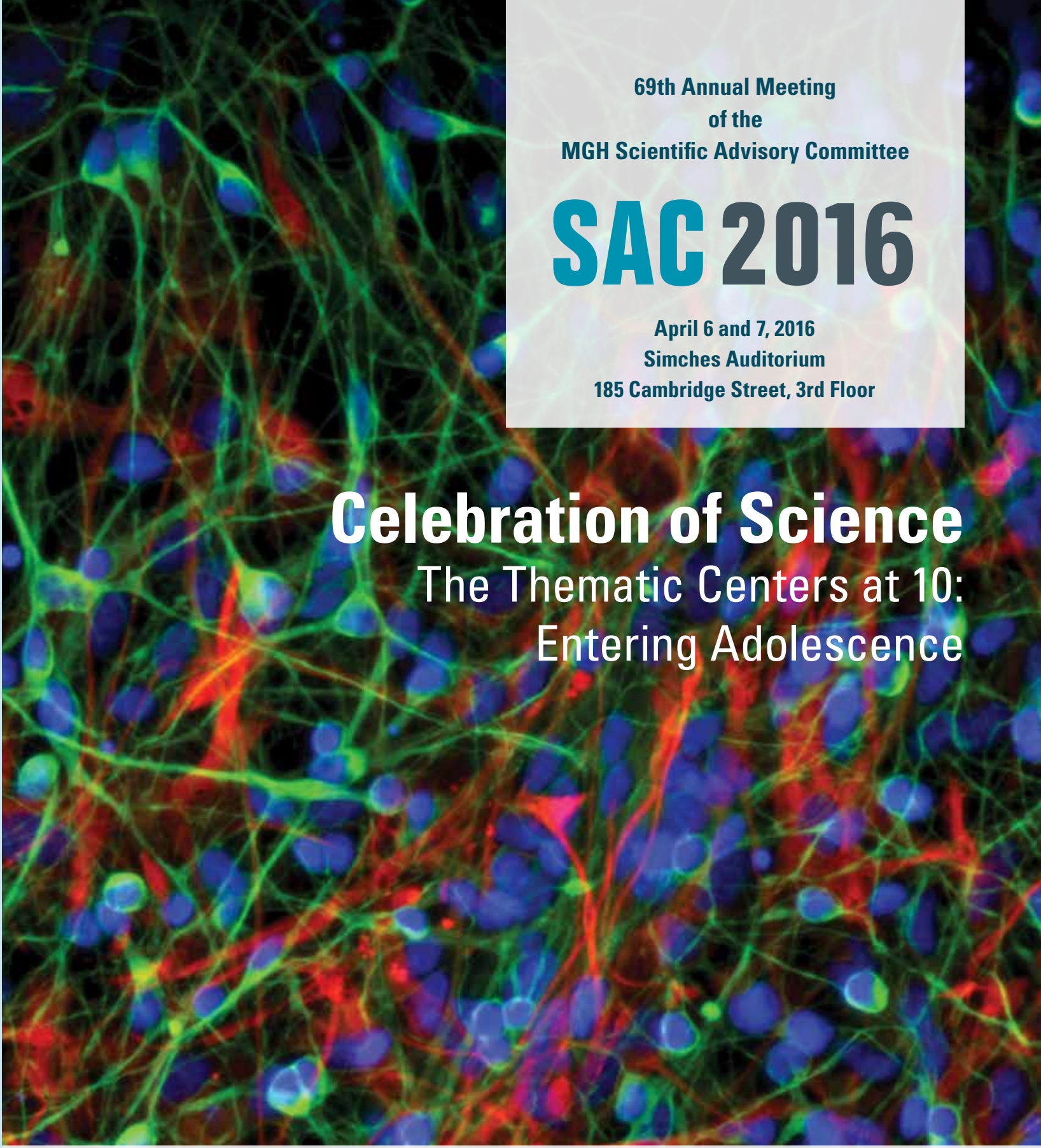


69th Annual Meeting
of the
MGH Scientific Advisory Committee

SAC 2016

April 6 and 7, 2016
Simches Auditorium
185 Cambridge Street, 3rd Floor

Celebration of Science

The Thematic Centers at 10: Entering Adolescence

MASSACHUSETTS GENERAL HOSPITAL
RESEARCH INSTITUTE

Executive Committee on RESEARCH
Fostering Innovation at MGH



Contents



Welcome

Welcome to the 69th Annual Meeting of the MGH Scientific Advisory Committee (SAC) on April 6th and 7th, 2016. Dr. Daniel K. Podolsky has graciously agreed to chair our SAC meeting again this year.

As in past years, we will begin our two-day SAC meeting with a Celebration of Science at MGH. Our poster session begins at 10:15 am on Wednesday, April 6, followed by an afternoon Research Symposium from 2:00 pm to 5:00 pm. The outstanding MGH researchers who will be presenting their work in our Symposium this year are the 2016 Howard Goodman Award recipient Robert Anthony, PhD, and the 2016 Martin Research Prize recipients, Filip K. Swirski, PhD, and Andrew T. Chan, MD. David N. Louis, MD, will begin the first day with an ECOR report and the announcement of the 2016 class of MGH Research Scholars.

The theme of SAC this year will be the five MGH Thematic Centers as they enter their *adolescence.* We are honored to have as our keynote speaker, Daniel K. Podolsky, MD, from the University of Texas Southwestern Medical Center, who will begin our morning on Thursday, April 7. After this keynote, Dr. Louis, will give a presentation on the Thematic Center Survey results. We will next turn our attention to presentations by the Directors of the five Thematic Centers at MGH who will discuss some of the major events over the past ten years, the remarkable science currently being done, and challenges that remain going forward.

Also on Thursday, SAC members will again have the opportunity to meet with small groups of MGH investigators in unstructured, informal conversations during lunch.

To maximize the time for discussion during the day, the annual MGH Research Institute Executive Report (formerly known as the MGH Research Administration Executive Report) and Financials for FY15 will be provided in these printed materials in advance of the meeting. Dr. Louis plans to highlight some of this information in his annual ECOR Report and there will be an opportunity for SAC members to ask questions about the written report.

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

Peter L. Slavin, MD
PRESIDENT

David N. Louis, MD
CHAIR, EXECUTIVE COMMITTEE
ON RESEARCH

Harry W. Orf, PhD
SENIOR VICE PRESIDENT
FOR RESEARCH

SAC 2016 Wednesday, April 6, 2016
Annual Celebration of Science at MGH

10:15 am–1:45 pm / Simches, Floors 2 & 3

SAC 2016 Poster Session (lunch available)
Session 1: 10:15–11:45 am
Session 2: 12:15–1:45 pm

2:00–5:00 pm / Simches 3.110

Scientific Presentations

Welcome
Peter L. Slavin, MD, President, MGH

Opening Comments, Introductions, and 2016 MGH Research Scholars
David N. Louis, MD, Chair,
Executive Committee on Research (ECOR)

2:15–3:00 pm

ECOR Report
David N. Louis, MD, Chair, ECOR

3:00–3:30 pm

2016 Martin Prize for Fundamental Research
Filip K. Swirski, PhD
Interleukin-3 amplifies acute inflammation and is a potential therapeutic target in sepsis

3:30–3:50 pm

Break

3:50–4:20 pm

2016 Martin Prize for Clinical Research
Andrew T. Chan, MD
Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants

4:20–4:50 pm / Simches 3.110

2016 Goodman Award
Robert Anthony, PhD
Glycan regulation of immunoglobulins

5:00–6:00 pm / Simches Cafe, Floor 3

Reception

Thursday, April 7, 2016

Annual Celebration of Science at MGH

SAC 2016

8:00–9:00 am / Simches 3.120

Executive Breakfast

9:00–9:30 am / Simches 3.110

Keynote Address—Thematic Centers: Experiments in Science

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

9:30–10:15 am

Thematic Center Survey Results

David N. Louis, MD
Chair, ECOR

10:15–10:45 am

Wellman Center for Photomedicine

R. Rox Anderson, MD

10:45–11:00 am

Break

11:00–11:30 am

Center for Systems Biology

Ralph Weissleder, MD, PhD

11:30 am–12:00 pm

Center for Computational and Integrative Biology

Brian Seed, PhD

12:00–1:30 pm / Simches 3.120 & 3.130

Lunch—SAC Members with invited Faculty

1:30–2:00 pm

Center for Regenerative Medicine

David Scadden, MD

2:00–2:30 pm

Center for Human Genetic Research

Sekar Kathiresan, MD

2:30–3:15 pm

MGH Thematic Centers: Open Discussion

3:15–3:45 pm / Simches 3.120

Executive Discussion (SAC Members only)

3:45–4:15 pm

Debriefing (SAC Members and ECOR Leadership)

Goodman & Martin Award Winners

2016 Howard M. Goodman Fellowship

The Fellowship honors Howard M. Goodman, 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's 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.

Immunoglobulin Glycosylation in Health and Disease

Robert Anthony, PhD
Assistant Professor
Medicine/Rheumatology, Allergy & Immunology

Martin Research Prize 2016 for Fundamental and Clinical 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.

Fundamental Research

Interleukin-3 amplifies acute inflammation and is a potential therapeutic target in sepsis

Filip K. Swirski, PhD
Associate Professor
Radiology & Center for Systems Biology

Clinical Research

Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants

Andrew T. Chan, MD
Associate Professor
Medicine/Gastrointestinal Unit

Scientific Advisory Committee 2016

Jennifer Waddell Photography

Constance L. Cepko, PhD
Professor, Genetics and Ophthalmology
Investigator, Howard Hughes Medical Institute
Harvard Medical School
Term: SAC 2015 through SAC 2018
(1st term)

Mark C. Fishman, MD
Past President and CEO
Novartis Institutes of Biomedical Research
Term: SAC 2016 through SAC 2019
(1st term)

Richard O. Hynes, PhD
Daniel K. Ludwig Professor for Cancer Research
Investigator, Howard Hughes Medical Institute
Massachusetts Institute of Technology
Term: SAC 2013 through SAC 2016
(1st term)

Chris Kaiser, PhD
Professor of Biology
MacVicar Faculty Fellow
Massachusetts Institute of Technology
Term: SAC 2013 through SAC 2016
(1st term)

Vivian S. Lee, MD, PhD, MBA
Senior Vice President for Health Sciences
Dean, School of Medicine
CEO, University of Utah Health Care
Term: SAC 2015 through SAC 2018
(1st term)

Richard P. Lifton, MD, PhD
Chairman Department of Genetics
Professor Genetics and Internal Medicine
Yale University School of Medicine
Term: SAC 2014 through SAC 2017
(2nd term)

Daniel Podolsky, MD
President
University of Texas Southwestern Medical Center
Term: SAC 2014 through SAC 2017
(1st term)

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
Term: SAC 2014 through SAC 2017
(2nd term)

Ex Officio
Jeffrey S. Flier, MD
Dean, Faculty of Medicine Harvard Medical School
Term: Ex Officio

Executive Committee on Research

Officers and Members 2016

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

VOTING MEMBERS

Galit Alter, PhD†
Ragon Institute
April 2012–March 2018

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

Katrina Armstrong, MD
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
Renal Unit/Nephrology
Elected Representative
Chair, MGH Research Council
January 2014–December 2017

James A. Brink, MD†
Chief, Imaging
April 2013–March 2019

Dennis Brown, PhD
Director, Office for Research Career Development (ORCD)
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

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

Robert Gerszten, MD
Cardiology
Co-Chair, Subcommittee on Review of Research Proposals (SRRP)
Ex-officio

Marcia Goldberg, MD†
Infectious Diseases
April 2012–March 2018

Allan Goldstein, MD
Pediatric Surgery
Elected Representative
January 2014–December 2016

Steven Grinspoon, MD
Director, MGH Program in Nutritional Metabolism
Elected Representative
January 2016–December 2018

James Gusella, PhD
Director, Center for Human Genetic Research
Ex-officio

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

Kurt J. Isselbacher, MD
Honorary Member

Ronald E. Kleinman, MD‡
Chief, Pediatrics
April 2010–March 2016

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

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

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

† Chair Appointment, ‡ Chief's Council

Executive Committee on Research

Officers and Members 2016

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

Joren Madsen, MD, DPhil†
Director, MGH Transplant Center
April 2012–March 2018

David Milan, MD
Cardiology
Elected Representative
January 2016–December 2018

Karen K. Miller, MD
Neuroendocrinology
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

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

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

Guillermo J. Tearney, MD, PhD†
Wellman Center for Photomedicine
December 2015–April 2021

Anne Thorndike, MD
General Medicine
Elected Representative
January 2014–December 2016

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
Ex-officio

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

NON-VOTING MEMBERS

Sarah Alger
Director, Paul S. Russell Museum
Contributing Member

Gaurdia Banister, RN, PhD
Executive Director,
Institute for Patient Care
Nursing Administration and Support Services
Contributing Member

Deverie Bongard, MBA
Associate Director, Technology & Communications, ECOR
Contributing Member

Meg Bourbonniere, RN, PhD
Director, Nursing Research and Innovation
Yvonne L. Munn Center for Nursing Research
Contributing Member

F. Richard Bringhurst, MD
Research Integrity Officer
Ex-officio

Andrew Chase
Vice President, Partners Research Management & Research Finance
Ex-officio

Anne Clancy, PhD
Director, Animal Welfare Assurance, MGH
Ex-officio

† Chair Appointment, ‡ Chief's Council

Executive Committee on Research

Officers and Members 2016

Christopher Coburn
Vice President, Partners Innovation
Ex-officio

Thilo Deckersbach, PhD
Director, Graduate Student Division
Ex-officio

Kim Durniak, PhD
Administrative Director, Partners Academic Programs and Policy
Contributing Member

Dianne Finkelstein, PhD
Director, Biostatistics Unit
Ex-officio

Michael L. Fisher, LPD
Director, Research Space Management Group (RSMG)
Ex-officio

Patrick Fortune, PhD
Market Sector Leader, Partners Innovation
Contributing Member

Mary L. Gervino
Director, MGH Research Compliance
Ex-officio

Katherine Gutierrez
Director, Development
Contributing Member

Mary Hanifin, MBA
Sr. Managing Director of Development
Contributing Member

Elizabeth L. Hohmann, MD
Partners, IRB Chair
Contributing Member

Donna Jarrell, DVM
Director, Center for Comparative Medicine (CCM)
Ex-officio

Tatiana Koretskaia, MBA
Director, Administration and Finance
Division of Clinical Research
Contributing Member

Donna Lawton, MS
Executive Director, Center for Faculty Development
Ex-officio

Diane Mahoney, PhD, RN, FAAN
MGH Institute of Health Professions
Ex-officio

Richard Masland, PhD
Ophthalmology
Massachusetts Eye and Ear Infirmary
Ex-officio

Susan R. McGreevey
Manager, Science & Research Communications
MGH Public Affairs
Contributing Member

Mary Mitchell
Director, Partners Research Compliance
Contributing Member

Elena Olson, JD
Executive Director, Center for Diversity and Inclusion (CDI)
Contributing Member

P. Pearl O'Rourke, MD
Director, Human Research Affairs, Partners
Ex-officio

John Parrish, MD
Director, CIMIT
Ex-officio

Kay Ryan
Director, Clinical Research Operations
Division of Clinical Research
Contributing Member

Joan Sapir, EdM, MBA
Sr. Vice President,
MGH Administration
Contributing Member

Ann Skoczenski, PhD
Program Manager,
Center for Faculty Development
Contributing Member

Gary Smith
Sr. Administrative Director,
MGH Research Management
Ex-officio

Scott T. Weiss, MD, MS
Scientific Director, Partners Center for Personalized Genetic Medicine (PCPGM)
Ex-officio

Winfred W. Williams, Jr., MD
Co-Chair, Center for Diversity and Inclusion Advisory Board
Contributing Member

MGH Research Institute

Executive Report for SAC 2016

Harry W. Orf, PhD
Senior Vice President for Research

A Research Community By Any Other Name…

The expanded name of this year's report, the MGH Research Institute Executive Report, represents not only the new name of our research community, but also the numerous initiatives now underway across the entire research enterprise, initiatives that will benefit our community for years to come. The Research Institute, launched this time last year and described in my 2014 Executive Report, is off to a running start under the direction of Dr. Susan Slaugenhaupt, the inaugural Scientific Director. New initiatives in philanthropy, formation of strategic alliances with industry, and marketing of the MGH research 'brand' are underway and described in Susan's write-up in the last section of my report, MGH Research—Progress in 2015. Similar advances, also described in this section, have been made in other elements of our research strategic plan under: 1) Dr. Maurizio Fava's leadership of the new Division of Clinical Research; 2) Dr. Mason Freeman's work on the new Translational Research Center; 3) Dr. Andrew Nierenberg's initiatives with the new RITE (Research Institute Training and Education) Committee; 4) Drs. Jordan Smoller and Susan Slaugenhaupt's efforts leading the Partners Biobank at MGH; 5) Dr. Carl Blesius and Deverie Bongard's work with the new RSIS (Research Support IS) Committee; and 6) the "Isuggest" Operations Improvement team (Katherine Abuhadal, Samantha Molle, Misha Pivovarov, and Gary Smith).

In addition to these strategic initiatives, other important results, events, and developments had a significant impact on MGH research in 2015. These include a major recovery in research revenues from the dip last year, a new indirect cost rate negotiated with the federal government, and major upgrades to our animal care and use program, an expanded account of which is given below in this year's report.

By the Number$—An Impressive Rebound to an All-Time High

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

In Fiscal Year 14 (FY14), research revenues decreased for the first time in over a decade from $786M to $760M, due to cuts and delays in federal funding resulting from sequestration. We are very pleased to report that research revenues not only recovered in FY15 but reached an all-time high, posting a $40M (5.2%) increase to just over $800M ($610M direct costs and $190M indirect). Our awarded dollars from the National Institutes of Health (NIH) in FY15 decreased slightly from $350M in FY14 to $349M, but, the percentage of funding awarded to MGH from the entire NIH extramural grant pool (market share) in FY15 grew from 1.5% to 1.6%. This is a testament to the perseverance and resilience of the MGH research faculty amid challenging budget times at NIH. With a proposed $2B increase to the NIH budget planned for this coming year, we are hopeful that our NIH funding will again 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" (14%), "Industry/Corporate" (26%) and "Non-Profit" (17%). Overall, MGH submitted 4,373 research proposals to all sponsors in FY15, up 10% from the prior fiscal year. DHHS success rates for MGH proposals are approximately 23%, six points higher than the NIH national average of 17%.

Research expenditures from direct DHHS funding (which consists mostly of NIH funding), now accounts for 43% of MGH research, down 1% from last year's 44%. Although the percentage of our DHHS research funding base went down, our DHHS-sponsored research expenditures increased

from $337M in FY14 to $343M in FY15. Again in 2015, MGH remains the largest recipient of NIH funding among independent hospitals and 13th nationally for all institutions.

We also saw increases in research expenditures for all of our other sponsor types. "Other Federal Gov't" increased 24% from $29M in FY14 to $38M in FY15. "Industry/Corporate" expenditures increased 5% to $61M in FY15. The remaining sponsors, which include non-profit organizations, subcontracts, foundations, internal, and gifts/endowments, showed an increase of 8%, to $396M in FY15 from $365M in FY14, as investigators have continued to turn to these sources to buffer the constraints on NIH support. The cumulative annual growth rate for FY11-FY15 across all sponsor types was 8%.

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.

Important Changes to the Indirect Cost Rate

MGH has historically negotiated a fixed, multi-year predetermined indirect cost rate with the federal government. The rates in effect for FY14 (74% for onsite research and 27% for offsite) were set years ago using FY06 as the base year. In FY15, this rate was extended as a provisional rate while we worked with federal negotiators to establish a new indirect cost rate using FY14 as the base year. After a year-long effort to document and substantiate indirect costs associated with our research enterprise, we reached an agreement on new rates for FY16 and FY17–71% onsite and 32% offsite. The 3% decrease in the onsite rate was due primarily to the fact that our research revenues have increased dramatically since our last base year calculation, but our research space (and associated operating costs) did not.

Aside from the lower indirect rate itself, the most important change imposed by the federal negotiators this year was a change to our rate-setting process. Beginning in FY16 and going forward, indirect rate agreements will have to be determined annually (i.e., based on an annual fixed rate) rather than the multi-year predetermined rate process we and other academic medical centers have traditionally used. In the annual rate setting process, any difference between actual and applied rates will be carried forward and used to establish the rate in subsequent years.

Because rates will now be adjusted at the beginning of each fiscal year, our investigators will now have to plan for (hopefully small) fluctuations in their grant budgets. Since most federal grants are awarded based on fixed total dollars, grants will get slightly more direct research dollars in years when the indirect rate decreases, and slightly less direct research dollars in years when the indirect rate increases. While the onsite indirect rate dropped this year by 3%, resulting in slight increases in direct research dollars to onsite grants, the unanticipated 5% increase in the offsite rate resulted in significant losses of direct research dollars for offsite grants. For investigators with large offsite grants whose programs were jeopardized, the hospital provided one-time internal funding to replace most of the direct research dollars lost.

As one might imagine, this new process requires full documentation of all indirect expenses each year and will impose an enormous (bureaucratic!) increase in workload for research management staff. Our new team of federal negotiators dictated this process change based on an archaic (40 year old) guideline stating that hospitals may not use predetermined fixed indirect rates if they receive any federal contracts. Since MGH receives approximately $11M in federal contracts annually (out of over $800M in combined grant and contract revenue), we are required to change our process to the annual fixed indirect rate. We believe the rationale for this process change is flawed and are working through our congressional representatives to have it retracted.

Awards and Recognition

The summer of 2014 saw the creation of the MGH Committee on Awards and Honors, chaired by Dr. Sam Thier, president of the hospital 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. It meets regularly and, in 2015, championed the nominations of more than 23 outstanding MGH scientists for major awards and society memberships.

National and International Awards. In 2015, MGH investigators continued to receive national recognition for their major research contributions. Rakesh Jain, PhD, Director of the Edwin L. Steele Laboratory for Tumor Biology, won the National Medal of Science, which is awarded by the President of the United States. This is the first time an MGH investigator was honored with this award and also marks the first time in 26 years that an HMS faculty member received the award. Jeannie Lee, MD, PhD, in the Department of Molecular Biology, was elected to the National Academy of Science. Emery N. Brown, MD, PhD, Department of Anesthesia, was elected into the National Academy of Engineering and named as a Fellow in the National Academy of Inventors. Joan W. Miller, MD, Department of Ophthalmology, was elected into the National Academy of Medicine. Hakho Lee, PhD (Center for Systems Biology), was named a Blavatnik National Awards for Young Scientists Finalist.

Other major awards and prizes received by MGH investigators in 2015 include the following:

Alliance for Aging Research Silver Innovator Award
Rudolph E. Tanzi, PhD (Neurology)

American Skin Association's David Marin Carter Mentor Award
Howard P. Baden, MD (Dermatology)

American Society of Anesthesiologists Award for Excellence in Research
Emery Brown, MD, PhD (Anesthesia)

American Association for Cancer Research (AACR) Academy Fellow
Bruce Chabner, MD (Cancer Center)

American Institute for Medical and Biological Engineering College of Fellows
Patrick Purdon, PhD (Anesthesia)

American Nurses Association Massachusetts' Excellence in Nursing Research Award
Sara Dolan Looby, PhD, ANP-BC, FAAN (Patient Care Services—Munn Center for Nursing Research)

Association for Research in Vision and Ophthalmology (ARVO) Proctor Medal
Patricia A. D'Amore, PhD, MBA (Pathology)

Association for Research in Vision and Ophthalmology (ARVO) Mildred Weisenfeld Award for Excellence in Ophthalmology
Joan Miller, MD (Ophthalmology)

Bill and Melinda Gates Foundation Grand Challenges Explorations (GCE)
Christina Faherty, PhD (Pediatrics), Alessio Fasano, MD (Pediatric Gastroenterology and Nutrition), Stefania Senger, PhD (Pediatrics) with researchers at MIT

Clinical Research Forum's Distinguished Clinical Research Achievement Award
Lee Schwamm, MD (Neurology)

Diabetes Research Center Outstanding Achievement in Clinical Diabetes Research Award
David M. Nathan, MD (Medicine)

Endocrine Society's Laureate Outstanding Mentor Award
Anne Klibanski, MD (Neuroendocrine)

Gastroenterology Research Group/American Gastroenterological Association Young Investigator Clinical Science Award
Hamed Khalili, MD, MPH (Gastroenterology)

MGH Research Institute

Executive Report for SAC 2016

Gerald D. Aurbach Award for Outstanding Translational Research
Steven Grinspoon, MD (Medicine)

German National Academy of Sciences
Ralph Weissleder, MD, PhD (Center for Systems Biology)

Guggenheim Fellowship for Applied Mathematics
Emery Brown, MD, PhD (Anesthesia)

HIV Medical Association HIV Research Award
Ingrid Bassett, MD, MPH (Infectious Disease)

International Society for Optics and Photonics Britton Chance Biomedical Optics Award
David Boas, PhD (Martinos Center for Biomedical Imaging)

Jacobson Innovation Award
Joseph Vacanti, MD (Pediatric Surgery at Mass General Hospital *for* Children)

John Eisenberg National Award for Career Achievement in Research
Nancy Rigotti, MD (Medicine)

Joseph B. Martin Dean's Leadership Award for the Advancement of Women Faculty
Merit Cudkowicz, MD (Neurology)

Kenneth Rainin Foundation Innovator Award
Kate Jeffrey, PhD (Medicine)

National Academy of Inventors—2015 Fellows
Emery Brown, MD, PhD (Anesthesia)
Gary Tearney, MD, PhD (Pathology and Wellman Center for Photomedicine)

National Institute on Drug Abuse Avenir Award
Alejandro B. Balazs, PhD (Ragon Institute of MGH, MIT and Harvard)

National Cancer Institute Outstanding Investigator Award
Rakesh Jain, PhD (Radiology)

National Institute of Neurological Disorders and Stroke (NINDS) Javits Neuroscience Award
Kevin Staley, MD (Pediatric Neurology)

NIH Director's Early Independence Award
Shadmehr Demehri, MD, PhD (Dermatology and the Cancer Center)

NIH Director's New Innovator Award
Alex K. Shalek, PhD (Ragon Institute of MGH, MIT and Harvard)

Paul Marks Prize for Cancer Research
Bradley Bernstein, MD, PhD (Pathology)

American Cancer Society Research Professorship
Bradley Bernstein, MD, PhD (Pathology)

International Association of Providers of AIDS Care Rising Star Award for Promising Early Career Scientist/Practitioner
Jessica Haberer, MD, MS (Center for Global Health)

Radiological Society of North America
G. Scott Gazelle, MD (Radiology)

Rogers Family Foundation Cara J. Rogers Endowed Scholar to Advance Bone Marrow Transplant Research
Yi-Ben Chen, MD (Cancer Center)

Smithsonian American Ingenuity Award
Rudolph E. Tanzi, PhD (Neurology) and Doo Yeon Kim, PhD (Neurology)

Society of Neuroscience
Keren Haroush, PhD (Neurosurgery)

Susan G. Komen Foundation Dare Award
Priscilla Brastianos, MD (Cancer Center)

Chemical and Engineering News Talented 12 (finalist)
Jacob M. Hooker, PhD (Radiology)

***Time* Magazine's "100 Most Influential People"**
Rudolph E. Tanzi, PhD (Neurology)

Executive Report for SAC 2016

MGH Research Scholars. As reported previously, the Executive Committee on Research (ECOR), in partnership with the MGH Development Office and its external Research Institute Advisory Council (RIAC), framed a strategic plan for a $100 million campaign in support of our researchers. This plan evolved into the MGH Research Scholars Program, providing research and salary support to outstanding MGH fundamental and clinical scientists engaged in cutting-edge, innovative research with the potential for significant impact on patient care. Scholars are awarded $100,000 per year for five years in support of their research. In 2011, the first five scholars were selected from among 115 applicants. Reflecting the donor gifts made to support these MGH Scholars, all five were "named" Scholars. Each donor gift was matched with funds from a $10 million anonymous donor gift made in 2010 that helped launch the program.

At our SAC 2015 event last April, we announced the fifth group of MGH Research Scholars. These eight recipients were selected from 77 applicants by a committee led by Nobel Laureate Jack Szostak, PhD, of the Department of Molecular Biology, and Bruce Walker, MD, Director of the Ragon Institute of MGH, MIT and Harvard. The 2015 MGH Research Scholars are:

- Harald Ott, MD, Surgery
- Mikael Pittet, PhD, Center for Systems Biology
- Mark Poznansky, MD, PhD, Infectious Disease
- Sridhar Ramaswamy, MD, Cancer Center
- Michael Talkowski, PhD, Neurology
- Elsie Taveras, MD, MPH, Pediatrics
- Lawrence Wald, PhD, Martinos Center
- Rochelle Walensky, MD, MPH, Infectious Disease

Martin Prizes. The Martin Fundamental and Clinical Research Prizes, established in 2008 to honor Joseph Martin, MD, PhD, former MGH Chief of Neurology and HMS Dean, were awarded again this year. These two $100,000 annual awards recognize the most outstanding work by MGH investigators published in the previous calendar year. The 2016 recipients for a 2015 publication are Filip Swirski, PhD, (Fundamental Science Award) for his Science paper entitled, "Interleukin-3 amplifies acute inflammation and is a potential therapeutic target in sepsis" and Andrew Chan, MD (Clinical Science Award) for his JAMA paper "Association of aspirin and NSAID use with risk of colorectal cancer according to genetic variants".

Goodman Award. The 2016 Howard Goodman Award recipient is Robert Anthony, PhD, from Rheumatology, Allergy and Immunology. This Fellowship honors Howard M. Goodman, founder and former Chief of the MGH Department of Molecular Biology. 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's 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 within Molecular Biology. Each year a Goodman awardee 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, supported at $150,000 direct costs annually.

Executive Report for SAC 2016

The Final Frontier (Space!)

The Research Space Management Group (RSMG) fulfills a number of critical objectives in support of the MGH Research Institute, with particular emphasis on development and implementation of space allocation strategies that support overall institutional research objectives.

Demand and Densities. MGH currently owns or leases approximately 1.2 million square feet of research space, of which 42% is in the Charlestown Navy Yard, 23% is on the MGH Main Campus, 22% in the Charles River Park, and the remainder is in various locations throughout Boston and Cambridge. During 2015, research vacated approximately 23,500 nasf at 100 Cambridge Street and other locations, which was replaced with 20,465 nasf at 125 Nashua Street. Because the Nashua Street space boasts a more efficient design, this actually represents a small increase in usable research square footage.

Indirect Cost density dropped slightly from $167 per square foot to $160 per square foot due primarily to minor changes in research space and the grant funder mix.

The Research Densification Committee, formed in 2009 and reconstituted in 2014 as the Research Space Advisory Committee (RSAC), a subcommittee of ECOR, works with RSMG to develop policies designed to improve research space utilization. At the beginning of 2015, RSMG presented RSAC with a list of requests from the research community for an additional 72,507 nasf of space. During the year, RSMG was able to satisfy 33,137 nasf of these requests primarily by partnering with a number of departments, assisting them in identifying and better using space already in their portfolio and, in a few cases, arranging for a transfer of space from one department to another. The list now includes requests from the departments for an additional 103,557 nasf of new space, of which 58% is for wet research and 42% is for dry research. This amount requested is up 40% from last year.

The large growth of the research enterprise over the past decade has not been accompanied by concurrent growth in research space. Accordingly, finding suitable space solutions for new and expanding programs requires imagination, negotiation, and cooperation. For example, in order to satisfy Molecular Biology's space needs for retention and recruitment, RSMG worked with adjoining departments and throughout the Simches Building to identify appropriate space that would fulfill the growing needs of the department. Another example of locating space for a strategic initiative is the conversion of a former patient care floor in the White Building into the Translational and Clinical Research Centers, a major project expected to be completed in Fall/Winter 2016.

Construction and Renovation Projects. RSMG serves as the client of record for all research construction and renovation projects, and is managing or overseeing $20M of ongoing small and medium projects. The value of new and ongoing projects will increase by $24M in FY16.

During 2015, a number of projects were completed at the cost of $9M. These included, installation of quench vents for Building 149 imaging equipment, renovation of Simches 3 labs for Cardiology, humidity mediation at our swine facility, a second recruiting/blood draw room for the MGH Biobank, and installation of two X-ray irradiators.

With the recent approval of the 2016 capital budget, work can finally begin in Building 149 (Charlestown) on a major renovation of the 10th and 2nd floors. This project will allow us to provide dry space for the Interdisciplinary Brain Center and the Institute for Innovation in Imaging on the 10th floor, and subject interview space, lab space, and a hot lab on the 2nd floor. Another major ongoing project involves renovation of Warren 6 to better accommodate the needs of Psychiatry research and the department's clinical consultation program. Two other exciting projects that are scheduled to start in FY16 are modification of space on Edwards 3 to provide specialized rodent housing and

procedure space for Cardiology, as well as conversion of a vacant imaging room on Edwards 1 into wet lab space.

Survey and Analytical Activity. We experienced substantial progress in the functionality of the Research Space Management System (RSMS) database application and report module over the past year. In conjunction with Brigham and Women's Hospital (BWH), RSMG worked closely with the Partners' RSMS development team to identify, review, and prioritize issues. Inefficiencies in process were identified and consensus achieved, allowing further development to proceed.

Discussions regarding the data needed to better manage space metrics were ongoing with BWH and the Partners report team throughout the year. Several new reports have been added and, overall, data presentation has been improved to make it easier for PI's to understand. Some of the new reports under development, in particular the Quality Density Report, will provide valuable space metrics across all levels of MGH's research organizational hierarchy.

RSMG also worked closely with Partners Research Reimbursement to survey research space usage as part of ongoing indirect cost (IC) negotiations. RSMG utilized the talents of three summer interns to survey MGH on-site research space to verify room utilization and to identify critical demographic data for occupants of every "seat" in this space. The hospital preparation was so successful that the auditors who were expected to visit the institution to audit space usage decided there was no need to do so and accepted the hospital's figures as submitted. Moving forward, IC rates will be negotiated annually and RSMG will continue to be an integral part of the preparation for the negotiation.

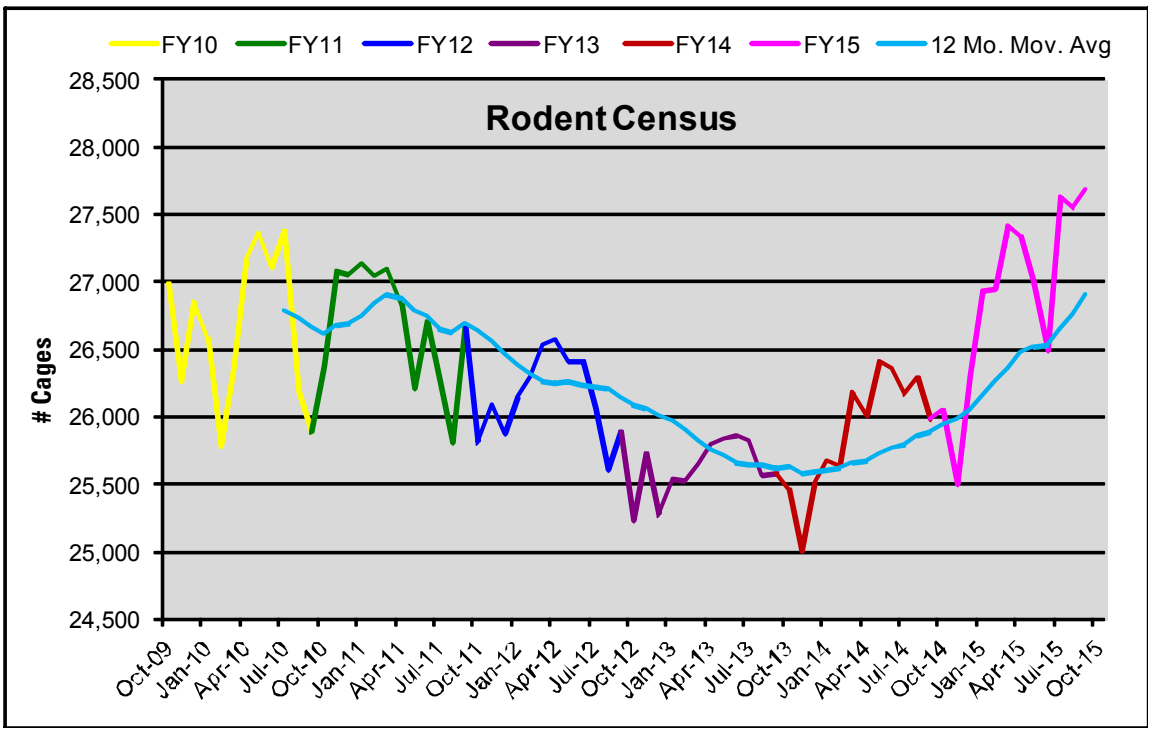
Animal Care (Center for Comparative Medicine) and Compliance (Institutional Animal Care and Use Committee)

On any given day, approximately 100,000 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 300 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, intra-institutional transportation, preventive and clinical veterinary care, training in animal manipulative techniques, surgery and post-operative support, mouse breeding and colony preservation, and consultation in animal modeling and protocol design. Over 125 employees, including seven staff veterinarians (five of whom are board-certified in laboratory animal medicine) and a leadership team of 17 mid- and director-level managers, provide these services throughout MGH.

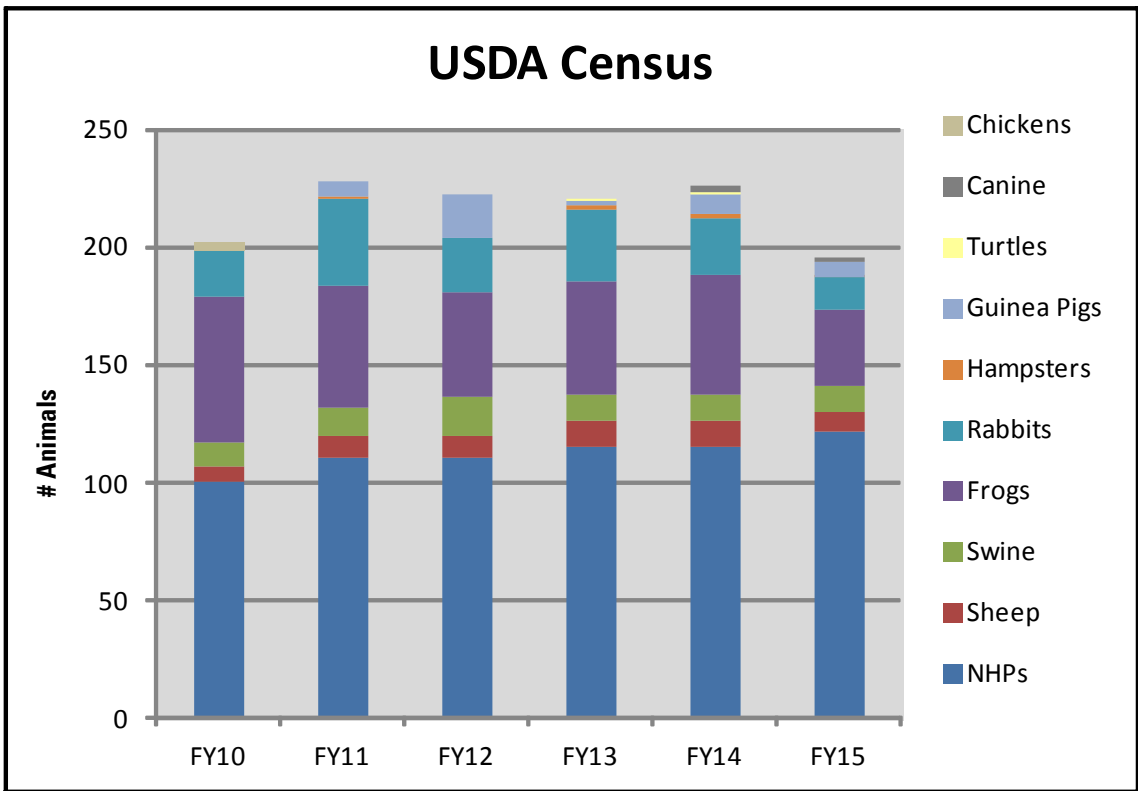
Executive Report for SAC 2016

Graph 1:



Over the past year, animal census has increased throughout all facilities to the highest year-end level in five years, with our rodent average daily census approaching 27,000 cages (Graph 1). For the USDA-regulated species (Graph 2), growth has fluctuated depending on the species with the non-human primate census continuing to increase the most. Rodents (the majority of animals maintained) and non-human primates census growth continue to put significant pressure on current resources for housing and procedural areas.

