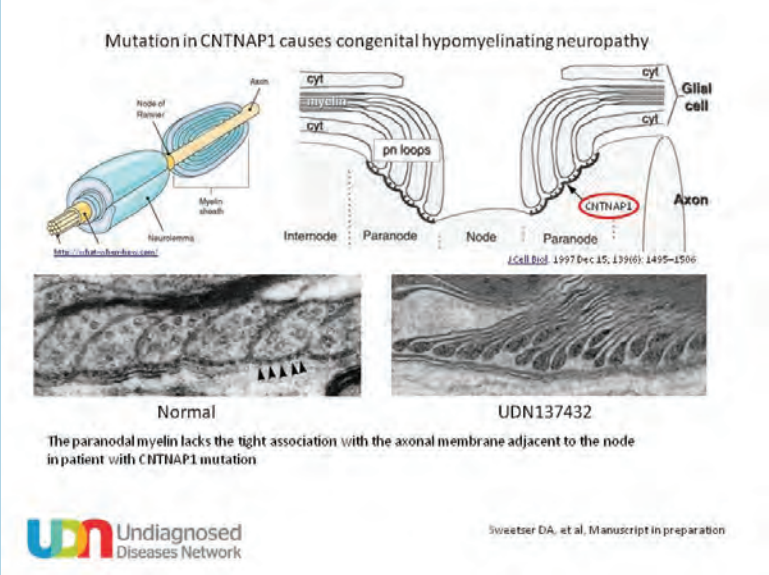
Medical Genetics and Metabolism

This past year has seen the full scale launch by the MGH Medical Genetics and Metabolism Division of the NIH sponsored Undiagnosed Diseases Network. Leveraging the unique combination of scientific and medical expertise and resources at the NIH and six new clinical sites around the country of the Undiagnosed Diseases Network this endeavor seeks to provide answers to patients with mysterious conditions that have long eluded diagnosis despite extensive analyses, and to advance medical knowledge about rare and common diseases. Of the 16 patients we have evaluated at MGH we made 4 diagnoses and are actively pursuing diagnoses in many of the other cases. The diagnoses made to date include PLA2G6-related neurodegeneration with brain iron accumulation, CNTNAP1-associated congenital hypomyelinating neuropathy, GABRG2-related seizure and intellectual disability disorder, and GNAO1-related movement disorder with mild intellectual disability. Many of these represent newly described and extremely rare orphan genetic disorders. Biological specimens collected and collaborations with model organism cores are further extending our understanding of these disorders.

Phenotypic Associations with CNTNAP Mutations Previously Known to Cause a Lethal Congenital Contracture Syndrome



A 13 month old child (UDN137432) with profound hypotonia, sensorineural hearing loss, slow nerve conduction velocities, cerebral atrophy, and dependency on CPAP and G tube feeds was referred to the MGH Undiagnosed Diseases Network for evaluation. Whole exome sequencing identified a homozygous mutation in CNTNAP1, a protein localized to the Node of Ranvier. As shown in the figure above, electron microscopy of a sural nerve biopsy demonstrates the poor association of paranodal myelin with the axonal membrane in this patient. This finding extends the phenotype associated with CNTNAP mutations previously known to cause a lethal congenital contracture syndrome.

Hematology/Oncology

The laboratory of Dr. David Sweetser has made major breakthroughs in determining the key signaling pathway controlled by the TLE/Groucho tumor suppressor genes, which act as major gatekeepers in blocking the action of numerous oncogenes. In two landmark papers published this last year, one in PNAS and the other in Leukemia Research, Dr. Sweetser showed, both in an AML leukemia cell line, as well as in a mouse knockout line, that these proteins act as major regulators of inflammatory pathways and that anti-inflammatory agents have a substantial anti-leukemia effect on subtypes of AML. These results also have broad implications to our understanding of a variety of autoimmune disorders.

Relevant References

1. Ramasamy S, Saez B, Mukhopadhyay S, Ding D, Ahemd AM, Chen X, Pucci F, Yamin R, Pittet MJ, Kelleher CM, Scadden DT, and Sweetser DA. Tle1 tumor suppressor negatively regulates inflammation in vivo and modulates NF-⊠B inflammatory pathway. PNAS 2016, 113:1871-6.
2. Shin TH, Brynczka, Dayyani F, Rivera M, and Sweetser DA. TLE4 Regulation of Wnt-mediated Inflammation Underlies its Role as a Tumor Suppressor in Myeloid Leukemia. Leuk Res. 2016;48:46-56.

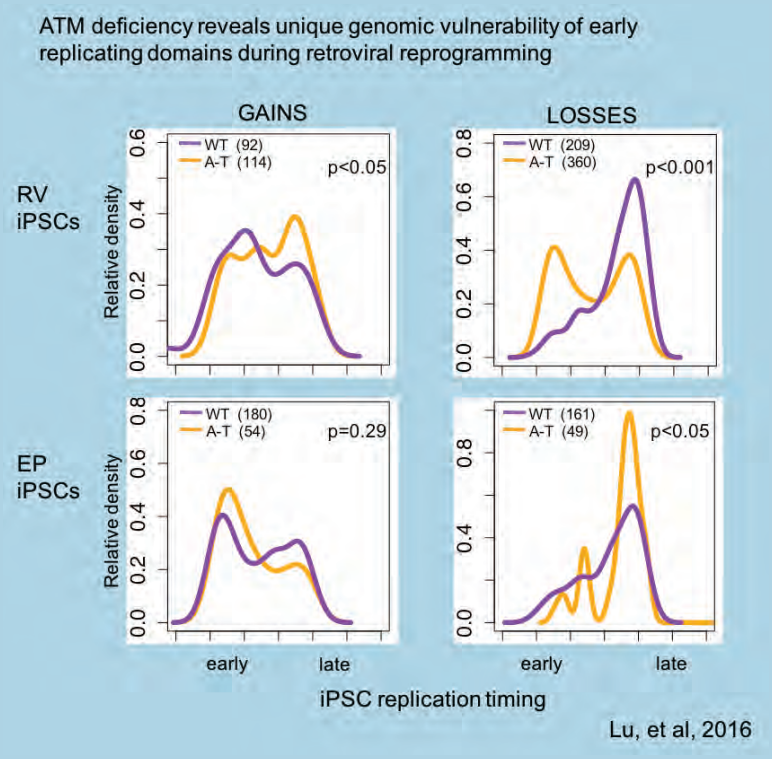
Infectious Disease

Dr. Jason Harris has been actively characterizing the B cell response to cholera and cholera vaccines analyzed at the individual cell / antibody level. He has identified the basis of partial serotype specificity and long term memory against the O antigen. In addition, he has identified several novel targets of the immune response to cholera including a sialidase that potentiates the effect of cholera toxin. This may impact the development of advanced Vibrio cholerae vaccines.

Neonatology and Newborn Medicine

Paul Lerou followed up prior work on the role of chromatin organization during cellular reprogramming and demonstrated that the early replicating genome (open chromatin) is uniquely vulnerable during reprogramming using integrating vectors (1). Beyond this basic science work, the division has welcomed five new clinical-translation studies into the NICU and newborn units reflecting the broad spectrum of newborns we care for. All these projects share a common mission, which is to advance scientific knowledge aimed at improving the care and treatment of our very vulnerable patients and their families. The improvement of our clinical-translational research portfolio division has been facilitated by the creation of a perinatal clinical research committee.

ATM Deficiency and Unique Genomic Vulnerability of Early Replicating Domains



Therapeutic and research potentials of human induced pluripotent stem cells (iPSCs) are critically limited by the presence of many forms of genomic variations, in particular copy number variations (CNVs). iPSCs from healthy volunteer (WT) or patients with ATM deficiency (A-T) were generated using integrating retroviral (RV) or non-integrating episomal (EP) vectors. Kernel density plots show the differential replication timing distribution of CNV gains and losses detected in these iPSCs, revealing vulnerability of early replicating genome to retroviral

Relevant References

1. Lu J, Li H, Baccei A, Sasaki T, Gilbert DM, Lerou PH. Influence of ATM-Mediated DNA Damage Response on Genomic Variation in Human Induced Pluripotent Stem Cells. Stem Cells Dev. 2016 May 1;25(9):740-7. PMID: 26935587

Nephrology

The Division of Nephrology extended its identification of novel genetic mutations associated with calcium phosphorus metabolism, including those found in a mother and her two sons affected by Jansen's metaphyseal chondrodysplasia, who are all carriers of the previously identified H223R mutation in the PTH/PTHrP receptor.