Graph 2:

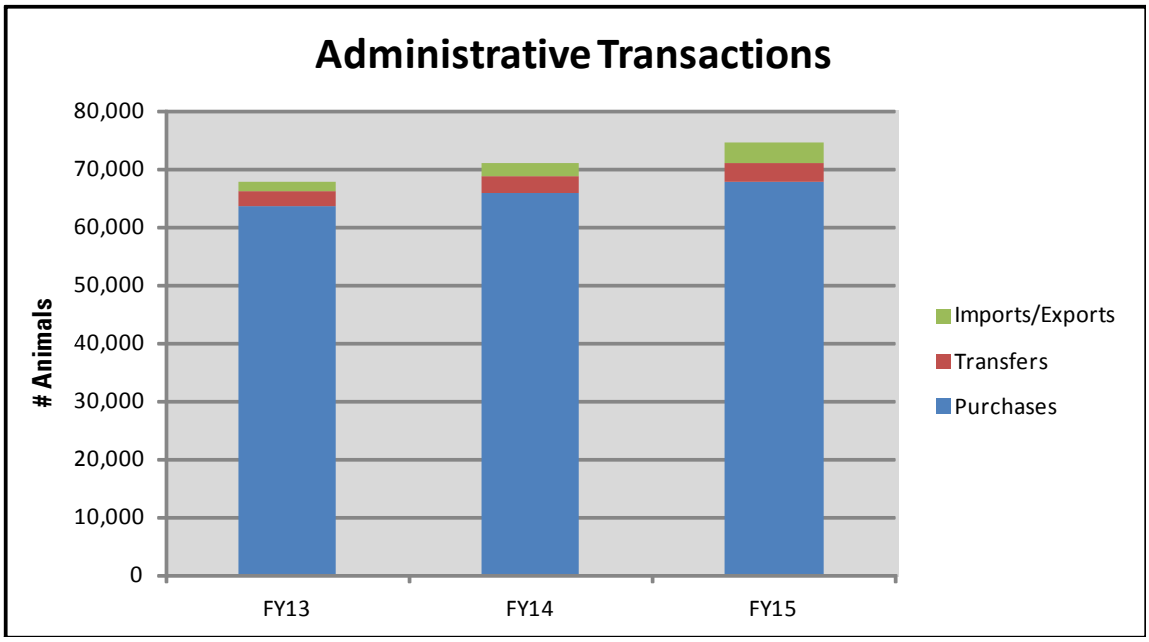


In addition, CCM continues to see an increase in requests for administrative (Graph 3) and technical (Graph 4) support from the research community in various husbandry and veterinary specialties. The most popular requests for these support services are in the areas of rodent procurement, rodent production/breeding support services, and experimental study conduct.

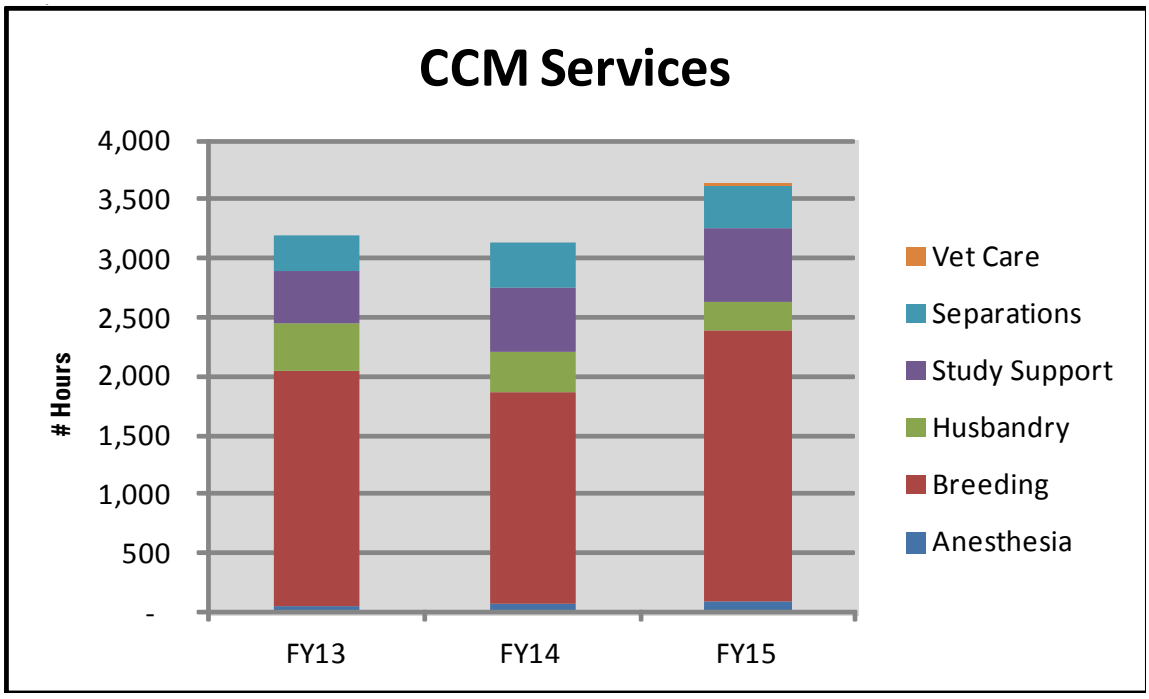
Through the application of lean operations management, made popular by the adaptation of the Toyota Production System, CCM has been able to respond to both the increasing census as well as the expansion of research support services provided to researchers without significant increases in costs. In some processes, costs have actually been decreased. For example, with a steady increase in animal importation (including quarantine) requests (Graph 3), the CCM Veterinary Services team successfully revised the rodent quarantine program resulting in a 57% decrease (from 44 days average to 19 days average) in length of quarantine. All of these savings were passed onto researchers by no increase in FY16 per diem charges from FY15.

Executive Report for SAC 2016

Graph 3:



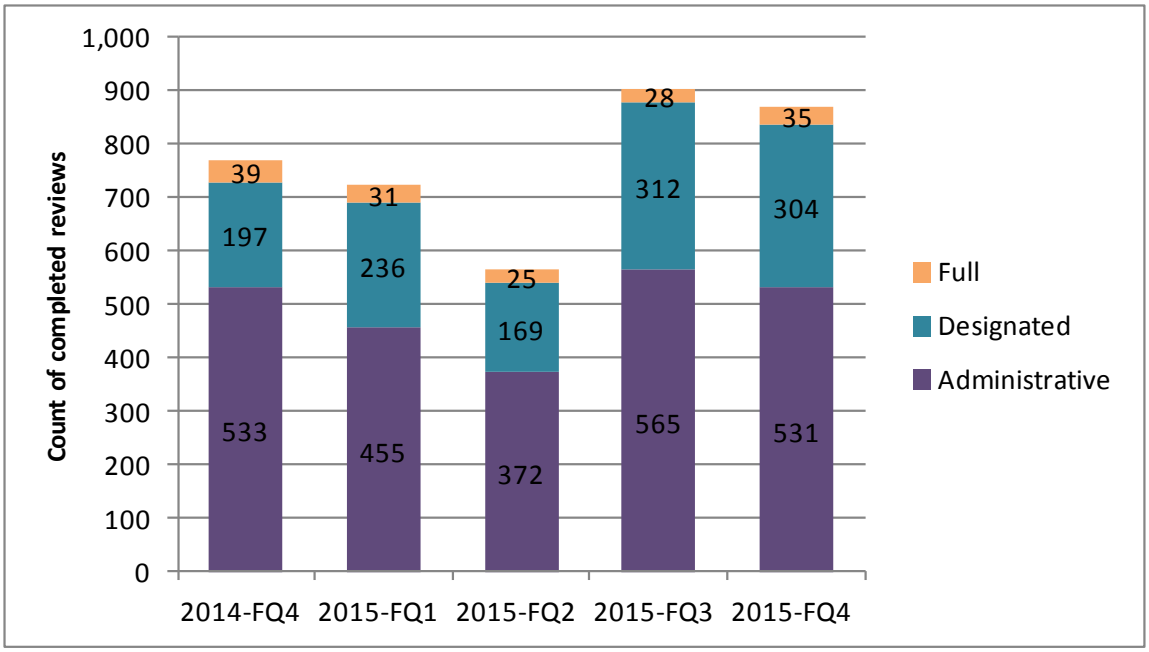
Graph 4:



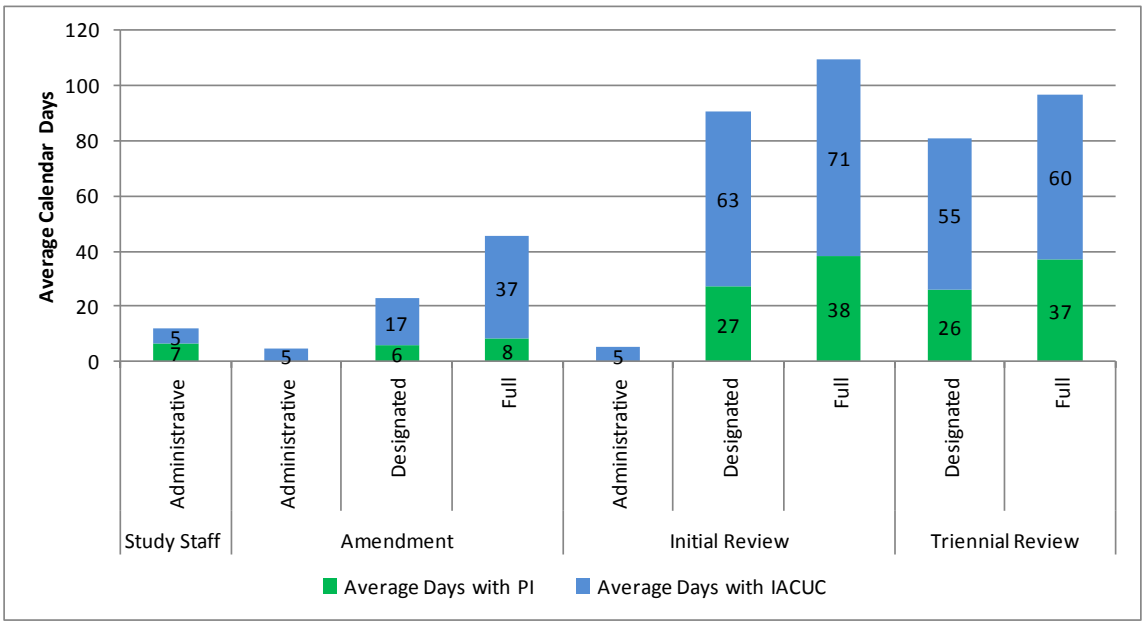
Lastly, CCM hosted over 30 visits in 2015 from research and laboratory animal leaders who have expressed interest in adopting a similar lean program operations model in their vivaria. Seminars and webinars on this subject were presented at annual conferences of the American College of Laboratory Animal Medicine, the Laboratory Animal Management Association, the American Association of Laboratory Animal Science, and the Public Responsibility in Medicine and Research. In 2015, CCM along with Harvard University and the Oklahoma Medical Research Foundation, co-founded the Vivarium Operations Excellence Network (http://www.voenetwork.com) to offer a platform for animal care and use programs to share program-based continuous improvement opportunities and solutions with participating members. In just one year the Network has grown to over 20 members, representing six countries and has offered more than 20 events to ~250 participants.

The Institutional Animal Care and Use Committee (IACUC) governs the use of research animals at MGH. The IACUC office and staff is led by Anne Clancy, PhD. MGH is registered/licensed by all federal and state agencies governing animal welfare and has been accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC) since 1993. Currently, there are more than 900 active protocols being performed by over 360 Principal Investigators. Approximately 750 transactions are processed quarterly by the MGH IACUC (Graph 5). For the fourth quarter 2015, approximate turn-around-times for review and approval of Initial (New) IACUC Applications, Triennial Review Applications and Amendments (reviewed by Full Committee or Designated Member Review processes) were 100, 90 and 34 calendar days, respectively (Graph 6). A major process improvement initiative, under the joint leadership of Drs. Clancy and Jarrell and with the full participation of their respective departmental leadership teams, has recently been started to reduce these turnaround times.

Graph 5: Volume of IACUC Approvals by Quarter-Summary
Number of Full, Designated and Administrative Reviews—Q4 FY14 to Q4 FY15



Graph 6: Average Turnaround Time of Reviews Completed in Q4 FY15
Split by Time with PI and IACUC



Updates to the overall animal care and use program in the past year:

- In June 2015 AAALAC International awarded MGH a status of Full Accreditation, following a review of the MGH animal research program in fall 2014.
- USDA conducted an annual inspection of the MGH animal research facility. The program received a citation for two incidents that were immediately addressed and rectified to the satisfaction of the agency.
- The City of Cambridge conducted its annual inspection of the MGH animal research facilities; no deficiencies were identified in the program.
- The IACUC office worked with the Insight team to make improvements to the eIACUC system in response to feedback from the researcher community and system issues impacting protocol forms. Examples of changes included better navigation and prompts, as well as improved communications regarding continuing review applications.
- The IACUC office, in collaboration with the Partners Research Analytics Group, has developed quarterly work activity reports available on Research Navigator:

https://partnershealthcare.sharepoint.com/sites/phrmResources/news/Pages/IACUC-Q4-FY15-Work-Activity-Report.aspx

- The IACUC and CCM continued to collaborate with RSMG 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 and Occupational Health Service streamlined the occupational health screening requirements and process to provide better service to the research community while continuing to meet our regulatory standards.

- The IACUC, in collaboration with CCM, established a new standardized process for managing animals in the facilities when IACUC approval expires. This program focused on prevention of expiration and ensuring compliance in our program while providing support to research programs during the renewal process.
- Dr. Clancy participated as Faculty in the 2015 National IACUC Conference hosted by Public Responsibility in Medicine and Research in a Panel Session entitled "Cultivating a Culture of Compliance." Robin Minkel represented MGH in an IACUC Best Practices Meeting sponsored in part by Office of Laboratory Animal Welfare (OLAW), NIH.
- The IACUC and CCM, along with representatives from the research community, continued to lead the Continuous Research Operations Improvement (CROI) Animal Care and Use Working Group to resolve suggestions received from the research community to make the research experience using animals at MGH more productive and successful.

Partners Research Management

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 (PRM) team. They work in close collaboration with Harry Orf, PhD, Senior Vice President of Research, at MGH and Paul Anderson, MD, PhD, 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, Vice President of Partners Innovation.

Partners Research Management (PRM) continues to successfully manage one of the largest and most complicated research portfolios in the world. Over the past year, PRM continued to make significant improvements to operations, systems and quality of service to MGH. System enhancements and reporting tools that were put in place last year have become more entrenched in day-to-day activities resulting in greater efficiencies. The resources gained through efficiency are now supporting an increased volume of proposals, awards and subcontracts.

Many of the improvements PRM has made for MGH are focused on more efficient ways to minimize compliance risks associated with federal regulations or new federal requirements. Two examples of these types of improvements over the past year are the automation of the compliance requirements associated with managing the NIH salary cap, and the transition in our reimbursement process from the federal government.

Complying with the NIH salary cap, which mandates a limit on salary charged to an NIH award, has been a tedious and administratively burdensome exercise for MGH research departments. Designing and then leveraging new functionality in PeopleSoft, PRM has developed a tool that guarantees compliance, reducing the risk to MGH associated with potential human errors and significantly decreasing the administrative time associated with this task.

NIH mandated a change in how award recipients get reimbursed, allowing the NIH greater transparency on spending activity on individual projects. While this change in the reimbursement process took effect for all new awards over the past year, this year all existing awards must be converted to comply with the new process. This conversion affects 500 projects. PRM has invested in IT enhancements to accommodate the change, developed new procedures, expanded trainings and increased communication with the research community to facilitate this change. Thus far, the transition to the new process has been successful and the first wave of existing awards has been converted.

Unfortunately, improvements made in previous years have been challenged by the ever increasing regulatory burden imposed by federal and non-profit sponsors. The recent consolidation of Federal Regulatory circulars into one "Uniform Guidance" (2 Code of Federal Regulations Part 200) has resulted in delays in our subcontract executions and invoice payments. The academic institutions with which we collaborate have interpreted the new regulations in unique ways that in turn create significant administrative burden on our support infrastructure. Addressing this new environment in a way that streamlines and speeds up our contracting is a key objective. PRM has reorganized the contracting group to allow for timelier front end review of agreements. We have been working with our largest academic collaborators to rationalize the interpretation of the Uniform Guidance and are engaged with other key research institutions in national forums to promote more standardization.

PRM remains focused on providing the highest level of support to the MGH research community and the office is well positioned to handle additional changes in the funding and regulatory environment to allow for the continued success of MGH research.

Partners Innovation

Partners Innovation, led by Vice President Chris Coburn, is MGH's commercialization arm. It is organized into nine clinical vertical units (e.g., neurosciences, cardiovascular and pulmonology, orthopedics and rheumatology, etc.) that are designed to strategically engage industry, enable internal priority setting, and drive larger and more frequent industrial outcomes. Four highly experienced industry leaders with senior investment, product development, R&D and supply chain experience lead the sectors. The market sectors complement the Partners Innovation Fund and the Business Development/Health IT groups, each which has had substantial success.

In 2015, Partners Innovation had a number of substantial outcomes, including the acquisition of the portfolio company, Adheron, by Roche for $580 million. This success drove the Fund IRR to nearly 30%—making it one of the most successful academic investment initiatives in the United States. This led to the launch of Fund II, which takes the total under management to $100 million. Also transacted last year was a $30 million deal with Health Catalyst to jointly develop population health management tools.

Finally, the World Medical Innovation Forum will be held April 25-27, 2016. It will feature the newest technologies to diagnose, treat and manage cancer. The World Medical Innovation Forum is a global gathering of more than 1,200 senior health care leaders hosted by Partners HealthCare in the heart of Boston. Speakers include industry CEOs, leading clinicians, innovators, investors and top journalists. In addition to examining the cutting-edge issues in the field, the forum will feature the "Disruptive Dozen"—12 emerging technologies with the potential to revolutionize the selected field over the next decade. Several dozen MGH faculty will participate in the Forum as panelists and speakers.

MGH Outcomes	FY14	FY15
Licensing Activity * (exclusive and non-exclusive licenses, options (amendments with $ or IPP added)	113	127
Material Transfer Agreements	1,073	987
New Disclosures (with material inventions)	408	318
Patents Filed (US)	253	228
Patents Filed (Int'l)	644	399
Patents Issued (US)	86	89
Patents Issued (Int'l)	172	120
Royalty and Licensing Income	$68.9M	$80M

** Excludes non-revenue bearing ("end-user") licenses.*

Partners Office for Interactions with Industry (OII)

In 2015, OII, led by Chris Clark, Esq., continued to refine and improve Partners policies and processes relating to the complex relationships between academic medicine and the for-profit biomedical sector. While the focus continues to be on ensuring that such relationships do not bias Partners charitable activities, OII is also committed to fostering these relationships as essential to Partners ability to carry out its missions. Thus OII, working with the oversight committees, constantly re-evaluates Partners policies and processes to ensure that they assure integrity while avoiding unnecessary impediments to healthy industrial relationships.

Significant accomplishments during FY15 included the following:

1. With the Committee on Outside Activities, took a leadership role in pressing HMS to re-evaluate hard-stop 1(b) rule, and actively participated with HMS and other affiliates in the review process, leading to a soon-to-be-announced major loosening of a rule perceived to be an impediment to appropriate industry relationships.
2. Streamlined the process for completing conflicts reviews of funded research projects.
3. With the Committee on Outside Activities, identified acceptable exceptions to the gift ban policy, streamlined the process for review of Institutional Officials, refined the policy provisions on "promotional activities" and "use of institutional resources."
4. Worked with senior leadership to revise chairs and members of Committee on Outside Activities to better represent appropriate constituencies of the community.
5. With the Education Review Board, instituted a two-year pilot that loosened the multi-funder rule for Harvard and Partners accredited grand rounds activities, and recognized a new sub-category of a Partners Educational Activity for programs not relating directly to clinical care, with more flexible rules.
6. Worked with Partners Research Applications Group to achieve major usability upgrades to the Insight Disclosure system, and to finalize and implement systems needed to capture all research investigators who are subject to Public Health System regulations, thereby addressing a major area of compliance concern.

MGH Research Institute

Executive Report for SAC 2016

MGH Research—Progress in 2015

The Mass General Research Institute—Dr. Susan Slaugenhaupt, Scientific Director
The Office of the Scientific Director is primarily charged with promoting science at Mass General, which includes marketing efforts, boosting philanthropic giving, and building new relationships with industry to broaden our research funding base.

Introducing the Research Institute. The Office of the Scientific Director has played a key role in introducing the Research Institute to the Mass General research community and spreading the word through a grass-roots speaking tour. The goal of this initiative was to increase awareness of the Institute among our investigators. In 2015, the Institute team made numerous appearances to promote the Institute, including speaking at or sponsoring:

- The Scientific Advisory Council Dinner
- Partners World Medical Innovation Forum
- Center for Human Genetic Research (CHGR) Retreat
- Research Council
- Research Staff Appreciation Day
- Clinical Research Council
- Nursing Research Day
- The Research Administrators Retreat
- The PhD Steering Committee
- The MGH Summer Picnic
- The Claflin Awards Luncheon
- Research Faculty Happy Hour
- The MGH Development Office All Staff Meeting
- MGH in London (Development Office event)
- Partners Innovation Advisory Board
- The Research Fellows Celebration
- Graduate Student and Post Doc BBQ
- Phillips Society Luncheon
- The MGH Board of Trustees
- The Department of Medicine
- HUBweek

Marketing
We have been steadily ramping up the marketing of research at Mass General, so we can spread the word about the amazing science that takes place here every day.

The Mass General Research Website and related research lab and center pages on massgeneral.org received 970,000 page views from over 270,000 individual users in 2015. More than half of these visitors were new to the site. Some of the most popular pages included job openings, faculty pages, our labs and centers directory, and the research sections of the psychiatry, neurology, pediatrics and orthopedics departments.

Facebook. Research-related Facebook posts continue to be some of the most popular on the Mass General Facebook site. Here are some highlights from 2015:

- Could meditating for 30 minutes a day actually change your brain structure? A neuroscientist at Mass General has compiled brain imaging data suggesting that it can. (Featuring Sara Lazar, PhD) *58,000 people reached*
- A new Mass General research study has found—for the first time—evidence of neuroinflammation in the brain in patients with chronic pain. (Featuring Marco Loggia, PhD) *29,000 people*
- A new gel-based capsule solution may hold the key to successfully transplanting insulin-producing islet cells into patients with Type 1 diabetes without the need for immunosuppressive drugs. (Featuring Mark Poznansky, MD, PhD) *24,000 people*
- Mass General's Dr. Rudolph Tanzi was recognized on TIME Magazine's list of 100 Most Influential People for his pioneering work in Alzheimer's research. *21,000 people*

Other Marketing Efforts. In the fall, the Research Institute played a major role at HUBweek, sponsoring the popular Women in Medicine speaking series at the Russell Museum. We created "The Science of You" handout cards (explaining how research at Mass General is helping to better our understanding of the human body) and handed them out during the lecture series and at other HUBweek events. The Research Institute was also featured in a full page advertisement in Proto Magazine's 10th anniversary issue. And this is only the beginning. We have lots of big plans for spreading the word about Mass General research in the coming year, including newsletters, stories, videos and more.

Communicating Science. Learning how to speak to a lay audience about research is an important tool to help our investigators garner more interest and funding for their work. The Research Institute recently received a donation that will be used to fund a series of "Communicating Science" programs. Some of the options we are exploring include interactive workshops, collaborations with artists, and roundtable idea-sharing forums.

Advancement (Philanthropy)
We are working 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.

In addition to a February 2015 trip to Palm Beach to speak at a large, annual Development dinner, Drs. Slaugenhaupt and Orf have promoted Mass General research at numerous other events, including the annual meeting of the Research Institute Advisory Council (RIAC) in May, a June donor event in London, and the Phillips Society luncheon in September.

The hospital's major gifts committee has been a valuable source of feedback as we are refining our marketing pitch for a naming donor. The donation that would accompany naming the Research Institute could provide a major new stream of revenue to support research at Mass General in these challenging times.

Plans are underway for a donor event in Florida in March, 2016 that will be titled "The Science of You." This event will once again introduce the Research Institute to a large donor audience and will highlight two Research Scholars, Nir Hacohen, PhD, and Sekar Kathiresan, MD.

The Research Institute Steering Committee also meets regularly with individual donors to discuss the initiatives of the Institute. In December 2015, the Research Institute was given its first donor gift—funding towards the exciting Communicating Science programs that were highlighted in

the marketing section of this report. In May, 2015, we created an Advancement Committee of the Research Institute Advisory Council. This committee is chaired by the past chair of ECOR, Robert Kingston, PhD.

Strategic Alliances (Working More Closely with Industry)
In 2015, we hired Gabriela Apiou, PhD, to be the Director of Translational Research Training and Development for the Research Institute. Together with Gabriela, we developed and launched the strategic alliance initiative with the objective of helping scientists engage in productive collaborations with industry at all stages of their work; from fundamental research and proof of concept (early translation), to development and transfer to market (late translation). We also established the Strategic Alliance (SA) Committee of the Research Institute Advisory Council (RIAC). The Strategic Alliance Committee is composed of key leaders in the field of biomedical research from industry and venture capital who are working with us to foster interactions with commercial partners.

We also initiated the pilot phase of the research portfolio development process as a key mechanism to:

(i) Build common understanding of the ongoing research at Mass General, a comprehensive scientific foundation for promoting our research

(ii) Enable programmatic efforts across departments and centers

(iii) Establish a sound basis to define well informed strategies and tactics for translational research push while taking into account the market pull

(iv) Assess potential collaborations with industry

We reached out to all of the Departments and Centers and asked them to suggest 'research themes' that highlight strengths at MGH. We meet with a core group of our RIAC Strategic Alliance committee every six weeks to review the research themes, and then work with teams of investigators to prepare and present the program to our full RIAC SA committee. We held our first meeting in December, 2015 and brought together 27 investigators to present two programs—Epigenetics and Cancer Immunotherapy. Remarkably, these themes represented four departments, three research centers, and brought together nine uniquely identified research themes. Soon we will host follow-up meetings with representatives from pharma and venture capital who are specifically interested in these areas. We are excited about this initiative and feel that it is off to a great start.

We have also developed the outline of a unique translational training program to teach MGH scientists:

(i) Why and how to think early on about potential applications of their research

(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.

Finally, we have coordinated the launch of the Sanofi iAwards Program at MGH that supports early translational research ideas and funds 24 projects per year for three years across seven academic centers. Massachusetts General Hospital submitted 56 pre-proposals, 14 full proposals and received five awards.

Executive Report for SAC 2016

The Division of Clinical Research—Dr. Maurizio Fava, Director

Founded in 1996 as the MGH Clinical Research Program (CRP), the newly-named Division of Clinical Research (DCR), is now entering its 20th 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.

Following DCR's mission as well as the MGH Strategic Plan recommendations, the following progress has been made in 2015:

DCR Centers	DCR Units
• 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) *NEW* •Think Tanks *NEW* • Bioinformatics Consortium *NEW*	• Clinical Research Support • Comparative Effectiveness • Drug Discovery Rounds *NEW* • Education • Electronic Health Records Research • Imaging Biomarkers • Information Technology • Omics • Patient-Centered Outcomes Research • Qualitative Analysis • Survey Research

Here are some of the highlights for the NEW Centers and Units as well as other DCR initiatives:

Drug Discovery Rounds are face-to-face advisory sessions with key advisors:

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

Pediatric Translational Research Center (PTRC), led by Alessio Fasano, MD, 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 PTRC 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, MD)
- Think Tank on Neuroinflammation (co-chaired by Rudy Tanzi, PhD, and Chris McDougle, MD)
- Think Tank on Microbiome (co-chaired by Alessio Fasano, MD, and Ashwin Ananthakrishnan MBBS, MPH)

Executive Report for SAC 2016

Bioinformatics Consortium, led by Ruslan Sadreyev, PhD. 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 a close partnership with Harvard Catalyst. Here is the snapshot of Harvard Catalyst Utilization by MGH:

July 1, 2014–June 30, 2015

Biostatistics Consultation

# Consultations	264
# Hours	1100

MS in Clinical and Translational Investigation

# Applicants	10
# Appointments	5

Education

# Attendees	226

Program in Clinical and Translational Science

# Applicants	13
# Appointments	7

Clinical Research Centers

# Studies Submitted	66
Average # Active Studies	98.5
# Inpatient days	243
# Outpatient visits	6039
# Lab-only Studies	10

KL2/CMeRIT

# Applicants	18
# Appointments	5

Pilot Awards

# Applicants	92
# Awards	12
Total Pilot $	$483,444

Master IRB Reliance Agreement

# Cede Review Requests Submitted	62
# Cede Review Requests Reviewed	57
# Determinations listing MGH as IRB	59

Renovations to and Expansion of the DCR Offices on Simches 2 are nearing completion and, when done, will provide one-stop shopping for clinical investigators by:

- Offering expanded resources for new clinical investigators
- Establishing an EPIC/eCare help center
- Creating a clinical research center satellite
- Consolidating and centralizing bioinformatics resources and referrals
- Proving on-site support by Partners staff from the IRB, Innovation, and the new Partners Clinical Trials Office.

An expanded version of the 2015 DCR progress report, including reports from all Centers and Units, can be found online (MGH Research Institute, DCR website at http://www.massgeneral.org/research/dcr/).

The MGH Translational Research Center (TRC)—Dr. Mason Freeman, Director
Shortly after the Trustees and senior hospital management approved the research strategic plan in March of 2014, Dr. Mason Freeman was named the inaugural Director of the TRC. With years of industrial drug development experience as head of the MGH Translational Medicine Unit, and as primary author of the TRC business plan, Dr. Freeman was both a logical and excellent choice. He, along with Dr. David Nathan, Director of the Clinical Research Center (CRC), were both named by Dr. Maurizio Fava, as Associate Directors of the new Division of Clinical Research.

The synergy of having Drs. Freeman and Nathan working together on our clinical research leadership team paid an opportunistic dividend in our search for a home for the TRC. The TRC will be an 18-bed unit co-located on White 12/13 with the CRC, which currently occupies White 13. This major renovation project ($13M) has an anticipated completion date within Fall/Winter of 2016. The TRC is working closely with the CRC staff to manage the hiring of new personnel in synchrony with the expected opening of the new combined Translational and Clinical Research Center (TCRC). With further clarity on the timing of the facility opening, we will begin to hire new trial staff and the small number of administrative personnel needed to oversee the operation of the unit. We are working closely with MGH Research administration to determine how the TCRC will be organized as a financial entity in the hospital and how the hospital investment in administrative support can be transitioned into a fully self-supporting entity. To build new partnerships with the TCRC, we need to strengthen our business development activities through recruitment of an experienced business development professional as well as work more closely with the MGH Research Institute Scientific Director's Office and the Partners Innovation Office.

The Partners Biobank at MGH—Drs. Jordan Smoller and Susan Slaugenhaupt
The Partners Biobank at MGH component of the research strategic plan 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 from patients that are linked to their electronic medical record. Resources at Partners were committed to expand the existing Partners Biobank currently in place for recruitment, storage, processing, and distributing biological samples to researchers. Resources at MGH were committed to add personnel, space, and equipment to jumpstart the consent and collection program here. In its first five years of operation, the Biobank collected only 8,500 samples across all of Partners. With the additional resources contributed these past two years, we have seen a dramatic increase in patient recruitment (to over 35,000), and our goal across Partners is to grow the Biobank to over 100,000 patient samples within the next five years.

Executive Report for SAC 2016

Through the dedicated efforts of MGH Biobank co-directors, Susan Slaugenhaupt, PhD, and Jordan Smoller, MD, ScD, Biobank manager Alison Hoffnagle, and their staff, the MGH program has enjoyed great success since the implementation of the strategic plan. The completed infrastructure work includes two new, dedicated Biobank consent/collection rooms - one on Wang 2, and another on Yawkey 3, and implementation of a training program for patient recruitment in Central Phlebotomy. Design is complete and acquisition is underway for electronic Biobank "kiosks" 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. We also launched the Community Advisory Panel in 2015, which has been a tremendous success with members contributing much-needed advice for patient engagement techniques. Most recently, Partners approved additional funding to genotype the first 25,000 Biobank samples, and, as anticipated, there has been a dramatic increase in investigator use as this data becomes available.

These new resources, together with the extraordinary efforts of the Biobank staff, have resulted in a major increase in subjects recruited. Through December 2015, consented subjects have exceeded 35,000 (with a monthly consent rate now exceeding 1,200), and actual sample collection is over 27,000. At MGH, face-to-face recruitment has continued to grow, with samples now being collected in both inpatient and outpatient settings, and the MGH team has consistently met their monthly recruitment FY15 targets. Goals for this coming year include installation of the kiosks, launch of recruitment at McLean hospital spearheaded by the MGH Biobank team, expansion of current recruiting efforts in the Chelsea Healthcare Center, and potential recruitment in other community health centers as feasible, 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, and full integration of sample consent and collection within the clinical phlebotomy operations of the hospital.

Research Support IS Committee (RSIS)—Carl Blesius, MD and Deverie Bongard, MBA

The Research Support IS Committee (RSIS) was created to serve as a more formal and coordinated interface for project teams across Partners to help coordinate technical efforts within the research community. To date the focus has been on addressing policy/procedural issues and designing research-oriented solutions that support cutting edge dynamic technical needs of the research community, within the confines of a healthcare-oriented enterprise.

The committee deals with strategic and tactical IS issues that impact the MGH Research community. Additionally, we look to prevent the duplication of technical efforts by leveraging local expertise and both consolidating and streamlining resources and services to promote a more responsible use of limited research resources.

Since the first standing meeting on April 29, 2015, the committee structure has been solidified to carry out this mission. It consists of members from Partners and MGH IS as well as MGH research community stakeholders (faculty, administration, staff, etc.). Areas of research community technical need have been identified and consolidated into discrete projects, which have been prioritized. Smaller working groups have been established to identify project requirements, resource needs, and implementation plans.

This year our top priority is the implementation of the Researcher Profiles Project. It is being created in partnership with the Partners Corporate Information Security Office and will leverage their nascent Enterprise Identity Management System to unify numerous data sources about individuals from across the enterprise. Once implemented, the project will allow programmatic information sharing across multiple platforms and institutions creating a solid foundation for subsequent high

priority RSIS projects (research training and education system, electronic communication support, infrastructure sharing, etc.).

Research Institute Training and Education Committee (RITE)—Andrew A. Nierenberg, MD
Training Survey and Personalized Course Directory. The RITE committee, in collaboration with the Laboratory of Computer Science (LCS), has developed and pilot-tested a system to help researchers comply with training requirements. In an expanding regulatory environment, researchers have had to complete, track, and update a large list of online and in-person training modules in the absence of any system that informed them or their supervisors of what they needed to do. Nor has there been any clear directory of trainings that were required or desired. In addition, MGH had no way of knowing the complete array of research being conducted by over 6,000 researchers in the system.

To fill these gaps, the RITE committee and LCS developed an online survey to personalize training. Using a branched logic approach, the survey developed a standard method to assign required training based on self-reported research areas and created a single portal where courses can be viewed and tracked. The survey generated links to all required courses—if all the questions are positive (an unlikely scenario with, for example, someone needing to train in shipping hazardous materials as well as having to do research with people, large animals, radiation, and lasers)—23 courses would be required. A more likely scenario is that a research coordinator who interviews human subjects, has access to personal health information, draws blood, ships biospecimens, and works in a wet lab would have to complete 12 courses. The system would also allow supervisors to view the training status of all of their staff.

The pilot phase was launched September 14, 2015 to 313 new hires with 272 completed surveys. The survey was sent to those who conduct basic, animal, and clinical research. Division of Clinical Research staff reviewed the surveys for accuracy and worked with the Compliance Office to refine the survey. Additional issues to be addressed include a personalized dashboard that will inform researchers about their compliance status as well as a transcript of completed courses and notifications of upcoming requirements.

Learning Innovation Platform. In addition to the survey to personalize compliance training, the LCS is developing an integrated and comprehensive learning management system to simplify training and certification, make training meaningful using the latest advances in teaching and education to better align certification and actual competencies of researchers, and to integrate training into the information technology fabric of MGH. The overall vision is to move beyond basic required trainings and provide opportunities for professional advancement. To these ends, the LCS is developing Hub 2.0 to manage all education logistics (identify management, course development and delivery, attendance, certificates) and use cutting edge methods for adult learning (e.g. spaced learning—see Make It Stick: The Science of Successful Learning by Brown, Roediger, and McDaniel).

In summary, the RITE committee is making good progress in its inaugural year to serve the training and education needs of the community of over 6,000 MGH researchers.

Isuggest—Expanding Research Operations Improvement Across Partners
As described in my previous two reports, the MGH Research Management Office, working in collaboration with ECOR and the Partners Research Management Office, announced in October, 2012 the official launch of the Continuous Research Operations Improvement (CROI) Program. This initiative provides straightforward ways for members of our research community to offer ideas that will help us improve our support of the research enterprise. Three years after launching the program, over 600 suggestions have been received and almost 300 implemented, with a similar number still being actively worked. 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.

Based on the success of the MGH CROI program, senior research leadership from Partners, BWH, and MGH have decided to expand the CROI program across all of Partners. This new initiative is called Isuggest and we project it to be fully implemented by March, 2016. Major improvements to the new program 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.

SAC-Inspired Research 'Road Shows' Continue to Roll

As reported last year, based on feedback received from the 2014 SAC lunch (where faculty members met privately without research leadership present to discuss issues on their mind) we learned our numerous efforts to communicate with the research community were still not reaching a majority of our target audience. While some faculty stated that processes and communication had clearly improved, others were still unaware of many of the initiatives or new resources available to them. We concluded that the most effective (and perhaps only!) way to really reach and educate our researchers was face-to-face at their own department or unit meetings. Accordingly, in summer of 2014, we presented 'road shows' for researchers consisting of two parts: 1) an overview of the research strategic plan and the new MGH Research Institute; and 2) a tutorial on the "Top Ten Things Every MGH Researcher Should Know, but Probably Doesn't".

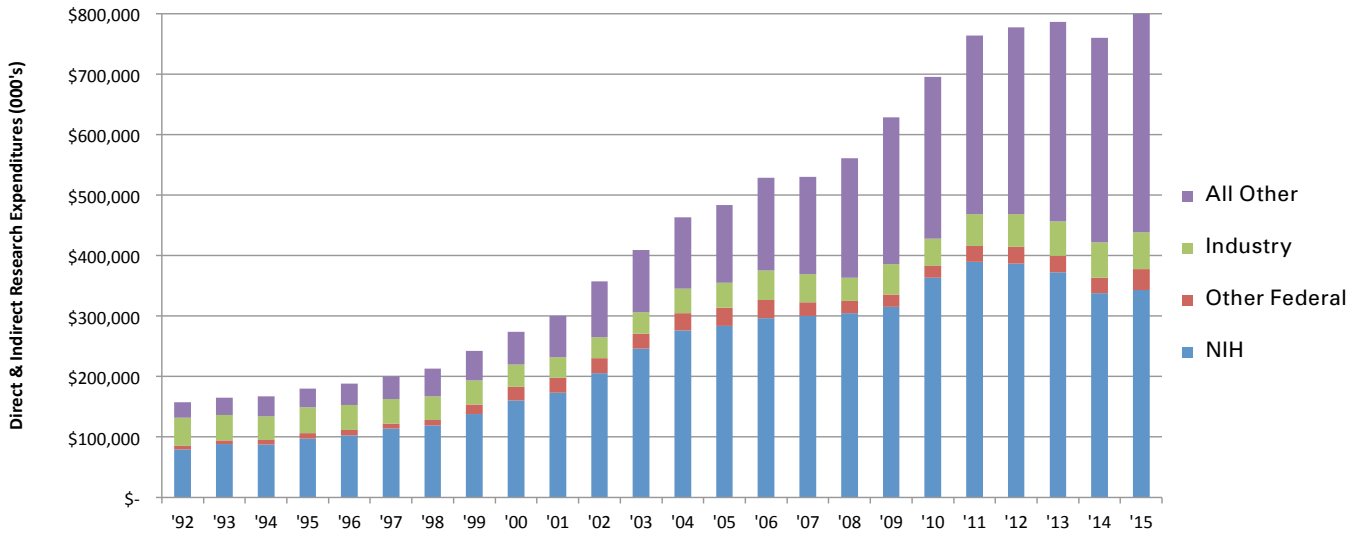
The road shows have 'put a face' on research support and have been very well received. At the end of 2014, we had held 14 road shows and directly reached over 300 researchers on their 'home turf'. Due to their popularity, word has spread and requests for them have continued unabated through 2015. This past year, we presented an additional dozen shows, bringing the number of faculty reached directly to over 800, and we have several more scheduled in 2016.

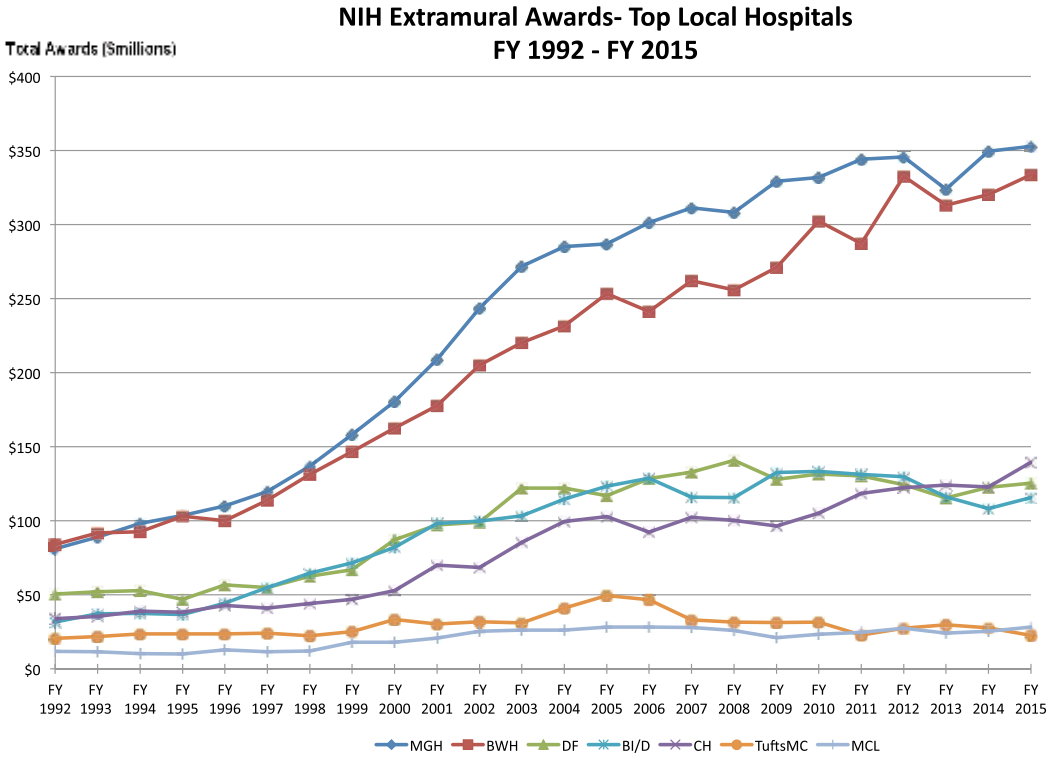
Overall, significant progress has been made in 2015 implementing the strategic plan for research and improving the services that support our research community. I am grateful to the many MGH and Partners research staff members who have affected these changes and appreciate the continued dedication and initiative they offer to constantly improve and strengthen our research enterprise.

Respectfully submitted,
Harry W. Orf, PhD

MGH Research has grown 325% over 20 years to $800M

MGH combined research has grown at a compounded annual growth rate of 7.4% between FY2000 and FY15. The 5-year moving average annual growth has decreased from 7.1% in FY10 to 4.2% in FY15; the FY14-FY15 growth was 5.3%, with increases across every sponsor category.

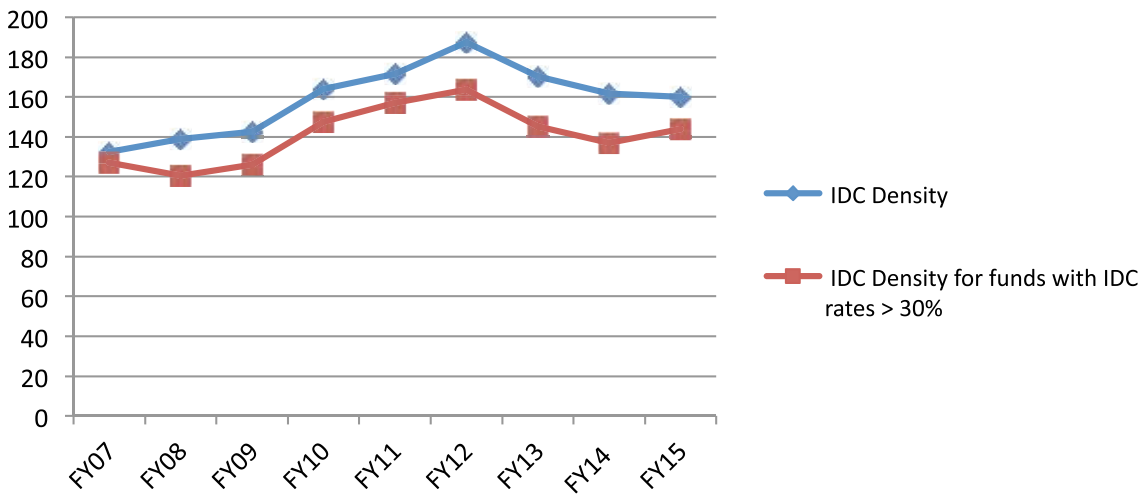




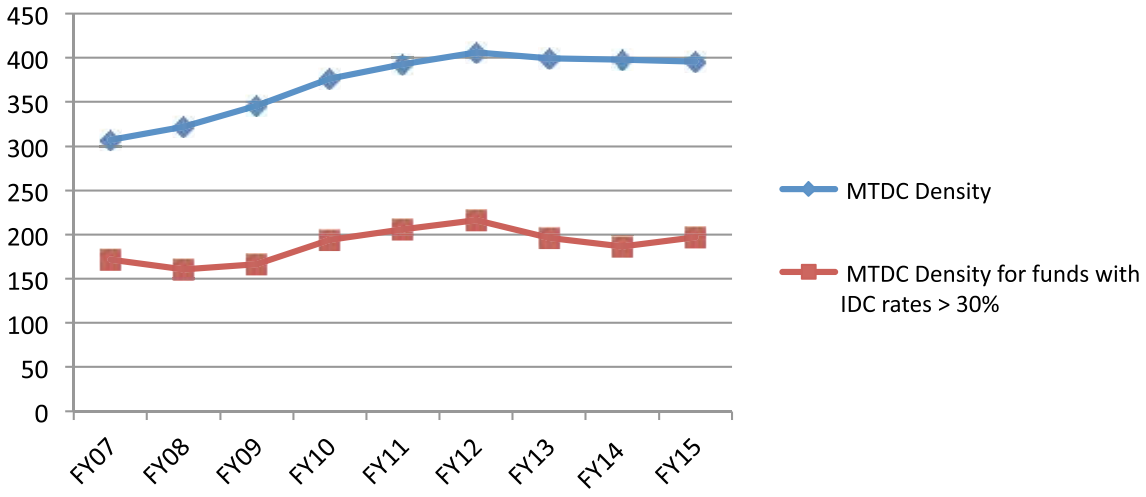
Note: FY15 data is Final.

Executive Report for SAC 2016

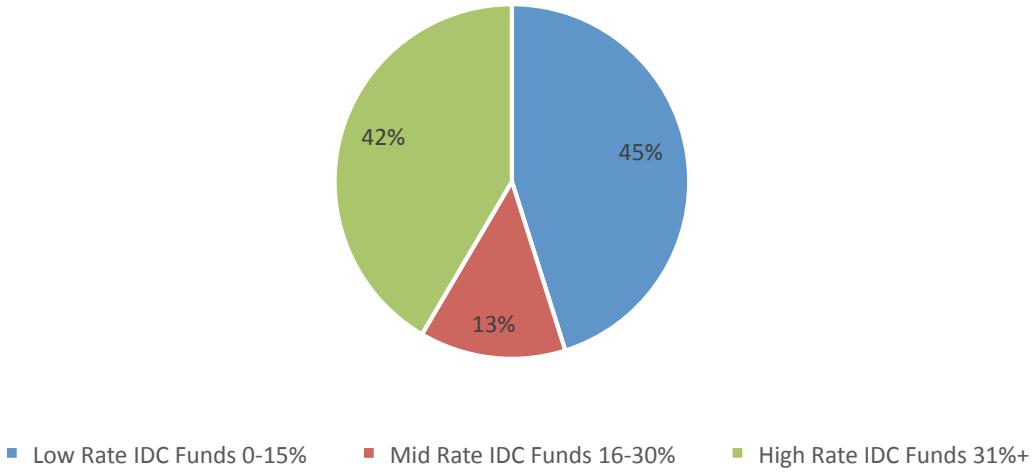
MGH IDC Density Trends



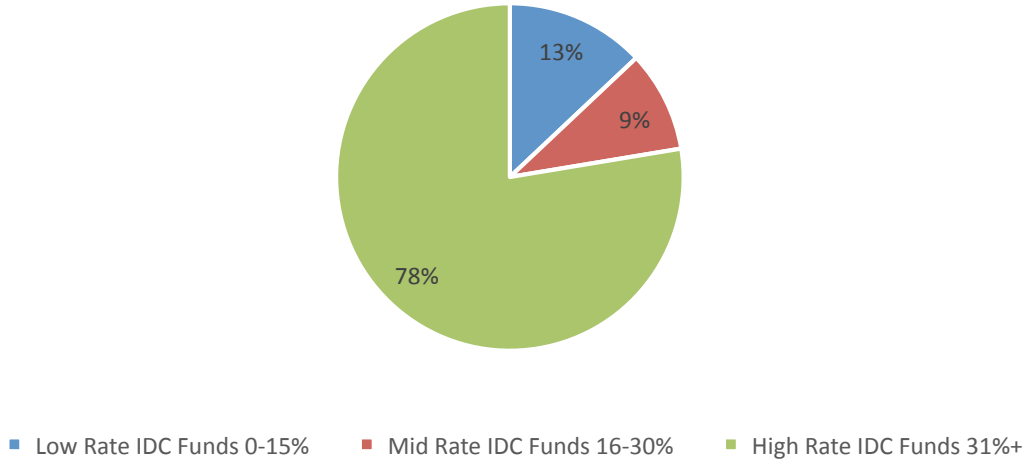
MGH MTDC Density Trends



FY15 MTDC Density Composition



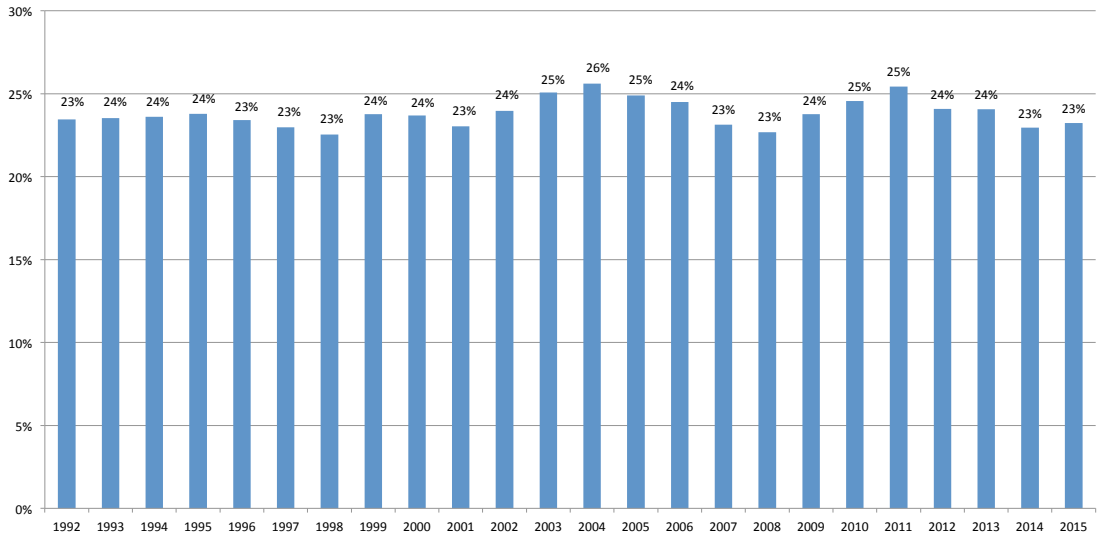
FY15 IDC Density Composition



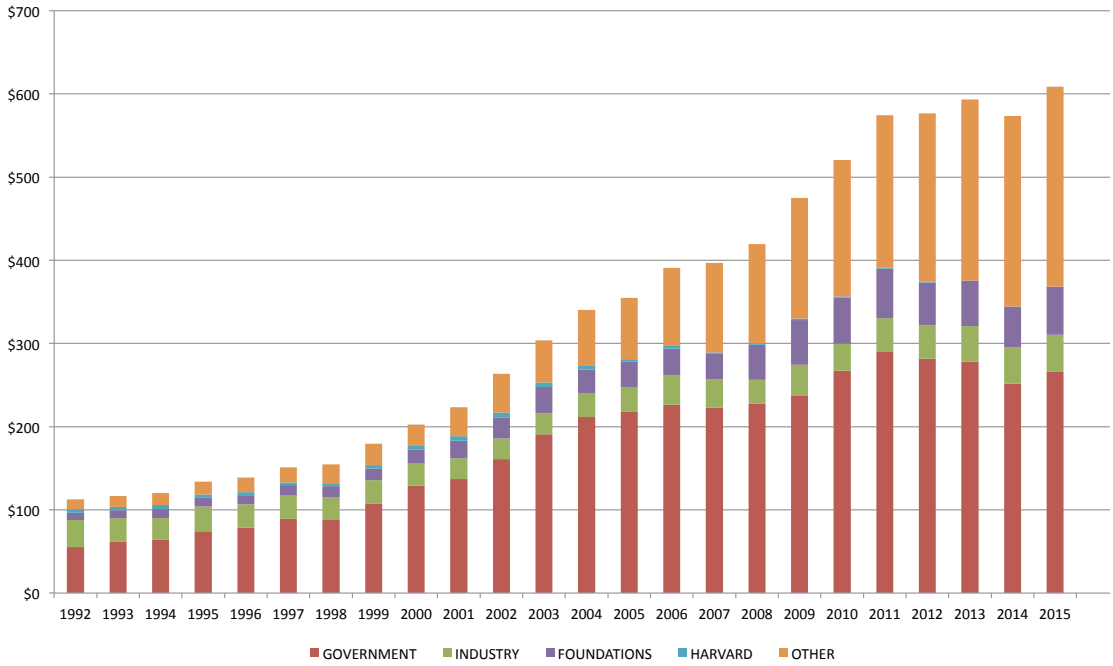
MGH Research Institute

Executive Report for SAC 2016

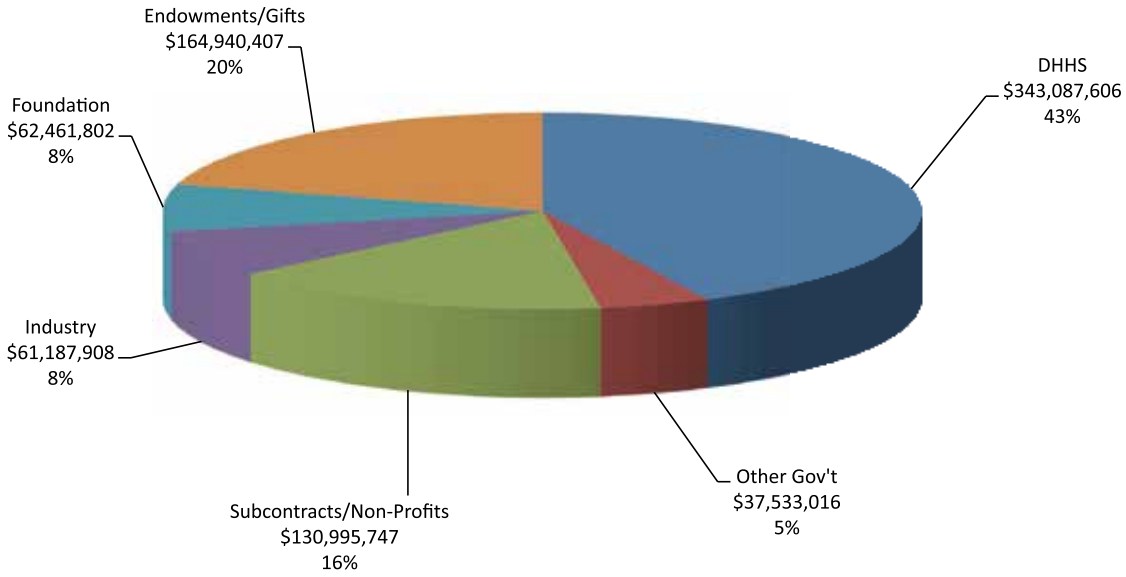
MGH Research Revenue as a Percentage of Total MGH Operating Revenue
FY1992 - FY2015 Actual



Massachusetts General Hospital
Direct Research Expenditures by Sponsor
FY1992 - FY2015
(in $Millions)



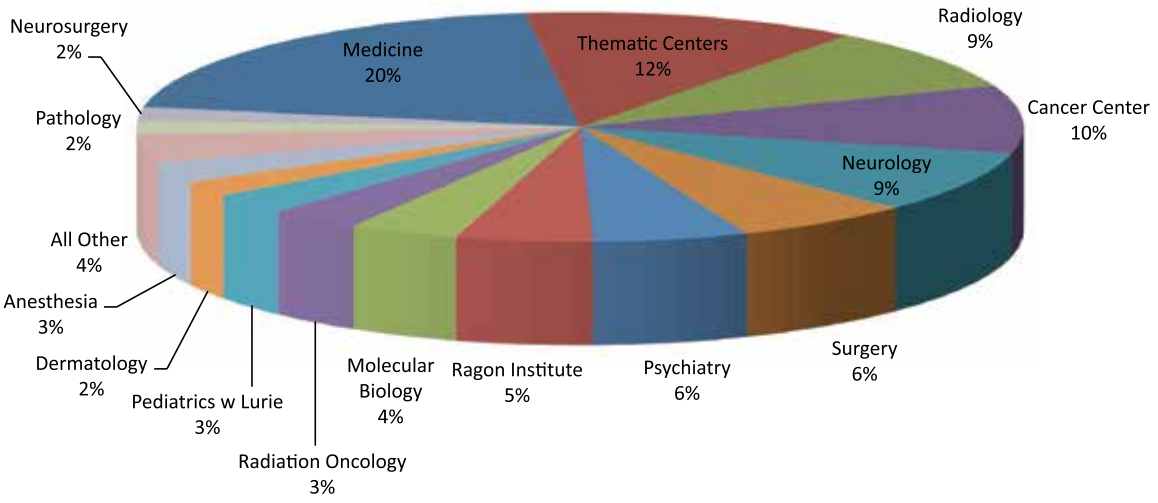
Massachusetts General Hospital
Total Research Expenditures FY 2015
$800,206,486



Notes:
1- DHHS includes ARRA funding
2- Other Gov't includes Other Federal and State/Local.

Executive Report for SAC 2016

FY 2015 MGH Research Expenditures by Department Direct & Indirect Expenditures $800M



Notes:
1- Expenditures include ARRA funding and Other Science
2- Surgery includes Pediatric Surgery, Oral Surgery and Urology.
3- Other includes Administrative Departments

MASSACHUSETTS GENERAL HOSPITAL
Science Activity by Sponsor

	Fiscal Year 10/01/14-09/30/15		
Type of Activity	***Direct***	***Indirect***	***Total***
Federal & State	*265,708,537*	*114,912,082*	*380,620,619*
Non-Federal	*345,139,436*	*75,146,863*	*420,286,299*
Total Expenses FY 15	*610,847,973*	*190,058,945*	*800,906,918*
Federal Activity by Sponsor			
DHHS	*232,046,476*	*103,656,629*	*335,703,105*
ARRA	*(10,844)*	*(386)*	*(11,230)*
DOD	*21,673,666*	*8,640,977*	*30,314,643*
AHRQ	*3,569,179*	*177,739*	*3,746,918*
FDA	*1,241,793*	*482,495*	*1,724,288*
NSF	*572,284*	*289,694*	*861,978*
Other Federal	*3,735,421*	*1,162,982*	*4,898,403*
Total Other Federal Activity	*30,792,343*	*10,753,887*	*41,546,230*
Subtotal Federal	*262,827,975*	*114,410,130*	*377,238,105*
State	*2,880,562*	*501,952*	*3,382,514*
Total State Activity	*2,880,562*	*501,952*	*3,382,514*
Total Federal and State	*265,708,537*	*114,912,082*	*380,620,619*
Non-Federal Activity by Sponsor			
Industry	*44,740,063*	*16,432,208*	*61,172,271*
Foundations	*58,072,485*	*5,819,181*	*63,891,666*
Subcontracts/Other Nonprofit	*101,598,031*	*33,292,486*	*134,890,517*
MGH Endowment & Gifts	*138,336,782*	*19,578,711*	*157,915,493*
Total Non-Federal Activity	*342,747,361*	*75,122,586*	*417,869,947*
Total Expenses	*608,455,898*	*190,034,668*	*798,490,566*
Harvard Medical School	*2,392,075*	*24,277*	*2,416,352*
Grand Total	*610,847,973*	*190,058,945*	*800,906,918*

Executive Report for SAC 2016

MASSACHUSETTS GENERAL HOSPITAL
SUMMARY OF DIRECT AND INDIRECT COST SCIENCE ACTIVITY
FY 1989 - FY 2015
(000 omitted)

Sponsor	***Actual 1989***	***Actual 1990***	***Actual 1991***	***Actual 1992***	***Actual 1993***	***Actual 1994***	***Actual 1995***	***Actual 1996***	***Actual 1997***	***Actual 1998***	***Actual 1999***
Government Grants & Contracts	*$58,752*	*$66,225*	*$76,509*	*$85,053*	*$95,098*	*$96,096*	*$110,610*	*$116,569*	*$129,576*	*$131,136*	*$157,705*
Industry	*$18,153*	*$21,536*	*$34,533*	*$46,575*	*$42,398*	*$39,582*	*$43,152*	*$41,424*	*$40,443*	*$38,983*	*$39,443*
Foundations	*$5,192*	*$6,241*	*$8,539*	*$9,100*	*$9,744*	*$11,509*	*$10,955*	*$11,403*	*$13,534*	*$14,205*	*$14,785*
HMS Grants & Endowments	*$7,916*	*$5,756*	*$5,130*	*$4,652*	*$4,357*	*$5,112*	*$5,160*	*$3,565*	*$3,303*	*$3,483*	*$4,179*
MGH Endowments & Gifts, Subcontracts /Other Nonprofit	*$15,551*	*$12,889*	*$14,961*	*$16,244*	*$18,764*	*$19,920*	*$21,734*	*$24,976*	*$25,120*	*$27,960*	*$30,922*
Total Direct & Indirect Costs	***$105,564***	***$112,648***	***$139,672***	***$161,624***	***$170,361***	***$172,219***	***$191,611***	***$197,937***	***$211,976***	***$215,767***	***$247,034***

Sponsor	***Actual 2000***	***Actual 2001***	***Actual 2002***	***Actual 2003***	***Actual 2004***	***Actual 2005***	***Actual 2006***	***Actual 2007***	***Actual 2008***	***Actual 2009***	***Actual 2010***
Government Grants & Contracts	*$186,881*	*$200,259*	*$233,155*	*$273,490*	*$305,360*	*$314,582*	*$327,225*	*$322,936*	*$325,259*	*$336,420*	*$383,775*
Industry	*$37,071*	*$34,178*	*$34,417*	*$34,760*	*$40,147*	*$41,184*	*$48,328*	*$46,622*	*$38,777*	*$50,142*	*$44,487*
Foundations	*$18,013*	*$22,065*	*$26,730*	*$33,318*	*$30,152*	*$32,884*	*$34,328*	*$32,861*	*$46,031*	*$58,325*	*$60,500*
HMS Grants & Endowments	*$5,115*	*$5,689*	*$5,785*	*$5,134*	*$4,689*	*$3,154*	*$2,920*	*$1,833*	*$1,719*	*$1,892*	*$1,374*
*MGH Endowments & Gifts, Subcontracts /Other Nonprofit**	*$31,307*	*$41,936*	*$57,134*	*$62,778*	*$82,585*	*$91,448*	*$115,820*	*$125,714*	*$148,899*	*$181,604*	*$205,563*
Total Direct & Indirect Costs	***$278,388***	***$304,127***	***$357,222***	***$409,481***	***$462,934***	***$483,252***	***$528,621***	***$529,967***	***$560,685***	***$628,384***	***$695,699***

Sponsor	***Actual 2011***	***Actual 2012***	***Actual 2013***	***Actual 2014***	***Actual 2015***
Government Grants & Contracts	*$415,951*	*$415,114*	*$400,740*	*$366,191*	*$380,621*
Industry	*$52,497*	*$53,864*	*$57,223*	*$58,439*	*$61,172*
Foundations	*$64,620*	*$56,385*	*$59,487*	*$53,490*	*$63,892*
HMS Grants & Endowments	*$1,258*	*$919*	*$1,553*	*$1,280*	*$2,416*
*MGH Endowments & Gifts, Subcontracts /Other Nonprofit**	*$229,719*	*$250,024*	*$267,509*	*$280,526*	*$292,806*
Total Direct & Indirect Costs	***$764,045***	***$776,307***	***$786,512***	***$759,926***	***$800,907***

**2007 data was restated*

**2008 forward data includes Animal Facility*

MASSACHUSETTS GENERAL HOSPITAL
SUMMARY OF ALL DIRECT COST SCIENCE ACTIVITY
FY 1983 - FY 2015
(000 omitted)

Sponsor	***Actual 1983***	***Actual 1984***	***Actual 1985***	***Actual 1986***	***Actual 1987***	***Actual 1988***	***Actual 1989***	***Actual 1990***	***Actual 1991***	***Actual 1992***	***Actual 1993***	***Actual 1994***	***Actual 1995***	***Actual 1996***
Government Grants & Contracts	*$24,057*	*$25,473*	*$26,236*	*$32,477*	*$39,202*	*$43,599*	*$45,865*	*$47,364*	*$50,102*	*$55,195*	*$61,989*	*$63,668*	*$74,386*	*$78,842*
Industry	*$6,235*	*$7,385*	*$7,993*	*$9,270*	*$9,770*	*$9,735*	*$14,086*	*$16,039*	*$24,323*	*$32,828*	*$28,240*	*$26,536*	*$29,898*	*$28,071*
Foundations	*$3,091*	*$3,285*	*$5,054*	*$5,113*	*$5,189*	*$6,447*	*$5,508*	*$5,793*	*$7,025*	*$8,469*	*$9,125*	*$10,718*	*$10,253*	*$10,623*
HMS Grants & Endowments	*$3,689*	*$3,339*	*$3,060*	*$3,903*	*$4,063*	*$5,201*	*$6,841*	*$5,730*	*$5,098*	*$4,613*	*$4,323*	*$5,064*	*$4,157*	*$3,540*
MGH Endowments & Gifts, Subcontracts /Other Nonprofit	*$4,696*	*$4,546*	*$6,516*	*$8,075*	*$8,343*	*$11,920*	*$12,001*	*$10,094*	*$10,463*	*$11,664*	*$12,945*	*$14,556*	*$15,062*	*$17,673*
Total Direct Costs	***$41,768***	***$44,028***	***$48,859***	***$58,838***	***$66,567***	***$76,902***	***$84,301***	***$85,020***	***$97,011***	***$112,769***	***$116,622***	***$120,542***	***$133,755***	***$138,750***

Sponsor	***Actual 1997***	***Actual 1998***	***Actual 1999***	***Actual 2000***	***Actual 2001***	***Actual 2002***	***Actual 2003***	***Actual 2004***	***Actual 2005***	***Actual 2006***	***Actual 2007***	***Actual 2008***	***Actual 2009***	***Actual 2010***
Government Grants & Contracts	*$89,031*	*$88,035*	*$107,445*	*$128,693*	*$137,045*	*$160,990*	*$190,583*	*$211,802*	*$218,199*	*$226,609*	*$222,759*	*$228,000*	*$236,810*	*$267,256*
Industry	*$28,037*	*$27,254*	*$28,225*	*$26,718*	*$24,965*	*$24,764*	*$25,554*	*$28,783*	*$29,455*	*$35,555*	*$34,252*	*$28,223*	*$37,370*	*$32,531*
Foundations	*$12,560*	*$13,180*	*$13,842*	*$17,031*	*$20,940*	*$25,303*	*$31,639*	*$27,763*	*$30,141*	*$31,831*	*$30,552*	*$42,191*	*$53,733*	*$55,602*
HMS Grants & Endowments	*$3,290*	*$3,482*	*$4,131*	*$5,125*	*$5,717*	*$5,785*	*$5,188*	*$4,645*	*$3,144*	*$2,976*	*$1,833*	*$1,719*	*$1,893*	*$1,374*
*MGH Endowments & Gifts, Subcontracts /Other Nonprofit**	*$17,988*	*$22,818*	*$25,673*	*$25,033*	*$34,440*	*$46,870*	*$50,548*	*$67,555*	*$73,791*	*$93,862*	*$100,372*	*$119,360*	*$144,989*	*$164,021*
Total Direct Costs	***$150,907***	***$154,769***	***$179,316***	***$202,599***	***$223,107***	***$263,713***	***$303,512***	***$340,547***	***$354,730***	***$390,833***	***$389,769***	***$419,492***	***$474,795***	***$520,785***

Sponsor	***Actual 2011***	***Actual 2012***	***Actual 2013***	***Actual 2014***	***Actual 2015***
Government Grants & Contracts	*$289,838*	*$281,588*	*$277,899*	*$251,897*	*$265,709*
Industry	*$40,643*	*$40,244*	*$42,927*	*$43,312*	*$44,740*
Foundations	*$59,462*	*$51,670*	*$54,787*	*$48,961*	*$58,072*
HMS Grants & Endowments	*$1,258*	*$919*	*$1,553*	*$1,280*	*$2,392*
*MGH Endowments & Gifts, Subcontracts /Other Nonprofit**	*$182,911*	*$202,196*	*$217,574*	*$229,409*	*$239,935*
Total Direct Costs	***$574,112***	***$576,616***	***$594,739***	***$574,859***	***$610,848***

**2007 MTDC is restated*
**2008 MTDC includes Animal Facility and adjustments*

Center for Faculty Development (CFD)

Programmatic Report

CFD

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

Focus

The Center for Faculty Development (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 is housed within the ORCD branch to address the needs of the graduate student community.

Achievements

In 2015 the CFD and its offices again saw continuing success in the integrated approach to providing services and resources to our faculty. 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 ***99 professional development programs with 3,287 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.

In addition, ***281 individuals*** visited the CFD and/or one of its offices this past year for a total of 327 office consultations. 173 of these individuals met with a CFD staff member (64% faculty, 36% fellows, graduate students, residents and other staff) and 108 met with an external advisor (42% faculty, 58% fellows, graduate students, residents, and other staff). The vast majority of the visits were for career advice and promotion.

Strategic Priorities

- In response to SAC recommendation, work to establish a dedicated Postdoctoral Fellow Division within the CFD if possible.
- Meet with all new Chiefs to review departmental faculty data and CFD resources.
- Deliver the CFD faculty mentoring program to the Hospital Medicine Unit.
- Provide professional development programs, workshops that meet the needs of our faculty, as well as to continue to provide networking opportunities for the faculty.
- 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.

CFD

- Continue to offer individual consultations to help faculty and research fellows with advice and guidance.
- Continue to facilitate consultation services to understand the usage of the Community of Science (COS) PIVOT database.
- Continue to monitor and report on the Annual Career Conference (ACC) statistics.
- Work with departmental liaisons on ACC quality data by using results from the ACC quality survey.
- Develop training to enhance the ACC experience.
- Collaborate with the Mass General Physician's Organization to expand the CFD CV Consulting Service.

ORCD—Dennis Brown, PhD, Director

Mission

The ORCD, Office for Research Career Development, 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 development pathways of research faculty in an academic medical center environment.
- Strengthen the career guidance and mentoring offered to trainees.
- 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 postdoctoral research fellows, including administering the MGH Guidelines for Research Fellows and advising the Mass General Postdoctoral Association (MGPA). In 2015, 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

Highlights of ORCD activity:

- Counseled 58 faculty, fellows and research staff in individual meetings aimed at career advice. Approximately 80 additional individuals sought guidance from an external career consultant, for a total of 173 consultations.
- Collaborated with the MGH Development office to offer ~ 60 individual consultations on **identifying research funding** opportunities.
- Continued to offer a six-seven session **Responsible Conduct of Research (RCR)** series designed for NIH trainees and open to all MGH researchers.
- Continued **English as a Second Language (ESL)** classes specifically designed for researchers. Each 15 week semester of ESL served 80-90 students. Classes were updated in 2015 with educational activities outside class time.
- The six Session N**ew Investigator Advancement Initiative (NIAI)** continued for MGH faculty who currently hold their first NIH R-level grant.
- Sponsored the 9th annual **Research Fellows Poster Celebration**, to recognize the excellent research conducted by MGH postdoctoral fellows. Approximately 70 posters on display highlighted postdoc's research accomplishments.

Center for Faculty Development (CFD)

Programmatic Report

CFD

- Continued multiple seminar series including **Communication Skills**, **Grant Writing Workshops** and an **Orientation Program** for research fellows.
- Advised the **MGPA**, which has been very active in forming new subcommittees and creating programs to meet the career and networking needs of postdoctoral fellows.
- Continued the **Career Explorations Series**, with seminars and panels on careers in academia, consulting, publishing, patient care and industry research.
- With the MGPA, offered educational programs to internationally trained MD researchers who wish to do US medical residencies.
- Updated the process for granting extensions on the 5-year Term limit on the research fellow position, by reviewing the CVs of postdocs requesting extensions beyond 6 years, offering targeted career advice to postdocs whose PIs request extensions.
- Developed the Career Pathways for Postdocs Internship program, which began a pilot phase in December 2015.

Strategic Priorities

- 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 loss of funding, including:
    - Supporting the use of the non-faculty track Research Scientist position in order to retain highly trained individuals and increase 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 MGH postdoc community to help form mentoring relationships between postdoc mentors and graduate student mentees.
- Complete the pilot phase of the Career Pathways for Postdocs Internship Program and evaluate results to determine next steps.

GSD—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.
- Attract more graduate students to MGH.
- Establish relationships with area graduate schools.

CFD

Focus

The GSD serves greater than 450 graduate students doing their research at MGH and provides assistance to the faculty working with graduate students. The focus of the GSD this past year was to strengthen the graduate student community by enhancing the sub communities at CNY and Simches, develop a better understanding of the international students and their needs, create international student orientation and provide information about funding resources specific to the international students, support communication and relationships with graduate schools administration, and to generate interest in recruiting more graduate students to MGH. The office continued to offer educational seminars designed to help graduate students build professional, communication, and networking skills.

Achievements

In the past year the GSD provided 21 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 continued to expand efforts to provide individual career counseling and networking opportunities for graduate students here at MGH by counseling 17 graduate students and connecting approximately 13 individuals with an external career consultant to offer a total of 33 office consultations. The office created and supported graduate student sub communities at the CNY and Simches locations. The GSD maintained the relationships with local school administrations and participated in Harvard-MIT HST Faculty Poster session.
The GSD started to develop mentoring relationships between more mature PhD Students and new incoming students to MGH. The office collaborated with HR and Police and Security departments to amend the MGH graduate student registration process that resulted in significant improvements in the registration process of the new PhD students joining MGH.

Strategic Priorities

- *Programming:* Sponsor and administer the ***GSD Graduate Student Travel Awards*** to help graduate students when traveling to an academic/society meeting which is directly related to his/her academic advancement.
- *Communication:* In collaboration with PHS Media develop, record and put into production MGH Graduate Student Division video to help to market and promote opportunities for the graduate students in research offered at MGH.
- *Community building:* Develop and support international student "Buddy" System to connect new international graduate students with the grad students who have been at MGH for a longer period of time and collaborate with ORCD to connect graduate students with MGH postdocs.
- *Networking and Education:* Work with the GSD committee to enhance networking and exposure to industry.
- *Knowledge:* Continue to 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.
- Enhance the relationships with area graduate schools.
- Generate interest in recruiting more graduate students to MGH by raising awareness on how to apply as graduate program faculty.
- Collaborate with relevant offices and committees at MGH, Harvard and other graduate schools.

CFD

OWC—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 multiple opportunities for women faculty to network with peers and with female role models in academic leadership positions.

Achievements

The OWC continued efforts to support and advance the careers of women faculty in 2015. Highlights of OWC activity:

- Partnered with individual departments, including Medicine (DOM) and Surgery, to support their internal efforts to promote the advancement of female faculty. For example, helped the DOM secure philanthropic funds to support the Celia White Tabor Women in Medicine lectureship. The funds support an annual visit by a distinguished female physician scientist to give Medical Grand Rounds and meet with residents, fellows, and junior faculty in the DOM. The OWC helped to recruit the first lecturer, Dr. Nancy Andrews, Dean of the Duke University School of Medicine.
- Organized a 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. Nancy Andrews.
- Presented an overview of gender issues to MGH's Diversity Committee, on which Dr. Rigotti is an invited member.
- 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 and the *Claflin Consultation Initiative* to provide individual assistance to applicants. Hosted the annual *Claflin Luncheon* to welcome the newest Scholars. (The timing of 2015 Claflins changed, leading to two rounds of applications and associated programs/initiatives).
- Sponsored a panel discussion on "Becoming a Leader," featuring three distinguished female leaders at MGH/Partners. Sponsored a program for women faculty on fundraising for research and clinical initiatives, and communicating with donors, in response to the relatively low rates of women who seek funding from potential donors.

CFD

- Continued 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.
- Continued the annual **Business of Life** workshop, to help faculty develop strategic plans to advance their career and personal life.
- Continued to include trainees where possible in OWC programs, and supported trainee-to-faculty transition programs.
- Counseled 15 women faculty in individual meetings aimed at career advice and supporting gender equity. Approximately 6 additional women faculty sought guidance from an external career consultant. These individuals visited the office for a total of 22 consultations.

Strategic Priorities

- 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.
- Plan and sponsor additional programs to support women in the critical trainee-to-faculty transition, especially in the areas of developing management skills and improving mentoring relationships by building developmental networks of mentors.
- 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.
- Represent the needs of women faculty and advocate for gender equity on the MGH/MGPO Diversity Committee, especially in area of equity in salary and resources.
- Continue to 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, and 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.
- Research and develop new ways for women faculty to network and support each other. Develop a private group on social media that allows MGH women faculty to fit communication with each other into their busy schedules.
- The OWC will participate in the planning for the annual Celia White Tabor Women in Medicine lecture and associated events.

Center for Faculty Development (CFD)

Programmatic Report

CFD

OCC—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

Highlights of OCC activity:

- Advised 83 faculty and fellows from a cross section of departments in 91 consultation sessions regarding: career advice, CV/cover letter critique, mentoring, and promotion.
- Worked with Advisory Council on what skills clinicians need (leadership training, teaching skills, "Speaking Up," and time management were the top discussion items).
- Sponsored 7 educational programs: Can I/Should I Be Promoted?, CV Narrative, Drafting Your Chief's Letter, and Scholarly Writing Seminar Series 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

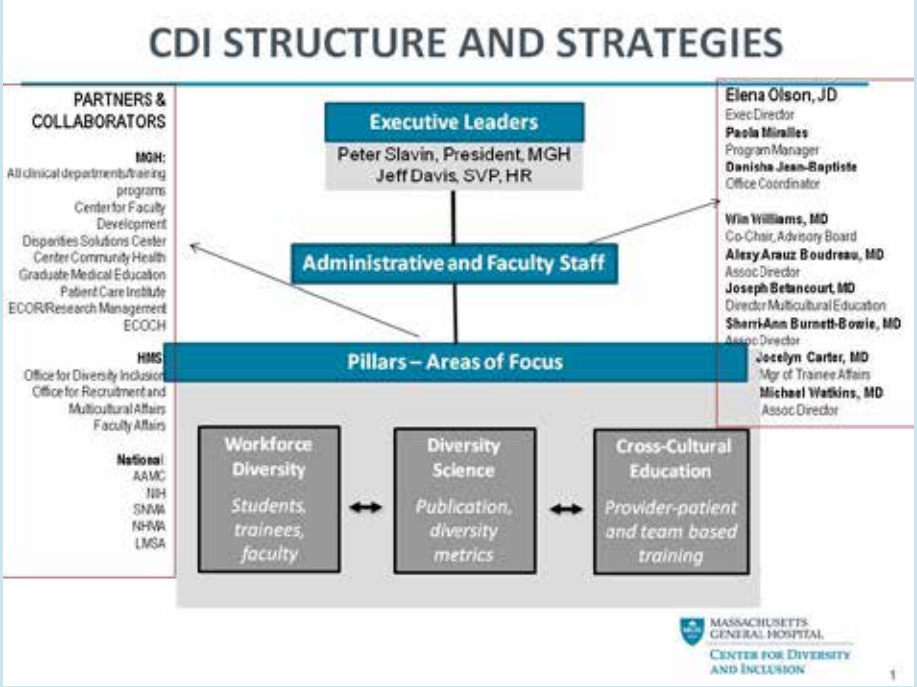
- Expand professional development programs and workshops to meet the needs of clinical faculty, stressing academic and career advancement.
- Collaborate with the *proposed* Postdoctoral Fellow Division within the Center for Faculty Development to address clinical fellow needs.
- Advocate for clinical faculty and their career and work life balance needs.
- Promote awareness of/celebrate clinical faculty promotions and academic achievements.
- Demystify and market the promotion process for clinical faculty.
- Continue to advise individual clinical faculty on career and academic advancement.
- Continue to 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.