Relevant References

1. Takatani R, Molinaro A, Grigelioniene G, Tafaj O, Watanabe T, Reyes M, Sharma A, Singhal V, Raymond FL, Linglart A, Jüppner H. Analysis of multiple families with single individuals affected by pseudohypoparathyroidism type Ib (PHP1B) reveals only one novel maternally inherited GNAS deletion. J. Bone Miner. Res. 2016;31:796–805. PMC4826817. PMID: 26479409
2. Tenhola S, Voutilainen R, Reyes M, Toiviainen-Salo S, Jüppner H, Mäkitie O. Impaired growth and intracranial calcifications associated with autosomal dominant hypocalcemia caused by a GNA11 mutation. Eur. J Endocrinol. 2016;175:211-218. PMID: 27334330
3. Nampoothiri S, Fernández-Rebollo E, Dhanya Yesodharan, Thomas J. Gardella, Eric T. Rush, Craig B. Langman, Jüppner H. Jansen Metaphyseal Chondrodysplasia due to heterozygous H223R-PTH1R mutations with or without overt hypercalcemia. J. Clin. Endocrinol. Metab. 2016;101:4283-4289.

Psychiatry

Department Report

Jerrold F. Rosenbaum, MD, Chief

Psychiatric disorders are the leading cause of disability worldwide. The MGH Department of Psychiatry is dedicated to alleviating the suffering and burden of mental illness through its four-fold mission:

Clinical Care: The Department of Psychiatry aims to provide the highest standard of care for our patients and their families across the full spectrum of psychiatric, psychological and substance use disorder, both for adults and children/adolescents. The department's more than 600 affiliated psychiatrists, psychologists and social workers serve as clinicians, researchers, supervisors and/or teachers, and include some of the field's most accomplished and recognized specialists, particularly in psychopharmacology, cognitive-behavioral therapy and behavioral medicine. For its exceptional results in patient care, the MGH Department of Psychiatry has been rated the #1 department of psychiatry in 19 of the past 22 years (during all of which we have been in the top three) in the annual "America's Best Hospitals" survey by US News & World Report.

Research Innovation: The Department's vast array of clinical, translational and basic research programs is dedicated to pioneering advances in neuroscience, genetics, therapeutics and the prevention of psychiatric disorders. The department has one of the three largest clinical research programs in the hospital. Using cutting-edge tools such as neuroimaging, genetics and genomics, and experimental animal and cellular models, Department of Psychiatry researchers are beginning to map the pathways through which brain biology interacts with life circumstances and events to produce psychiatric illnesses. This research is making it possible to pinpoint affected areas of the brain; understand inherited risk factors and the role of environmental stress; develop more effective psychotherapies, medications, and neurotherapeutic treatments; and ultimately to prevent these illnesses from occurring by intervening early. In FY16, the Department had more than $58 million in research support, continuing its record of successful funding despite an increasingly challenging funding environment.

Professional Education: The Department of Psychiatry offers in-depth postgraduate education that trains the next generation of mental health professionals. For our colleagues at MGH and across the globe, our experts share the latest clinical and research advances to help improve access to and quality of psychiatric care. Each year, we train 100 adult and child psychiatry residents, psychology interns and clinical fellows to be leaders in their areas of specialization. And our education reaches another 65,000 psychiatrists, non-psychiatric physicians and other health professionals through the Psychiatry Academy and its dozens of webinars, simulations, online courses, live conferences and more. In addition, the Department educates professionals in education, law enforcement, clergy and the military who work with patients and families affected by psychiatric conditions. Through an array of programs, our experts provide them with an enhanced understanding of mental health techniques they can use to assist affected individuals.

The Massachusetts General Hospital Psychiatry Academy was tapped by the New York Office of Mental Health to coordinate education and facilitate specialty consultation in child psychiatry. The Psychiatry Academy received a five year $4.9 million contract to run New York's Project TEACH Statewide Coordination Center, with a goal of expanding the program's reach throughout the state. Project TEACH, short for "Training and Education for the Advancement of Children's Health," links pediatric primary care providers with child psychiatrists who provide immediate consultations to help connect pediatric patients to appropriate care. This innovative program aims to help close the gap between the rising need for pediatric behavioral health services and available providers who can help. The Psychiatry Academy has been selected to operate this center, while also evaluating the program to assess its impact on the health of New York's youth population.

Last year the Psychiatry Academy began another new program, Mass General Visiting. Visiting's goal is to reduce the risks and disparities associated with the physician shortages, patient outcomes, education and quality leadership in health care systems. Partnering with health care organizations of all sizes, we create high-level quality improvement programs that mitigate the impact of physician shortages and treatment shortfalls. We do this by leveraging the extensive faculty and resources of Massachusetts General Hospital and Harvard Medical School. We utilize that expertise to provide customized solutions for provisional clinical services, telehealth, interim leadership personnel, continuing medical education, and clinical and financial consultation.

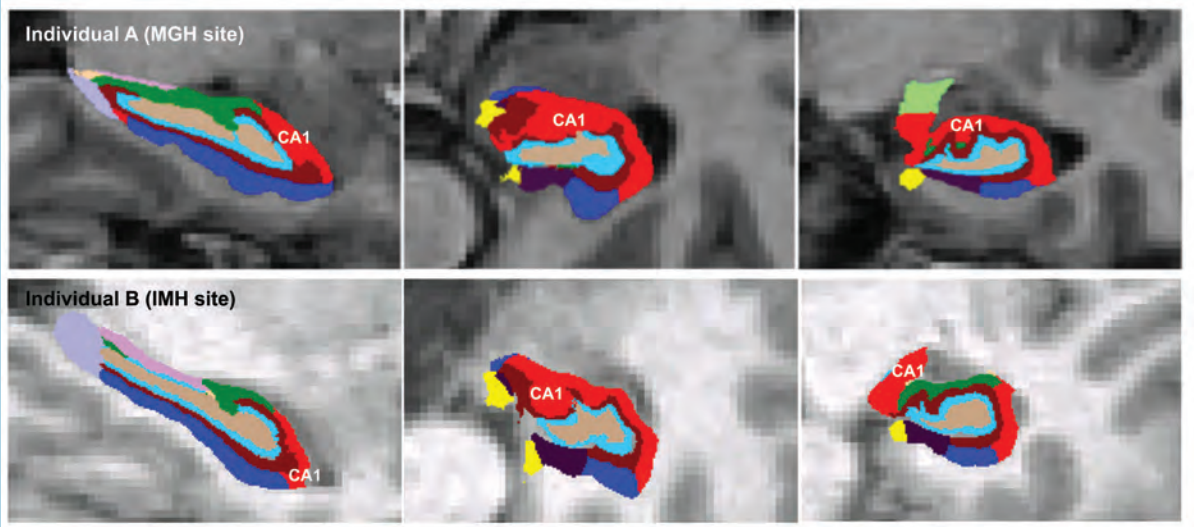
Community Service: To address the mental health needs of people who live in MGH neighborhoods and suffer from mental illness, substance use disorders, poverty, immigration challenges, homelessness and multiple trauma, the Department of Psychiatry partners with local organizations through its Division of Public and Community Psychiatry. Last year and continuing, as part of the MGH Strategic Plan, and with the Department of Medicine, we are engaged in a hospital wide Substance Use Disorders (SUDS) initiative, one feature of which involves the inclusion of people in recovery from addiction ("recovery coaches") as part of the treatment team. The Department also offers free patient and family education programs in Boston through its Psychiatry Academy. To serve the hospital's global neighbors, the Chester M. Pierce, MD Division of Global Psychiatry, the first hospital global psychiatry program in the United States, addresses the acute

shortage of mental health professionals in developing countries through program development and training.