Elena B. Olson, JD, Executive Director

CDI

Mission

The Center for Diversity and Inclusion's (CDI) 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

Current Strategic Priorites

- Integrating above focus areas into all MGH mission areas and the fabric of the institution
- Enhancing branding and marketing to reflect our new name
- 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 and social determinants of health
- Developing outcome measurement for all CDI programs
- Disseminating knowledge and innovation through publications and national presence

Center for Diversity and Inclusion (CDI)

Programmatic Report

CDI

Achievements for the 2015 Year

4.1. Overall

Center for Diversity and Inclusion: With our recent name change we have continued our efforts in branding and marketing, and are soon to premiere an online video which shares testimonials from trainees, clinicians and physician/scientists on the value of CDI and working at MGH.

4.2. Professional Leadership and Workforce Diversity

Developing the Student Pipeline: Our student pipeline efforts begin with our signature Summer Research Trainee Program (SRTP), which brings in college and medical students to conduct novel research at MGH. After 23 years and over 285 students we conducted a comprehensive online survey of past participants to potentially determine SRTP's career impact on alum. A manuscript undergoing final edits describes our data and program and soon will be ready for submission to a peer-reviewed journal. This work has all been in collaboration with colleagues at the Mongan Institute for Health Policy.

Promoting Leadership at Harvard Medical School: CDI provides active outreach, mentorship and guidance to URM HMS students. In the past we have principally sponsored the Student National Medical Association (SNMA) Region VII annual conference with the help of the President's Office and the Department of Medicine. CDI continues to mentor HMS students during their Primary Clinical Experience (PCE) and those doing rotations at MGH through the Visiting Clerkship Program which we help co-sponsor. HMS URM students remain actively engaged with the CDI's Resident and Fellow Committee (RFC), especially in providing community outreach through local health fairs. This year the RFC participated in a panel at HMS for SNMA and the Latino Medical Society Association (LMSA) discussing tips on how to prepare for PCE. In partnership with the Lazarex-MGH Cancer Care Equity Program, CDI helped increase MGH's presence in Boston, Mattapan, Cambridge and Chelsea.

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 2015, we matched overall almost 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.

During this year's recruitment season, CDI met individually with leadership from all 19 MGH affiliated residency programs and department chairs to discuss URM and female recruitment and retention at the trainee and faculty levels. These meetings provide an opportunity to enhance the individual efforts of each clinical department in increasing diversity, as well as further develop the priorities set forth by the department's diversity action plans. Additionally, the CDI hosted 10 receptions (embedded within the interviewing schedule of all MGH and joint residency programs) to contribute to URM recruitment. These receptions were well attended by applicants, trainees and faculty from all MGH departments.

MGH Trainee Mentoring: The Career Development Liaison Program (CDLP) matches URM interns 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

CDI

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: Motivated by Ginther *et al*'s article "Race, Ethnicity, and NIH Research Awards" and a report to the Advisory Committee to the NIH Director by a working group on diversity in the biomedical research workforce, CDI convened a research workforce workgroup with the Center for Faculty Development and the Executive Committee on Research to address this issue locally. At MGH, similar to the national landscape, the low percentage of NIH funded investigators who are Black and Latino remains a challenge. MGH does not have one single Black R01 funded investigator, and only 7 Latinos, which represents 2.5% of the R01 funded investigators at MGH. MGH's numbers fall below the national NIH data.

Led by workgroup recommendations, CDI began 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. As a direct outcome of CDI's efforts in faculty development, ECOR has committed to funding a second Physician/Scientist Development Award as of 2015.

Promoting Clinical and Research Faculty through the Minority Faculty Development Award Program (MFDA): To date, CDI has awarded a total of 38 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 stated above, ECOR funded a second PSDA this year.

4.3. Cross-cultural Education

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. Three critical initiatives include: 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.

4.4. 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.

CCIB

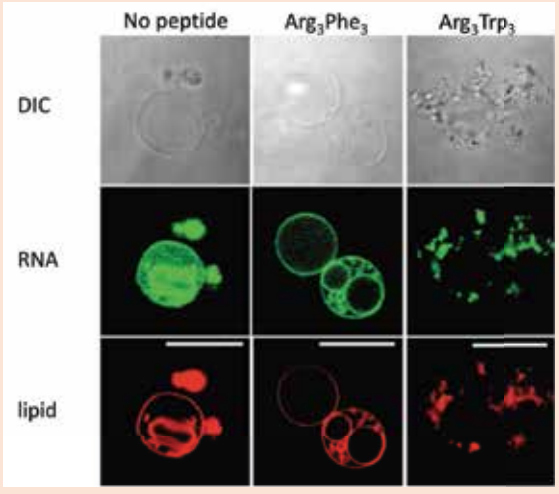
Brian Seed, PhD, Director

The Center for Computational and Integrative Biology (CCIB) is a collection of faculty members whose interests often lie outside the traditional purview of academic medicine, and include chemistry-centered investigations of potential mechanisms underlying the origin of life, technologies and instrumentation for the detection of life outside our planet, the role of microbial communities in the establishment of supportive environmental networks that mutually benefit eukaryotes and prokaryotes, translational medicine and therapeutic discovery. The mission of the unit is to support its investigators and to facilitate studies that are often interdisciplinary in scope and require unusual resources or fall outside the conventional scope of NIH-funded single investigator awards.

The exploration of new approaches to the treatment of human diseases and the clinical evaluation of candidate therapies is the principal focus of the Translational Medicine Group at MGH, which is led by Mason Freeman, MD and housed in CCIB. The Translational Medicine Group supports the most diverse collection of activities of the Translational Research Center at MGH and comprises a committed group of clinical management professionals who carry out studies both within the institution and externally, by managing clinical research organization providers or by providing direct trial support and supervision. Within MGH a new 18-bed clinical trial facility will provide dedicated space for institutionally-affiliated investigator-initiated studies as well as studies partnered with external biopharmaceutical companies. The longest-standing and largest program supervised by the Translational Medicine Group is a multi-trial investigation 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.

One of the key issues for the development of life from prebiotic chemical reactions is a mechanism for sequestration of reaction products to prevent dissipation of newly synthesized molecules, as well as mechanisms that concentrate the precursors needed to support prebiotic macromolecular assembly. The Szostak lab has pioneered the investigation of micellar lipid structures that may represent proto-cellular templates that have the capability of providing the critical sequestration functions. Recently they have discovered that in the presence of lipid membranes, small molecules and short peptides such as undecylimidazole and Arg3Phe3 or Arg3Trp3 that are both cationic and hydrophobic can mediate the localization of RNA to membranes. The figure below demonstrates the peptide-mediated localization. In primitive protocells membrane localization of RNA could facilitate the assembly of larger complexes, the activity of ribozymes on hydrophobic substrates, or even RNA replication.

Electrostatic Localization of RNA to Protocell Membranes by Cationic Hydrophobic Peptides Neha P. Kamat, Sylvia Tobé, Ian T. Hill, and Jack W. Szostak, Angew. Chem. Int. Ed., 54, 1 – 6 2015

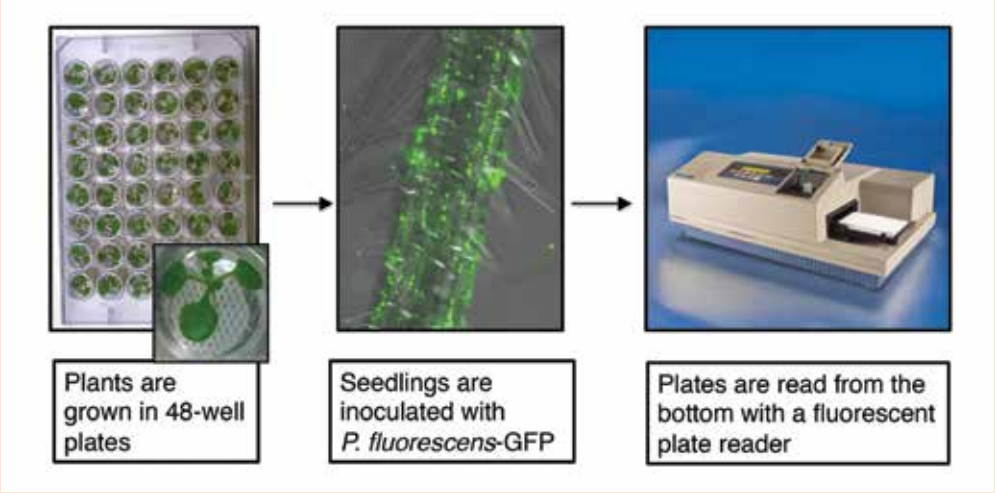


Microscopy of encapsulated RNA localization to lipid membranes with peptides. Confocal images show that RNA (green) encapsulated in lipid vesicles (containing a rhodamine-labeled lipid, red) becomes localized to the membrane after an overnight incubation with Arg3Phe3 and Arg3Trp3 peptides.

CCIB

Host-associated microbiomes influence host health in both plants and animals. Whether genotypic variations in host organisms influence the microbiome in ways that have adaptive consequences for the host was studied. Wild strains of *Arabidopsis thaliana* differ in their ability to associate with the root-associated bacterium *Pseudomonas fluorescens*, with consequences for plant fitness. From a screen of 196 naturally occurring Arabidopsis strains, lines that actively suppress *Pseudomonas* growth under gnotobiotic conditions were identified. 16S ribosomal RNA sequencing revealed that strain-specific differences in the microbial communities were largely limited to a subset of Pseudomonadaceae species. These strain-specific differences in *Pseudomonas* growth resulted in enhanced or impaired fitness that depended on the host's ability to support *Pseudomonas* growth, the specific *Pseudomonas* strains present in the soil and the nature of the stress. These results suggest that small host-mediated changes in a microbiome can have large effects on host health.

Associations with rhizosphere bacteria can confer an adaptive advantage to plants Cara H. Haney, Buck S. Samuel, Jenifer Bush and Frederick M. Ausubel Nature Plants 15051 2015.

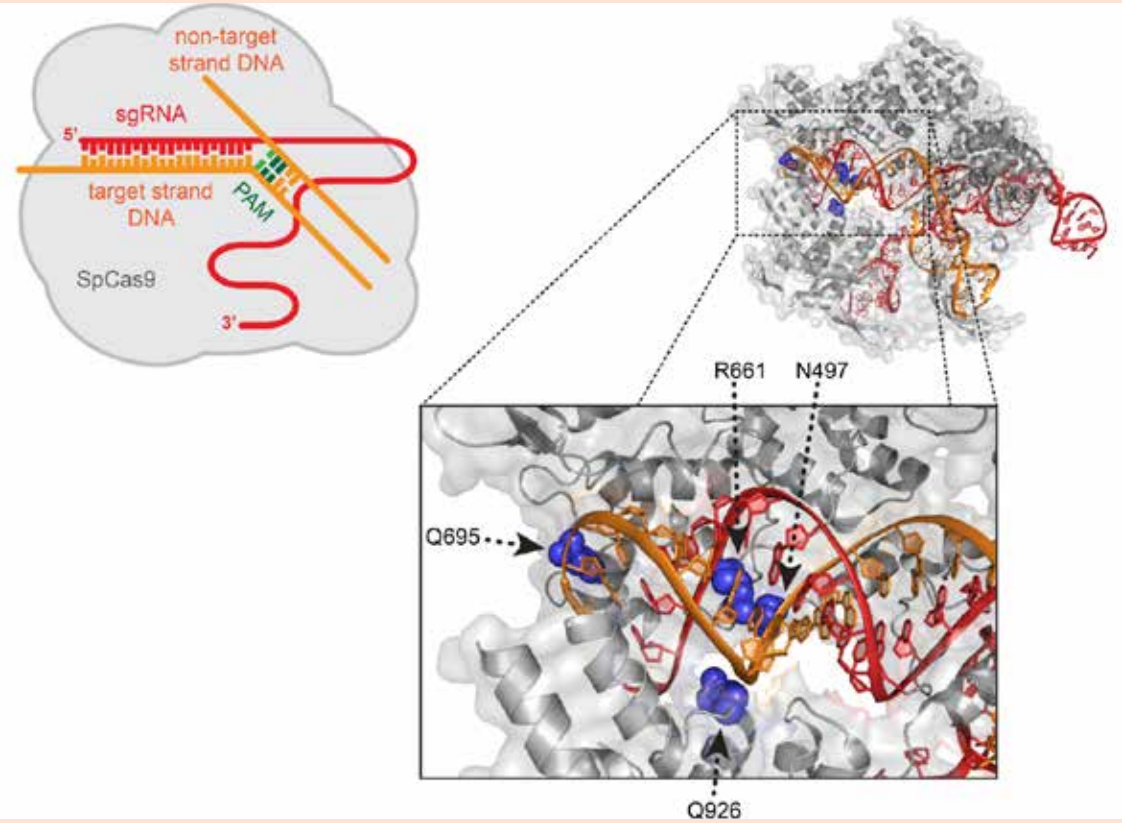


Semi-automated workflow to quantitate host-microbe interactions in plants. Arabidopsis plants are grown in 48 well plates, one plant to a well (inset). The seedlings are inoculated with Pseudomonas fluorescens that expresses Green Fluorescent Protein, allowing the Pseudomonas density to be quantitated with a fluorescent plate reader.

CRISPR–Cas9 nucleases are widely used for genome editing but can induce unwanted off-target mutations. Existing strategies for reducing genome-wide off-target effects of the widely used *Streptococcus pyogenes* Cas9 (SpCas9) are imperfect, possessing only partial or unproven efficacies and other limitations that constrain their use. A high-fidelity variant harboring alterations designed to reduce non-specific DNA contacts was created. SpCas9-HF1 retains on-target activities comparable to wild-type SpCas9 with >85% of single-guide RNAs (sgRNAs) tested in human cells. Notably, with sgRNAs targeted to standard non-repetitive sequences, SpCas9-HF1 rendered all or nearly all off-target events undetectable by genome-wide break capture and targeted sequencing methods. Even for atypical, repetitive target sites, the vast majority of off-target mutations induced by wild-type SpCas9 were not detected with SpCas9-HF1. With its exceptional precision, SpCas9-HF1 provides an alternative to wild-type SpCas9 for research and therapeutic applications.

High-fidelity CRISPR–Cas9 nucleases with no detectable genome-wide off-target effects Benjamin P. Kleinstiver, Vikram Pattanayak, Michelle S. Prew, Shengdar Q. Tsai, Nhu T. Nguyen, Zongli Zheng and J. Keith Joung. Nature.

CCIB



Schematic diagram and structural representation of the CRISPR-Cas9 target recognition complex, with the critical residues that were converted to alanine in the high fidelity variant highlighted as blue space-filling spheres.

James F. Gusella, PhD, Director

CHGR

The MGH Center for Human Genetic Research (CHGR) is a thematic center that has grown from 10 faculty members at its inception to now house 40 resident faculty, with a commensurate growth in research funding to approximately $40 million dollars per year. The CHGR is truly interdisciplinary and cross-departmental, with resident faculty representing the Departments of Anesthesiology and Pain Medicine, Medicine, Neurology, Pediatrics and Psychiatry being complemented by more than 60 Associate Faculty in these and other Departments. The mission of the CHGR has been to investigate fundamental mechanisms in all areas of human biology and disease using the unbiased power of human genetics. CHGR Faculty have had great success in this mission by organizing their efforts around the Genetic Research Cycle, a paradigm for disease research that begins 1) by comparing human phenotypes and genetic variation to identify genes of importance in human disease, then 2) moves on to characterizing the mechanisms by which the underlying DNA differences lead to phenotypic differences in disease using models driven by human genotype-phenotype relationships, and 3) is completed when the knowledge gained delivers benefit back to the patient population in the forms of improved disease diagnosis, prevention, management and treatment. The CHGR has pursued this mission through individual and collaborative faculty investigations at each stage of the genetic research cycle paradigm and, in the process, has made seminal contributions to characterizing variation in the human genome, interpreting its meaning with respect to health and disease, facilitating the translation of such genetic interpretation into clinical practice, and pursuing genetics-driven understanding of disease processes and intervention in humans, human cells and genetics-based model systems ("Systems Genetics") in order to fulfill the promise of disease-modifying treatments. The mission of the CHGR and strategic priorities going forward remain uncertain as the MGH is currently searching for a new Director which will have a profound impact on the future activities of this thematic center.

Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium. *Identification of Genetic Factors that Modify Clinical Onset of Huntington's Disease.* Cell 2015; 162:516-26.

This paper elaborates a novel strategy to understand early events in pathogenesis of Huntington's disease (HD), a familial late-onset neurodegenerative disorder that for decades has presaged successful research strategies later applied to more frequent adult-onset disorders. The findings of the GeM-HD Consortium, an international, interdisciplinary collaborative group led by CHGR investigators point to an entirely new route to developing and testing potential therapeutic interventions in HD, for which no disease-modifying treatment is known. Convinced that the tools of modern genetics, which have been applied mainly to discovering genes underlying disease risk, could be applied in a novel way to point to potential therapeutic avenues for late-onset disease, the GeM-HD Consortium combined the efforts of molecular geneticists, medical geneticists, neurologists, psychiatrists, and many other health professionals worldwide to assemble DNA and clinical phenotypes from the largest collection of HD subjects ever subjected to genetic analysis. Shortly after discovery of the HD genetic defect in 1993, it was recognized that the age at onset of motor symptoms, which underlie HD clinical diagnosis, is negatively correlated with the length of the CAG repeat mutation in *HTT* that causes the disease. The CHGR HD team established that the methods widely-used for statistical analysis of this genotype-phenotype relationship were flawed and went on to develop a new, robust statistical approach which demonstrated that HD is a completely dominant disorder in which the expanded CAG repeat both causes the disease and largely determines the rate of the pathogenic process that leads to onset. However, remaining variation in onset suggested the existence of genetic modifiers. To discover these modifiers, the GeM-HD Consortium studied more than 4,000 HD subjects, in part through collaboration with clinical investigators in several large natural history studies of HD, including the Pharos, Cohort-HD and Predict-HD studies of the Huntington Study Group and the Registry study of the European

CHGR

Huntington's Disease Network. The Consortium performed genome-wide genotyping of single-nucleotide polymorphisms in a Genome-Wide Association (GWA) design. Importantly, this GWA was not performed in the traditional mode of detecting risk alleles, since HD risk is entirely conferred by the expanded CAG repeat, but in an innovative manner aimed at identifying modifiers of the disease process that do not themselves contribute to disease risk. The GeM-HD Consortium identified multiple modifier loci with effect sizes larger than most complex disease risk alleles, suggesting that this route will be valuable to identify modifiers in many disorders beyond HD. Importantly, the identification of these modifiers both establishes the proof-of-principle that HD pathogenesis can be influenced prior to emergence of clinical disease and also points to specific processes as targets for rational therapeutic development that are already validated in the human patient. Thus, the GeM-HD Consortium has opened a route to disease-modifying treatments to delay or potentially prevent onset of this devastating neurodegenerative disorder. The GeM-HD findings emphasize the potential to better understand the early disease process and the need to move treatment efforts to the period prior to emergence of clinical symptoms. Importantly, they also provide a scientifically effective route to do so. In addition, the genetic findings will support more efficient and less costly clinical trials by allowing selection of subjects and analysis of outcomes that takes into account the genetic modifier status of the trial participants. Overall, the work of this team provides a clear demonstration of the value of merging clinical insight with basic science techniques to gain fundamental information from the human patients themselves concerning disease-modification and clinical trial design issues. It also sets a compelling example that can be widely applied in human disease to develop disease-modifying treatments.

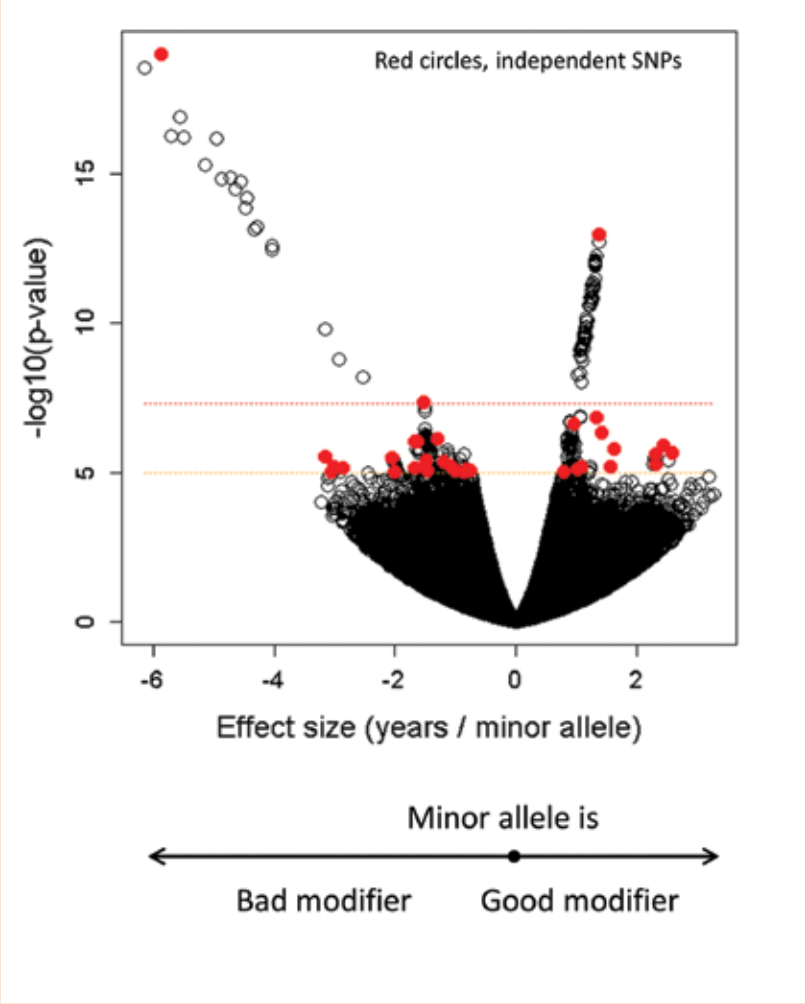
Derek J C Tai, Ashok Ragavendran, Poornima Manavalan, Alexei Stortchevoi, Catarina M Seabra, Serkan Erdin, Ryan L Collins, Ian Blumenthal, Xiaoli Chen, Yiping Shen, Mustafa Sahin, Chengsheng Zhang, Charles Lee, James F Gusella, Michael E Talkowski. *Engineering microdeletions and microduplications by targeting segmental duplications with CRISPR.* Nature Neuroscience 2016; in press.

Recurrent, reciprocal genomic disorders in which microdeletions and microduplications result from non-allelic homologous recombination (NAHR) between near-identical segmental duplications (SDs) are a major cause of human disease, often producing phenotypically distinct syndromes. The genomic architecture of flanking SDs presents a challenge for modeling these syndromes but the ability to efficiently generate reciprocal copy number variants (CNVs) that mimic NAHR would represent a valuable modeling tool. In a novel application of CRISPR/Cas9 genome editing, CHGR investigators introduced a new approach, single-guide CRISPR/Cas targeting of repetitive elements (SCORE), to model reciprocal genomic disorders. As proof-of-principle, they demonstrated that SCORE can efficiently generate reciprocal CNVs of 16p11.2 and 15q13.3, including alteration of one copy-equivalent of the SDs that mediate NAHR *in vivo*. The method was reproducible, and RNA sequencing reliably clustered transcriptional signatures from human subjects with *in vivo* CNVs and their corresponding *in vitro* models. This new approach will provide broad applicability for the study of genomic disorders, which are particularly relevant to neurodevelopmental defects such as autism, and, with further development, may also permit efficient correction of these defects.

Durst R, Sauls K, Peal DS, deVlaming A, Toomer K, Leyne M, Salani M, Talkowski ME, Brand H, Perrocheau M, Simpson C, Jett C, Stone MR, Charles F, Chiang C, Lynch SN, Bouatia-Naji N, Delling FN, Freed LA, Tribouilloy C, Le Tourneau T, LeMarec H, Fernandez-Friera L, Solis J, Trujillano D, Ossowski S, Estivill X, Dina C, Bruneval P, Chester A, Schott JJ, Irvine KD, Mao Y, Wessels A, Motiwala T, Puceat M, Tsukasaki Y, Menick DR, Kasiganesan H, Nie X, Broome AM, Williams K, Johnson A, Markwald RR, Jeunemaitre X, Hagege A, Levine RA, Milan DJ, Norris RA, Slaugenhaupt SA. *Mutations in DCHS1 cause mitral valve prolapse.* Nature. 2015; 525:109-13.

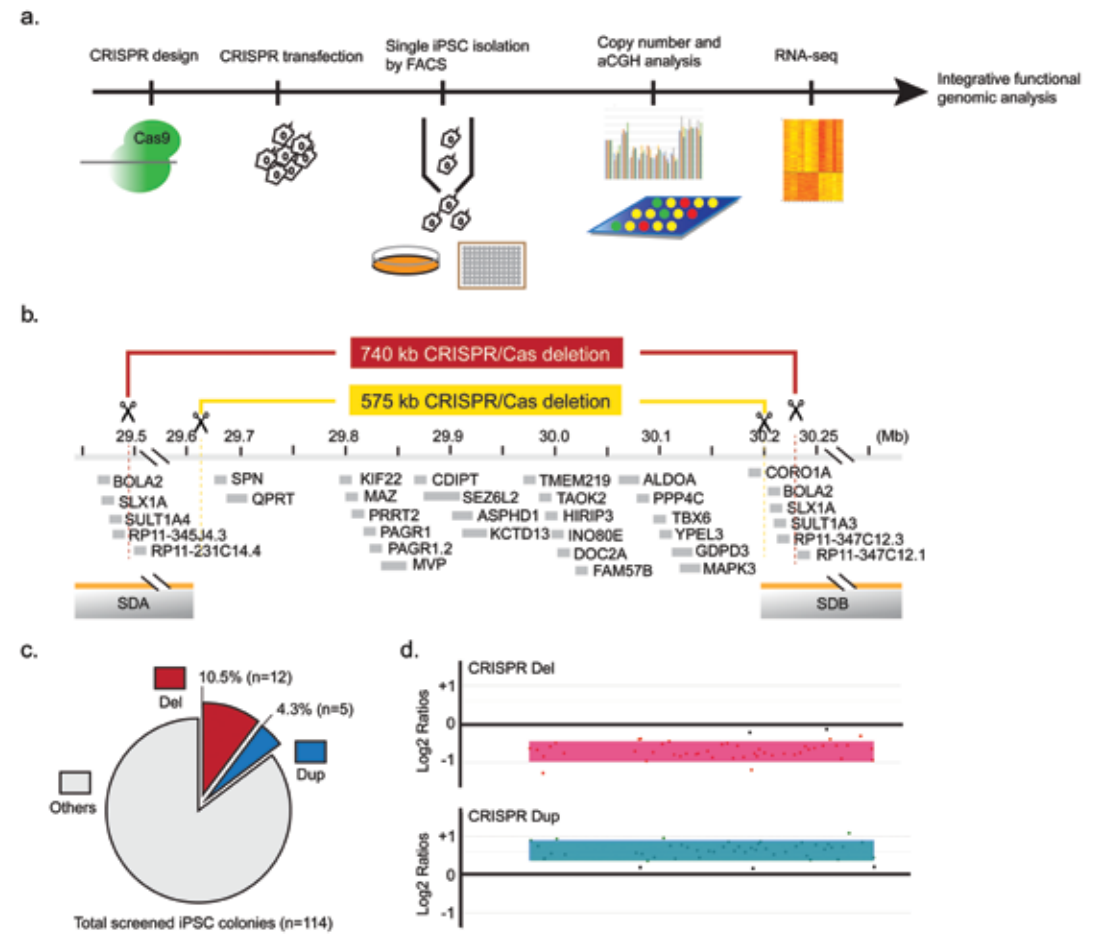
CHGR

Mitral valve prolapse (MVP) is a common cardiac valve disease that affects nearly 1 in 40 individuals. It can manifest as mitral regurgitation and is the leading indication for mitral valve surgery. Despite a clear heritable component, the genetic etiology leading to non-syndromic MVP has remained elusive. CHGR investigators and their collaborators had previously demonstrated genetic linkage of a heritable form of MVP to a region of chromosome 11 in a unique large family. In this study, they captured and sequenced the DNA of this region from four affected members of this large multigenerational family. They identified a missense mutation in *DCHS1*, the human homologue of the *Drosophila* cell polarity gene *dachsous (ds),* that segregates with MVP in this family. Morpholino knockdown of the zebrafish homologue *dachsous1b* resulted in a cardiac atrioventricular canal defect that could be rescued by wild-type human *DCHS1* mRNA, but not by *DCHS1* messenger RNA with the familial mutation. Further genetic studies identified two additional families in which a second deleterious *DCHS1* mutation segregates with MVP. Both *DCHS1* mutations reduce protein stability as demonstrated in zebrafish, cultured cells and, notably, in mitral valve interstitial cells (MVICs) obtained during mitral valve repair surgery of a proband. *Dchs1(+/-)* mice had prolapse of thickened mitral leaflets, which could be traced back to developmental errors in valve morphogenesis. *DCHS1* deficiency in MVP patient MVICs, as well as in *Dchs1(+/-)* mouse MVICs, result in altered migration and cellular patterning, supporting these processes as etiological underpinnings for the disease. Discovery of a role for *DCHS1* in mitral valve development and MVP pathogenesis now opens a route to potential novel therapeutic insights for this very common disease.



The Volcano plot shows the effect size in years for all SNPs in a GWA seeking modifiers of age at clinical onset in Huntington's disease, with the genome-wide significance threshold of 5x10-8 noted as a doted red line. Red dots indicate peak SNP in each independent region that achieved a P value <10-5 (dotted orange line).

CHGR



The proof-of-principle application of the SCORE method in generating 740 kb microdeletions and microduplications equivalent to the autism-associated 16p11.2 rMDS region: a) Study design; b) SCORE targeting (740 kb segment) of segmental duplications produces both microdeletions and microduplications, compared with dual-guide CRISPR approach (575 kb microdeletion) that fails to alter segmental duplications; c) Pie chart indicating efficiency and d) microarray confirmation of dosage change.

David Scadden, MD, Director

CRM

The Center for Regenerative Medicine is dedicated to understanding how tissues are formed and may be repaired. Our primary goal is to develop novel therapies to regenerate damaged tissues and overcome debilitating chronic disease. The success of this effort requires a cohesive team of scientists and clinicians with diverse areas of expertise, but with a shared mission and dedication to the larger goal.

Stem cells need and provide a niche. (Nature. 2015 Jul 30;523(7562):597-601)
Stem cells integrate inputs from multiple sources. Stem cell niches provide signals that promote stem cell maintenance, while differentiated daughter cells are known to provide feedback signals to regulate stem cell replication and differentiation. Recently, stem cells have been shown to regulate themselves using an autocrine mechanism. The existence of a 'stem cell niche' was first postulated by Schofield in 1978 to define local environments necessary for the maintenance of haematopoietic stem cells. Since then, an increasing body of work has focused on defining stem cell niches. Yet little is known about how progenitor cell and differentiated cell numbers and proportions are maintained. In the airway epithelium, basal cells function as stem/progenitor cells that can both self-renew and produce differentiated secretory cells and ciliated cells. Secretory cells also act as transit-amplifying cells that eventually differentiate into post-mitotic ciliated cells . Here we describe a mode of cell regulation in which adult mammalian stem/progenitor cells relay a forward signal to their own progeny. Surprisingly, this forward signal is shown to be necessary for daughter cell maintenance. Using a combination of cell ablation, lineage tracing and signalling pathway modulation, we show that airway basal stem/progenitor cells continuously supply a Notch ligand to their daughter secretory cells. Without these forward signals, the secretory progenitor cell pool fails to be maintained and secretory cells execute a terminal differentiation program and convert into ciliated cells. Thus, a parent stem/progenitor cell can serve as a functional daughter cell niche.

> **Parent stem cells can serve as niches for their daughter cells.** Pardo-Saganta A, Tata PR, Law BM, Saez B, Chow RDz, Prabhu M, Gridley T, **Rajagopal J**. Nature. 2015 Jul 30;523(7562):597-601. doi: 10.1038/nature14553. Epub 2015 Jul 6.

Changing cell 'code' (Nature Biotechnology. 2015; Jul;33:761-8)
It is well accepted that forced expression of the embryonic transcription factors Oct4, Sox2, Klf4 and c-Myc (abbreviated OKSM) is sufficient to reprogram adult skin cells into induced pluripotent stem cells that acquire the potential to give rise to any cell type of the body. More recently, numerous studies showed that the same four genes can directly convert one adult cell type into another adult cell type (e.g., a skin cell into a brain stem cell) without ever going through a pluripotent state, a process coined transdifferentiation. Transdifferentiation was suggested to be a safer approach than reprogramming because no pluripotent cells are ever generated, which have the unwanted side effect of growing into tumors if they remain undifferentiated. Using a battery of genetic tools, our lab made the observation that cells undergoing "transdifferentiation" transiently pass through a pluripotent intermediate state and subsequently differentiate rather than convert from one mature cell type directly into another mature cell type as has been assumed. These unexpected results suggest that pluripotent stem cells are the default product, albeit short-lived, when embryonic genes are expressed in differentiated cells under conditions that favor transdifferentiation. From a therapeutic point of view, our data argue that it will be important to exclude the presence of rare pluripotent cells when using available transdifferentiation strategies in combination with embryonic transcription factors.

> **Lineage conversion induced by pluripotency factors involves transient passage through an iPSC stage.** Bar-Nur O, Verheul C, Sommer AG, Brumbaugh J, Schwarz BA, Lipchina I, Huebner AJ, Mostoslavsky G, **Hochedlinger K.** Nat Biotechnol. 2015 Jul;33(7):761-8. doi: 10.1038/nbt.3247. Epub 2015 Jun 22.

CRM

Bone cells drive T cell competence (Journal of Experimental Medicine. 2015 May 4;212:759-74.)
Production of the cells that ultimately populate the thymus to generate /βT cells has been controversial, and their molecular drivers remain undefined. We reported that specific deletion of bone-producing osteocalcin (Ocn)-expressing cells *in vivo* markedly reduces T-competent progenitors and thymus-homing receptor expression among bone marrow hematopoietic cells. Decreased intrathymic T cell precursors and decreased generation of mature T cells occurred despite normal thymic function. The Notch ligand DLL4 is abundantly expressed on bone marrow Ocn(+) cells, and selective depletion of DLL4 from these cells recapitulated the thymopoietic abnormality. These data indicate that specific mesenchymal cells in bone marrow provide key molecular drivers enforcing thymus-seeding progenitor generation and thereby directly link skeletal biology to the production of T cell-based adaptive immunity.

> **Specific bone cells produce DLL4 to generate thymus-seeding progenitors from bone marrow.** Yu VW, Saez B, Cook C, Lotinun S, Pardo-Saganta A, Wang YH, Lymperi S, Ferraro F, Raaijmakers MH, Wu JY, Zhou L, **Rajagopal J**, Kronenberg HM, Baron R, **Scadden DT**. J Exp Med. 2015 May 4;212(5):759-74. doi: 10.1084/jem.20141843. Epub 2015 Apr 27.

Making lungs (Nature Biotechnology. 2015 Oct;33:1097-102.)
Bioengineered lungs produced from patient-derived cells may one day provide an alternative to donor lungs for transplantation therapy. Here we report the regeneration of functional pulmonary vasculature by repopulating the vascular compartment of decellularized rat and human lung scaffolds with human cells, including endothelial and perivascular cells derived from induced pluripotent stem cells. We describe improved methods for delivering cells into the lung scaffold and for maturing newly formed endothelium through co-seeding of endothelial and perivascular cells and a two-phase culture protocol. Using these methods we achieved 75% endothelial coverage in the rat lung scaffold relative to that of native lung. The regenerated endothelium showed reduced vascular resistance and improved barrier function over the course of in vitro culture and remained patent for 3 days after orthotopic transplantation in rats. Finally, we scaled our approach to the human lung lobe and achieved efficient cell delivery, maintenance of cell viability and establishment of perfusable vascular lumens.

> **Engineering pulmonary vasculature in decellularized rat and human lungs.** Ren X, Moser PT, Gilpin SE, Okamoto T, Wu T, Tapias LF, Mercier FE, Xiong L, Ghawi R, **Scadden DT**, Mathisen DJ, **Ott HC**. Nat Biotechnol. 2015 Oct;33(10):1097-102. doi: 10.1038/nbt.3354. Epub 2015 Sep 14.

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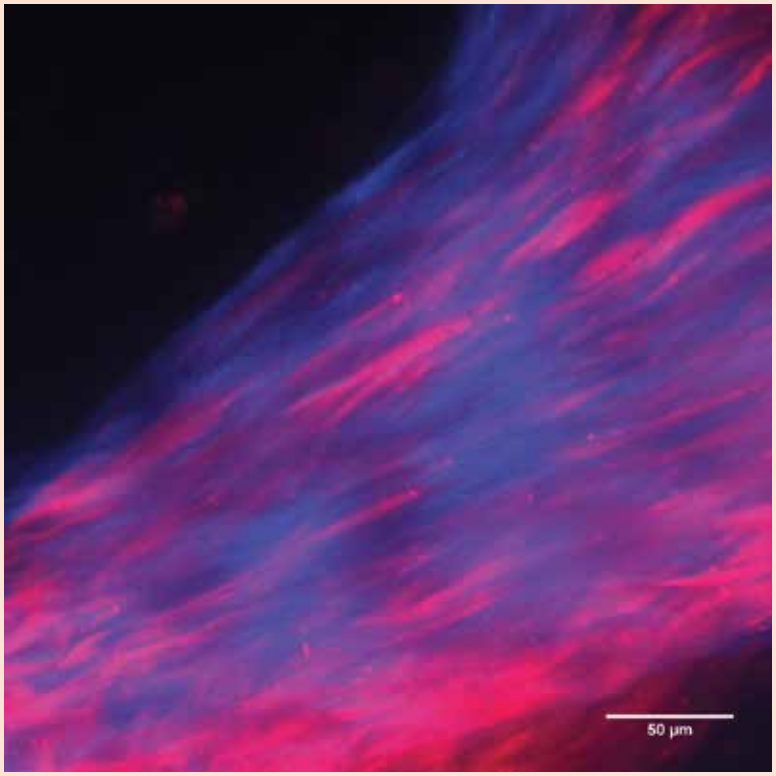
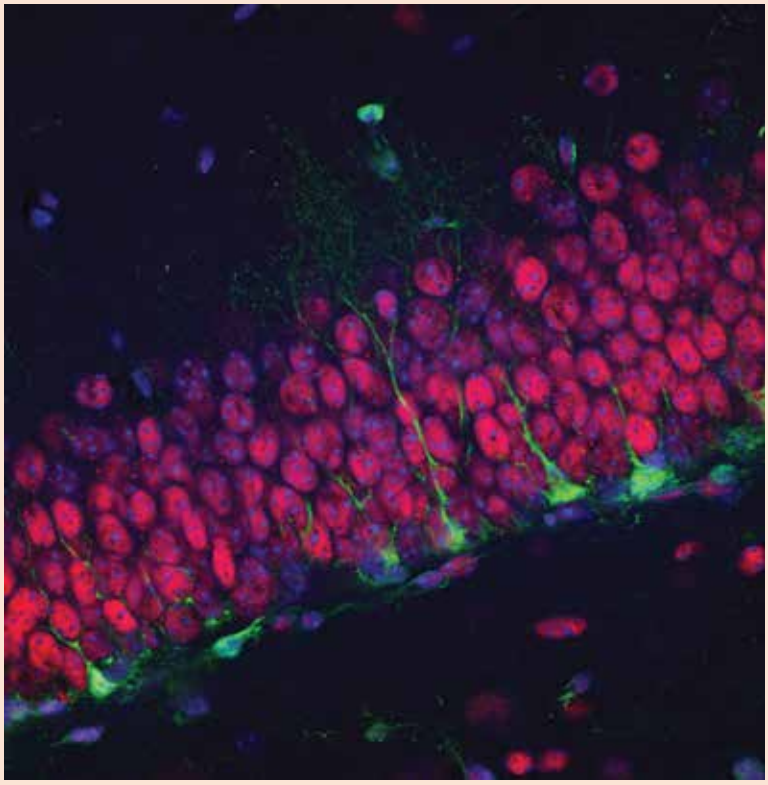


Multiphoton Microscopy image of adult zebrafish tendons
(Jenna Galloway, PhD)



Confocal Microscopy image of Neural stem cells and progenitor cells (in green) in the subgranular zone of the hippocampal dentate gyrus region in the adult mouse brain
(Amar Sahay, PhD)

CSB

Ralph Weissleder, MD, PhD, Director

The mission of the Center for Systems Biology (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 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 expertise in bioimaging, chemistry, engineering, biology, physiology, 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, 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 171 full time employees, including 41 faculty.