Achievements

Daphne J. Holt, M.D., Ph.D.: Understanding disease progression in the early stages of schizophrenia using MRI. A reduction in the volume of the hippocampus is one of the most replicated findings of investigations of the neurobiology of schizophrenia. However, the sequence of events and pathophysiological mechanisms that underlie this observation have been difficult to identify. Recently, new clues about this observation have come from applications of advanced neuroimaging methods to this question; studies which have used novel techniques to examine the distinct subfields of the hippocampus separately have found that the CA1 subfield is selectively affected early in the course of schizophrenia. Moreover, a recent study conducted at MGH and the Institute of Mental Health in Singapore by Ho et al demonstrated that the atrophy that is initially limited to the CA1 subfield spreads to other hippocampal subfields as the disease progresses. This progressive decline in hippocampal volume during the early stages of schizophrenia correlates with symptomatic worsening. Based on this emerging body of work, the hope is that further confirmation and a deeper understanding of the mechanisms underlying this specific pattern of hippocampal atrophy in schizophrenia can provide a clearly defined target for investigations of the molecular basis of this brain-based phenotype and novel treatments for the illness.

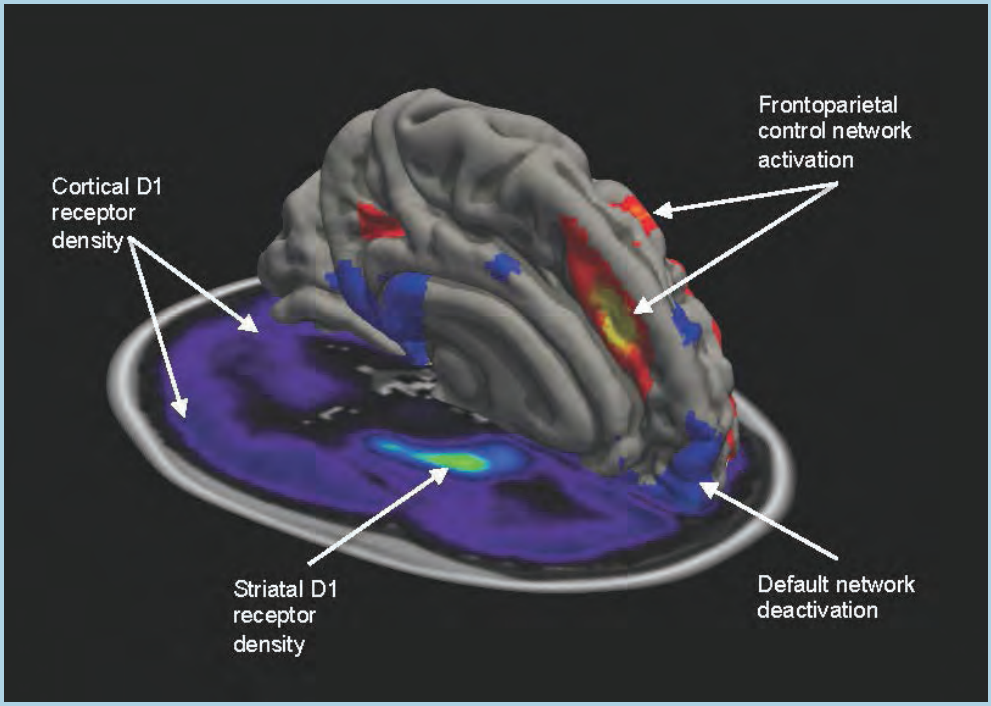
Ho N-F, Iglesias JE, Sum MY, Kuswanto CN, Sitoh YY, De Souza J, Hon Z, Fischl B, Roffman JL, Zhou J, Sim K, Holt DJ. Progression from selective to general involvement of hippocampal subfields in schizophrenia. Molecular Psychiatry. advance online publication, 23 February 2016; doi:10.1038/mp.2016



The borders of the subfields of the human hippocampus can be accurately identified in the MRI scans of human brains using an automated segmentation procedure developed at the MGH/HST Athinoula A. Martinos Center for Biomedical Imaging.

Joshua L. Roffman, M.D.: Dopamine D1 signaling organizes network dynamics underlying working memory (published online in Science Advances on 6/3/16). Working memory dysfunction is a common, debilitating, and currently untreatable aspect of schizophrenia. While functional MRI studies of schizophrenia patients clearly demonstrate abnormalities in the brain networks that underlie working memory performance, it is critical to link these altered cortical dynamics with underlying cellular mechanisms in order to develop effective treatments. Using simultaneous PET-MRI scans, a new technology developed at the Martinos Center, we were the first to relate variation in dopamine signaling to cortical network dynamics that underlie working memory in real time. We discovered that cortical dopamine helps to uncouple the network that is primarily responsible for working memory performance (the frontoparietal control network) from a second network that is active at rest (the default network). This network dissociation echoes the known effects of dopamine on the cellular level, where it improves the tuning of cortical pyramidal neurons to task-relevant stimuli. Our results provide new anatomical and functional insights into dopamine signaling, and take an important step toward developing personalized interventions to improve working memory deficits in schizophrenia.

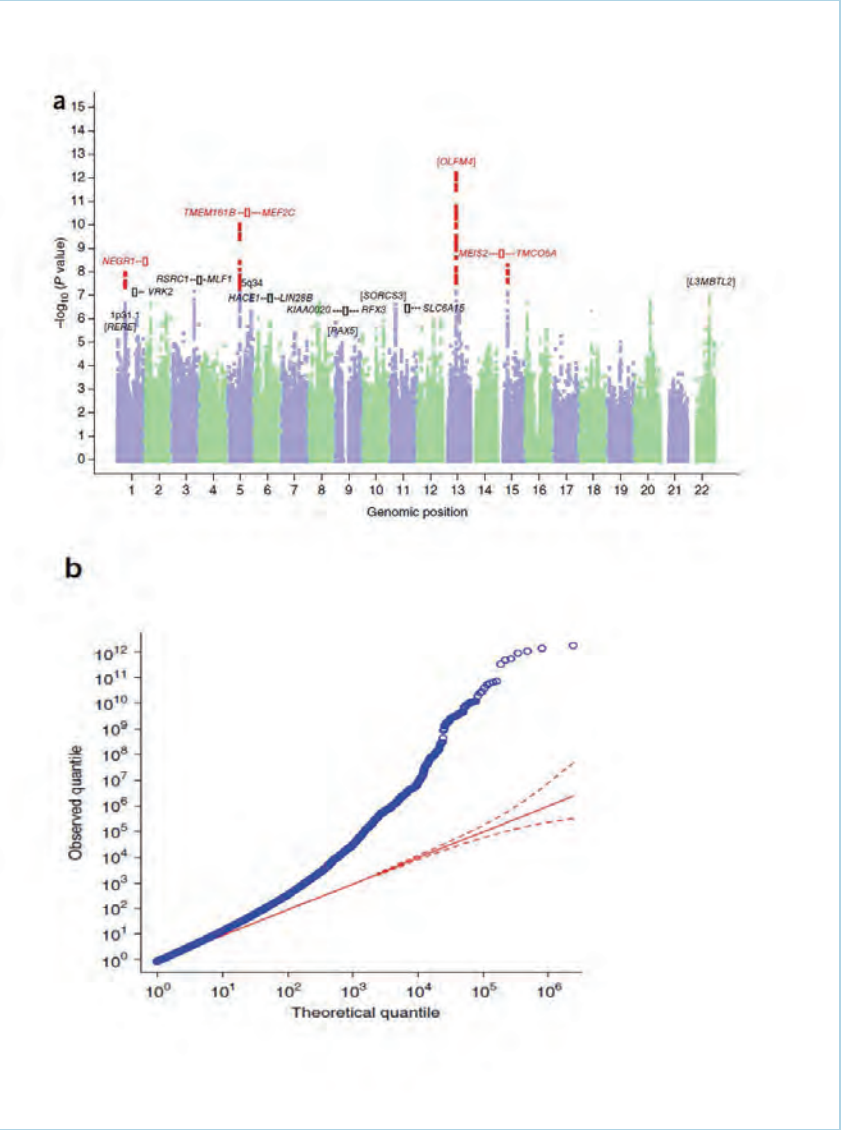
Joshua L. Roffman, Alexandra S. Tanner, Hamdi Eryilmaz, Anais Rodriguez-Thompson, Noah J. Silverstein, New Fei Ho, Adam Z. Nitenson, Daniel B. Chonde, Douglas N. Greve, Anissa Abi-Dargham, Randy L. Buckner, Dara S. Manoach, Bruce R. Rosen, Jacob M. Hooker, Ciprian Catana



Simultaneously obtained functional MRI and PET data relate working memory-related network activity to dopamine D1 signaling in real time. From: Roffman JL et al, Science Advances, 2016.

Roy Perlis, MD, MSc: Genome regions associated with major depression: Dr. Perlis and colleagues identified the first regions of genome associated with major depressive disorder. Previous smaller genome wide association studies had failed to reliably identify any risk variants in individuals of Northern European descent, prompting Dr. Perlis to consider alternative and less costly means of studying large clinical cohorts. Specifically, Perlis and colleagues partnered with the consumer genomics company 23andme to study more than 75,000 individuals diagnosed with depression, and more than 200,000 healthy controls. They found 15 regions of genome associated with risk; these loci were enriched for genes implicated in brain development. These genes provide a new perspective on the biological investigation of one of the most common and disabling brain diseases. More generally, they demonstrated the viability of using large-scale consumer genomics data to discover risk genes for complex diseases, an approach which may be applied across medicine.

Craig L Hyde, Michael W Nagle, Chao Tian, Xing Chen, Sara A Paciga, Jens R Wendland, Joyce Y Tung, David A Hinds, Roy H Perlis & Ashley R Winslow: Identification of 15 genetic loci associated with risk ofmajor depression in individuals of European descent
Nature Genetics, August 1, 2016; doi:10.1038/ng.3623



Figures a and b: Discovery-phase meta-analysis of 23andMe self-report ascertainment of major depression (75,607 cases and 231,747 controls) and PGC MDD (9,240 cases and 9,519 controls). (a) Manhattan plot of the discovery-phase 23andMe GWAS. The intercept calculated by LD score regression was used for inflation correction. The threshold for genome-wide significance (P < 5 × 10−8) is represented by the horizontal purple line. Red dots correspond to SNPs with P values smaller than the genome-wide significance threshold. Regions labeled in black denote loci that reached genome-wide significance in the joint analysis. The hg19 release of the UCSC Genome Browser was used for mapping. SNP location is denoted by []. If the SNP occurs between genes, then the distance from those genes is denoted by dashes: no dash, ??1 kb; -, ??10 kb; --, ??100 kb; ---, ??1,000 kb. (b) Quantile–quantile plot for the 23andMe MDD GWAS.

Radiation Oncology

Department Report

Jay S. Loeffler, MD, Chief

The Edwin Steele Laboratories for Tumor Biology – The Steele Laboratories include a highly interactive and multidisciplinary team of Principal Investigators directed by Professor Rakesh K. Jain. Their complementary research goals are, 1) To gain further mechanistic understanding of the vascular, interstitial and cellular barriers to the delivery and efficacy of molecular– and nano-medicines in solid tumors; 2) To develop new strategies to overcome these barriers using state of the art imaging techniques and animal models; 3) To translate these insights into the clinic to improve treatment outcome in cancer patients; and 4) To educate basic scientists, bioengineers, and oncologists in the integrative biology of cancer.

Achievements

Rakesh K. Jain, PhD, the Andrew Werk Cook Professor of Tumor Biology at HMS, received the United States National Medal of Science, our nation's highest honor for achievement and leadership in advancing the field of science, in May 2016. This year, Dr. Jain was also a Princess Takamatsu Cancer Research Fund International Lecturer (Japan), delivered the R. B. Trull Lecture, University of Texas, Austin, and was named "One of the Most Influential/Cited Authors" on the 75th Anniversary of Cancer Research journal. He remained one of the top 1% cited researchers in Clinical Medicine, Thomson Reuters (http://highlycited.com) (Web of Science).

On May 19, 2016 the White House hosted the recipients of the National Medals of Science and Technology including Rakesh Jain, PhD, director of the Edwin L. Steele Laboratories for Tumor Biology in the Department of Radiation Oncology.

Dan G. Duda, DMD, PhD, Associate Professor, received the 2016 Heroes of Hope Award from the Granara-Skerry Trust for Pancreatic Cancer Research. This year, he was also appointed to Translational Research Director for GI Radiation Oncology, and delivered a State-of-the-art Lecture at the 26th IASGO World Congress, Seoul, Korea, a Plenary Lecture at the 5th Metronomics and Anti-Angiogenesis Meeting in Mumbai, India, and invited lectures at Johns Hopkins University, Duke University, Kyoto University, Nagasaki University, and Humanitas University Milan.

Dai Fukumura, MD, PhD, Associate Professor, was elected as a Fellow of the American Institute of Medical and Biological Engineering (AIMBE), the highest honor for a biomedical engineer.

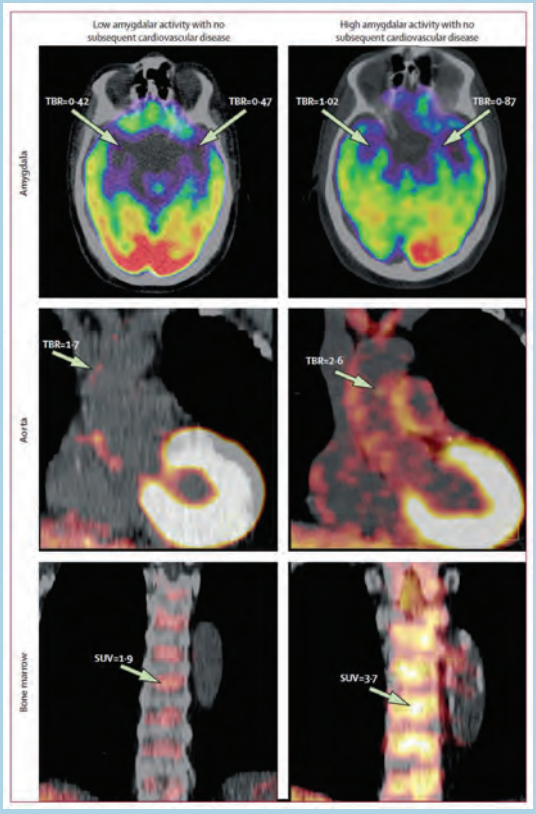
Lance Munn, PhD, received a new R01 from NCI to study the role of glycocalyx mechanobiology in cancer metastasis.

On April 9, 2016, Granara-Skerry Trust hosted their second Kathy's Gala of Hope at the Marriott Hotel in Burlington, Massachusetts. Drs. Dan G. Duda received the Heroes of Hope Award. From left to right: Carlos Fernandez-del Castillo, MD; Dan G. Duda, DMD, PhD; Nabeel Bardeesy, PhD; Krushna Patra, PhD; Andrew X. Zhu, MD, PhD; David P. Ryan, MD; and Yasutaka Kato, MD (all MGH).

James A. Brink, MD, Chief

The Department of Radiology provides excellence in patient care, teaching and research. The research mission of the Department includes: 1) development of novel technologies (instrumentation and algorithms) for data acquisition and analysis to discover and/or measure novel biological structures and processes e.g. fMRI, in vivo membrane potential; 2) design and synthesis of molecular agents (PET, MR, optical) for assessment of receptors, abnormal proteins and other biological targets of disease; 3) assessment of novel instrumentation and molecular imaging agents in preclinical disease models and in clinical research; 4) translation of these discoveries, in concert with industry, into patient care and; 5) development and application of analytic tools to support economically-based assessment of medical imaging technologies and outcomes research. Our strategic priority is the continuous development of intellectual and physical resources to enable researchers within and outside of Radiology to further their research goals into clinical applications. This is achieved through three Centers (The Martinos Center, The Gordon Center and The Center for Clinical Data Science; The Institute of Technology Assessment; several research laboratories and three Core Facilities: The MRI Core, The PET Core and the Tumor Imaging Metrics Core.