A new lead in sepsis (Science 2015;347:1260)
The complication of an infection known as sepsis (or "blood poisoning") is extremely dangerous, claiming up to half a million lives in the United States every year. A study from the Swirski lab has shown that a growth factor called interleukin-3 (IL-3) amplifies inflammation in sepsis and potentiates septic shock, the most severe form of sepsis. The authors show that IL-3 induces the emergency production of inflammatory monocytes and neutrophils, which are sources of the hallmark cytokines that comprise a lethal cytokine storm. A subset of B-1 B cells, discovered in the Swirski lab and named IRA B cells, are abundant sources of IL-3 in sepsis. Patients diagnosed with sepsis with high IL-3 in their blood die more often than those containing low IL-3.

> Weber GF, Chousterman BG, He S, Fenn AM, Nairz M, Anzai A, Brenner T, Uhle F, Iwamoto Y, Robbins CS, Noiret L, Maier SL, Zönnchen T, Rahbari NN, Schölch S, Klotzsche-von Ameln A, Chavakis T, Weitz J, Hofer S, Weigand MA, Nahrendorf M, Weissleder R, Swirski FK
>
> Interleukin-3 amplifies acute inflammation and is a potential therapeutic target in sepsis.
>
> Science. 2015;347(6227):1260-1265 - PMID: 25766237

Single cell epigenetic profiling (Nat Biotechnol. 2015;33:1165)
Chromatin profiling provides a versatile means to investigate functional genomic elements and their regulation. However, current methods yield ensemble profiles that are insensitive to cell-to-cell variation. In a recent study from the Bernstein lab they combined microfluidics, DNA barcoding and sequencing to collect chromatin data at single-cell resolution. They demonstrate the utility of the technology by assaying thousands of individual cells and using the data to deconvolute a mixture of ES cells, fibroblasts and hematopoietic progenitors into high-quality chromatin state maps for each cell type. The data from each single cell are sparse, comprising on the order of 1,000 unique reads. However, by assaying thousands of ES cells, they identified a spectrum of subpopulations defined by differences in chromatin signatures of pluripotency and differentiation priming. They corroborated these findings by comparison to orthogonal single-cell gene expression data. The method for single-cell analysis reveals aspects of epigenetic heterogeneity not captured by transcriptional analysis alone.

> Rotem A, Ram O, Shoresh N, Sperling RA, Goren A, Weitz DA, Bernstein BE
> Single-cell ChIP-seq reveals cell subpopulations defined by chromatin state.
> Nat Biotechnol. 2015;33(11):1165-72 - PMID: 26458175

CSB

Smartphone Sees Cancer (Proc Natl Acad Sci. 2015;112:5613)
With their ubiquitous presence and superb computation power, smartphones now bring unprecedented opportunities to realize mobile healthcare. Investigators from the Weissleder and Lee labs have developed a new smartphone-based system, D3 (digital diffraction diagnosis), for on-the-spot molecular detection. This system, complete with a custom App, was used for cervical cancer screen and diagnosing aggressive lymphomas, prevalent cancers in low and middle-income countries. This technology for the first time allows molecular diagnostics in a point of care setting and will be tested in a large scale clinical trial in Botswana.

Im H, Castro CM, Shao H, Liong M, Song J, Pathania D, Fexon L, Min C, Avila-Wallace M, Zurkiya O, Rho J, Magaoay B, Tambouret RH, Pivovarov M, Weissleder R*, Lee H*
Digital diffraction analysis enables low-cost molecular diagnostics on a smartphone
Proc Natl Acad Sci U S A. 2015;112(18):5613-8 - PMID: 25870273.

Macrophages act as drug delivery depots of nano medicines (Sci Transl Med. 2015;7:314)
Solid tumors often contain large numbers of immune cells including macrophages that feed cancer growth and metastasis. Investigators from the Weissleder lab discovered that these tumor associated macrophages can be co-opted by nanomaterials to serve as drug depots, gradually delivering chemotherapy to neighboring cancer cells. Driven by new intravital imaging technology, this research presents a new paradigm for therapeutic design and for selecting patients into clinical trials. In related research, the investigators have discovered a way to repurpose FDA-approved magnetic nanoparticles for predicting how effectively nanomedicines can accumulate in tumors. This "companion diagnostic" approach suggests that clinical imaging can be used to select patients most likely to benefit from the most advanced nanomedicine treatments.

Miller MA, Gadde S, Pfirschke C, Engblom C, Sprachman MM, Kohler RH, Yang KS, Laughney AM, Wojtkiewicz G, Kamal N, Bhonagiri S, Pittet MJ, Farokhzad OC, Weissleder R
Predicting therapeutic nano-medicine efficacy using a companion MR imaging nanoparticle.
Sci Transl Med. 2015;7:314 - PMID: 26582898.

Miller MA, Zheng YR, Gadde S, Pfirschke C, Zope H, Engblom C, Kohler RH, Iwamoto Y, Yang KS, Askevold B, Kolishetti N, Pittet M, Lippard SJ, Farokhzad OC, Weissleder R
Tumour-associated macrophages act as a slow-release reservoir of nano-therapeutic Pt(IV) pro-drug. Nat Commun. 2015;6:8692 - PMID: 26503691.

CSB

The VATPase interactome (Sci Rep. 2015;5:14827)

V-ATPases (H(+) ATPases) are multisubunit, ATP-dependent proton pumps that regulate pH homeostasis in virtually all eukaryotes. They are involved in key cell biological processes including vesicle trafficking, endosomal pH sensing, membrane fusion and intracellular signaling. They also have critical systemic roles in renal acid excretion and blood pH balance, male fertility, bone remodeling, synaptic transmission, olfaction and hearing. Furthermore, V-ATPase dysfunction either results in or aggravates various other diseases, but little is known about the complex protein interactions that regulate these varied V-ATPase functions. Investigators from the Brown and Breton labs performed a proteomic analysis to identify V-ATPase associated proteins and construct a V-ATPase interactome. The analysis using kidney tissue revealed V-ATPase-associated protein clusters involved in protein quality control, complex assembly and intracellular trafficking. ARHGEF7, DMXL1, EZR, NCOA7, OXR1, RPS6KA3, SNX27 and 9 subunits of the chaperonin containing TCP1 complex (CCT) were found to interact with V-ATPase for the first time in this study. Knockdown of two interacting proteins, DMXL1 and WDR7, inhibited V-ATPase-mediated intracellular vesicle acidification in a kidney cell line, providing validation for the utility of the interactome as a screen for functionally important novel V-ATPase-regulating proteins. The data provide new insights and directions for the analysis of V-ATPase cell biology and (patho)physiology.

Merkulova M, Punescu TG, Azroyan A, Marshansky V, Breton S, Brown D

Mapping the H(+) (V)-ATPase interactome: identification of proteins involved in trafficking, folding, assembly and phosphorylation.

Sci Rep. 2015;5:14827 - PMID: 26442671

For a complete list of ~ 130 publications from CSB in 2015, please see here: https://csb.mgh.harvard.edu/publications?year=2015

CSB

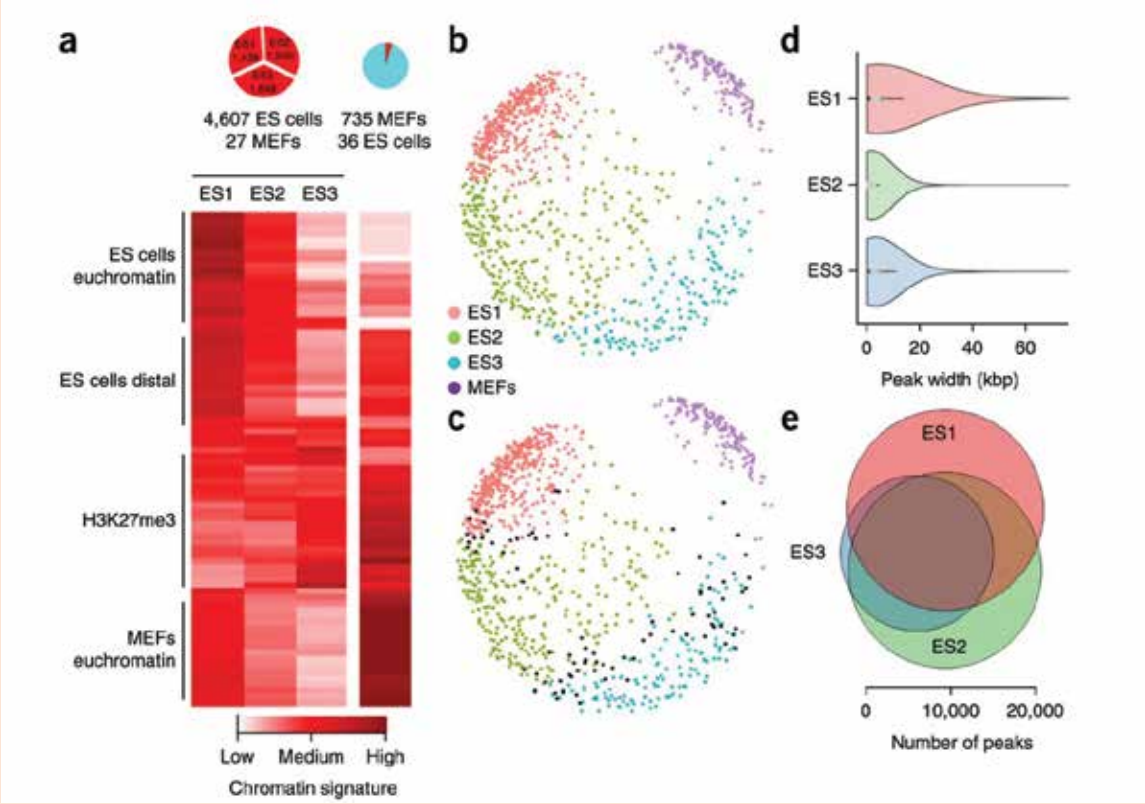


Fig. 1 (Nat Biotechnol. 2015;33:1165). A spectrum of ES cell subpopulations with variable chromatin signatures for pluripotency and priming. (a) Single-cell H3K4me2 data for 4,643 ES cells and 762 MEFs were subjected to agglomerative hierarchical clustering based on their scores in 91 signature sets of genomic regions (see Online Methods). Pie chart at left depicts the proportions of individual ES cells that cluster into each of three clusters (1,436 cells in ES1, 1,550 cells in ES2 and 1,648 cells in ES3), and pie chart at right depicts the relative numbers of ES cells and MEFs that cluster into a fourth group, which corresponds to MEFs. Heat map (below) depicts the mean signature scores (rows) for each cluster (columns). (b) Multidimensional scaling (MDS) plot compares the chromatin landscapes of single ES cells and MEFs (colored dots). The distance between any two dots (cells) approximates the distance between their 91-dimensional signature vectors. The plot shows 1,000 single cells (randomly sampled from the 5,405 cells with H3K4me2 data), colored on the basis of their cluster association. Tight co-localization of the MEF cluster and, to a lesser degree, the ES1 cluster suggests that the corresponding landscapes are relatively more homogeneous. In contrast, the ES2 and ES3 clusters are more broadly distributed and may reflect a gradient of single cell states. (c) MDS plot as in b, but with cells that frequently switched clusters in bootstrapping tests on varying subsets of cells indicated in black (see Online Methods). These unstable cells are exclusively located on the borders between clusters. (d) Violin plots show the distribution of peak widths for peaks called from aggregate ES1, ES2 or ES3 profiles (see Online Methods). (e) Venn diagram depicts the relative numbers and overlaps of peaks called from aggregate ES1, ES2 or ES3 profiles. The ES1 cluster is notable for higher pluripotency-signature scores, larger numbers of peaks and tighter internal concordance. In contrast, the ES3 cluster has higher activity over Polycomb signatures and increased heterogeneity, potentially reflecting a mixture of primed states .

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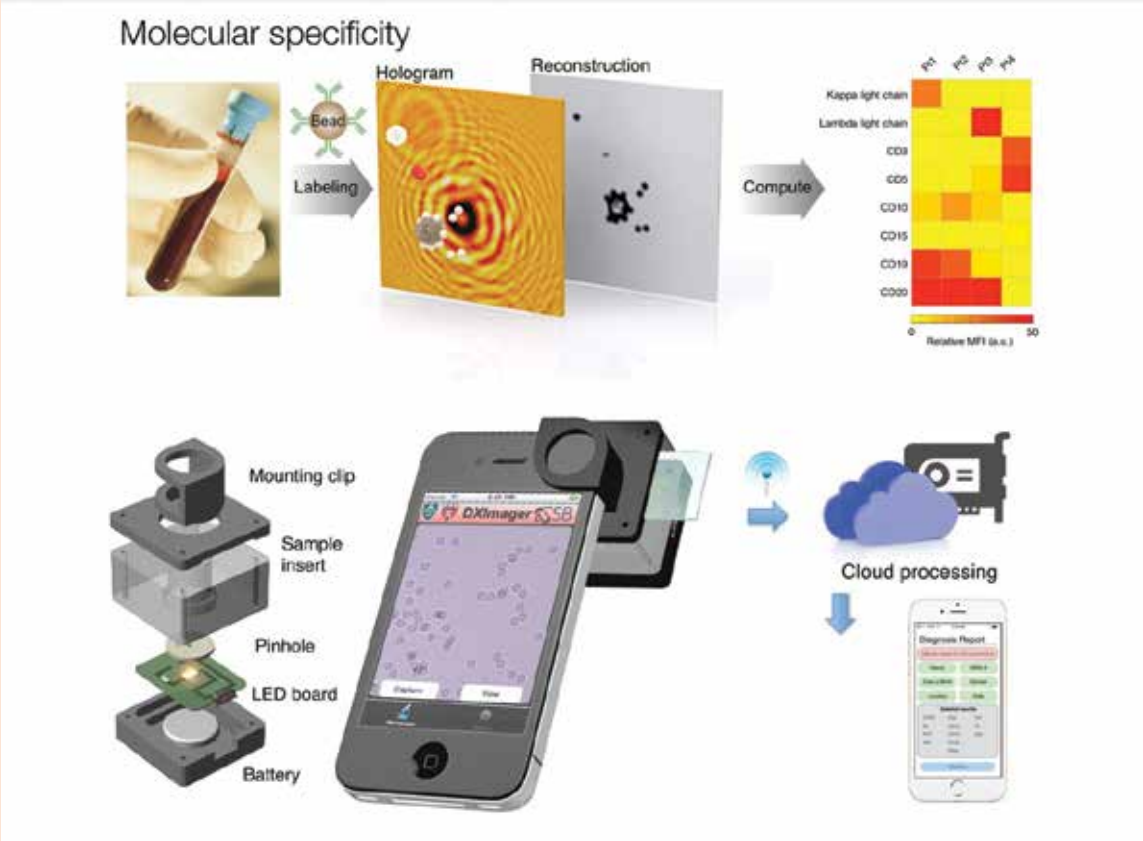

FIG. 2 (PROC NATL ACAD SCI. 2015;112:5613). Design and implementation of the D3 smartphone diagnostic system.(Top) Blood or fine needle aspirate samples are labeled by molecular-specific microbeads and imaged without washing steps by the real-time holographic method. The images of cancer cells are reconstructed from recorded holograms using a multi-core graphics processing unit (GPU) implemented computing systems for rapid calculation. The detection results are quantitative. (Bottom) Schematic of the holographic, D3 detection system mounted on a smartphone. Mathematical reconstruction of holograms is done via cloud processing in seconds and results in diagnostic reports.

R. Rox Anderson, MD, Director

WCP

Our mission at the Wellman Center for Photomedicine is to improve people's lives through research, development, innovation, and education. 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 rapidly expanding field.
- Wellman Center was a major source of MGH and Partners royalty income this year.
- Prevalent research topics include: point-of-care optical diagnostics, novel immunization strategies, cancer treatment, 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, advanced microscopy, mammalian photobiology, and bio-inspired optical technologies.
- We collaborate broadly at MGH, are part of the MIT-Harvard H.S.T. program, work with many other universities, teach graduate courses, CME and fellowships, fund graduate students and host a yearly undergraduate summer school.
- Wellman has over 250 personnel, spending > $25M a year on research.
- We initiated a $25M investment fund during 2015, which will support tech transfer from the Center. Part of the fund is immediately available to support discovery and feasibility-stage research at the Wellman Center.

Strategic priorities

- *Leadership in the field of photomedicine.* Biomedical optics is expanding rapidly; we now have unprecedented access, for unprecedented imaging and optical treatments of essentially any organ system.
- *Medical impact.* Light is powerful and versatile. Wellman is uniquely poised to actually solve problems in medical practice, access, cost-effectiveness and capability.
- *Return value to MGH.* Wellman works closely with the research and clinical communities of MGH, and our faculty serves many roles. This year, our translational research core also served as a model for the MGH Research Institute.
- *Funding that is diverse, sustained and well spent.* The Center operates on a healthy mix of NIH, DOD, royalty, industry and some philanthropy.
- *Create new support for discovery, and technology transfer.* A new $25M investment fund linked to Wellman was created this year, to foster these goals.
- *Appropriate growth.* We have grown steadily at 5-10% per year since becoming a Thematic Center in 2004. Several new faculty members should be strategically recruited. We have outgrown our available space at MGH.
- *Our greatest need:* 10% more space. We have an urgent need for ~4500 SF of nearby research space. Our laboratories are already spread out, in 10 floors of 7 buildings in 3 cities—Boston, Charlestown and Cambridge. Even after consolidation and renovations now underway, the Center cannot meet its goals without additional space. Wellman Center's density is already 150% of the MGH 2015 target.

Wellman Center for Photomedicine

Thematic Center Report

WCP

Research Highlights of 2015

We published 160 research papers and received 20 new US patents in 2015. For a deeper look at the Wellman Center, visit www.massgeneral.org/wellman

Discoveries and New Feasibilities

Men and women get different melanomas. Hensin Tsao MD PhD discovered a complex interplay between gender, mutations and survival from melanoma skin cancer. Melanomas of men harbor a significantly higher burden of mutations, than those of women. Surprisingly, tumors with more mutations also exhibited significantly better clinical outcome.

Gupta S, Artomov M, Goggins W, Daly M, Tsao H. Gender Disparity and Mutation Burden in Metastatic Melanoma. J Natl Cancer Inst. 2015;107(11).

The bone marrow micro-environment. Functionally distinct blood vessel subtypes in bone marrow were re-defined using intravital microscopy, by Charles Lin PhD in collaboration with David Scadden MD of the MGH Center for Regenerative Medicine. Both immature hematopoietic cells and mature leukocytes traffic to the bone marrow exclusively through sinusoidal blood vessels, which exhibit high vascular permeability and increased levels of reactive oxygen species. These observations reveal distinct microenvironments that regulate stem cell maintenance and cell trafficking. (*Nature* 2016, in revision)

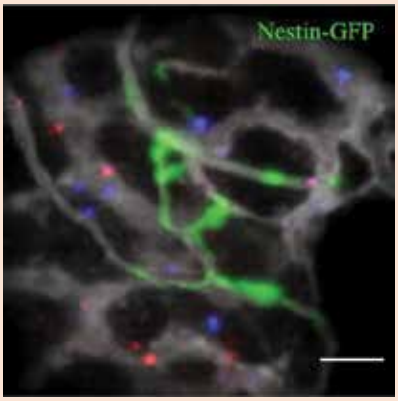

Figure 1: Intravital image of adoptively transferred hematopoietic progenitor cells (red) and mature leukocytes (blue) localizing to nestin-negative sinusoidal vessels (gray), in vivo, in situ. Scale bar = 50 μm.

Gluing cells together. Can different cell types be "glued" together, survive and function *in vivo* as a potential new cell-based therapeutic strategy? In collaboration with the MGH Center for Systems Biology, Andy Yun PhD and coauthors reported a nontoxic click-chemistry way to bind two or more cells together, while preserving both viability and cell function. They propose to combine targeting/trafficking cells, with effector cells to create targeted new therapies. H Koo, M Choi, E Kim, SK Hahn, R Weissleder, SH Yun. Bio-orthogonal Click Chemistry Based Synthetic Cell Glue. Small. 2015 Dec;11(48):6458-66

Seeing the mechanics of cells in action.
The mechanical properties that underlie cell adhesion, shape, structure and motility, have not been studied without perturbing the system—until now. Brillouin scattering microcopy, an invention from Andy Yun's laboratory, was used to map in detail the micro-mechanical properties of cells as they respond to stimuli. In the lower figure, a cell stiffens in response to mobility signals.

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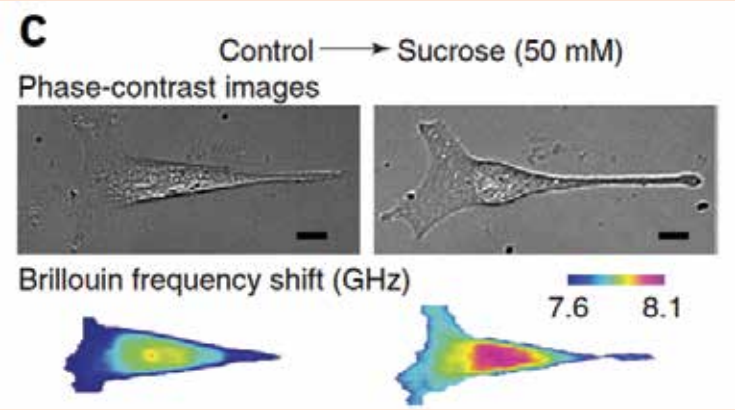
Figure 2: In the image, below, a cell stiffens in response to mobility signals.



G Scarcelli, WJ, Polacheck, HT Nia, K Patel, AJ Grodzinsky, KRD Kamm, SH Yun. Non-contact three-dimensional mapping of intrcellular hydromechanical prperties by brillouin microscopy. Nature Methods 12 (12), 1132-1134, 2015.

Living lasers. A breakthrough was achieved when the first live-biological laser was built and demonstrated at Wellman Center about 5 years ago. This year, Yun's laboratory discovered that cells can be individually identified by fine structure of their laser emission, which in the future could allow very high numbers (billions) of cells to be individually identified. M Humar, SH Yun. Intracellular Microlasers. Nature Photonics 2015;9:572-576.

Diagnostics and Human Imaging

Wellman Center has been leading a revolution in human live microscopy and point-of-care diagnostics that is already impacting the practice of medicine. We invent, design, build and test a host of novel catheters and devices at MGH. Intrinsic optical signals provide image contrast, functional and chemical identification that rivals conventional histopathology and is being used to direct therapy.

Coronary artery imaging. Three teams at Wellman Center are engaged in coronary artery imaging for diagnosis and guided treatment. Prof. Brett Bouma's group reported the first-in-human images of smooth muscle in coronary arteries using birefringence and optical frequency-domain imaging (OFDI), a previous Wellman invention that images tissue structures. This year, Ben Vakoc's laboratory also developed an OFDI method for 3-D imaging of lymphatic vessels *in vivo*.

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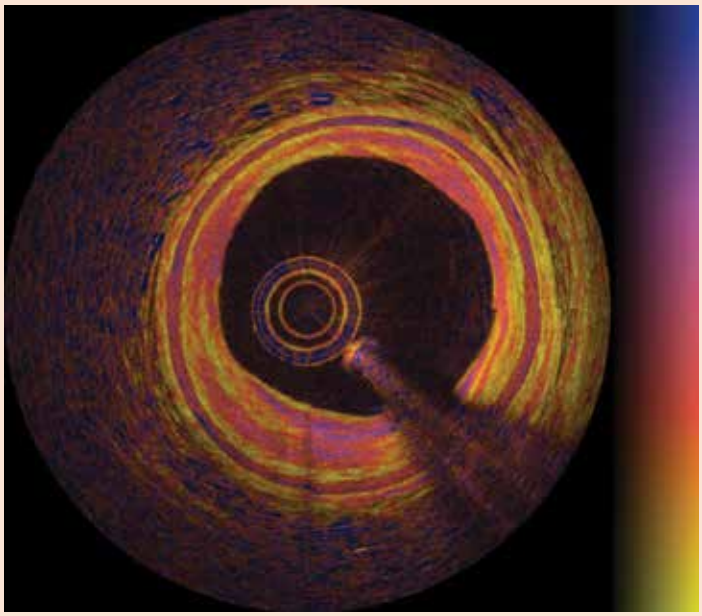

Figure 3: An image of smooth muscle in coronary arteries using birefringence and optical frequency-domain imaging [OFDI].

Prof. Gary Tearney and colleagues performed the first-in-human intracoronary OFDI that is combined with near-infrared autofluorescence to demarcate high-risk lesions based on detection of oxidative chemical changes. The new technology promises insights into human coronary artery pathology, and could be used clinically to identify the highest-risk lesions that may cause heart attacks.

GJ Ughi, H Wang, E Gerbaud, J Gardecki, AM Fard, E Hamidi, P Vacas-Jacques, M Rosenberg, FA Jaffer, GJ Tearney. First-In-Human Dual-Modality OCT and Near-Infrared Autofluorescence Imaging of Coronary Artery Disease. JACC: Cardiovascular Imaging, 2016 (in press).

Entire-esophagus live microscopy. The Tearney group also demonstrated spectrally encoded confocal microscopy (SECM), a technology that can quickly image the entire esophagus at *single-cell resolution*, in living patients. The microscope has a swallow-able capsule. In collaboration with Leigh Simmons MD (MGH Medicine) tethered capsule endomicroscopy, a Wellman invention commercialized and recently cleared by FDA, was demonstrated to work well in a primary care setting. High quality, three-dimensional microscopic images of the esophagus were taken quickly, without the need for sedation.

Coagulopathy detection. Bleeding from poorly controlled anti-coagulant drugs kills more people in the US than automobile accidents. Seemantini Nadkarni PhD invented, developed and this year demonstrated using blood from MGH patients, an optical diagnostic for blood coagulation testing. The test is rapid, uses only a drop of blood, and will be developed for point-of-care or home use. A small camera detects changes the interference pattern of reflected laser light, known as speckle, due to Brownian motion (figure 4). Her lab has also made a coronary artery catheter that uses laser speckle modulation to find unstable plaques, based on distinct mechanical properties.

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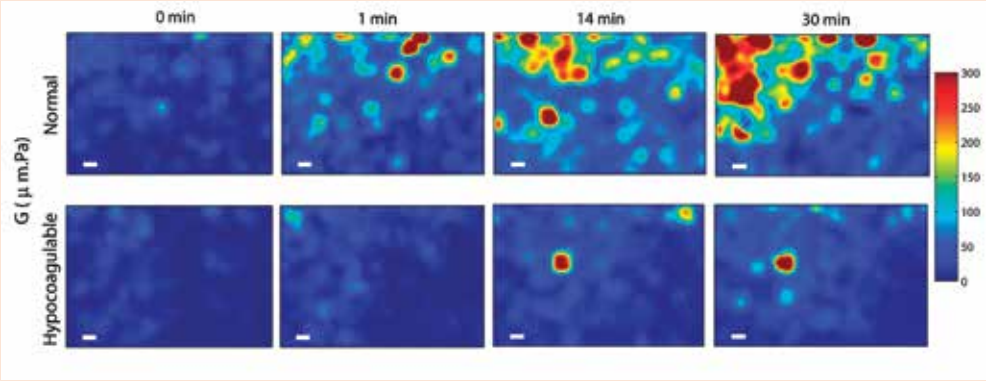
Figure 4: Blood Clot formation detected by Laser Speckle Rheology.



The color maps show clot stiffness (G) changes during clotting from a drop of blood obtained from a normal patient (top row) and a hypo-coagulable patient with low levels of clotting factors (bottom row) at 0, 1, 14, and 30 minutes after clotting activation. Micro-clots of significant G values appear at early times (~1 min) and continue to progress to form a large blood clot over 30 min in the normal patient. (In contrast, in the hypocoagulable sample, micro-clots of comparable G are only visible at 14 min and the extent and overall clot strength is considerably reduced compared to the normal patient even at 30 min. Scale bars are 100μm long. Hajjarian Z, Tripathi MM, Nadkarni SK. Optical Thromboelastography to evaluate whole blood coagulation. J Biophotonics. 2015 May;8(5):372-81.

A dressing that reports tissue pO2 . The lab of Conor Evans PhD has synthesized very bright oxygen-sensing phosphorescent reporter molecules, and incorporated them into transparent wound dressings. The pO2 of underlying tissue is reported with enough intensity that simply looking at the dressing, or taking a smart phone camera image, shows an accurate map of tissue pO_2. The technology is being developed for burns, ischemic conditions, monitoring and surgical wound care.

Roussaki E, Li Z, Nowell NH, Nichols AJ, Evans CL. Bright, "clickable" porphyrins enable visualization of oxygenation under ambient light. Communication, Wiley-VCH, 2015; 1-5.

Potential new therapies

Long-lasting analgesia without drugs. In a phase I clinical trial, Rox Anderson's laboratory found that a single non-invasive treatment of controlled tissue cooling can selectively inhibit sensory function for 1-2 months, followed by full recovery of sensation. Previously, the lab developed a now popular non-invasive treatment that locally removes subcutaneous fat, based on the discovery that lipid-rich cells are selectively sensitive to mild cold injury. A similar process occurs in the lipid-rich myelin sheath that surrounds nerve axons, affecting both myelinated and non-myelinated pathways in mixed nerves. In recent ongoing work, prolonged sensory nerve block was safely produced in animals, using a novel strategy for injectable tissue cooling.

Garibyan L, Cornelissen L, Sipprell W, Pruessner J, Elmariah S, Luo T, Lerner EA, Jung Y, Evans C, Zurakowski D, Berde CB, Anderson RR: Transient Alterations of Cutaneous Sensory Nerve Function by Noninvasive Cryolipolysis. J Invest Dermatol 2015 Nov;135(11):2623-31.

Passivating tissue response after surgery. In collaboration with MGH Surgery, Robert Redmond PhD is developing photochemical tissue passivation (PTP) to improve outcomes after vascular and other surgery. PTP stabilizes the extracellular tissue matrix by collagen crosslinking, without causing cytotoxicity. Rose Bengal, an FDA approved dye, is applied to the tissue and activated by green light for a few minutes. When PTP is applied at the time of creating an arterio-venous shunt, subsequent distension of the vein.

Wellman Center for Photomedicine

Thematic Center Report

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Increasing flu vaccine efficacy. Ironically, elderly people at greatest risk of mortality from influenza often have weak or nil response to flu vaccines. A simple laser treatment may substantially improve response. Mei Wu's laboratory reported that non-ablative fractional laser treatment of skin given at the time of flu vaccination, potently activates dermal antigen presenting cells. A human study is planned.

Wang J, Li B, Wu MX. Effective and lesion-free cutaneous influenza vaccination. Proc Natl Acad Sci U S A. 2015 Apr 21;112(16):5005-10.

Near-infrared light treatment for brain injury and neurodegenerative diseases. Modest doses of near-infrared light at specific wavelengths can rescue neurons and other cells under hypoxic, metabolic or oxidative stress. Photon absorption in the cytochrome C complex stimulates more efficient electron transport, increases ATP level, down-regulates entry into apoptosis, and initiates cell signaling. Mike Hamblin's laboratory has shown in brain-injured mice that treatment activates neuronal stem cells in the hippocampus, increases the key cytokine BDNF, and increases synaptogenesis. Based on positive pre-clinical animal work in Hamblin's lab, a phase I randomized controlled clinical trial is now underway at MGH, testing transcranial near infrared light treatment in patients with acute brain injury. Pilot trials were completed this year for treatment of depression and Alzheimer's, with encouraging results.

Xuan W, Agrawal T, Huang L, Gupta GK, Hamblin MR. Low-level laser therapy for traumatic brain injury in mice increases brain derived neurotrophic factor (BDNF) and synaptogenesis. J Biophotonics. 2015 Jun;8(6):502-11.

Light-activated cocktails for cancer. The impressive progress in new cancer drugs that inhibit a specific tumor survival pathway, are mitigated when cancer cells "escape" by other pathways.

Photodynamic therapy of cancer uses light-activated drugs, reducing the risks of systemic toxicity. Prof. Hasan's laboratory focused this year on several promising strategies for light-activation of synergistic agents. In a realistic murine model of pancreatic cancer, the topoisomerase inhibitor irinotecan was shown to be synergistic with photodynamic therapy, by inhibiting compensatory mechanisms. In a separate study, the monoclonal antibody VEGF inhibitor drug bevacizumab, was delivered in a photoactivated liposome containing the photodynamic drug benzoporphyrin, with excellent synergy for treatment of pancreatic cancer.

Huang H-C, Mallidi S, Liu J, Chiang CT, Mai Z, Goldschmidt R, Rizvi I, Hasan T. Photodynamic therapy synergizes with irinotecan to overcome compensatory mechanisms and improve treatment outcomes in pancreatic cancer. Cancer Research doi: 10.1158/0008-5472.CAN-15-0391 Published online: December 30, 2015.

Anesthesia, Critical Care and Pain Medicine

Department Report

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. **(1)** DACCPM research activities have an international reputation and encompass a broad range of disciplines with active research units focused in the areas of cardiac and pulmonary pathophysiology, molecular and system neuroscience, pharmacology, pain neurobiology, neuroimaging, stem cell research, genetics, comparative outcome research, biomedical engineering, and new drug and medical device development. **(2)** DACCPM has over 200 research staff including MD and/or PhD investigators, post-doctoral fellows, and graduate students. **(3)** The laboratories and clinical research units are mostly located on the main MGH campus and at the MGH-East research facility at the Charlestown Navy Yard. **(4)** Research activities at DACCPM are supported by 70-80 grants per year including 25-30 NIH grants. **(5)** The DACCPM faculty publishes annually over 200 journal articles and numerous books/book chapters.

There are three strategic research priorities at DACCPM. **(1)** Retaining and expanding a premier research team: we have a long-term plan to foster the growth of three tiers of investigators, including a) T32 and K08 trainees, b) junior and mid-level investigators, and c) well-established senior investigators. Over years, we have provided significant investment in expanding and retaining our research staff, including salary support to T32/K08 trainees, gap funding for MD and/or PhD investigators, and supplemental salary support for basic science and clinical researchers. **(2)** 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. **(3)** Using innovation to advance translational research and expand the overall scope of basic science and clinical research: we have an internal funding mechanism that supports invention and innovation through fruitful translational research. A significant number of pending or awarded patents from our department offer a promising pipeline of innovative products that will ultimately advance patient care and provide sustainable support for research activities in the department. This effort is further strengthened over the last several years.

In 2015, the DACCPM faculty published over 200 journal articles as first authors, senior authors, or co-authors. The following are four representative achievements from our research faculty.

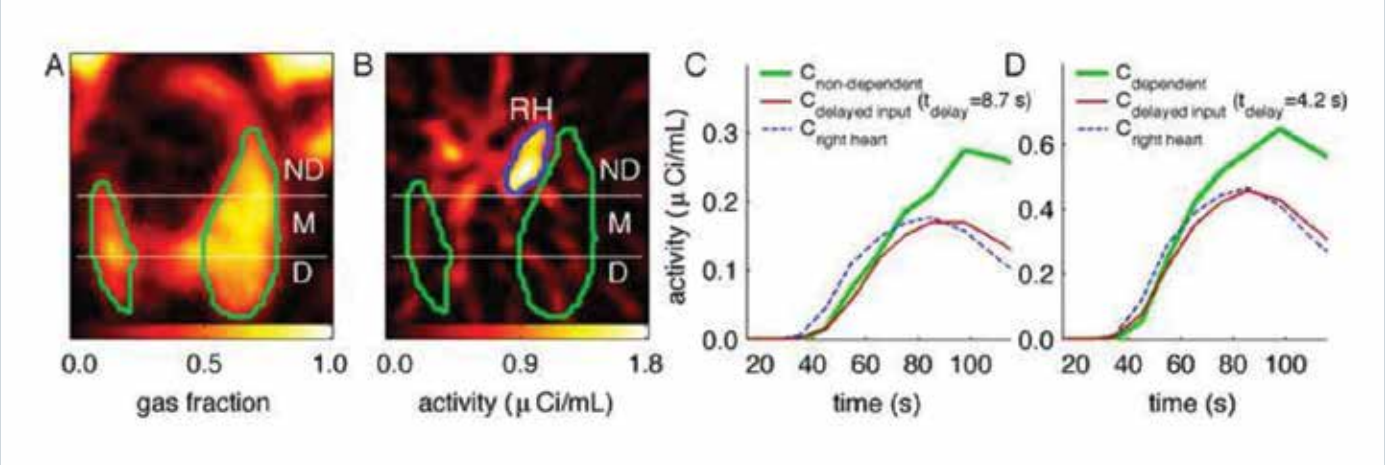
(1) Innovative portable device producing nitric oxide for inhalation therapy: The Lab led by Dr. Warren Zapol designed, constructed and tested, in lambs and humans with pulmonary hypertension, a lightweight, economical, portable electric nitric oxide (NO) generator. Inhaled NO therapy, a life-saving treatment for babies with pulmonary hypertension of the newbornβis unavailable in many parts of the world or in patients' homes because of the cumbersome delivery system and high cost $14,000 for 5 days of treatment for one newborn. To make inhaled NO more widely available, the Zapol lab designed a lightweight, inexpensive, and portable system that produces a therapeutic range of NO (5-80 ppm) from air, using a pulsed electrical discharge. It is demonstrated at MGH that electrically generated NO is equivalent to NO delivered from a standard NO/N_2 cylinderβthe current clinical gold standard. This new, economical technology for NO inhalation therapy will liberate patients from costly, cumbersome tanks and complicated delivery systems and will facilitate long-term, home use of inhaled NO. We anticipate that the availability of this device will permit investigators to identify novel indications for NO inhalation therapy in pulmonary hypertension, including the treatment of chronic lung diseases and congestive heart failure. These findings were published in *Science: Translational Medicine* in 2015.

(2) Understanding the brain mechanism of sleep and sleep disorders: A joint research team from Massachusetts General Hospital and Massachusetts Institute of Technology (MIT), led by

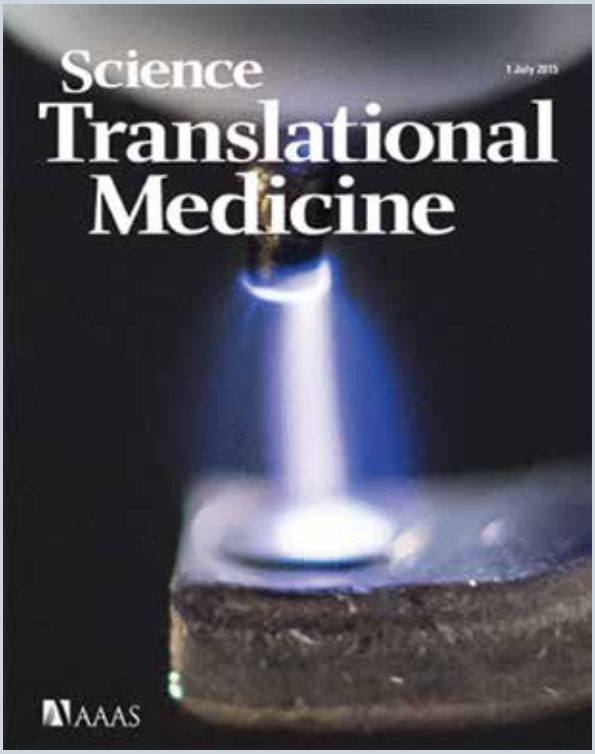
Drs. Emery Brown and Patrick Purdon, is a step closer to understanding the science of sleep. Using a scanning method that can activate light-sensitive proteins, the researchers found that the activation of cholinergic neurons (those that release the neurotransmitter acetylcholine) in two structures of the brain stem are key to inducing REM (rapid-eye movement) sleep in lab models. Both REM and non-REM sleep perform important functions, but current sleep aids cannot effectively replicate the cycling between each stage that occurs during natural sleep. By gaining a better understanding of the mechanisms that underlie sleep, investigators may be able to develop more effective remedies for sleep disorders. For his work, Dr. Patrick Purdon was elected into the American Institute for Medical and Biological Engineering (AIMBE) College of Fellows. Since 1991, AIMBE's College of Fellows has led the way for technological growth and advancement in the fields of medical and biological engineering. Fellows have helped revolutionize medicine and related fields to enhance and extend the lives of people all over the world. They have also successfully advocated for public policies that have enabled researchers and business makers to further the interests of engineers, teachers, scientists, clinical practitioners and ultimately patients.