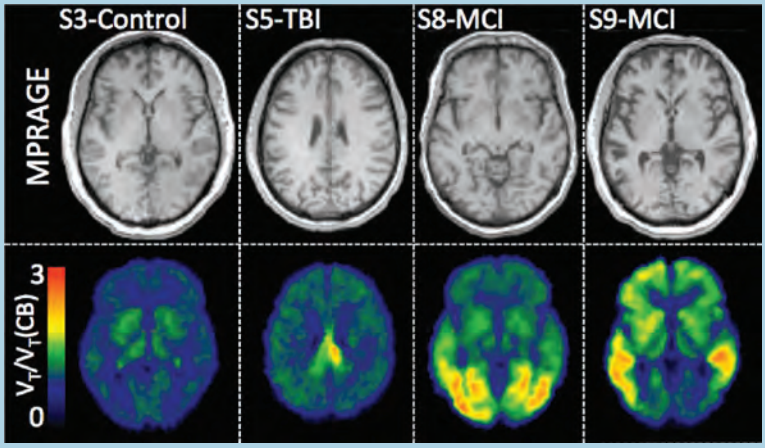
The Department is recognized as the national leader in Radiology research based on its scientific output and NIH funding. For the past 15 years among all academic Radiology departments, MGH has held the #1 ranking in NIH funding. Approximately 200 Radiology faculty members serve as principal investigators on one or more grants, either from the NIH or other funding sources, with total funding of ~$80 million. Through its major programs and Core facilities the Department has significantly enabled the research efforts of many investigators in Cardiology, Emergency Medicine, Neurology, Oncology, Psychiatry, Radiation Medicine, Surgery and other MGH Departments.



Amygdala, arterial, and bone-marrow uptake of 18F-FDG in individuals with and without subsequent cardiovascular events. Axial views of amygdala (upper left and right), coronal views of aorta (middle left and right), and coronal views of bone marrow (lower left and right) are shown. 18F-FDG uptake was increased in the amygdala, bone marrow, and arterial wall (aorta), in a patient who experienced an ischemic stroke during the follow-up period (right) compared with a patient who did not (left). 18F-FDG = 18f fluorodeoxyglucose.

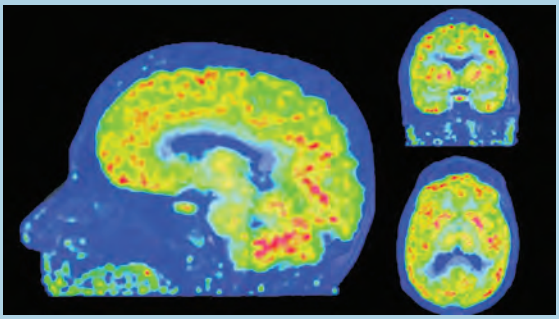
The Cardiac MR PET CT Program has expanded its scope of work in translational research further supporting the necessity to assess biological processes such as inflammation or stress as conduits for manifestation of adverse cardiovascular events and key points for potential clinical interventions. We demonstrated that newly initiated combined Anti Retroviral Therapy in treatment-naive individuals with HIV infection to restore immune function results in different central (aorta) versus peripheral (axillary lymph nodes) inflammatory response, suggesting more complex interactions between the immune and inflammatory system (Zanni, et al, JAMA Cardiology 2016). We further observed that the anti-inflammatory impact of statins is substantially greater within coronary plaques that contain high risk features, explaining individuals with more advanced atherosclerotic disease disproportionately benefit from statins (Singh Circulation CV Imaging 2016). Lastly, a cutting edge study suggests that metabolic activity in the amygdala strongly predicts both the risk for and the timing of subsequent heart attack and stroke, describing an amygdala-bone marrow-arterial axis that might explain the majority of stress-related CVD (Tawakol, et al, Lancet 2017).

Keith Johnson and colleagues from the Gordon Center published key finding in the Annals of Neurology 2016, demonstrating the first in vivo assessment of the defining pathologic lesions of AD, amyloid plaques and tau tangles. PET measures compared in AD patients and normal elderly explored the central paradox of the disease, that while amyloid pathology precedes tau in cortex, and probably initiates the disease, it is tau pathology that directly relates to the dementia. These findings have been replicated by others and contributed to making tau PET a standard component of observational and therapeutic trials exploring aging and dementia. In a related work, Jorge Sepulcre reported in J. Neuroscience and Nature Medicine 2016 on the in vivo Tau, Amyloid, and Gray Matter Profiles in the Aging Brain. Also related to imaging Tau in the brain, Normandin, Wooten and colleagues have reported the first pharmacokinetic evaluation of the Tau PET radiotracer F-18-AV-1451 in human subjects demonstrating rapid clearance from plasma and properties suitable for in vivo tau quantification with PET. Furthermore, promising imaging findings were reported in traumatic brain injury (TBI) in addition to mild cognitive impairment.



MR images (top) and Tau PET images (bottom) demonstrating that the increase in Tau uptake correlates with the severity of traumatic brain injury.

Epigenetic dysfunction is implicated in many neurological and psychiatric diseases, including Alzheimer's disease and schizophrenia. Consequently, histone deacetylases (HDACs) are being aggressively pursued as therapeutic targets. In the August issue of Science Translational Medicine 2016, the Martinos Center's Jacob Hooker and colleagues reported the first-in-human evaluation of neuroepigenetic regulation in vivo (Figure 3). Using positron emission tomography with [11C]Martinostat, an imaging probe selective for class I HDACs (isoforms 1, 2, and 3), they found that HDAC expression is higher in cortical gray matter than in white matter, with conserved regional distribution patterns within and between healthy individuals. Among gray matter regions, HDAC expression was lowest in the hippocampus and amygdala. Through biochemical profiling of postmortem human brain tissue, they confirmed that [11C]Martinostat selectively binds HDAC isoforms 1, 2, and 3, the HDAC subtypes most implicated in regulating neuroplasticity and cognitive function. This study quantifies HDAC expression in the living human brain and provides the foundation for gaining unprecedented in vivo epigenetic information in health and disease.



The first images of Epigenetics in the human brain using the PET agent [11C]Martinostat demonstrating greater signal from [11C] Martinostat in the cortical gray vs white matter consistent with higher levels of histone deacetylases (HDACs)

The Program in Neuroprotection Research is focused on experimental and translational research in stroke and neurodegeneration. Tools in our unit comprise a mix of molecular/cell biology, in vivo pharmacology, and in vivo imaging. In collaboration with XuanWu Hospital in Beijing, we recently found potential evidence for inter-cellular transfer of mitochondria as a mechanism of "help-me signaling" between different CNS cell types (Hayakawa et al, Nature 2016). We have also collaborated with Seoul National University in Korea to define novel mechanisms of crosstalk between pericytes and neuronal stem cells that can be potentially leveraged to improve recovery after CNS injury and disease (Choi et al, Nature Medicine 2016).

Bruce D. Walker, MD, Director

The Ragon Institute of MGH, MIT and Harvard was officially established in February 2009 with a dual mission: to contribute to the accelerated discovery of an HIV/AIDS vaccine and to establish itself as a world leader in the collaborative study of immunology. Founded with an original commitment of expendable funds of $10 million per year for 10 years from Mr. and Mrs. Ragon, and an additional commitment to extend this funding through 2023, the Institute is structured and positioned to significantly contribute to a global effort to develop an HIV/AIDS vaccine by:

- Catalyzing non-traditional partnerships among outstanding scientists and engineers with different but complementary backgrounds;
- Providing infrastructure and novel technologies to open new avenues of research;
- Providing a means for rapidly funding promising studies and emerging concepts in the field;
- Integrating key facets of current vaccine development efforts that have tended to follow separate tracks;
- Providing a substantial pool of accessible, flexible funding that will help lower the threshold for scientists to pursue risky, unconventional yet potentially high benefit avenues of study that are unlikely to attract funding from traditional sources. Such funding encourages innovation, compresses the time it takes to conduct bench-to-bedside research and attracts new minds to the field.

The Institute creates a singular opportunity and environment to engage scientists, engineers and clinicians in challenging research for which there may be no greater benefit – saving lives and curing the ill.

Achievements

Establishment of 2 MIT and 2 HMS Endowed Chairs

The year 2016 saw the establishment of four new endowed chairs at the Ragon Institute. These endowments, gifted by the Phillip T. and Susan M. Ragon Foundation, create four faculty positions, two at Harvard Medical School (HMS) and two at the Massachusetts Institute of Technology (MIT) for researchers who will be appointed to the Ragon Institute. The Ragon chairs represent a stable funding endowment which will allow researchers and their laboratories to pursue the goal of harnessing the immune system to prevent and cure human disease.

Ragon's new Associate Director, Dr. Facundo Batista was appointed the Phillip and Susan Ragon Professor of Microbiology and Immunobiology at HMS, effective January 2016. Ragon Institute Director, Dr. Bruce Walker was appointed as the Ragon Professor of Medicine at HMS, effective March 2016.

The joint Ragon/MIT chairs were announced at a ceremony held on June 6, 2016 at InterSystems in Cambridge and was attended by Susan and Terry Ragon, Dr. Bruce Walker, Dr. L. Rafael Reif, President of MIT, and Dr. Peter Slavin, President of Massachusetts General Hospital (MGH). A search is currently underway for the recruitment of these positions.

The Ragon Institute is pleased to have the continued support from Mr. and Mrs. Ragon and to further strengthen ties with MIT and Harvard to continue pursuing the goal of developing a vaccine for HIV/AIDS, with the broader goal of harnessing the immune system to prevent and cure human disease.

Recruitment of Facundo Batista, Ph.D.

Drs. Bruce Walker (left) and Facundo Batista (right)

In January 2016, after an international search conducted in conjunction with the Microbiology and Immunobiology Department at Harvard Medical School, the Ragon Institute hired Dr. Facundo D. Batista as the Ragon Institute's first Associate Director and the first recipient of the Phillip and Susan Ragon Professorship at Harvard Medical School. The creation of this new position, established through the generosity of the Phillip T. and Susan M. Ragon Foundation, strengthens the breadth of the Institute's leadership while deepening our research capabilities and expertise.

Ragon Institute of MGH, MIT and Harvard

Department Report

Ragon Institute employees - 400 Technology Square in Cambridge, MA

Dr. Batista is an internationally renowned expert in the field of B cell activation, high-resolution imaging and in vivo microscopy. His research focuses on the cellular and molecular events that lead to the activation of B cells and how these events affect the ability of B cells to produce antibodies, which are key for vaccine development. Dr. Batista will continue his B cell immunobiology research at the Ragon Institute.

Dr. Batista comes to Harvard and MGH from The Francis Crick Institute, a biomedical research center in London. He graduated from the University of Buenos Aires, Argentina and received his PhD at the International School of Advanced Studies, Trieste, Italy. As a postdoctoral European Molecular Biology Organization (EMBO) fellow, he then trained in the laboratory of Michael Neuberger at the Laboratory of Molecular Biology, Cambridge, England. In 2002, Dr. Batista established his own independent lab at the London Research Institute (now The Francis Crick Institute).

Dr. Batista's appointment provides an important combination of administrative and research support, ensuring the smooth continuation and carefully managed expansion of the institute's basic research efforts across disciplines; translational research efforts that can move advances in the lab to patients' bedsides; and training programs to create a pipeline of exceptional biomedical research leaders.

Identification of distinct antibody functional profiles that differentiate latent from active TB

Lu LL, Chung AW, Rosebrock TR, Ghebremichael M, Yu WH, Grace PS, Schoen MK, Tafesse F, Martin C, Leung V, Mahan AE, Sips M, Kumar MP, Tedesco J, Robinson H, Tkachenko E, Draghi M, Freedberg KJ, Streeck H, Suscovich TJ, Lauffenburger DA, Restrepo BI, Day C, Fortune SM, Alter G. A Functional Role for Antibodies in Tuberculosis. Cell. 2016 Oct 6;167(2):433-443.e14. PubMed PMID: 27667685.

While a third of the world carries the burden of tuberculosis, disease control has been hindered by a lack of tools, including a rapid, point-of-care diagnostic and a protective vaccine. In many infectious diseases, antibodies (Abs) are powerful biomarkers and important immune mediators. However, in Mycobacterium tuberculosis (Mtb) infection, a discriminatory or protective role for humoral immunity remains unclear. Using an unbiased antibody profiling approach, Ragon Institute investigators under the leadership of Galit Alter and Sarah Fortune show that individuals with latent tuberculosis infection (Ltb) and active tuberculosis disease (Atb) have distinct Mtb-specific humoral responses, such that Ltb infection is associated with unique Ab Fc functional profiles, selective binding to Fc□RIII, and distinct Ab glycosylation patterns. Moreover, compared to Abs from Atb, Abs from Ltb drove enhanced phagolysosomal maturation, inflammasome activation, and, most importantly, macrophage killing of intracellular Mtb. Combined, these data point to a potential role for Fc-mediated Ab effector functions, tuned via differential glycosylation, in Mtb control.

Identification of a limited number of host dependency factors required for HIV infection

Park RJ, Wang T, Koundakjian D, Hultquist JF, Lamothe-Molina P, Monel B, Schumann K, Yu H, Krupzcak KM, Garcia-Beltran W, Piechocka-Trocha A, Krogan NJ, Marson A, Sabatini DM, Lander ES, Hacohen N, Walker BD. A genome-wide CRISPR screen identifies a restricted set of HIV host dependency factors. Nat Genet. 2016 Dec 19. [Epub ahead of print] PubMed PMID: 27992415.

Host proteins are essential for HIV entry and replication and can be important nonviral therapeutic targets. Large-scale RNA interference (RNAi)-based screens have identified nearly a thousand candidate host factors, but there is little agreement among studies and few factors have been validated. In this study led by Ragon Institute investigators and involving collaborations with Broad Institute investigators, a genome-wide CRISPR-based screen was employed to identify HIV host factors (dependency factors) in a physiologically relevant cell system. Five factors, including the HIV co-receptors CD4 and CCR5, that are required for HIV infection yet are dispensable for cellular proliferation and viability. Two additional factors, tyrosylprotein sulfotransferase 2 (TPST2) and solute carrier family 35 member B2 (SLC35B2), function in a common pathway to sulfate CCR5 on extracellular tyrosine residues, facilitating CCR5 recognition by the HIV envelope. A fifth factor, activated leukocyte cell adhesion molecule (ALCAM) mediates cell aggregation, which is required for cell-to-cell HIV transmission. Investigators validated these pathways in primary human CD4+ T cells through Cas9-mediated knockout and antibody blockade. These findings indicate that HIV infection and replication rely on a limited set of host-dispensable genes and suggest that these pathways can be studied for therapeutic intervention.

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

The research mission of the Department of Surgery is to guide and foster basic, translational, and outcomes research activities in a broad range of surgical subspecialties with a goal of advancing knowledge and improving patient care. To accomplish this goal, scientists and clinicians engage in multiple scientific disciplines to solve everyday challenges in clinical medicine. We serve a diverse group of patients, and our research enterprise is similarly diverse, being distributed among multiple Centers and clinical Divisions.

Surgical Research Council

The Surgical Research Council (SRC), co-chaired by Laurence Turka, MD, and Richard Hodin, MD, was established to help the Department achieve its research mission. The SRC has a broad membership that includes the Department Chair, the Division Chiefs and Center Directors, and other members representative of each division and the large community of PhD and MD researchers. The SRC meets quarterly and holds research town hall meetings twice a year that bring the entire department research community together in a forum designed to exchange information and promote collaboration.

Centers of Excellence

The Department of Surgery has four specialized centers of excellence in research that are designed to enhance the research environment, foster collaboration, and leverage expertise and resources to expand the productivity and output in areas of particular interest.

Center for Transplantation Sciences (CTS)

The CTS is a multidisciplinary research center working at the interface between basic science and clinical applications in transplantation immunology and related fields with Joren C. Madsen, MD, DPhil, James F. Markmann MD, PhD, and Laurence A. Turka, MD, serving as co-directors. The mission of the CTS is to improve the number and the lives of recipients with organ, tissue and cell transplants by:

- Better understanding the mechanisms underlying the immune response
- Developing novel means of inducing immune tolerance
- Finding creative ways of increasing the supply of donor organs

Center for Surgery, Innovation and Bioengineering

The Center is a clinically driven enterprise built upon decades of collaborative clinical, basic science, and engineering activities at MGH and MIT. Clinically inspired engineers, physicians, and human biologists use creative scientific approaches to improve diagnostics and therapeutics for patient care worldwide. Within this MGH Center, and under the same roof, the most promising discovers are nurtured and supported into therapies, devices, and diagnostics in a direct and rapid fashion. The Center's position within the MGH clinical and research environments enables not only the traditional academic triad of sciences, technology, and clinical medicine, but its position also enables a fourth dimension – innovation. Serving as co-directors; Ronald Tompkins, MD, ScD, Mehmet Toner, PhD, and Martin Yarmush, MD, PhD.