(3) Understanding the interaction between adrenergic signaling and cardiac signaling: Dr. Fumito Ichinose and his team revealed that the rise and fall of calcium levels inside cardiomyocytes controls their contraction and relaxation. This contractility can be modulated by beta-adrenergic receptor (βAR) signaling, which leads to the phosphorylation of calcium-handling proteins in these cells. Chronic activation of βAR and a sustained increase in intracellular calcium can lead to left ventricular hypertrophy and heart failure. Therefore, a thorough understanding of the molecular signals downstream of βAR activation would provide insights into the disease mechanism. Recent evidence suggests that βAR not only phosphorylates calcium handling proteins, but it also increases the production of nitric oxide (NO) by stimulating nitric oxide synthase. Dr. Ichinose and colleagues have now examined this parallel role of βAR activation more closely and discovered that βAR-induced NO production leads to S-nitrosylation of calcium handling proteins—specifically phospholamban and cardiac troponin C. Importantly, they found that suppression of S-nitrosylation prevented left ventricular hypotrophy in mice that were subjected to chronic βAR stimulation. These results suggest that S-nitroslylation of phospholamban, troponin C or other calcium handling proteins might be novel processes to target in future heart failure therapies. These findings were published in *Circulation Research* in 2015.

(4) Improving respiratory function in ICU patients. Obese patients in ICU are more likely to require invasive mechanical ventilation for primary respiratory failure than non-obese patients. Current ventilation guidelines do not take into consideration specific positive end-expiratory pressure (PEEP) titration techniques for mechanical ventilation in obese patients, exposing them to the risks of hypoxemia or lung damage, ultimately leading to failed liberation from mechanical ventilation and ventilator-dependence. Dr. Lorenzo's Berra's group hypothesized that an individualized approach to mechanical ventilation with the implementation of PEEP titration techniques can improve oxygenation and respiratory system mechanics. They included 14 mechanically ventilated obese patients. They observed that routinely set PEEP levels are not adequate in morbidly obese patients - these levels result in reduced functional residual capacity, lower oxygenation and worse elastic properties of the lung and respiratory system. Both an esophageal-titrated PEEP and a decremental PEEP trial after lung recruitment yielded similar results. Recruitment maneuvers and PEEP titration are able to restore normal lung volumes, improving oxygenation and the elastic properties of the respiratory system. These findings are published in *Critical Care Medicine* in 2015.



Dr. Marcos Vidal Melo's pulmonary pathophysiology lab **developed a technique to measure regional pulmonary blood flow using the lung kinetics of the tracer fluorodeoxyglucose. The figure below shows coronal sections of a sheep lung with its aeration (gas fraction, A) and immediately following central venous tracer injection (B), when most of the tracer is in the right heart (RH, high activity). Exploring the delay times between the heart and the lungs (C, D), regional pulmonary blood flow can be accurately computed in non-dependent (ventral), middle (M), and dependent (dorsal) lung regions.**



ONLINE COVER: It's Electric! An iridium electrode›s spark generates nitric oxide from ambient air. In this issue, Yu and colleagues (*from Dr. Zapol's lab at Massachusetts General Hospital*) packaged this spark into a portable, lightweight device, so that nitric oxide can be easily delivered to patients in emergency rooms or in their own homes. The respiratory device was first tested in lambs with pulmonary hypertension, performing as well as traditional tank-delivered nitric oxide.

Cancer Center

Department Report

Daniel 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 ***focused*** 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, and expanding our efforts in patient-derived preclinical models and their application in combination targeted therapies. We are also building a leading cancer immunology program, focused on both 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 Heme/Onc and Clinical Director of the Cancer Center. **Total annual research funding** for CCR and Heme/Onc is 50M (including16.4M in industry clinical trials contracts).

Highlighted 2015 accomplishments for the Cancer Center are grouped into four thematic areas:

1) Targeted Cancer Therapies

The highly specific molecular targeting of oncogenic drivers in cancer leads, in many cases, to acquired resistance.Considerable progress is being made in identifying mechanisms of resistance associated with specific therapies.*Dr. Ryan Corcoran* and colleagues have found that reactivation of the MAPK pathway in colorectal cancers targeted in combination therapies with RAF inhibitors (1). *Drs. Jeff Engelman* and co-workers discovered that EGFR mutant lung adenocarcinomas develop resistance to targeted therapy by transforming to small-cell lung cancers, and found that mutation of *RB1* is a critical event in this process (2).In some cases, resistance to targeted therapies can be overcome by the use of second and third generation inhibitors. *Dr. Alice Shaw* and coworkers found that mutations that provide resistance to one class of ALK inhibitors can sensitize, and even resensitize, lung tumors to other classes of inhibitors (3).Tumor heterogeneity has been identified as a major obstacle for targeted therapies, contributing to both lesion specific responses (4) and the emergence of resistance clones (5, 6).The competition between drug sensitive and resistance clones is evident in lesion specific radiographic responses and can be monitored in circulating tumor DNA (4, 5).Importantly, genomic analyses of brain metastases shows that clinically actionable alterations are frequently present that are not detected in primary biopsies (7), indicating that the molecular diagnostic strategies are needed to sample material from all sites.

(1) Ahronian LG, *et al.*, Clinical Acquired Resistance to RAF Inhibitor Combinations in BRAF-Mutant Colorectal Cancer through MAPK Pathway Alterations. *Cancer Discov.* 2015; 4:358-67.

(2) Niederst MJ, *et al.*, RB loss in resistant EGFR mutant lung adenocarcinomas that transform to small-cell lung cancer. *Nat Commun.* 2015; 6:6377.

(3).Shaw AT, *et al.*, Resensitization to Crizotinib by the Lorlatinib ALK Resistance Mutation L1198F. *N Engl J Med.* 2015 Dec 23.

(4) Russo M, *et al.*, Tumor heterogeneity and lesion-specific response to targeted therapy in colorectal cancer. *Cancer Discov.* 2015; pii: CD-15-1283.

(5) Kwak EL, *et al.*, Molecular Heterogeneity and Receptor Coamplification Drive Resistance to Targeted Therapy in MET-Amplified Esophago gastric Cancer. *Cancer Discov.* 2015; 5(12):1271-81.

(6) Piotrowska Z, *et al.*, Heterogeneity Underlies the Emergence of EGFRT790 Wild-Type Clones Following Treatment of T790M-Positive Cancers with a Third-Generation EGFR Inhibitor. *Cancer Discov.* 2015; 5(7):713-22.

(7) Brastianos PK, *et al.*, Genomic Characterization of Brain Metastases Reveals Branched Evolution and Potential Therapeutic Targets. *Cancer Discov.* 2015; 5(11):1164-77.

2) Cancer Genetics and Epigenetics

In addition to the mutational events that drive tumor progression, epigenetic changes can have a major impact on tumor biology and the past year has seen important advances in our understanding of the epigenetic events that help to establish cell identity, the changes in the organization of topological domains in cancer genomes, and the consequences of altered activity of chromatin regulators.

Function-based screens enabled *Dr. Konrad Hochedlinger* and colleagues to identify chromatin regulators that are key for transcription-factor–mediated reprogramming of mouse fibroblasts to induced pluripotent stem cells (1).Unexpectedly, subunits of the chromatin assembly factor-1 complex play a key role in this process, and act by regulating the accessibility of enhancer elements during programming.Disruption of the organization of chromosomal domains was also found to play an important role in IDH mutant gliomas (2).Here widespread changes in the methylation of CpG islands was discovered to alter the binding sites for CTCF, a key regulator of topological domains, allowing enhancer elements to aberrantly interact with the PDGFR gene, an important glioma oncogene. Novel approaches for the detection of genomic rearrangements and enhancer activity revealed novel mechanisms for oncogene activation in B-cell Lymphoma (3).

Other studies have identified unexpected consequences of altering the levels of known chromatin regulators. *Dr. Shyamala Mahreswaran* and colleagues found that the lysine methyltransferase SETD1A suppresses the expression of antiproliferation gene BTG2 by inducing the expression of several miRNAs that target BTG2.*Dr. Johnathan Whetstine* and co-workers demonstrated that the lysine demethylase KDM4A is not only a regulator of histone modifications but that it is also found in the cytoplasm where it associates with the translation machinery and regulates protein synthesis (5).Remarkably, nucleotide polymorphisms in KDM4A alter cellular sensitivity to mTOR inhibitors (6).In the nucleus, KDM4A promotes transient site specific copy gains, an activity that regulated by hypoxia (7), suggesting that variation in KDM4A levels can affect both copy number heterogeneity and drug sensitivity in cancer. Another elegant connection between chromatin regulators and drug sensitivity was provided by *Dr. Lee Zou's* studies of the chromatin remodeling protein ATRX (7).The Zou laboratory discovered an association between the inactivation of ATRX and the pathways that cells use to maintain telomere length and to overcome replicative mortality.Cells lacking ATRX use the ALT pathway to maintain telomere length, and were found to be highly sensitive to ATR inhibitors. This sensitivity raises the possibility that these inhibitors may have general utility for the treatment of ALT-positive cancers.

(1) Cheloufi S, *et al.*, The histone chaperone CAF-1 safeguards somatic cell identity. *Nature.* 2015; 528(7581):218-24.

(2) Flavahan WA, *et al.*, Insulator dysfunction and oncogene activation in IDH mutant gliomas. *Nature.* 2015; Dec 23.

(3) Ryan RJ, *et al.*, Detection of Enhancer-Associated Rearrangements Reveals Mechanisms of Oncogene Dysregulation in B-cell Lymphoma. *Cancer Discov.* 2015; 5(10):1058-71.

(4) Tajima K, Yae T, *et al*., SETD1A modulates cell cycle progression through a miRNA network that regulates p53 target genes. *Nat Commun*. 2015; 6:8257.

(5) Van Rechem C, Black JC, Boukhali M, Aryee MJ, Gräslund S, Haas W, Benes CH,Whetstine JR. Lysine demethylase KDM4A associates with translation machinery andregulates protein synthesis. *Cancer Discov.* 2015; 5(3):255-63.

(6) Van Rechem C, *et al*., A coding single-nucleotide polymorphism in lysine demethylase KDM4A associates with increased sensitivity to mTOR inhibitors. *Cancer Discov*. 2015; 5(3):245-54.

(7) Black JC, *et al*., Hypoxia drives transient site-specific copy gain and drug-resistant gene expression. *Genes Dev.* 2015; 29(10):1018-31.

(8) Flynn RL, *et al*., Alternative lengthening of telomeres renders cancer cells hypersensitive to ATR inhibitors. *Science.* 2015; 347(6219):273-7.

3) Cancer Metabolism

Changes in tumor cell and systemic metabolism are central to the biology of many cancers. Understanding these alterations provides important insights into the ways that tumors develop and grow, and suggests new approaches for detection, prevention, and treatment. It is now clear that specific changes in metabolic circuits are associated with well-known driver mutations such as p53, mutant Ras, and most recently *RB1* (1). The mutation of metabolic enzymes is a recurrent theme in cancer genomes, although the underlying tumor-promoting mechanism is often unclear. Studies by *Dr. Nabeel Bardeesy* and co-workers (2) have provided critical insight into the effects of mutations in isocitrate dehydrogenase 1 and 2 (IDH1 and IDH2), lesions that are common in intrahepatic cholangiocarcinoma (ICC) and that also occur on subsets of neural, haematopoietic and bone tumors.Mutant IDH1 acquires an abnormal enzymatic activity leading to the accumulation of 2-hydroxyglutararate (2HG). In ICC, 2HG suppresses the activity of HNF-4α, a master regulator of hepatocyte identity and quiescence, resulting in impaired differentiation, elevated cell proliferation, and an aberrant response to hepatic injury.

In contrast, the pathogenesis of pancreatic ductal adenocarcinoma (PDA) requires high levels of autophagy, a conserved self-degradative process.Another seminal study by *Dr. Nabeel Bardeesy* and colleagues revealed that the induction of autophagy in PDA is part of a broader transcriptional program, mediated by the MiT/TFE family of transcription factors, that coordinates the activation of lysosome biogenesis and scavenging of nutrients (3). The discovery that MiT/TFE proteins are master regulators of metabolic reprogramming in PDA not only uncovered a novel hallmark of this aggressive malignancy but also identified new targets for therapeutic intervention.In additional studies that explored the natural variability of metabolic control in the human population, *Dr. Anders Naar* and colleagues examined the relationship between genome variants and human pathologies associated with altered lipid metabolism (3).Meta-analysis of genome-wide association data identified 69 miRNAs at loci associated with abnormal levels of circulating lipids.Several of these miRNAs control the expression of key proteins in cholesterol-lipoprotein trafficking, suggesting that altered miRNA expression contributes to abnormal blood lipid levels and may predispose individuals to cardiometabolic disorders.

(1) Nicolay BN, *et al*., Proteomic analysis of pRb loss highlights a signature of decreased mitochondrial oxidative phosphorylation. *Genes Dev*. 2015; 29(17):1875-89.

(2) Saha SK, *et al*., Corrigendum: Mutant IDH inhibits HNF-4α to block hepatocyte differentiation and promote biliary cancer. *Nature.* 2015; 528(7580):152.

(3) Perera RM, *et al*., Transcriptional control of autophagy-lysosome function drives pancreatic cancer metabolism. *Nature.* 2015; 524(7565):361-5.

(4) Wagschal A, *et al*., Genome-wide identification of microRNAs regulating cholesterol and triglyceride homeostasis. *Nat Med.* 2015; 21(11):1290-7.

4) Cancer Immunology

Groundbreaking work from *Dr. Nir Hacohen* and colleagues explored the concept that the genomic landscape of a tumor shapes, and is shaped by, anti-tumor immunity. Using large-scale genomic data sets from biopsies of 18 types of solid tissue tumors, they examined and quantified the cytolytic activity of the local immune infiltrates and identified associated properties (1, 2). The number of MHC Class I-associated neoantigens was lower than predicted, providing evidence for immunoediting in tumors. Analysis of this data identified recurrently mutated genes and amplified regions that are associated with cytolytic activity, and also uncovered mechanisms of tumor-intrinsic resistance to cytolytic activity.

(1) Rooney MS, *et al.*, Molecular and genetic properties of tumors associated with local immune cytolytic activity. *Cell.* 2015; 160(1-2):48-61.

(2) Shukla SA, *et al.*, Comprehensive analysis of cancer-associated somatic mutations in class I HLA genes. Nat Biotechnol. 2015; 15;33(11):1152-1158.

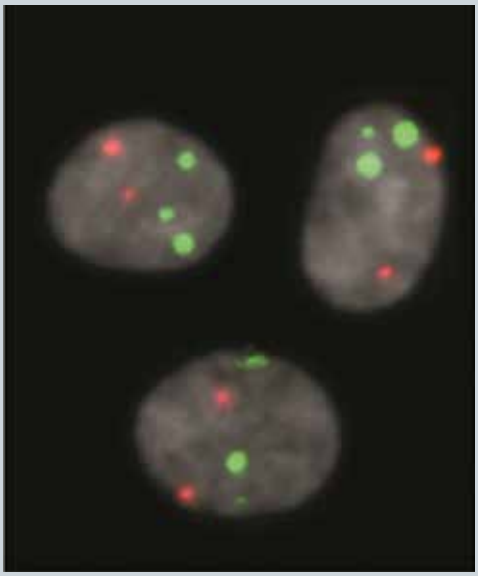


IMAGE Joshua C. Black, PhD

WHETSTINE LABORATORY
Human cells exposed to hypoxia generate extra DNA-copes containing drug resistant genes (green). The nucleus is white and a control DNA region is red.

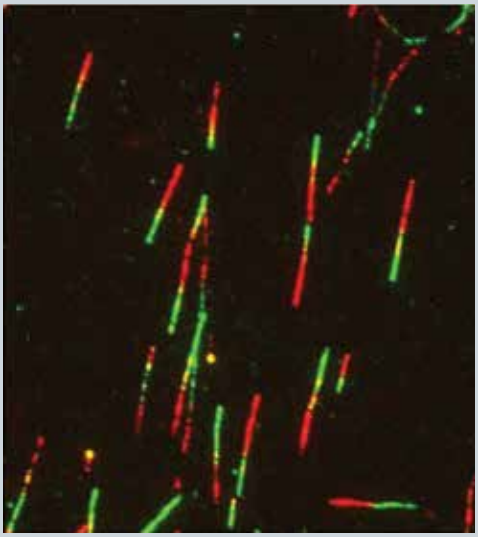


IMAGE Stephanie Yazinski, PhD

ZOU LABORATORY
Immunofluorescence image of DNA fibers from BRCA1-deficient ovarian cancer cells.Replicating cells are pulsed with nucleotide analogs, CldU (red) followed by IdU (green), the DNA is spread, and the analogs are stained which enables monitoring of replication progression and fork stability.

Consortia for Improving Medicine Through Innovation and Technology (CIMIT)

Department Report

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://www.cimit.org/about-clinical-impact-study.html) 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 now comprises more than 10 former founders and CEOs of medtech companies who fully understand the medical device and diagnostic markets and clinical implementation (http://www.cimit.org/services-accelerator.html). 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 2015, CIMIT was the recipient of large awards from three 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://www.cimit.org/poctrn.html). 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.

Consortia for Improving Medicine Through Innovation and Technology (CIMIT)

Department Report

Key achievements in 2015

Joint Warfighter Program new funding to CIMIT provided $1.8M of direct costs towards the research of three MGH investigators in cutting-edge, commercializable projects: 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 will be presented to the Department of Defense in February 2016. The bid on the second-phase $8M contract is in review.

CIMIT's CRAASH Course

In the summer CIMIT, held its first healthcare commercialization boot camp. 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 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. The second course starts at the end of January 2016.

CIMIT CRAASH Course Mentors (L-R): Eric Evans, Mike Dempsey, Marc Filerman, Joel Weinstein, John Collins, Josh Tolkoff, Alain Hanover and Wolfgang Krull

Team #1 Urinary Incontinence (L-R): Marshall Collins, Mei-Mei Chow and Carlos Estrada

Dermatology

Department Report

David E. Fisher, MD, PhD, Chief

The Department of Dermatology at MGH delivers world-class care to patients from around the globe and around the corner. Its core mission to deliver such care is coupled to a deep commitment to push the edge of innovation and discovery. This work is carried out in a broad set of research laboratories which seek to translate laboratory-based discoveries into innovations in dermatologic care. Towards this end the Department maintains an extremely busy clinic that sees >1000 patients per week, plus an Inpatient Consult Team and cutaneous malignancy care within MGH Cancer Center. It is also comprised of a series of subspecialty clinics in multiple fields, which include Pigmented Lesions (the first such clinic in America), Pediatric Dermatology, Rheumatologic Dermatology, Phototherapy, Cosmetic Dermatology, Dermatologic Surgery, High-risk non-melanoma Skin Cancers, and others. The Dermatology Department also houses a busy Clinical Trials Unit which typically runs a portfolio of 15-20 clinical trials. Beyond the clinic, the Department houses the Cutaneous Biology Research Center (CBRC), which is the home to 14 laboratory investigators, who run independent research programs. Their research covers numerous fields that examine the fundamental pathophysiologic mechanisms active in skin disease as well as mediators of healthy skin. Some of the topics investigated at CBRC include molecular/cellular biology of the epidermis, stem cells, epigenetics, immunobiology, chemical biology/drug-screening, topical drug delivery, itch, UV-protection, metabolism, cancer biology, inflammation, pigmentation, hair follicle biology, laser applications, and tumor immunology. Additional research faculty whose academic home is in Dermatology include multiple researchers in the Wellman Center for Photomedicine, an MGH Thematic Center that has made numerous seminal contributions to the current practice of dermatology.

In the year 2015, research and scholarly activities undertaken by faculty in the Department of Dermatology gave rise to 224 publications, as well as 235 speaking engagements. $17.2M 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. Two junior faculty members received perfect scores on KO8 grant applications at NIH in 2015. A new research program in Cancer Immunotherapy was initiated during the past year as a partnership with MGH Cancer Center. The Program has recruited 4 outstanding investigators, who include physician-scientists and world class experts in immunology and the therapeutic opportunities it offers. A Dermatologic Epidemiology initiative was also introduced during the past year, with new faculty recruitment and a partnership with Harvard Medical School's Population Medicine Department. Collectively, these efforts are driving innovation in both our understanding of skin biology, improvements in care of the dermatology patient, and strategies to prevent or diagnose skin diseases. The MGH Department of Dermatology is also proud of its Community Service and Educational missions, which are part of the daily mission of the department. These activities include free skin cancer screenings, dermatologic care to the homeless, and teaching of trainees from numerous constituencies, including high school, undergraduate college, medical school, and postgraduate clinical or research stages. Many trainees come to MGH Dermatology from overseas, and return to share the teachings at their home institutions. Finally, Dermatology prides itself on the extensive cross-departmental collaborative activities in which it is engaged. These include interactions with the Cancer Center, Pathology, Anesthesia, Plastic Surgery, Radiation Oncology, Psychiatry, Infectious Diseases, Rheumatology, and others.

Yoon KW, Byun S, Kwon E, Hwang S-Y, Chu K, Hiraki M, Jo S-H, Weins A, Hakroush S, Cebulla A, Sykes DB, Greka A, Mundel P, Fisher DE, Mandinova A, Lee SW. Control of signaling-mediated clearance of apoptotic cells by the tumor suppressor p53. **Science** 2015 Jul 31;349(6247).

This study, from the lab of Sam W. Lee, PhD, identified a new transcriptional target of the p53 tumor suppressor called DD1α. As a key regulator of apoptotic death, p53 was now found to also modulate clearance of dead/apoptotic cells, through this transmembrane protein which forms homotypic interactions between the apoptotic cell and engulfing macrophages. In addition to demonstrating this novel clearance mechanism, the study also examined DD1α as a potentially key homolog of the immune modulatory family represented by TIM, PDL1, and PD1. Through homotypic interactions across T cells, DD1α appears to inhibit T cell activation state because targeted knockout of DD1α in mice an autoimmune phenotype. This study suggests that DD1α blockade could represent a new form of immune checkpoint therapy.

Procopio MG, Laszlo C, Al Labban D, Kim DE, Bordignon P, Jo SH, Goruppi S, Menietti E, Ostano P, Ala U, Provero P, Hoetzenecker W, Neel V, Kilarski W, Swartz MA, Brisken C, Lefort K, and Dotto GP Combined CSL and p53 downregulation promotes cancer-associated fibroblast activation. **Nature Cell Biology** 17(9):1193 (2015)

This project, under the guidance of G. Paolo Dotto studied regulation of fibroblast senescence or activation within human cutaneous tumors. Focusing upon the Notch pathway effector CSLthe studies revealed its suppression of multiple senescence associated genes as well as cancer-associated-fibroblast genes. CSL appears to interact with p53, whose activity it represses. Within human premalignant skin lesions, CSL expression is downregulated, and p53 is lost upon conversion to frank malignancy (squamous cell carcinoma). Simultaneous loss of CSL and p53 overcomes senescence to produce both stromal and cancer cell population expansion.

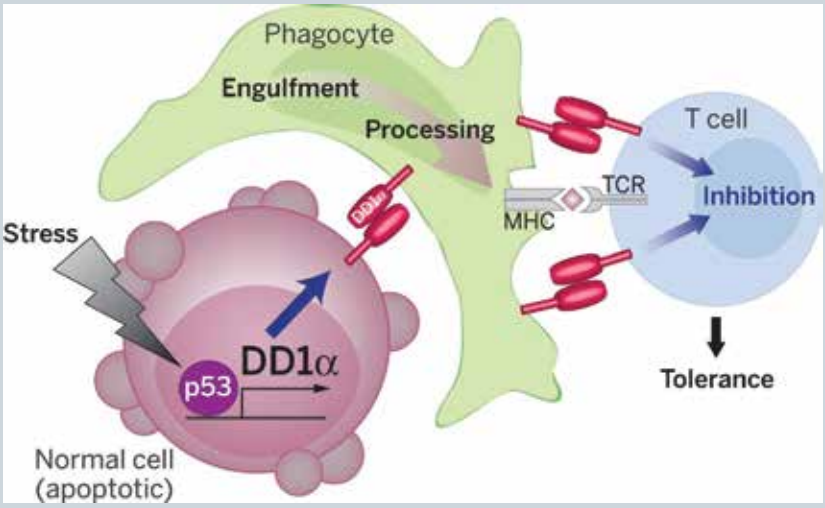


Figure 1 depicts the actions of DD1a, a transmembrane receptor which forms homotypic interactions between apoptotic cells and macrophages to facilitate clearance, and between T cells where it suppresses T cell activation in a manner related to immune checkpoint blockade. (from Yoon et al Science 2015 Jul 31;349(6247))

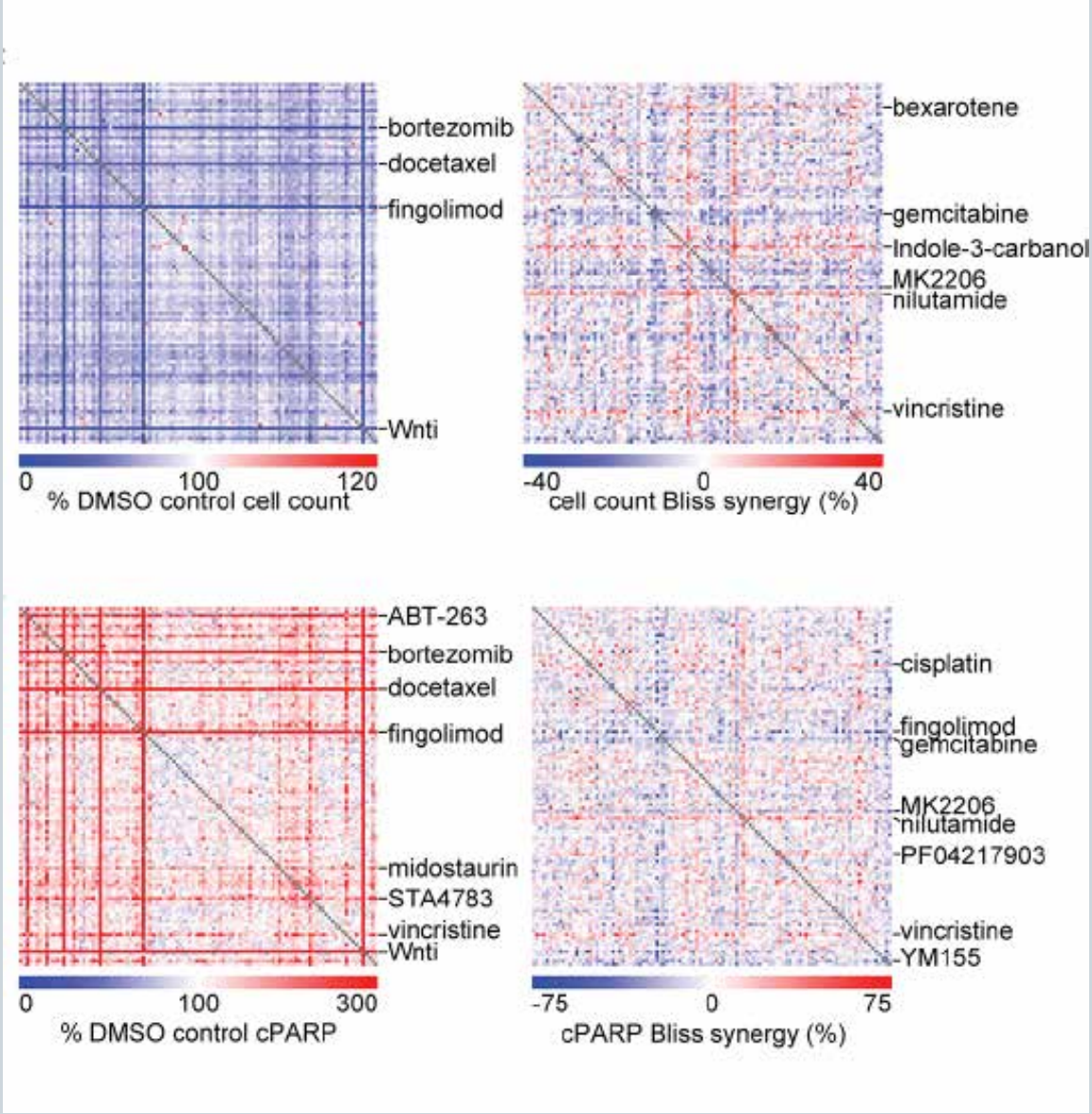


Figure 2 represents heatmaps from a large-scale combinatorial drug screen designed to identify 2-way targeted drug combinations that selectively kill melanoma cells. The automated, robotics based screen successfully identified both drugs and actionable molecular targets in a "phenotypic screening" strategy that may be implemented for personalized cancer therapy. (from Friedman *et al* PLOS One 2015 Oct 13;10(10))

David F. M. Brown, MD, Chief

Mission

The Emergency Medicine department's research mission is to perform innovative studies that improve the diagnosis and treatment of patients needing emergency care. This research spans the spectrum from basic science to individual patient care to population health.

Focus

Emergency physicians intervene in acute illness with the aim of preventing loss of life or limb. As specialists in health emergencies, our research focus is to develop and validate new diagnostic strategies and treatments across a broad range of injuries and illnesses and to investigate new emergency care delivery systems. Areas under 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, physiologic monitoring, and emergency care access, workforce, and policy.

Strategic priorities for the past year included:

A. Expanding our portfolio and broadening it to include basic/translational science, pediatrics, geriatrics, vascular emergencies, and trauma care and injury prevention.

B. Increasing our research support from federal funding sources.

C. Continuing to grow our research faculty, fellows, and clinical research coordinator team.

D. Increasing our research space (new office space at 125 Nashua Street and 326 Cambridge Street) and research storage capacity (e.g., -80C freezer).

1. **Burke TF, Ahn R, Nelson BD, Hines R, Kamara** J, **Oguttu M, Dulo L**, **Achieng E, Achieng B, Natarajan A,** Maua J, Kargbo S, **Altawil Z**, **Tester K**, **De Redon E**, Niang M, Abdalla K, **Eckardt M**. A postpartum hemorrhage package with condom uterine balloon tamponade: a prospective multi-center case series in Kenya, Sierra Leone, Senegal, and Nepal. BJOG. 2015 Jul 21. doi: 10.1111/1471-0528.13550

The Every Second Matters for Mothers and Babies Uterine Balloon Tamponade (ESM-UBT) device rapidly halts blood loss in women suffering from uncontrolled post-partum hemorrhage (PPH). The device comprises a condom tied to a Foley catheter, inflated by a maternal health worker with clean water through a syringe and one-way stopcock. Developed at MGH, the device is in the process of multinational implementation. This pilot project provided the first published evidence for ESM-UBT as a clinically promising and safe method to arrest uncontrolled PPH and save women's lives.

2. **Goldstein JN**, Refaai MA, Milling TJ Jr, Lewis B, Goldberg-Alberts R, Hug BA, Sarode R. Four-factor prothrombin complex concentrate versus plasma for rapid vitamin K antagonist reversal in patients needing urgent surgical or invasive interventions: a phase 3b, open-label, non-inferiority, randomised trial. Lancet. 2015 May 23;385 (9982):2077-87.

This multicenter randomized controlled trial compared plasma with prothrombin complex concentrates for emergency anticoagulation reversal. The results showed faster time to intervention and improved perioperative hemostasis. This trial led to FDA approval of Kcentra (4 factor PCC) which is now in widespread use across the United States, including MGH.

3. **Hasegawa K**, Jartti T, Mansbach JM, Laham FR, Jewell AM, **Espinola JA**, Piedra PA, **Camargo CA Jr**. Respiratory syncytial virus genomic load and disease severity among children hospitalized with bronchiolitis: Multicenter cohort studies in the US and Finland. *J Infect Dis* 2015; 211:1550-1559. PMID: 25425699

In this analysis of two multicenter cohort studies (in the US and Finland) of 1764 children hospitalized for bronchiolitis, we demonstrated an association with higher respiratory syncytial virus genomic load and higher disease severity (defined by longer hospital length-of-stay and intensive care use). This finding supports the concept that reductions of RSV (genomic) load may decrease disease severity in children with bronchiolitis.

4. **Lee J**, Kaafarani HM, Cropano C, Chang Y, Raybould T, Klein E, Gervasini A, Petrovick L, DePesa C, **Camargo CA Jr**, Velmahos GC, Masiakos P. The impact and sustainability of the graduated driver licensing program in preventing motor vehicle crashes in Massachusetts. J Trauma Acute Care Surg. 2015 Feb;78(2):265-70; PMID: 25757110

This paper examined and found that implementing a stricter Graduated Drivers Licensing (GDL) program in Massachusetts resulted in a decrease in motor vehicle crashes (MVCs) among teenage drivers. Overall, MVCs decreased in all age groups studied, but teenage drivers decreased at a much greater rate. The study is the first to evaluate the impact of the GDL program in Massachusetts.

One of our Division of Global Health fellows and our Kenya team, performing an emergency surgery despite no available anesthesiology services through invoking our award winning safe rescue anesthesia package (ESM-Ketamine).

(**Burke, T.**, Manglani, Y., **Altawil, Z.**, Dickson, A., Clark, R., Okelo, S., & **Ahn, R.** (2015). A Safe-Anesthesia Innovation for Emergency and Life-Improving Surgeries When no Anesthetist is Available: A Descriptive Review of 193 Consecutive Surgeries. World journal of surgery, 39(9), 2147-2152).

MGH clinicians are pictured in appropriate personal protective equipment (PPE) training with a special isolation unit (an isopod) designed for transport of a patient with Ebola who is producing large amounts of fluids.

(Herstein JJ, Biddinger PD, Kraft CS, Saiman L, Gibbs SG, Smith PW, Hewlett AL, Lowe JJ. Initial costs of Ebola treatment centers in the United States. Emerg Infect Dis.2016 Feb. http://dx.doi.org/10.3201/eid2202.151431; Savoia E. Agboola F, Bernard, D, Biddinger PD. Development of an Online Toolkit for Measuring Performance in Health Emergency Response Exercises. Prehosp and Disast Med. Prehosp Disaster Med. 2015;30(5):1-6).

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 2015 spread across the four following themes: genomic science, innate immunology and immune tolerance, therapeutic interventions, and population health.

The Department of Medicine has made multiple key achievements throughout 2015. Achievement in **genomic science** of cardiovascular disease included Anthony Rosenzweig, MD, and colleagues, who identified a potential mechanism of undesirable remodeling of the heart. They profiled microRNA expression in two models of exercise and found miR-222 was upregulated in both. They further determined that mice with inducible cardiomyocyte miR-222 were resistant to adverse cardiac remodeling and dysfunction. These studies reveal a potential strategy for protecting the heart against adverse remodeling. (1) Cardiology researchers have also contributed to a collaborative effort to discover genes that cause mitral valve prolapse. The team demonstrated that mutations in the gene DCHS1 cause mitral valve prolapse in a subset of individuals with this disease. The investigators identified DCHS1 mutations in affected individuals from a large multigenerational family and using zebrafish, mice, and cultured cells, demonstrated that the mutations cause developmental errors in valve morphogenesis. Understanding the role of DCHS1 in mitral valve development provides fundamental insights into the very common disease of mitral valve prolapse. (2) Andrew Chan, MD, MPH, led a study that provides proof-of-principle of the potential for using genomically-based "precision medicine" approaches to tailor cancer prevention. Until now, "precision medicine" in cancer has largely been focused on somatic profiling of tumors to guide therapeutic intervention for cancer patients. Although these are exciting advances, progress has been slower for "precision medicine" in the field of cancer prevention. Dr. Chan's work provides some of the earliest evidence that it may be possible to use germline profiling of healthy individuals to provide actionable information to guide chemoprevention. If validated in larger populations, these findings have the potential to transform the field of preventive medicine in cancer and other chronic diseases. (3) Significant accomplishments in genomic science for diabetes include completion of enrollment of the 1000th and final participant in the Study to Understand the Genetics of the Acute Response to Metformin and Glipizide in Humans (SUGAR-MGH) by Jose Florez, MD, PhD, and Geoffrey Walford, MD. This study will serve as a pharmacogenetic resource designed to evaluate genetic predictors of antidiabetic drug responses and use of pharmacological perturbations to interrogate gene function. (4) Joseph Avruch, MD, Vamsi Mootha, MD, Amit Majithia, MD, and David Altshuler, MD, published their findings on mice null for the type 2 diabetes-associated *Igf2bp2* (*Imp2*) gene (6). These mice

are resistant to diet-induced obesity and experience longer life spans, as well as increased insulin sensitivity. The proposed mechanism involves enhanced translation of Ucp1, a mitochondrial oxidative phosphorylation uncoupling protein abundant in brown fat. (5) Lee Kaplan, MD, PhD, and colleagues published new findings on the mechanisms involved—or not involved—in the effects of the most common form of bariatric surgery, which suggest that combining surgery with a specific type of medication could augment the benefits of the procedure. Investigators report that the effects of Roux-en-Y gastric bypass (RYGB) do not utilize neurologic pathways controlled by the serotonin 2C receptor. Since that receptor is a proven target for the FDA-approved anti-obesity drug lorcaserin, the findings imply that the two methods could have complementary effects, producing even more weight loss than achieved with either one alone. This is the first reported example of a rational, mechanism-based strategy for combining bariatric surgery with medication to treat obesity. The finding that not all potential weight-loss-activating pathways are engaged after surgery suggests that those unengaged pathways could be good targets for complementary therapies to improve surgical outcomes. (6) Cosmas Giallourakis, MD, and colleagues demonstrated a novel mechanism of action of DNA control elements called enhancers which regulate gene expression. (7) Given the importance of autophagy in a number of human diseases, Ramnik Xavier, MD, PhD and colleagues have identified small-molecule modulators of autophagy that affect disease-associated phenotypes in relevant cell types. BRD5631 and related compounds can serve as tools for studying how autophagy regulates immune pathways, and for evaluating the therapeutic potential of modulating autophagy in a variety of disease contexts. Deeper investigation into their mechanisms of action may reveal proteins and pathways that could serve as relevant targets for future therapeutic discovery. (8)

The department had a multitude of achievements in **innate immunity and immune intolerance** in 2015. A study by Robert Anthony, PhD, and colleagues revealed that immunoglobulin (IgE) antibodies that mediate allergic reactions have a key vulnerability to environmental antigens. The ability of IgE to trigger an allergic reaction through its interaction with mast cells is dependent on a single site of antibody glycosylation. IgE is tightly bound to mast cells through interaction with the high-affinity Fcε receptor (FcεRI) such that IgE antibodies are stably immobilized on the immune cells, sensitizing them to specific antigens for extended periods of time. The investigators showed that glycosylation of IgE is essential for both FcεRI binding and the triggering of mast cell degranulation and that IgE effector function is dependent on an oligomannose glycan at a single glycosylation site in IgE. The unusual presence of oligomannose glycans at this critical site offers an opportunity to specifically target this structure to shut down the allergic response. (9) To establish self tolerance, the immune system deletes T cell clones that recognize self antigens during their development in the thymus. However, due to the technical challenges of studying low frequency antigen-specific T cells in their natural environment, it is unclear how efficiently this process occurs for “tissue-restricted” self antigens that are not expressed in the thymus. James Moon, PhD, and colleagues used peptide:MHC tetramer-based cell enrichment methods to directly analyze CD4+ T cells with specificity to a model self antigen expressed in specific tissues of transgenic mice and showed that in contrast to the case of a ubiquitous self antigen, T cells with specificity for several tissue-restricted self antigens were not deleted at all. They further demonstrated that in some tissues (lung and intestine) , tolerance was maintained by the enhanced presence of antigen-specific Foxp3^{+} regulatory T cells (Treg) and that unlike deletional tolerance, Treg-mediated tolerance could be broken by repeated immunization with the self antigen. Collectively, these findings reveal that for some tissue-restricted self antigens, tolerance relies entirely on nondeletional mechanisms that are less durable than T cell deletion. These findings may explain why autoimmunity is often tissue-specific and offer a rationale for cancer vaccine strategies targeting tissue-restricted tumor antigens. (10) A study led by Terry K. Means, PhD, has uncovered a role for the protein TREML4 in activating an inflammatory pathway linked to the development of the autoimmune disease systemic lupus erythematosus (SLE). The research suggests that TREML4 could be a promising drug target for SLE. They identified TREML4 as a protein that may modulate the activity of the TLR7 pathway, which contributes to the development and

exacerbation of SLE. They found that mice that lack TREML4 produced lower levels of inflammatory molecules in response to TLR7 activation compared to normal mice, Land that upus-prone mice that lack TREML4 produced markedly lower levels of inflammatory molecules than their TREML4-producing littermates. In addition, they were partially protected from lupus-associated kidney failure, and survived significantly longer. The identification of TREML4's role in lupus represents a significant step forward in drug treatment for lupus, because it could lead to the development of new medicines that are more specific and less toxic to patients (11) Genital inflammation has long been attributed to increasing HIV acquisition risk, but the culprits of this inflammation were thought to be traditional sexually transmitted infections like chlamydia, gonorrhea, and herpes simplex virus. Doug Kwon, MD, PhD, and colleagues reported the surprising discovery that genital inflammation is most highly associated with the commensal bacteria that normally live within the female genital tract, rather than the handful of pathogens that the field has focused on in the past. They identified the bacterial properties that elicit an inflammatory response from genital epithelial cells and antigen presenting cells. This paper has unveiled a new interventional target for the prevention of HIV acquisition in women at highest risk, while providing new insights into the role of the microbiome in health and disease. (12) Jayaraj Rajagopal, MD, and colleagues demonstrated the existence of a 'stem cell niche' in the lung. In the airway epithelium, basal cells function as stem/progenitor cells that can both self-renew and produce differentiated secretory cells and ciliated cells. The investigators describe a mode of cell regulation in which adult mammalian stem/progenitor cells relay a forward signal to their own progeny. Surprisingly, this forward signal is shown to be necessary for daughter cell maintenance. Without these forward signals, the secretory progenitor cell pool fails to be maintained and secretory cells execute a terminal differentiation program and convert into ciliated cells. (13) Innate immune responses to allergens by airway epithelial cells (AECs) help initiate and propagate the adaptive immune response associated with allergic airway inflammation in asthma. A team led by Benjamin Medoff, MD, PhD, demonstrated that the protein CARMA3 is essential for activation of the transcription factor NF-βB in AECs by allergens or secondary mediators via G protein-coupled receptors (GPCRs). They then show that genetically modified mice with CARMA3-deficient AECs have reduced airway eosinophilia and proinflammatory cytokine production. Additionally, the investigators demonstrated that these mice have impaired dendritic cell maturation in the lung and that these dendritic cells have impaired Ag processing. These findings show that AEC CARMA3 helps mediate allergic airway inflammation and that CARMA3 is a critical signaling molecule that bridges the innate and adaptive immune responses in the lung. (14) The Golgi complex has a central role in the intracellular sorting of secretory proteins. Anterograde transport through the Golgi has been explained by the movement of Golgi cisternae, known as cisternal maturation. Roy Soberman, MD, and colleagues showed that the coat protein I (COPI) complex sorts anterograde cargoes into the tubules that connect the Golgi cisternae in human cells. In explaining how anterograde Golgi transport is achieved, these findings reveal that COPI tubular transport complements cisternal maturation and that bidirectional COPI transport is modulated by environmental cues through the small GTPase CDC42. (15) Kate Jeffrey received a 2015 Innovator Award from the Kenneth Rainin Foundation for her research on the interaction of the inflammatory bowel disease (IBD) virome with the innate immune sensors RIG-I and MDA-5. The Rainin Foundation supports research projects that are potentially transformative to diagnosing, treating and curing IBD. Awardees are selected for their ground-breaking, pioneering research and projects that demonstrate the potential to yield transformative discoveries and create major new insights about IBD. (16) Ramnik Xavier, MD, PhD and colleagues have used a rare CARD9 variant, a central component of anti-fungal innate immune signaling via C-type lectin receptors, which confers protection against inflammatory bowel disease as an entry point to investigating CARD9 regulation. Xavier's team showed that the protective variant of CARD9, which is C-terminally truncated, acted in a dominant-negative manner for CARD9-mediated cytokine production, indicating an important role for the C terminus in CARD9 signaling. They identified TRIM62 as a CARD9 binding partner and showed that TRIM62 facilitated K27-linked

poly-ubiquitination of CARD9. They've identified K125 as the ubiquitinated residue on CARD9 and demonstrated that this ubiquitination was essential for CARD9 activity. Xavier's team has also showed that similar to *Card9*-deficient mice, *Trim62*-deficient mice had increased susceptibility to fungal infection. (17)

Additional accomplishments were made in the area of **therapeutic interventions**. In their osteoporosis therapeutic trial, Benjamin Leder, MD and colleagues addressed the issue of how best to use sequential therapy for severe osteoporosis. The long-term use of many of the most effective osteoporosis therapies is discouraged due to efficacy and safety concerns. Thus, most patients at high risk of fracture are treated sequentially with two or more drugs. This is especially relevant to the use of the most potent osteoporosis therapies; the anabolic agent teriparatide and the antiresorptive agent denosumab. With both of these drugs, discontinuation results in rapid decline in bone density. The effects of transitioning from one medication to the other were unknown and were addressed in this study of postmenopausal osteoporotic women. The results showed that while switching from either teriparatide or combination therapy to denosumab resulted in additional increases in bone density at all anatomic sites (hip, spine, and radius), switching from denosumab to teriparatide resulted in rapid and significant bone loss and very high rates of bone resorption. Notably, at the end of all four years of treatment , women treated with denosumab followed by teriparatide have significantly lower bone mineral density than those treated with either of the other two sequences. This study demonstrated that the order in which denosumab and teriparatide are used has a significant impact on overall treatment efficacy in postmenopausal osteoporosis. These results should significantly impact the approach to the initial and sequential treatment of osteoporotic women, particularly those at very high risk of fragility fracture. (18) Steven Russell, MD, PhD, and Edward Damiano, PhD, continued their studies on the "bionic pancreas", a closed-loop dual hormone device that allows patients with insulin-dependent diabetes to manage their glucose levels with fewer incidents of hypoglycemia and no active intervention on their part. (19) By investigating how HIV attacks the body and how the body defends itself, Bruce Walker, MD, and his team identified molecular targets that have the potential to be exploited for a rationally designed HIV vaccine. By identifying and studying individuals prior to seroconversion, they determined the earliest immune responses to HIV infection. The study cohort of young women based in the Umlazi Township in KwaZulu-Natal, South Africa, is very unique because HIV-prevalence rates rise from less than 1% at age 15 to 66% at age 23. The project (termed FRESH, for Females Rising through Education, Support and Health) has two interlinked objectives: (1) provision of an intensive empowerment, life-skills and job readiness curriculum, coupled with HIV prevention education, and (2) screening of participants twice weekly by finger-prick plasma HIV RNA for evidence of acute HIV infection. The results show that the onset of plasma viremia is associated with a massive HIV-specific CD8 T cell response, the magnitude and rapidity of which are associated with set point viral control. The results also show that this period of acute infection leads to rapid immune dysregulation and failure to develop long term memory, providing key insights for understanding lack of control of chronic viremia. (20) The shortage of organs for transplantation is a major barrier to the treatment of organ failure. Jay Fishman, MD, and colleagues have been working to enhance the safety of porcine-to-human xenotransplantation. Multiple strains of miniature swine that carry immunological advantages for transplantation into baboons and humans have been developed. Limiting the safety of porcine-to-human xenotransplantation are a family of porcine endogenous retroviruses (PERVs), described by Dr. Fishman's group in 1998. PERVs have infectivity for human cells in vitro, raising concerns regarding transmission of PERVs to immunosuppressed human recipients of porcine organs. This paper demonstrates that the genomic eradication of all PERVs in a porcine kidney epithelial cell line using CRISPR-Cas9 technology resulted in the complete loss of infectivity of PK-15 cells for human targets over up to 60 days in culture. This study shows that PERVs can be inactivated for use in the derivation of pig strains for clinical application to porcine-to-human xenotransplantation. (21) Relatively high plasma levels of soluble urokinase-type plasminogen activator receptor (suPAR) have

been associated with focal segmental glomerulosclerosis and poor clinical outcomes in patients with various conditions. Whether elevated suPAR levels in patients with normal kidney function are associated with future decline in the estimated glomerular filtration rate (eGFR) and with incident chronic kidney disease was unknown. Work of Sanja Sever, PhD, and colleagues showed that a higher suPAR level at baseline was associated with a greater decline in the eGFR during follow-up. Participants with a normal eGFR at baseline had the largest suPAR-related decline in the eGFR. The risk of progression to chronic kidney disease in the highest quartile of suPAR levels was 3.13 times as high as that in the lowest quartile. In the groups studied, an elevated level of suPAR was independently associated with incident chronic kidney disease and an accelerated decline in the eGFR. (22) Sylvie Breton, PhD, and colleagues showed that, in addition to being stem/progenitor cells, basal cells, which are located in pseudostratified epithelia, are sensors of luminal stimuli and transmitters that modulate epithelial function via cell-cell crosstalk. The investigators demonstrated that basal cells have narrow body projections—which they term axiopodia—that periodically extend and retract over time. They found that the sSrc and MEK1/2-ERK1/2 pathways control the periodic axial motility of axiopodia, and therapeutic inhibition of tyrosine kinase activity induces axiopodia retraction. These previously unknown effects may explain observed toxicities of some tyrosine kinase inhibitors and might provide novel therapeutic opportunities. (23) Dennis Brown, PhD, and colleagues used a proteomics approach to identify, map and create the first "interactome" of cellular proteins that associate with and regulate a major cellular proton pump, the H^+ATPase. The definition of this interactome will advance the understanding of how the pump regulates a variety of acid-secreting processes that are crucial for cell, organ and whole body function. The protein is involved in many cellular, organ and body functions, and defects in its activity or structural mutations lead to a range of human disorders that include renal tubular acidosis, bone disorders, deafness, dysosmia and infertility. (24)

Throughout 2015, the Department of Medicine has shown immense progress in **population health** research. Seth Berkowitz, MD, and colleagues evaluated the impact of a population health management program for cancer screening on decreasing disparities in care within a large primary care network. There have been concerns that population health interventions optimizing care for the overall population might increase disparities in care for vulnerable subgroups. The study showed that a multifaceted population management intervention sensitive to the needs of vulnerable patients modestly narrowed disparities in colorectal cancer screening, while also increasing overall screening rates. These results suggest that embedding interventions for vulnerable patients within larger population management systems represents an effective approach to increasing overall quality of care while also decreasing disparities. (25)Travis Baggett, MD, MPH, and colleagues examined causes of death in 28,033 adults seen at Boston Health Care for the Homeless Program in 2003–2008 and used epidemiologic methods to determine the proportion of deaths attributable to tobacco, alcohol, and drug use. After accounting for overlap, an estimated 52% of all deaths in the study cohort were attributable to the use of any of these substances. In comparison with Massachusetts adults, tobacco-attributable mortality rates were 3 to 5 times higher, alcohol-attributable mortality rates were 6 to 10 times higher, and drug-attributable mortality rates were 8 to 17 times higher. These findings demonstrate the substantial health impact of substance use disorders among homeless individuals and suggest the need for comprehensive addiction treatment services targeting this vulnerable population. (26) David Nathan, MD, continued to direct the observational follow-up of the Diabetes Control and Complications Trial-Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC). The investigations showed that intensive glycemic control influenced the likelihood of ocular surgery (27), complementing what was confirmed regarding retinal complications in this cohort (28). The DCCT-EDIC investigators also showed that intensive glucose control has an effect on overall mortality (29). Work led by Linda Delahanty, MS, Deborah Wexler, MD, and David Nathan, MD, in the Diabetes Unit showed that a lifestyle intervention administered in a group setting was effective in helping participants achieve weight loss and medication reduction. (30)

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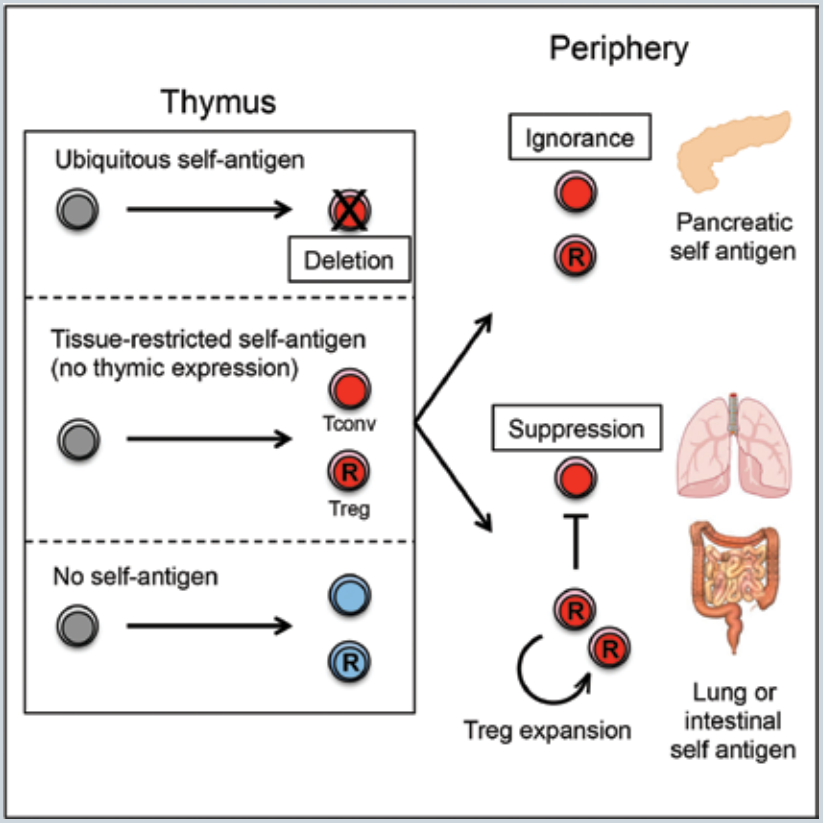

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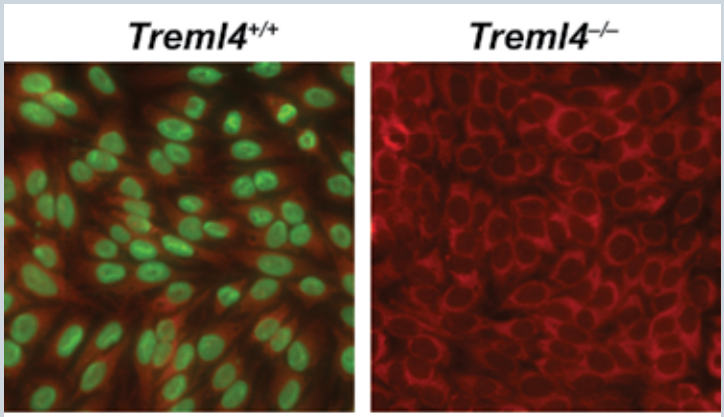
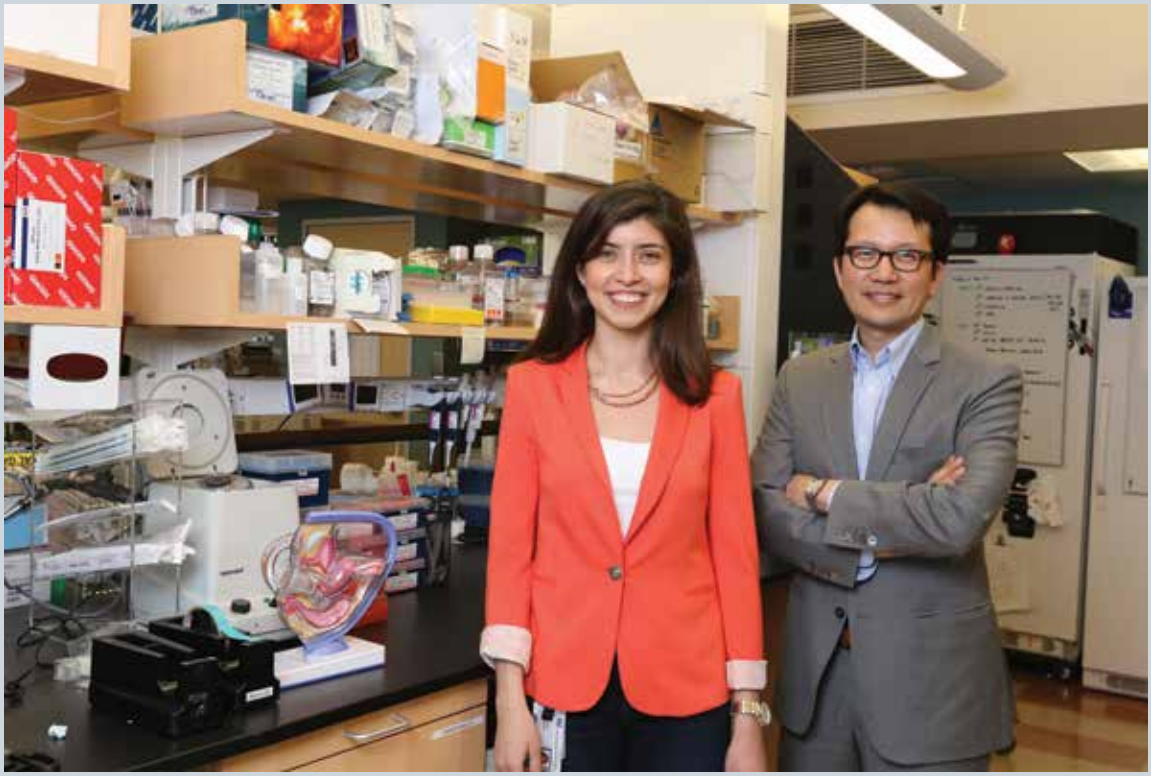


Ameliorated autoimmunity in lupus-prone MRL/lpr mice lacking TREML4. Anti-nuclear antibody immunofluorescence (green) staining pattern of HEp-2 cells with serum from 16-week old *Treml4*$^{+/+}$ or *Treml4*$^{-/-}$ MRL/lpr mice.

Reference #11—TREML4 Receptor Regulates Inflammation and Offers a Novel Drug Target for Lupus. Ramirez-Ortiz ZG, Prasad A, Griffith JW, Pendergraft WF III, Cowley GS, Root DE, Tai M, Luster AD, El Khoury J, Hacohen N, Means TK. Nature Immunology 16: 495-504 (2015).



Reference # 12 - Anahtar MN, Byrne EH, Doherty KE, Bowman BA, Yamamoto H, Soumillon M, Padavattan N, Ismail N, Moodley A, Sabatini M, Ghebremichael MS, Nusbaum C, Huttenhower C, Virgin HS, Ndung'u T, Dong KL, Walker BD, Fichorova RN, and Kwon DS. Cervicovaginal microbiota modulate host inflammatory responses in the female genital tract. Immunity, 2015 May 19; 42, 965–976.Therapeutic interventions

Molecular Biology

Department Report

Robert E. Kingston, PhD, Chief

The Department of Molecular Biology at Massachusetts General Hospital is a part of both the research community of the hospital and the Division of Medical Sciences of the Harvard Graduate School of Arts and Sciences. Members of the Department carry out basic genetic and molecular biological research on a variety of topics at the cutting edge of the discipline. At present, approximately 170 people, including 14 faculty and over 120 postdoctoral fellows and graduate students comprise the Department of Molecular Biology. The Department is a major component of the Department of Genetics at Harvard Medical School. All Molecular Biology faculty, postdoctoral fellows and graduate students have concurrent appointments at Harvard, mostly in HMS Genetics. Our current 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).
- 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).
- 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).

Broadly, our mission and priority is to advance the frontiers of basic and translational biological science. To that end, we are grateful to be embedded within a nexus of medical science in Boston.

We wish to bid Fred Ausubel farewell as he prepares to wind down a 40-plus-year career in science. Fred has made extraordinary progress in the fields of host-microbe interaction and innate immune signaling. He trained a number of notable scientists, including our very own Gary Ruvkun. He has received numerous awards in recognition of his contributions to science, including election to the National Academy of Sciences in 1994 and culminating in the Thomas Hunt Morgan Medal in 2014. Fred will reduce his research activity over the next few years, all the while maintaining a presence in the Department of Molecular Biology, his scientific home since 1982.

Congratulations to Jeannie Lee, who was elected to the National Academy of Sciences in 2015. Jeannie 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 Jeannie, including the Pew Scholar Award, the Basil O'Connor Starter Scholar Research Award, and the Molecular Biology Award of the National Academy of Sciences.

Over the course of the past year, our faculty have published several highly regarded publications in a number of important fields. For example, Konrad Hochedlinger's lab published a description of the role played by histone chaperone CAF-1 in determination of somatic cell fate (*Nature.* 2015 Dec 10;528(7581):218-24); Gary Ruvkun's lab used an RNAi screen in *C. elegans* to identify genes that are required for induction of the xenobiotic response to inhibition of germline translation by drugs or mutations (*Nat Cell Biol.* 2015 Oct;17(10):1294-303); Jeannie Lee's lab has furthered our understanding

of how Xist, a long noncoding RNA, induces silencing of the X-chromosome by effecting compositional and conformational changes in the chromosome (*Science.* 2015 Jul 17;349(6245)); and Jack Szostak's lab developed a 2-dimensional chromatographic method for direct sequencing of noncanonical small RNAs (*J Am Chem Soc.* 2015 Nov 18;137(45)).

Fred Ausubel winding down a 40-plus year career at MGH Molecular Biology.

Cliff Tabin, Harry Orf, Jeannie Lee and Bob Kingston, celebrating Jeannie's election to the National Academy of Sciences.

Neurology

Department Report

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 (with more than 8 strategic research recruits in the past two year and more on the horizon). 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 8% over the prior year, bringing in $84.5M in total research revenue.

Departmental Strategic Research Priorities

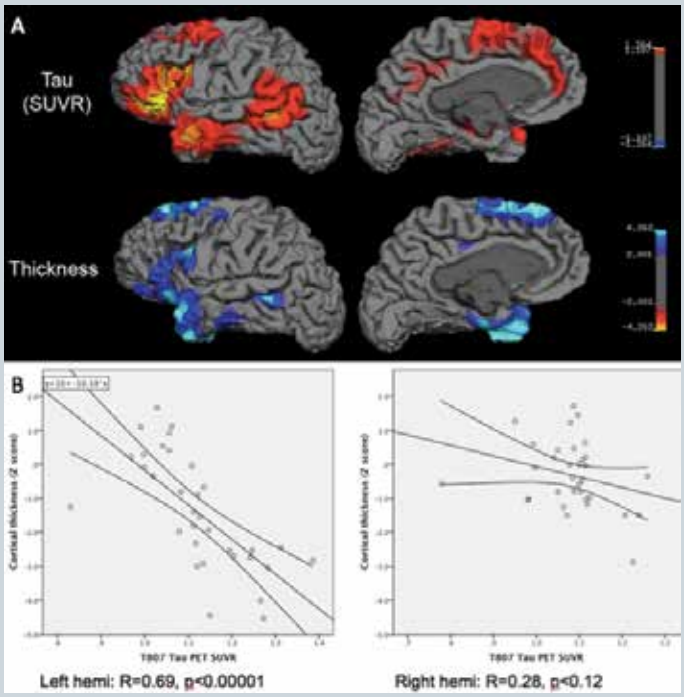
1. Unite department around a common vision: leadership in therapeutic research to better understand/treat diseases
2. Build cohesive community and partnerships, within and beyond department, that fosters collaboration and innovation
3. Target investment in a few key areas where we are best positioned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

Better Diagnostics

Tau PET Imaging

In research led by Dr. Brad Dickerson, MD, Director of the MGH FTD Unit (www.ftd-boston.org), efforts are underway to develop and validate tau PET tracers to image this form of neurodegenerative pathology in living patients. For example, Primary Progressive Aphasia (PPA) is a progressive syndrome caused by one of several neurodegenerative pathologies primarily in the frontal and anterior temporal lobes, including tau or TDP-43 forms of Frontotemporal Lobar Degeneration (FTLD) or Alzheimer's disease (AD). An important strategy for treatment development in PPA is to target one of the types of molecular pathology. Despite the fact that candidate compounds for treating tau pathology have begun to be identified in preclinical studies, a critical obstacle has hindered movement into clinical phases of development: biomarkers are not yet established that would enable patients to be selected for a clinical trial of a compound targeted against the subtypes of PPA that are due to tauopathies. We have begun to close this gap, in collaboration with investigators in the MGH Department of Radiology, by testing the utility of new PET ligands (e.g., [F18]-T807 for *in vivo* imaging of tau pathology. In one of our scans of a PPA case, the spatial topography of [F18]-T807 retention show prominent frontal, insular, and anterior temporal signal, sparing posterior regions. We mapped T807 signal onto this PPA patient's own cortical surface and compared it to the patient's regional cortical atrophy compared with an age-matched control group: atrophy strongly co-localizes with T807 signal (Figure, A), with T807 signal showing a larger penumbra around the zones of atrophy. Quantitative analysis of all FreeSurfer cortical regions of interest (ROI) from each hemisphere shows

that the magnitude of T807 signal within each ROI strongly correlates with the magnitude of atrophy relative to controls in the left hemisphere (R = 0.69, p<0.00001; Figure, B) but the relatively low T807 signal in the homologous right hemisphere ROIs does not relate to cortical thickness, where there is little atrophy (R = 0.28, p=0.12).



T807 signal co-localizes and correlates with atrophy.

mRNA Sequencing of Tumor-Educated Blood Platelets

The Tannous laboratory focuses on the development of novel cancer therapeutics and blood-based diagnostics with a primary focus on brain tumors. This year, Dr. Bahkos Tannous and colleagues show that mRNA sequencing of tumor-educated blood platelets distinguishes cancer patients from healthy individuals with 96% accuracy, differentiates between six primary tumor types of patients with 71% accuracy, and identifies several genetic alterations driving the tumors. The study was Highlighted by MGH press release, Cancer Cell, Nat Rev Genet, Genet Engin News, Med Res News, Science Daily, I F. Love Science and many others and was featured on CBC/Radio Canada.

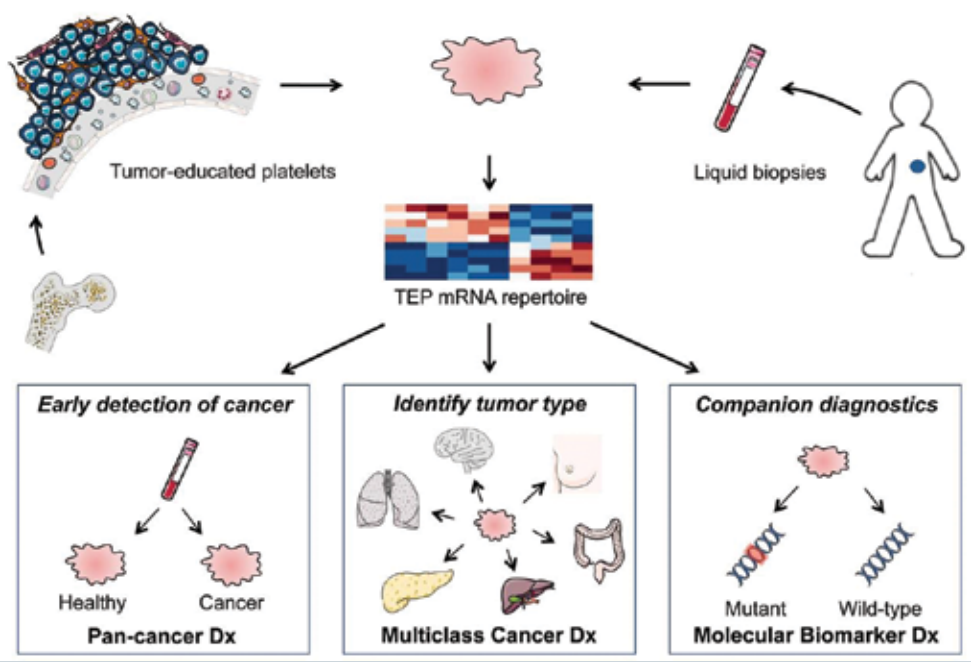
Highlights

- Tumors ''educate'' platelets (TEPs) by altering the platelet RNA profile
- TEPs provide a RNA biosource for pan-cancer, multiclass, and companion diagnostics
- TEP-based liquid biopsies may guide clinical diagnostics and therapy selection
- A total of 100–500 pg of total platelet RNA is sufficient for TEP-based diagnostics

Best M, Sol N, Tannous J, Westerman B, Rustenburg F, Schellen P, Verschueren H, Post E, Koster J, Ylstra Bm Ameziane N, Dorsman J, Smit EF, Verheul HM, Noske DP, Reijneveld JC, Nilsson JA, Wesseling P*, Wurdinger T*, **Tannous BA***. RNA-seq of tumor-edicated platelets enables blood-based pan-cancer, multiclass and molecular pathway cancer diagnostics. Cancer Cell. 2015.28:666-676. *Co-senior authors.

Imaging Neuroinflammation in People with ALS

Led by Dr. Nazem Atassi, investigators at the Neurological Clinical Research Institute (NCRI) are building new brain imaging platforms to measure and track neurodegenerative processes in Humans. Over the past year, the NCRI team was able to use PBR28 positron emission tomography (PET) and showed increased inflammation in the brain in people with ALS. The anatomical location of inflammation corresponds to the clinical phenotype and the degree of inflammation correlates with functional disability. The team is expanding this imaging platform by acquire longitudinal scans and include people with primary lateral sclerosis (PLS), ALS-FTD, and asymptomatic ALS gene carriers. This work was published in NeuroImage Clinical Journal 2015 and laid the groundwork for conducting a large multi-center PET imaging study in collaboration with General Electric (TRACK ALS) and two



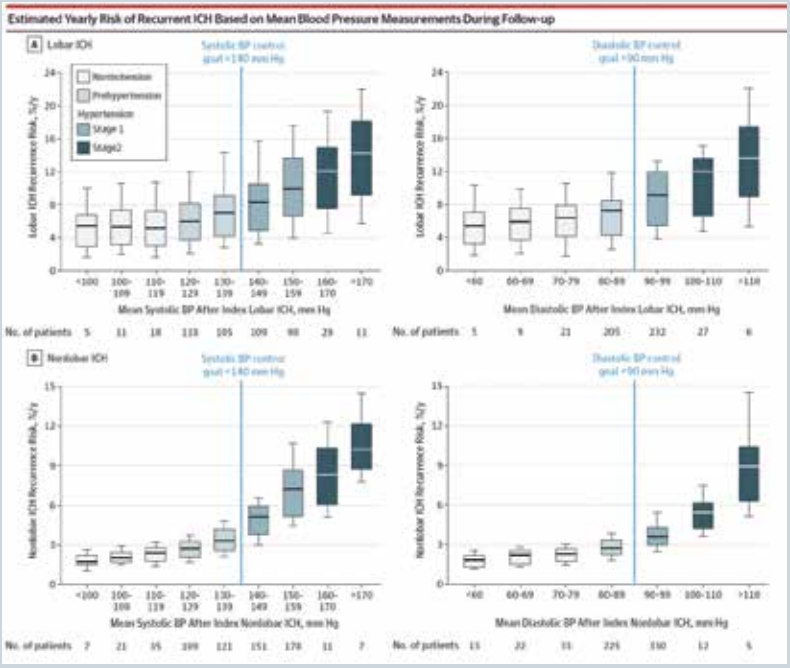
ALS clinical trials that use this imaging platform as readout for drug response.

Zürcher N, Loggia M, Lawson R, Chonde D, Izquierdo-Garcia D, Yasek JE, Akeju O, Catana C, Rosen B, Cudkowicz M, Hooker JM**, Atassi N*. Increased *in vivo* glial activation in patients with amyotrophic lateral sclerosis: Assessed with [11C]-PBR28. NeuroImage: Clinical. 2015. 7:409–414.

Developing Treatments for Neurological Disorders

Blood Pressure and Risk for Recurrence of Intracerebral Hemorrhage.

Dr. Alessandro Biffi, MD working in Jonathan Rosand's lab published findings from the largest longitudinal study of Intracerebral Hemorrhage (ICH) to date (including over 1,100 subjects enrolled at MGH). ICH is the most severe form of acute stroke, and survivors are at very high-risk for rebleeding. While Blood Pressure (BP) control represents the cornerstone of secondary ICH prevention, current guidelines are based on limited and often contradictory data. This study answered a number of clinically relevant questions regarding the relationship between BP and ICH recurrence. First, both lobar and deep ICH recurrence risks were found to associate with elevated BP. Prior findings emphasized the importance of hypertension primarily in deep ICH (often referred to as "hypertensive" ICH). Second, this study has provided evidence that even moderately elevated BP (previously referred to as "pre-hypertension") is associated with increased risk of ICH recurrence. Previous studies failed to identify these associations (likely because of their smaller sample sizes), thus leading to ICH prevention guideline advocating treatment only for frankly hypertensive BP measurements. Finally (and perhaps most importantly), Dr. Biffi and colleagues highlighted the large gap between expected and achieved performance in BP control among ICH patients. Findings from this article were selected for presentation at the opening plenary session of the 2016 Annual American Academy of Neurology Meeting. Following publication of these findings and partly informed by them, the American Stroke Association 2015 ICH Guidelines revised BP control goals, recommending treatment to lower acceptable thresholds. Dr. Biffi and colleagues are now conducting additional studies to: 1) explore the effect of BP on other ICH-related conditions, such as vascular cognitive impairment and vascular depression; 2) develop high-precision tools for individualized assessment of individuals' risk for ICH recurrence; 3) explore the complex interplays between genomics and hypertension in ICH biology.



Association Between Blood Pressure Control and Risk of Recurrent Intracerebral Hemorrhage. Biffi A, Anderson CD, Battey TW, Ayres AM, Greenberg SM, Viswanathan A, Rosand J. JAMA. 2015 Sep 1;314(9):904-12.

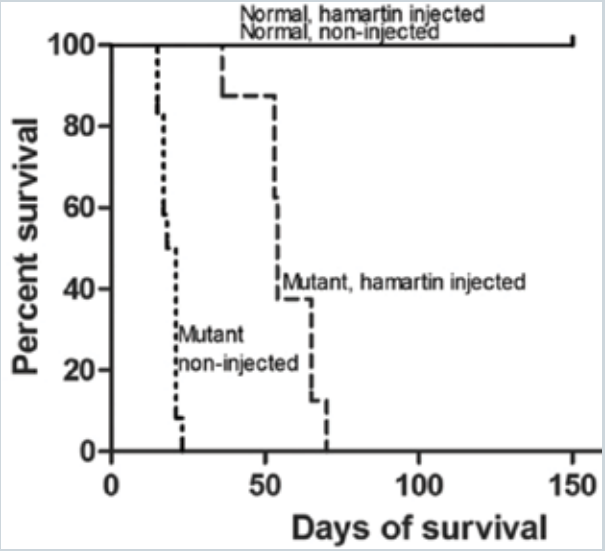
Tau in Alzheimer's Disease

The Hyman lab focuses on research in neural system failure underlying cognitive loss in Alzheimer's disease. In a recent paper Dr. Hyman and colleagues describe a rare oligomeric form of tau that appears to be responsible for spreading of tau aggregates across the brain in Alzheimer disease and in experimental models, accounting for "propagation". In subsequent work we have been able to detect this in ventricular and lumbar CSF of Alzheimer patients. This may provide a target for therapeutic intervention to prevent progression of disease.

Takeda S, Wegmann S, Cho H, DeVos SL, Commins C, Roe AD, Nicholls SB, Carlson GA, Pitstick R, Nobuhara CK, Costantino I, Frosch MP, Müller DJ, Irimia D, Hyman BT. Neuronal uptake and propagation of a rare phosphorylated high-molecular-weight tau derived from Alzheimer's disease brain. Nat Commun. 2015 Oct 13;6:8490.

Gene Therapy for Tuberous Sclerosis—Preclinical Efficacy

Dr. Breakefield's laboratory has focused for many years on developing gene therapy strategies for inherited neurologic diseases. Her team is the first to develop a gene replacement protocol for tuberous sclerosis (TSC type 1). This hereditary disease, caused by loss of hamartin which controls the mTOR pathway, affects multiple organs in the body. Brain involvement underlies epilepsy, developmental delays, autism and sleep disorders. Current treatment uses rapamycin analogs to prevent cell overgrowth, but this can have some toxicity and cause developmental problems. Dr. Breakefield's team used a mouse model in which the hamartin gene is knocked out in all neurons in the brain, starting early in embryonic development, leading to abnormal brain morphology, epilepsy and hydrocephalus. By injecting an adeno-associated virus (AAV) vector encoding the missing gene into the brain ventricles at birth, they were able to markedly extend survival, improve motor behavior, and normalize neuron size in the brains of these mice. This strategy for gene therapy has the advantages that therapy can be achieved from a single application, as compared to repeated treatment with drugs, and that AAV vectors have been found to have minimal-to-no toxicity in clinical trials for other neurologic conditions. Although there are many additional issues to be addressed, these preclinical studies strongly support gene therapy as a beneficial approach in TSC patients, with the potential for systemic delivery to decrease the size of benign tumors throughout the body.



Gene therapy for mice which lack hamartin in neurons in the brain. Tsc1SynCrecw++ mice were crossed with Tsc1cc– mice to obtain offspring which were either null (mutants, Tsc1SynCrecc+) or heterozygous for wild-type (normals, Tsc1SynCrecw+) hamartin in neurons in the brain. At P0, littermates were injected ICV in both ventricles (2 × 1010 g.c. in 2 µl into each ventricle) with an AAV vector encoding hamartin, or were left non-injected. Mice were monitored for survival, shown as Kaplan–Meier curves for non-injected normal mice (N=11), hamartin vector-injected normals (N=11), non-injected mutants (N=12) and hamartin vector-injected mutants (N=10). There was a highly significant difference between non-injected and vector injected mutants, p<0.0001

Survival benefit and phenotypic improvement by hamartin gene therapy in a tuberous sclerosis mouse brain model. Prabhakar S, Zhang X, Goto J, Han S, Lai C, Bronson R, Sena-Esteves M, Ramesh V, Stemmer-Rachamimov A, Kwiatkowski DJ, Breakefield XO. Neurobiol Dis. 2015. 82:22-31.

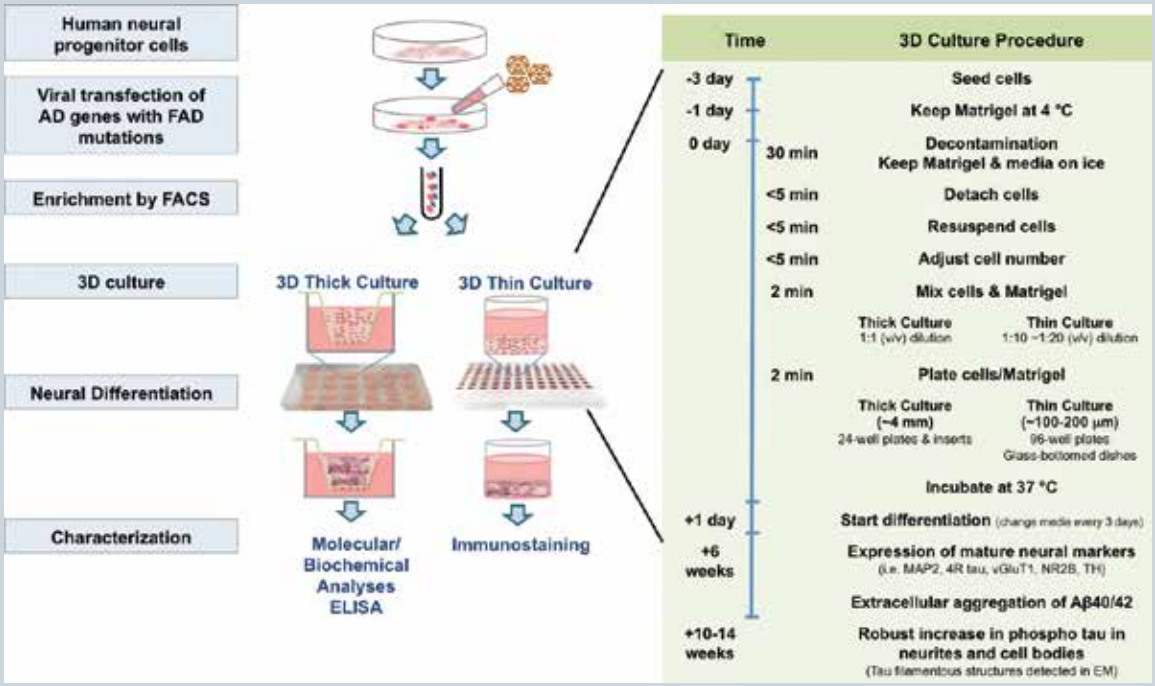
A 3D Human Neural Cell Culture System for Alzheimer's Disease Drug Discovery

Previously, Doo Yeon Kim, PhD (in collaboration with Tanzi lab in Neurology's Genetics and Aging Research Unit) published a paper that described a novel 3D human neural cell culture model of Alzheimer's disease (AD), which recapitulates both amyloid-β plaques and neurofibrillary tangles "in a dish" for the first time (Choi *et al.*, Nature, 515, 274–278, 2014). This year, Kim's lab published a follow-up article that comprehensively explained technical backgrounds and a step-by-step protocol for generating 3D human neural culture system in 24-well and 96-well formats (Kim *et al.*, Nature protocols, 2015). This unique human neural cell culture system of AD can be easily adapted for large-scale high-throughput screening of novel therapeutic targets in human brain-like environment, which has not been feasible in current AD mouse models. This study has been listed as one of the "10 Breakthrough Technologies 2015" by "MIT Technology Review," and chosen for 2015 Smithsonian American Ingenuity Award (Drs. Kim and Tanzi). Using this 3D culture model of AD, Kim and Tanzi labs started testing ~1200 FDA-approved drug library to find drug candidates that can reduce both amyloid-β plaques and neurofibrillary tangles.