Vital Organ Engineering and Tissue Regeneration

Joseph P Vacanti, MD, and his team continue to focus on the development of implantable tissue engineered living devices to replace structures damaged by disease, trauma, or congenital deformities. Currently, they are focusing on neural innervation of skeletal muscle, CNS implants, and hepatic tissue for implantation. In addition, they are applying their engineered blood vessel expertise to produce an in vitro model of a physiologic vasculature to be commercialized for drug testing applications. Harald Ott, MD, and his research lab focuses on developing novel strategies to generate personalized solid organ grafts for transplantation and to repair damaged organs in vivo and ex vivo.

Codman Center for Clinical Effectiveness in Surgery

The Codman Center's mission is to deliver the safest, highest value patient care through innovative research and education. Local, regional and national initiatives analyze and promote the clinical effectiveness of surgical care. The Codman Center collaborates with Partners HealthCare hospitals and other hospitals throughout the state to promote quality improvement in Massachusetts. Nationally, the center's leaders are the architects of quality and safety metrics used in hospitals across the country with Matthew Hutter, MD, serving as the medical director, David Shahian, MD, serving as the associate director, and David Chang, PhD, as the director of healthcare research and policy development.

Achievements

Unlocking a biological mystery

What initiates the selection of the primordial follicle to advance from the earliest stage to progressive ovulation has for years been a biologic mystery. David Pepin, PhD, has made the observation in recent work in the Pediatric Surgical Research Laboratories that mice given long term Mullerian Inhibiting Substance (MIS) delivered by a single AAV viral vector injection to treat primary ovarian cancer xenografts in work funded by the Department of Defense, caused shrinkage of the normal ovary. When sectioned histogically, the follicles were found to be all in the primordial stage, which represents the ovarian reserve.

Transplantation of these small ovaries back into control animals given the AAV-GFP showed that this effect was reversible. He could recapitulate these effects with purified recombinant human MIS protein, showing that the effect was both MIS-specific and reversible. Given these observations, he tested whether ovaries subjected to chemotherapy, the most common cause of premature ovarian failure in young women undergoing cancer treatment, could be protected by co-treatment with MIS. The ovaries of young mice were protected by MIS whether treated with doxorubicin, carboplatin, or cyclophasphamide. In addition to oncoprotection during chemotheraphy, it was noted that these animals while under treatment had fewer or no pups with continued breeding, suggesting that MIS could also function as a contraceptive agent.

Based upon this work, Dr. Pepin and Patricia Donahoe, MD, co-founded Provulis, LLC, and received funding from the Bill and Melinda Gates Foundation. Since MIS acts as an inhibitor of primordial follicle development. The laboratory is also actively searching for molecules which activate this process. This observation has potentially broad clinical application in the areas of oncoprotection, contraception, in vitro fertilization, and potential treatment for genetic causes of premature ovarian failure. Work is in progress to study its effects on the more common ovarian disorders, thereby having an even broader reach.

A fast, scar-free biopsy device

Over the past three decades, the incidence of skin cancer has been greater than all other cancers combined. According to the National Cancer Institute, 50% of Americans who live to age 65 will be diagnosed with skin cancer. When patients present to a dermatologist with a skin lesion, an invasive biopsy is performed for conformational diagnosis and management guidance. Biopsies are not only routinely performed on atypical moles and pigmented lesions, but also on rashes and blisters and for evaluation of autoimmune disorders.

Currently three biopsy options exist: punch, shave, and excisional. All result in significant cosmetic disfigurement, so the least invasive technique is employed primarily. However, with less tissue sampling, pathological evaluation suffers. Frequently, results show unclear pathology, and questionable margins or depth. In these cases, appropriate management cannot be complete without more invasive procedures and associated costs.

Jay Austen Jr., MD, was selected to receive a Partners Innovation Discovery Grant. The funding will allow Dr. Austen and his research team to develop a micro-biopsy device that will enhance the standard of care as follows: promote early screening, increase early cancer detection, lower healthcare cost, and remove cosmetic disfigurement.

Professional development for surgical residents & faculty

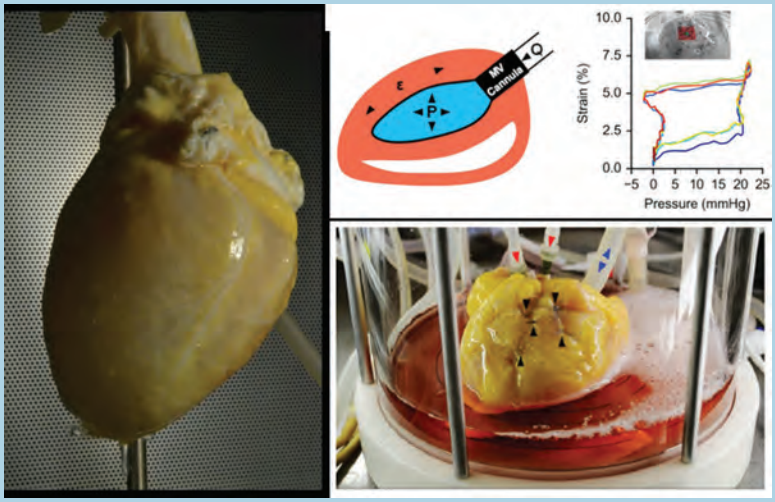
David Chang, PhD, has successfully established an academic and professional development program for residents and faculty of the Department of Surgery. He has implemented a dynamic mentorship curriculum that includes didactics, hands-on practicum in study design and data analysis and interpretation, manuscript publication, and clinical application of findings. Moreover, he has developed a structured curriculum for innovative research proposals and grant writing. During the last two years, Dr. Chang has published more than 60 manuscripts with MGH residents and faculty, and many of his mentees have been successful in securing internal and external grants. He has invigorated the academic culture for health services research, quality improvement, and health policy in the Department of Surgery, as well as in the larger Massachusetts General Hospital community.

Improving organ preservation for transplantation

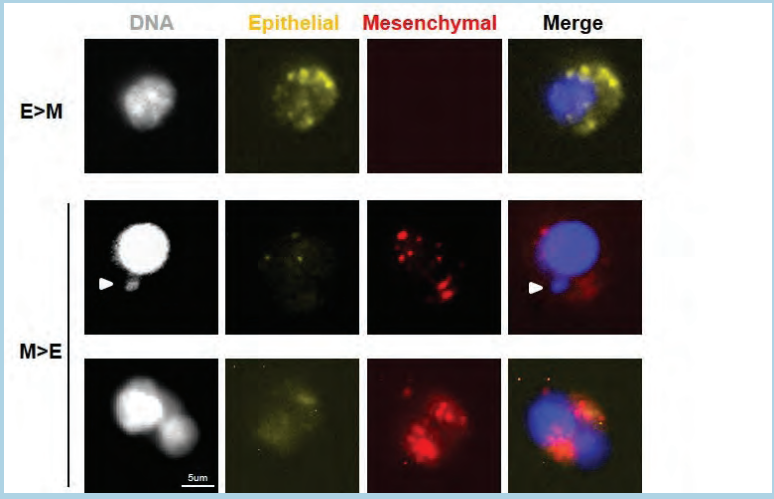
The transplant team, headed by James Markmann, MD, and Heidi Yeh, MD, has been collaborating with the MGH Bioengineering group led by Korkut Uygun, PhD, to develop ex vivo liver perfusion as an improved means to store livers in preparation for transplant. The group has now studied more than 50 discarded human livers to help find the optimal conditions for preserving the liver under physiologic conditions to allow its assessment and improved function in preparation for transplant. Recently, the Transplant team worked with a local company, Transmedics, to use their ex vivo perfusion device in an early phase clinical trial to demonstrate safety of this preservation approach in humans. The team performed the first warm ex vivo liver perfusion in the US in early 2016, and has since enrolled 9 patients in the randomized trial of the 20 patients included in Phase I. The team is convinced that this approach will rapidly become the standard of care and

will lead to more organs being available for transplantation. The trial has recently reopened to a much larger, 300 patient registration trial, with a plan to involve 20 sites.

In other work designed to make more organs available for transplant patients, a study being led by Parsia Vagefi, MD, has devised a new approach to improve survival of pig livers in non-human primates as a translational step to using pig livers in humans. The team's work targets coagulation incompatibilities between primates and humans that causes a coagulation disorder upon transplantation of a pig organ into the primate that causes graft loss within hours to a few days. By continuously supplying human clotting factors, the team achieved dramatic improvement in survival from less than a week to almost a month, by far the longest pig liver survival in a primate that has ever been reported. With further refinement, it is hoped that these studies will allow the initial assessment of pig liver function in humans by using it as an ex vivo support or a bridge to definitive transplant.



In 2016, the Ott lab created functional, electrically active human myocardium from clinically relevant matrix and cell sources. This is the first report of human myocardium of clinically relevant scale regenerated from pluripotent stem cells within a human heart matrix in ex vivo whole organ culture. This figure shows a perfused native de-cellularized human heart (left panel). Functional schematic and validation data for our human heart bioreactor (top right). A reseeded human heart being cultured in our biomimetic bioreactor system (bottom right; cell injections – black arrows, perfusion – red arrows, LV pump – blue arrows).



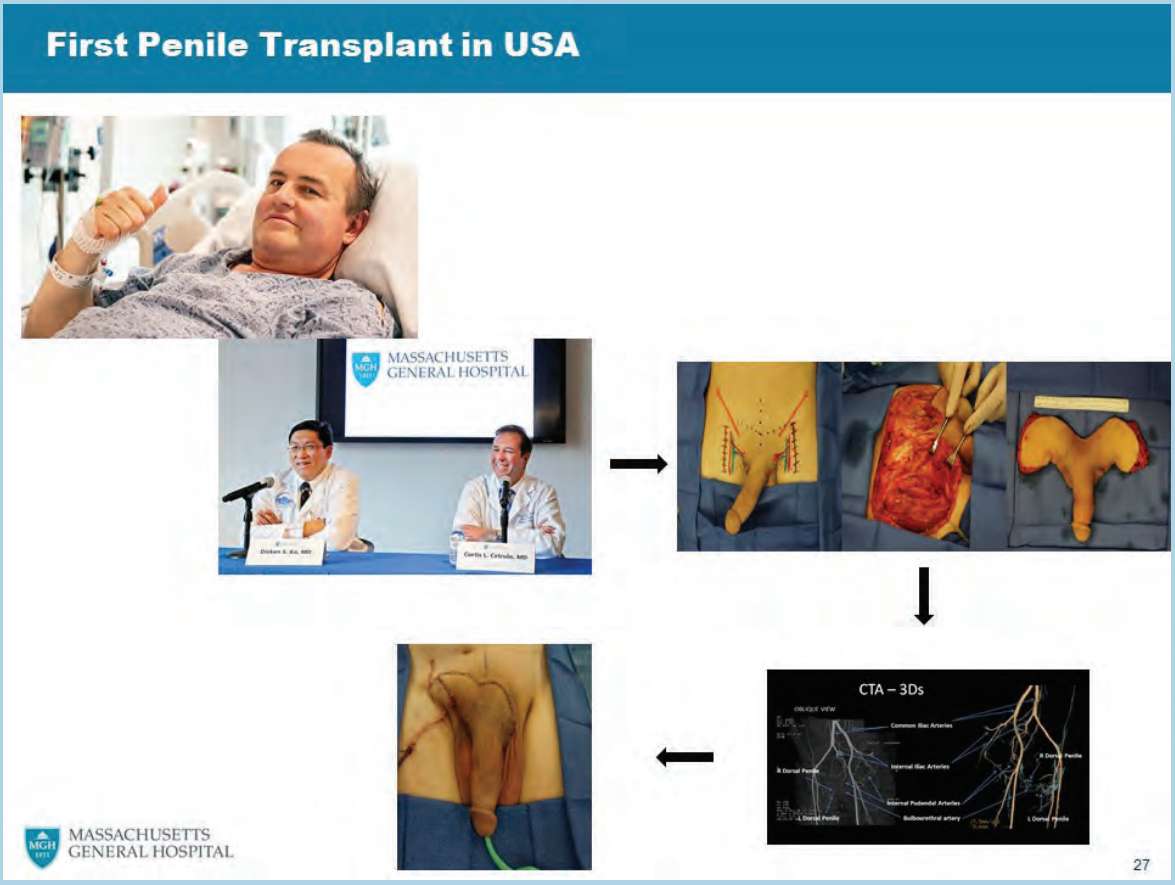
Circulating breast cancer circulating cells isolated using a chip developed with Mehmet Toner, PhD, Co-Director, Center for Surgery, Innovation, and Bioengineering. Cells from patients showing more of either an epithelial phenotype (E) or mesenchymal phenotype (M).

Michael L. Blute, Sr., MD, Chief

The Department of Urology is focused on a significant growth phase. We have had an expansion of our clinic space into the newly rennovated Charles River Plaza - 7th floor with 13,000+ square footage of clinic space in the new moder clinic area. Along with the space expansion, we plan to increase our faculty recruits in the areas of female urology, reconstructive urology and urologic oncology. With our faculty recruits, we plan to expand the research focus in our department. We have targeted clinical and basic reserach faculty who have demonstrated success as physician scientist in different areas of urologic research.

Achievements

The Department of Urology, in close collaboration with the Division of Plastic Surgery, completed the first genitourinary reconstructive (penile) transplant. The successful complex procedure that was led by Dr. Dicken Ko (Urology) and Dr. Curtis Cetrulo (Plastic Surgery) gained national attention, and the patient (Mr. Thomas Manning), a penile cancer survivor, had an outstanding result. The procedure served as a model for other institutions around the country which may use the footprint of the works at Mass General Hospital for future patients who may require a such a complex reconstructive procedure.



The Department of Urology held another symposium in conjunction with Johns Hopkins Medical Center, the Urotrack, which was the second conference jointly held between the two institutions. The well-received conference was held in Baltimore, MD this year, and will be held in the Boston area for its 3rd inaugural meeting in September 2017.

The Department had key publications in several areas of research:
Dr. Michael Blute was a co-author on the key publication on Comprehensive Molecular Characterization of Papillary Renal Cell Carcinoma Cancer Genome Atlas Research Network. Engl J Med. 2016 Jan 14;374(2):135-45.

Dr. Jack Elder from our Pediatric Urology Division published the following key manuscript about disparities in management of testicular torsion.
Treatment patterns, testicular loss and disparities in inpatient surgical management of testicular torsion in boys: a population-based study 1998-2010. BJU Int. 2016 Dec;118(6):969-979.

Dr. Feldman published the largest series on genitourinary melanoma.
Sanchez A, Rodríguez D, Allard CB, Bechis SK, Sullivan RJ, Boeke CE, Kuppermann D, Cheng JS, Barrisford GW, Preston MA, Feldman AS. Primary genitourinary melanoma: Epidemiology and disease-specific survival in a large population-based cohort. Urol Oncol. 2016 Apr;34(4):166.e7-14.

Dr. Cigdem (Cori) Tanrikut published an article that was highlighted by the Journal of Urology regarding the changes in hematocrit levels in men using supplemental testosterone.
Hayden RP, Bennett NE, Tanrikut C. Hematocrit Response and Risk Factors for Significant Hematocrit Elevation with Implantable Testosterone Pellets. J Urol. 2016 Dec;196(6):1715-1720.

In collaboration with Department of Radiation Oncology, Dr. Ross Krasnow (Urologic Onclogy Fellow), published the clinical outcomes of histologic variants bladder cancer.
Krasnow RE, Drumm M, Roberts HJ, Niemierko A, Wu CL, Wu S, Zhang J, Heney NM, Wszolek MF, Blute ML, Feldman AS, Lee RJ, Zietman AL, Shipley WU, Efstathiou JA. Clinical Outcomes of Patients with Histologic Variants of Urothelial Cancer Treated with Trimodality Bladder-sparing Therapy. Eur Urol. 2016 Dec 28. pii: S0302-2838(16)30899-5.

Dr. Zongwei Wang, from the research laboratory of Dr. Aria Olumi, received research funding from a very competitive pool of applicants through the American Urological Association/Urology Care Foundation. The research grant will help supplement Dr. Wang's research efforts in the Department of Urology.