A 3D human neural cell culture system for modeling Alzheimer's disease. Young Hye Kim, Se Hoon Choi, Carla D'Avanzo, Matthias Hebisch, Christopher Sliwinski, Enjana Bylykbashi, Kevin J Washicosky, Justin B Klee, Oliver Brüstle, Rudolph E Tanzi, and Doo Yeon Kim. Nature Protocol, 2015 vol. 10 (7) pp. 985-1006.

The Rare Disease Initiative and Center for Rare Neurological Diseases (CRND)

Collaborations between clinicians and basic scientists have been at the heart of the MGH mission and successfully implemented through programs such as the Center of Human Genetics Research (CHGR) and the Neurological Clinical Research Institute (NCRI). However, there has been a gap in translating insights in gene discovery and disease mechanisms into actionable treatment and interventions for rare diseases. This gap represented a perfect opportunity for a cross-departmental, cross-disciplinary effort endorsed by Drs. Merit Cudkowicz (Neurology department) and Maurizio Fava (MGH Division of Clinical Research (DCR). A Think Tank on Rare Diseases was created in the DCR that brings together leaders within the Harvard community and local biotechnology community. The Think Tank provides strategic guidance in understanding opportunities and challenges in the



Overview of the 3D human neural cell culture protocol. The experimental procedure begins with the generation of human neural progenitor cell lines virally transfected with APP and/or PSEN1 FAD mutations and enriched based on GFP and/or mCherry signals by FACS. The right-hand column shows in detail the timing for each step of the 3D culture method. Day 0 indicates the day on which cells are mixed with Matrigel. MAP2, microtubule-associated protein 2; NR2B, N-methyl d-aspartate receptor subtype 2B; TH, tyrosine hydroxylase; vGluT1, vesicular glutamate transporter 1; 4R tau, 4-repeat tau isoform.

rare disease field. In parallel, a Center for Rare Neurological Diseases (CRND) was created and began having meetings of clinicians and scientists in an effort to identify the needs of rare disease research in the Neurology department. The overall goal of the CRND is to eradicate rare disorders by leveraging the power of biological insights towards design and implementation of clinical trials. First steps entail identifying basic science insights with potential clinical benefit that lack a translational path to trial development (e.g. preclinical gene therapy research), facilitating partnerships with patient advocacy organizations (e.g. lysosomal and mitochondrial disease advocacy groups) and mentoring young clinical or basic science investigators by providing access to resources that aid career development. The CRND is working with Partners Innovation to create new fellowships sponsored by industry and venture capital. Lastly platforms, such NeuroBANK, are harmonizing and standardizing efforts around data collection and trial design and implementation.

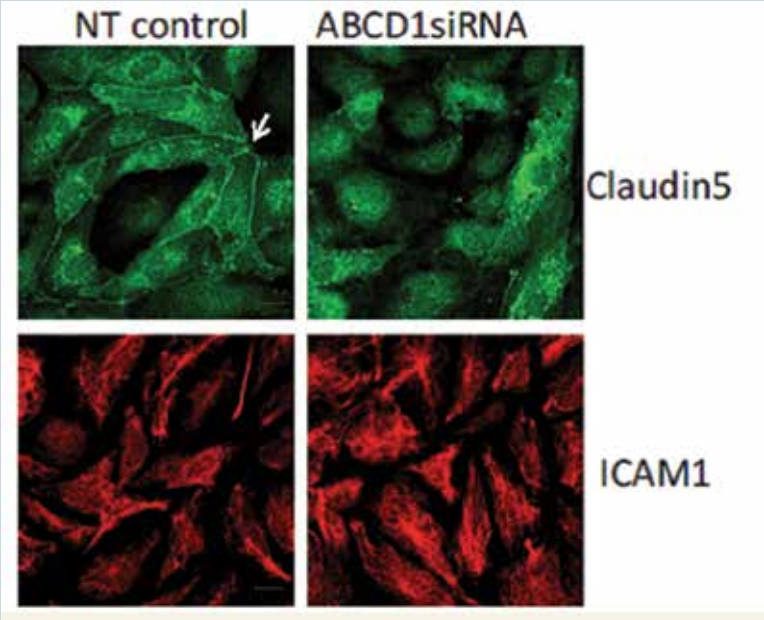
Sherman, Alexander 1, 2; Karaa, Amel 1, 4; Breakefield, Xandra 1; Aziz-Bose, Razina 1; Dickerson, Bradford Dickerson 1; Fridman, Vera 1; Gusella, James F 3; Haggerty, Stephen 3; Maguire, Casey 1; McArthur, Daniel 5; Merker, Vanessa 1; Musolino, Patricia 1; Ramesh, Vijaya 3; Tsvang, Inna 1; Thiele, Elizabeth 1; Walker, Melissa 1; Walsh, Kailey 1; Swoboda, Katherine J 1, 3 ; Eichler, Florian 1, 3

1. Neurology, Massachusetts General Hospital, Boston, MA, United States. 2. Neurology, NCRI, Boston, MA, United States. 3. CHGR, Boston, MA, United States. 4. Pediatrics, Genetics, Boston, MA, United States. 5. ATGU, Boston, MA, United States.

Blood–Brain Barrier Breakdown in Adrenoleukodystrophy (ALD)

Dr. Musolino *et al* unraveled for the first time some of the molecular mechanisms that underlie blood–

brain barrier breakdown in adrenoleukodystrophy (ALD). Using ALD brain tissue, and human brain microvascular cells (HBMECs) in which the ABCD1 (ALD) gene was silenced via siRNA, they demonstrate an upregulation of intercellular adhesion molecule 1 (ICAM1) and vascular cell adhesion protein 1 (VCAM1) expression that reflected endothelial activation and that facilitated monocyte adhesion. This correlated with the displacement of two members of the endothelial tight junction complex, claudin 5 (CLDN5) and ZO-1, from the membrane to the cytoplasm of endothelial cells: a clear indication that the blood–brain barrier had been breached, boosting the ingress of proinflammatory lymphocytes and monocytes into the white matter.



Effect of ABCD1 silencing on the expression of tight-junction proteins and adhesion molecules. HBMECs seeded in 8 well slide chambers were silenced with NT-control or ABCD1siRNA and fixed for Claudin5 and ICAM1 immunofluorescence staining. White arrow indicates membrane Claudin5 staining which is diminished in ABCD1siRNA treated HBMECs.

Since the discovery (by serendipity) that very long chain fatty acids accumulate in tissues, cells and plasma of patients with ALD, the accepted dogma has been that all pathogenic processes observed in ALD (cerebral demyelination, spinal cord axonopathy, adrenal insufficiency) are due to the 'toxic' accumulation of these fatty acids. Musolino *et al* show that changes in CLDN5 expression and localization observed in ABCD1- silenced HBMECs were seen before any increase in C26:0 lysophosphatidylcholine (C26:0-LPC) could be detected. This has created a paradigm shift in the field that was highlighted in an editorial by Patrick Aubourg (BRAIN 2015: 138; 3132–3140).

Musolino PL, Gong Y, Snyder JM, Jimenez S, Lok J, Lo EH, Moser AB, Grabowski EF, Frosch MP, Eichler FS. Brain endothelial dysfunction in cerebral adrenoleukodystrophy. Brain. 2015;138(Pt 11):3206-20.

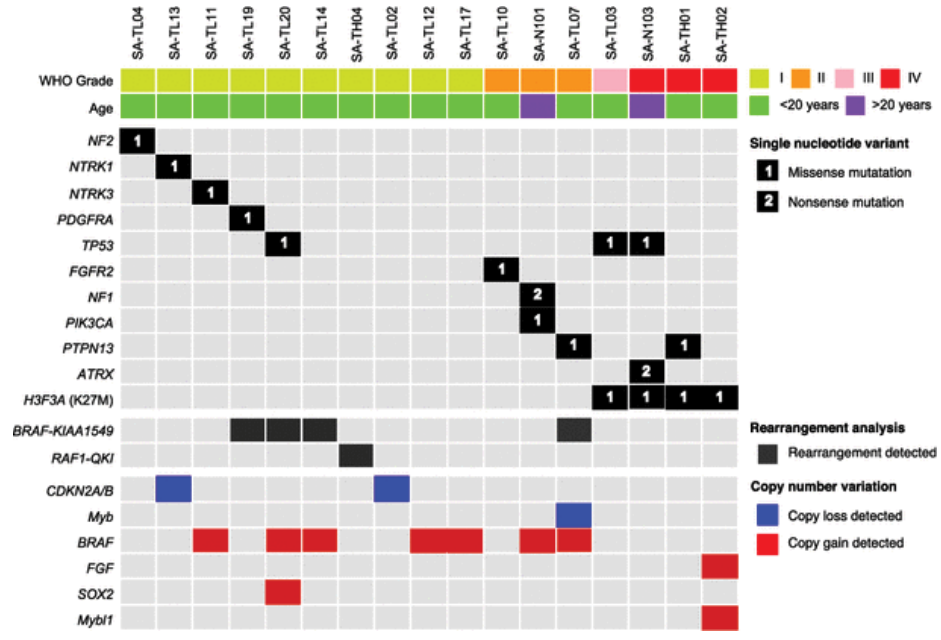
Robert L. Martuza, MD, FACS, Chief

Neurosurgery at MGH encompasses one of our nation's top-ranked neurosurgical services, a vibrant research effort dedicated to translating laboratory discoveries into more effective treatments and a rigorous training program that is preparing future leaders in academic neurosurgery. Patients of all ages and their families come to the MGH from around the nation and the world for the diagnosis and treatment of a full spectrum of diseases that attack the nervous system, from life-threatening brain tumors and aneurysms to movement disorders, epilepsy, neck and back pain and otherwise untreatable psychiatric illnesses. Clinical and research expansion are fueled by advances that promise to reshape the landscape of neurosurgical care. These include advances in imaging with intra-operative MRI and CT scanning, neuro-stimulation therapy for psychiatric, learning and behavioral problems, endovascular treatment of aneurysms, arteriovenous malformations, and stroke, and the study of the molecular underpinnings of CNS tumor growth and experimental therapies to treat these tumors including the development of oncolytic viruses and vaccines for the treatment of nervous system tumors.

Eskandar and colleagues in an article in Scientific Reports demonstrated in a primate model that coordinated stimulation of both dorsal and ventral striatum synergistically enhances associative learning. This has implications for improvement of functional outcomes in various cognitive disorders.

Shankar et al. in an article in Acta Neuropath demonstrated that specific genetic mutation can identify resectable (lower-grade) vs. unresectable (higher grade) tumors in the spinal cord. This is the first time this has been done and opens the path for genetically based intraoperative decision making.

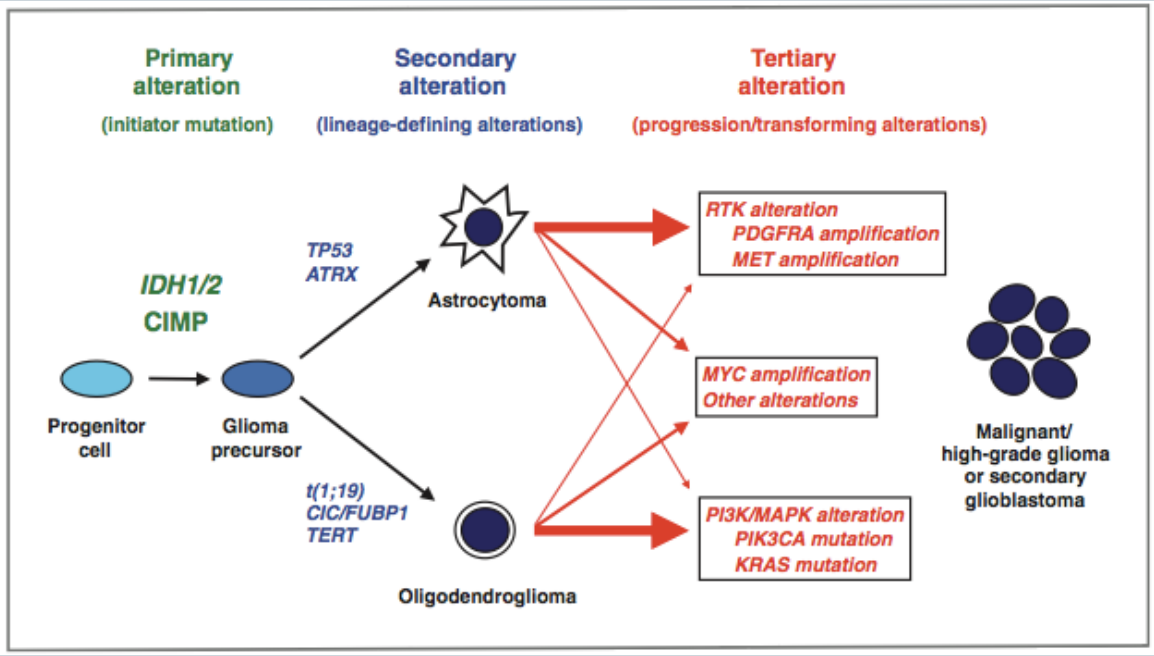
Precision medicine for spinal cord tumors: mutations that identify resectable (lower-grade) versus unresectable (high-grade) tumors. Ganesh Shankar *et. al. Acta Neuropath, 2015*



Wakimoto et al. in an article in Clinical Cancer Research defined the genetic framework of progession in the subset of gliomas with an IDH mutation and identified so-called "driver genes" for these tumors which may provide an opportunity for the development of targeted therapies.

Brastianos, Barker, and colleagues in an article in JNCI demonstrated for the first time a useful precision medicine approach to craniophayngioma. Given the presence of the BRAF V600E mutation in the patient's tumor, they used the oral BRAF inhibitor dabrafenib, which is FDA approved for BRAF-positive melanoma. The MRI revealed the enhancing tumor volume to be reduced by 85%. The patient remained clinically stable; toxicity was limited to one day of low-grade fever.

Genetic framwork of progressive IDH glioma



Wakimoto *et.al.* Clin Can Res, 2014

Jeffrey L. Ecker, MD, Chief

Overview of Department of Obstetrics & Gynecology: mission, focus, and strategic priorities
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.

Infertility The basic science lab lead by Ning Wang, PhD has dedicated their efforts to the understanding of gamete-producing germline stem cells by using spermatogonial stem cell (SSC) as a model. In their first study (Ferder 2015), they reported that age-related increase in Plzf expression represents a novel molecular signature of SSC aging by functionally arresting their differentiation. In their second study (Xiong 2015), they reported p53-mTORC1 pathway plays a critical role in maintaining the homeostasis of early SSC differentiation. Additionally, they developed a novel flow cytometry-based approach to separate SSC differentiation at consecutive differentiation stages. Of note, the lead authors of both studies received *Lalor Foundation Merit Awards* from 48th Society for the Study of Reproduction (SSR) Annual meeting held in San Juan, Puerto Rico in June 2015.

Gynecology Caroline Mitchell, MD, M.P.H. published a paradigm-shifting article in the American Journal of Obstetrics & Gynecology demonstrating the uterine cavity's colonization by bacteria in 95% of women (Mitchell, Haick 2015). This was formerly thought to be a sterile environment in healthy women.

Dr. Mitchell published an article showing vaginal colonization by *Lactobacillus* strains which produce hydrogen peroxide, which have historically been associated with better reproductive health outcomes, are associated with lower levels of vaginal inflammatory cytokines independent of the presence of bacterial vaginosis (Mitchell, Fredricks 2015). A proposal focused on identifying additional characteristics of *Lactobacillus* species associated with beneficial reproductive health outcomes was the basis of Dr. Mitchell's successful application for an MGH Claflin Scholar Award in 2015. In addition in 2015, she received both a bridge award from the American Association of Obstetricians & Gynecologists Foundation and an R21 from the NIH. In collaboration with Dr. Moran Yassour of the Broad Institute, Dr. Mitchell initiated the OriGiN study, an observational cohort study that is designed to identify where infants derive their gastrointestinal microbiota. This project actively enrolling participants, and is supported by philanthropic funds from the Broad Institute.

Gynecologic Oncology Endometrial cancer harbors increased expression of p95HER2 variant compared to breast carcinoma. Dr. Growdon and colleagues recently identified endometrial cancers over-express a truncated HER2 (ERBB2) variant called p95HER2 that has been associated with trastuzumab resistance in HER2 over-expressing breast cancer (Growdon 2015). This finding may explain why HER2 over-expressing endometrial cancers have failed to respond to the wide array of HER2 targeted therapy. In their study, a the novel VeraTag™ platform was used to quantitate continuously full length and truncated HER2 levels in large sets of breast (black points) and high grade endometrial tumors. The finding that across histologies, endometrial cancers express a higher proportion of p95HER2 with lower overall total HER2 expression provides scientific rationale for anti-HR2 therapy resistance and highlights multiple avenues for overcoming this resistance.

Obstetrics The recent introductions of cell-free DNA (cfDNA) screening and chromosomal microarray analysis have increased both the number of options available and the complexity of prenatal testing decision making as patients and providers weigh the trade-offs not only between screening and diagnostic testing, but between multiple different screening options (Kaimal 2015). Working with collaborators from UCSF, Dr. Anjali Kaimal of the Maternal-Fetal Medicine Division used decision and cost-utility analysis to investigate the clinical outcomes, maternal quality-of-life effects, and cost-effectiveness of currently available screening and diagnostic prenatal testing strategies. Weighing all of the tradeoffs involved in the complex menu of options that is currently available, she found that the current paradigm of traditional multiple marker screening, not newly-introduced cfDNA screening, is the optimal initial strategy for most women who desire prenatal testing. As women approach 40, the larger proportion of chromosomal abnormalities represented by the common aneuploidies makes cell-free DNA a more reasonable first-line test, as it provides excellent detection of the chromosomal problems most common at older maternal ages. As policy makers and professional organizations continue to refine their recommendations regarding prenatal testing, this analysis provides important information regarding the optimal way to integrate the current testing options.

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2. Xiong M, Ferder IC, Ohguchi Y, Wang N. Quantitative analysis of male germline stem cell differentiation identifies a role for p53-mTORC1 pathway in spermatogonial differentiation. *Cell Cycle.* 2015;14(18):2905-13.
3. Mitchell CM, Haick A, Nkwopara E, Garcia R, Rendi M, Agnew K, Fredricks DN, Eschenbach D. Colonization of the upper genital tract by vaginal bacterial species in nonpregnant women. Am J *Obstet Gynecol*. 2015 May;212(5):611.e1-9.
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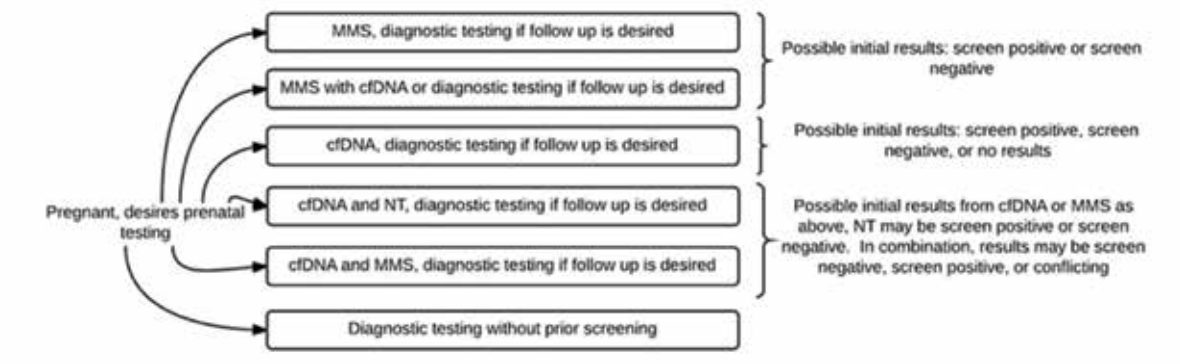
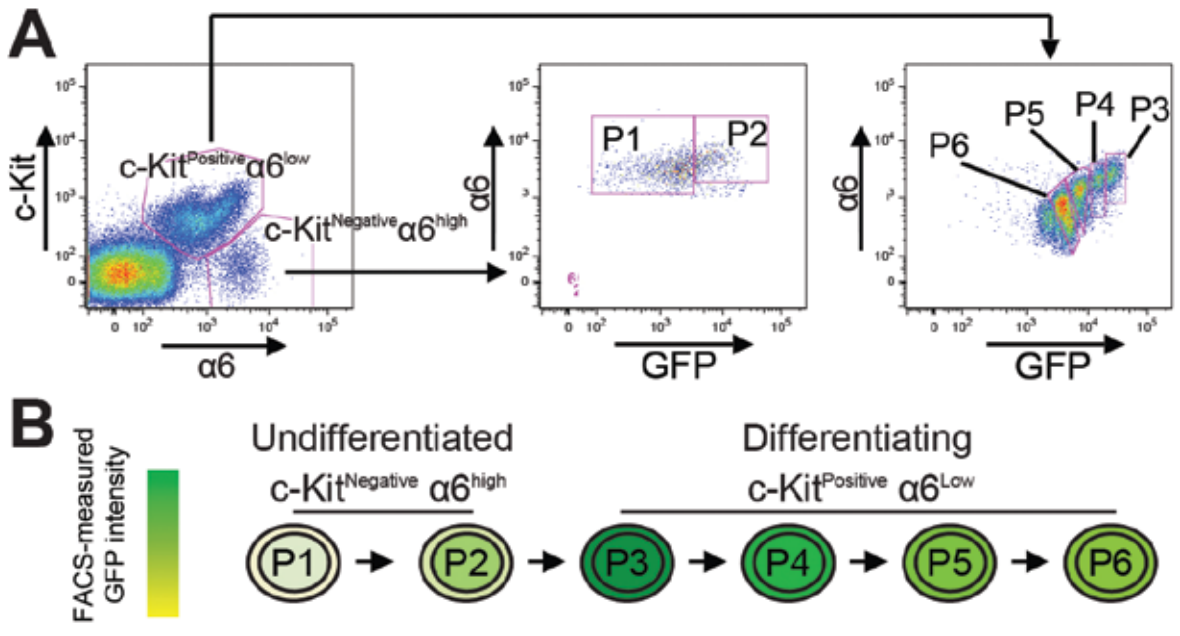
5. Kaimal AJ, Norton ME, Kuppermann M. Prenatal Testing in the Genomic Age: Clinical Outcomes, Quality of Life, and Costs. *Obstet Gynecol*. 2015 Oct;126(4):737-46.
6. Growdon WB, Groeneweg J, Byron V, DiGloria C, Borger DR, Tambouret R, Foster R, Chenna A, Sperinde J, Winslow J, Rueda BR. HER2 over-expressing high grade endometrial cancer expresses high levels of p95HER2 variant. *Gynecol Oncol*. 2015 Apr;137(1):160-6.



Anjali Kaimal, M.D, M.A.S.



Ning Wang, Ph.D

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 intense 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. Today, the Department pursues a programmatic research strategy focused on areas of greatest unmet medical need, including retinal degenerations and AMD, diabetic eye disease, and optic neuropathies, particularly glaucoma. Our largest investment is directed toward developing our genetics and genomics programs—with significant emphasis and support in the areas of retina and glaucoma—as 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, cataract surgical teaching, vision rehabilitation and perception.

Researchers Resurrect Ancient Viruses in Hopes of Improving Gene Therapy

Luk H. Vandenberghe, PhD, of the Grousbeck Center for Gene Therapy and Ocular Genomics Institute as well as colleagues at Schepens Eye Research Institute of Mass. Eye and Ear have reconstructed an ancient virus that is highly effective at delivering gene therapies to the liver, muscle, and retina. This approach, published June 30, 2015 in *Cell Reports*, could be used to design a new class of genetic drugs that are safer and more potent than those currently available. So far, adeno-associated viruses (AAVs) used for gene therapy are those that naturally circulate throughout the human population. However, many patients already have immunity to the virus and therefore, are ineligible for gene therapy. Engineering new AAVs could increase the number of people to whom a given gene therapy could be administered. Dr. Vandenberghe and his colleagues turned to evolutionary history for guidance. Over time, AAV ancestors have preserved their structural integrity and innate function while undergoing external surface changes, which may alter various viral functions and host interactions. These include the ability to bind host cells, stimulate immune responses, and transfer genes to target cells and tissues. One particular challenge in rational gene therapy vector design

has been modifying viral functions while retaining structural integrity. The researchers were able to recreate an evolutionary timeline of the changes and generate nine synthetic ancestral viruses. When injected into mice, Anc80, one of the ancestral viruses, successfully targeted liver, muscle, and retina without producing toxic side effects. Dr. Vandenberghe and colleagues hope to use the knowledge they have gained in this study to design next-generation viruses for use as vectors in gene therapy for patients.

Targeting the Immune System to Prevent Vision Loss

Kip M. Connor, PhD, and other vision researchers at Mass. Eye and Ear have taken an initial step in solving the problem of preserving photoreceptor cells to avoid irreversible vision loss in patients following retinal detachment. By analyzing innate immune system regulators in the eyes of human patients with retinal detachment and correlating their findings in an experimental model, Dr. Connor and his colleagues demonstrated that there were significant increases in the immune system's "alternative complement pathway" following retinal detachment. Researchers also found that this pathway facilitated early photoreceptor cell death after injury. Injured photoreceptors lose important proteins that normally protect them from complemented-mediated cell death, allowing for selective targeting by the alternative complement pathway. Blocking the alternative complement pathway, through both genetic and pharmacologic means, also protected photoreceptors from cell death.

Mass. Eye and Ear Launches its Most Ambitious Fundraising Campaign

In October, Mass. Eye and Ear officially launched its largest and most ambitious fundraising campaign in the hospital's 191 year history—Bold Science. Life-Changing Cures. The Campaign for Mass. Eye and Ear—with a public goal of $200 million by 2020. Led by President & CEO John Fernandez; Board Chairman, Wyc Grousbeck, and Chairs of the Harvard Departments of Ophthalmology and Otolaryngology Drs. Joan W. Miller and D. Bradley Welling, the goal of the campaign is to accelerate discoveries and make new cures possible by providing critical resources to HMS Ophthalmology and Otolaryngology faculty. Mass. Eye and Ear will use funds to create endowed chairs for its medical and scientific leaders; and to ensure that the hospital continues to recruit exceptional talent to its doors. Funds also will be used to strengthen and expand Mass. Eye and Ear research programs, while investments in facilities and infrastructure will keep the hospital a state-of-the-art research hub and world-class institution. The initial "quiet phase" of the campaign began in 2012, co-chaired by Mass. Eye and Ear leaders Wyc Grousbeck, Diane Kaneb, Charles de Gunzburg, and Fred Thorne. To date, the campaign has raised $105 million.

Ophthalmology

Department Report

Joan W. Miller, MD, FARVO Elected to the National Academy of Medicine

In October, 2015 Joan W. Miller, MD, FARVO, the Henry Willard Williams Professor of Ophthalmology and Chair of Ophthalmology at Harvard Medical School, and Chief of Ophthalmology at Massachusetts Eye and Ear and Massachusetts General Hospital, was elected to membership in the prestigious National Academy of Medicine (NAM). Dr. Miller is an internationally recognized expert on retinal disorders, including age-related macular degeneration (AMD). Established in 1970 by the National Academy of Sciences, the NAM—formerly named the Institute of Medicine—is a national resource for independent, scientifically informed analysis and recommendations on health issues. NAM serves alongside the National Academy of Sciences and the National Academy of Engineering to "address critical issues in health, medicine and related policy and to inspire positive action across sectors." With a current membership of over 2,000, the NAM elects no more than 70 national and 10 international members each year. Current active members elect new members through a selective process that recognizes eminent professionals who have made major contributions to the advancement of the medical sciences, health care, and public health and who are committed to volunteer service in activities of the National Academies of Sciences, Engineering, and Medicine.

Mass. Eye and Ear Chairman of the Board, Wycliff (Wyc) Grousbeck, announces a historic campaign goal of $200 million by 2020 during the hospital's sixth annual Sense-action! Gala in October 2015.

Maria J. Troulis, DDS, MSc, Chief

Virtual surgery, treatment and management of benign tumors and regenerative medicine were the highlighted subjects of the Research and Education Summit for the American Association of Oral and Maxillofacial Surgery May 2015. For 15 plus years, the department has been studying 3D treatment planning, navigation, tissue engineering, minimally invasive surgery and benign pathology. The department is strong in all these areas. We need to expand the minimally invasive surgery to the midface and orbit, study pain, and initiate OI/Safety and Education/Simulation research!

The focus of our department's research is a thematically-driven translational research program organized into two Centers: Skeletal Biology Research Center (SBRC) and Center for Advanced Clinical Investigation (CACI).

Skeletal Biology Research Center (SBRC): is based at the departmental laboratory on Thier 5 (approx.1500 sq ft). Translational science focuses on bone biology, rare tumor biology (Giant Cell Tumor). Also intensely studied in-vivo tissue engineering (distraction osteogenesis) and ex vivo tissue engineering and Giant Cell Tumors. (We recently received a grant to study Clear Cell Odontogenic Carcinoma). A minipig model for the study of the biology of distraction osteogenesis has been developed and has become a standard model throughout the world to study distraction. In addition to the biology of distraction, other components of the program include: Device design, 3-D imaging and treatment planning and minimally invasive techniques for reconstruction. Projects in surgical navigation, simulation, development of a totally buried, miniature, automated distraction device, bone tissue engineering and scaffold design, sialendoscopy and the molecular biology of rare jaw tumors are ongoing.

Center for Advanced Clinical Investigation has played a significant role in evidenced based studies related to diagnosis, management and outcomes of common problems in our specialty: wisdom teeth, dental implantology and medication related osteonecrosis of the jaws, maxillofacial pathology, orofacial pain and temporomandibular joint surgery outcomes.

A new focus of our research includes research on Safety and Quality outcomes and Education and simulation research.

A. TISSUE ENGINEERING:

Konopnicki S and Troulis MJ: Mandibular Tissue Engineering, Past, Present and Future. J Oral Maxillofac Surg (Special Supplement), 2015

Konopnicki S, Sharaf B, Resnick C, Patenaude A, Pogal-Sussman T, Huang KG, Abukawa H and Troulis MJ: Tissue engineered bone with three-dimensionally printed B-TCP/PCL Scaffolds and early implantation: An in vivo pilot study in a porcine mandible model. J Oral Maxillofac Surg May 73 (5); 2015

In collaboration with the Vacanti laboratory, we have already grown part of a jaw, but it lacked blood supply and bone in the center of the scaffolds (constructs). By changing protocols and early implantation, bone and blood supply throughout the scaffold was achieved. This was a major achievement this past year (Figure 1) and was a poster presentation at SAC (April 1, 2015) which was chosen as a finalist for best poster! Tissue engineering will continue to be a focus of the upcoming year. (Figures 1 & 2)

B. OPIOD CRISIS:

Coincidentally, an achievement this year was obtaining an NIH grant on opiod use and education. Timing is everything as the opiod crisis has come to national attention. Dentists have been identified as frequent prescribers of opiod analgesics for acute pain. Furthermore, drug-seekers often masquerade as having "dental pain". This department with 3 residencies (OMFS, General Dental and Orofacial Pain) is strategically positioned to effect change! Fortunately, the 2 key achievements stated below have set the foundation to educate all practitioners in pain management. We also need to find non-opiod pain management methods such as laser and cryotherapy, in discussion with Mrs. Gabriela Apiou and Dr. Rox Anderson.

Keith D: The prescription monitoring program in Massachusetts and its use in Dentistry. Journal of the Massachusetts Dental Society.

June 2012-July 2015, Sept 17, 2015- Sept 16 2020. NIH Pain Consortium Centers of Excellence in Pain Education sponsored by the National Institute on Drug Abuse, NIH Contract # HHSN271201500075C Reference #: NO1DA-15-4427

The goal is to enhance pain management knowledge and appropriate opiod prescribing by education using case-based training modules in small student groups at the intra and inter-professional level across health care institutions. Jeffrey Shaefer is the co-PI for National Institutes of Health (NIH) Pain Consortium Grant which designated HSDM to serve as one of 12 Centers of Excellence in Pain Education. Tasked with creating online case–based modules to teach the principles of pain management to individuals and small Intra and Inter professional groups.

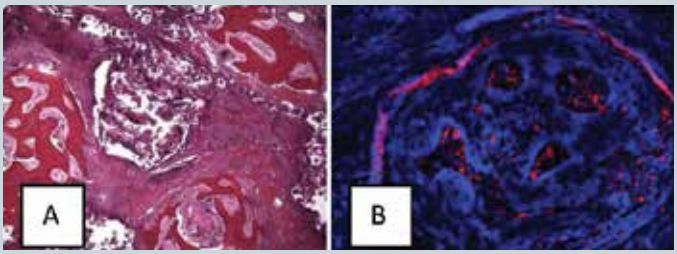


Figure 1 A. H&E: with bone seen in center of the construct. B. CD34 staining shows angiogensis in center of construct. (Konopnicki 2015)

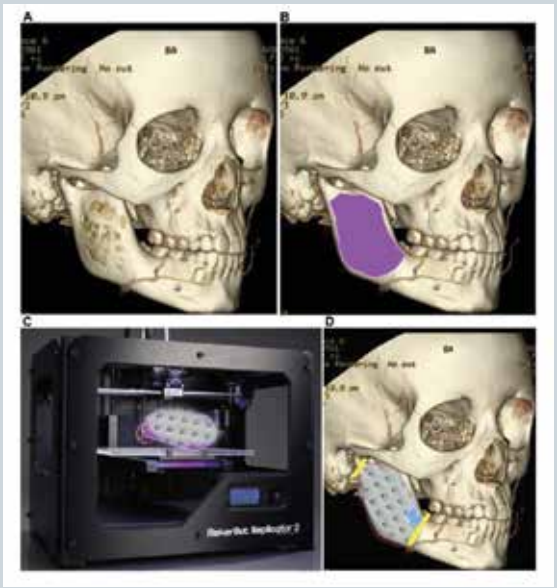


Figure 2 A Prediction for the future: combining all existing technologies, in collaboration with Drs. Vacanti, Yelnick, and Anderson's groups: A, B) a case will be virtually planned, C) the required scaffold printed, D) the patient's own cells or "banked" cells from discarded tissue like teeth, resulting in a co-construct, the resection will be performed with a laser, immediately reconstruct the resected tissue, weld it in place, cure it for strength.

Harry E. Rubash, MD, Chief

The Department of Orthopaedic Surgery at Massachusetts General Hospital is over a century old. Our mission is to provide the highest quality musculoskeletal patient care, teaching and research with a commitment to leadership in the field. Our research is problem-based and hypothesis-driven, and includes both basic and clinical translational research. We encourage our clinicians to integrate the investigation of new ideas and concepts into our daily patient activities. The MGH Orthopaedic Laboratories are:

1. Bioengineering Laboratory, PIs: Guoan Li, PhD, and Harry Rubash, MD
2. Dinesh Patel Arthroscopy Learning Laboratory, PI: Dinesh Patel, MD
3. Harris Orthopaedic Laboratory (HOL), PIs: Henrik Malchau, MD, PhD, Orhun Muratoglu, PhD, Ebru Oral, PhD and Charles Bragdon, PhD
4. Laboratory for Musculoskeletal Tissue Engineering, PI: Mark Randolph, MS
5. Monoclonal Antibody and Immunotherapy Laboratory, PIs: Soldano Ferrone, MD, PhD, and Joseph Schwab, MD, MS
6. Pediatric Orthopaedic Laboratory for Tissue Engineering and Regenerative Medicine, PIs: Craig Neville, PhD, and Brian Grottkau, MD
7. Sarcoma Molecular Biology Laboratory, PIs: Francis Hornicek, MD, PhD, and Zhenfeng Duan, PhD
8. Shoulder Biomotion Laboratory (SBL), PIs: Jon Warner, MD, Matthew Provencher, MD, Guoan Li, PhD, and Daniel Massimini, PhD
9. Technology Implementation Research Center (TIRC), PIs: , Orhun Muratoglu, PhD, Kartik Mangudi Varadarajan, PhD and Harry Rubash, MD
10. Musculoskeletal Genetics and Regenerative Biology Laboratory (MGRBL), PI: Jenna Galloway, PhD
11. Dual Fluoroscopy Laboratory, PIs: Young-Min Kwon, MD, PhD and Guoan Li, PhD
12. Foot & Ankle Laboratory, PI: Christopher DiGiovanni, MD

The Harris Orthopaedic Laboratory (HOL) has over five decades of experience addressing problems in adult reconstructive surgery by innovating new surgical techniques, devices, joint implant designs, and joint implant materials. Notably, this laboratory developed several clinical implant formulations of highly cross-linked ultrahigh molecular weight polyethylene (UHMWPE), stabilized by re-melting or vitamin E, for large scale usage in implant manufacturing. Currently, several million patients are using implants developed in this laboratory. The core cross-linking technology in these implants has changed the landscape of joint replacement by reducing the number of wear particles and instances of osteolysis associated with total joint implants. Under the direction of Orhun Muratoglu, the laboratory's current focus area of the pre-clinical material development team is improving the longevity of joint implants through advancing material development and treating diseases associated with implants by using material technology. The materials research team collectively brings experience in material and polymer science, polymer chemistry, biomaterials and biomechanics testing, and bench-to-clinic implant development, as well as follow-up testing of explanted devices to analyze *in vivo* effects. The team welcomes collaboration in all areas of orthopaedics.

Another major focus is follow-up and analysis of clinical implant performance to provide evidence-based feedback to patients and clinicians. Under the direction of Henrik Malchau, MD, PhD, the clinical research team conduct prospective national and international clinical studies on alternative bearing materials and new implant designs. This provides fast and valuable information on the performance of newly developed implants and helps compare them to historical standards. These studies also provide feedback on surgical techniques and skills to improve clinical outcomes. The

clinical team is currently developing these capabilities into an Academic Coordinating Organization, ACRO in order to perform comparative prospective multi-center studies as well as to augment these studies with performance data obtained from national and regional registries. In this way, they will be able to provide more timely data to industry and regulatory bodies as well as provide a sustainable, independent scientific and academic environment for research fellows, pre-medical and medical students.

A second important MGH orthopaedic laboratory, the Sarcoma Laboratory, experienced two noteworthy achievements this year. One significant topic was "Targeting Cdk11 in osteosarcoma cells using the CRISPR-cas9 system." (Feng Y, Hornicek FJ and Duan Z. *J Orthop Res. 2015 Feb;33(2):199-207*) Osteosarcoma is the most common type of primary malignant bone tumor. Patients with regional osteosarcoma are routinely treated with surgery and chemotherapy, and many patients with metastatic or recurrent osteosarcoma show poor prognosis with current chemotherapy agents. Therefore, it is important to improve the general condition and overall survival rate of patients with osteosarcoma by identifying novel therapeutic strategies. Recent studies have revealed that CDK11 is essential in osteosarcoma cell growth and survival by inhibiting CDK11 mRNA expression with RNAi. We applied the Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 system, a robust and highly efficient novel genome editing tool, to determine the effect of targeting endogenous CDK11 genes at the DNA level in osteosarcoma cell lines. We showed that CDK11 could be efficiently silenced by CRISPR-Cas9. Inhibition of CDK11 is associated with decreased cell proliferation and viability, and induces cell death in osteosarcoma cell lines KHOS and U-2OS. Furthermore, the migration and invasion activities are also markedly reduced by CDK11 knockout. These results demonstrate that the CRISPR-Cas9 system is a useful tool for modifying endogenous CDK11 gene expression. CRISPR-Cas9-targeted CDK11 knockout may be a promising therapeutic regimen for treatment of osteosarcoma. "Development and potential applications of CRISPR-cas9 genome editing technology in sarcoma." (Liu T, Hornicek FJ and Duan Z. *Cancer Lett. 2016 Jan 21*)

The other key topic was "Prevention of multidrug resistance (MDR) in osteosarcoma by NSC23925." (Yang X, , Hornicek FJ, Duan Z. *British Journal of Cancer (2014), 1–9.*) The major limitation to the success of chemotherapy in osteosarcoma is the development of multidrug resistance (MDR). Although preventing the emergence of MDR during chemotherapy treatment has been a high priority of clinical and investigational oncology, it remains an elusive goal. NSC23925 has recently been identified as a novel and potent MDR reversal agent; however, whether NSC23925 can prevent the development of MDR is unknown. Therefore, this study was designed to evaluate the effects of NSC23925 on preventing the development of MDR in osteosarcoma.

We exposed human osteosarcoma cell lines U-2OS and Saos to increasing concentrations of paclitaxel alone or in combination with NSC23925 for six months. Cell sublines selected at different times were evaluated for drug sensitivity, drug transporter P-glycoprotein (Pgp) expression and activity. We observed that tumor cells selected with increasing concentrations of paclitaxel alone developed MDR with resistance to paclitaxel and other Pgp substrates; cells cultured with paclitaxel-NSC23925, however, did not develop MDR and remained sensitive to chemotherapeutic agents. Paclitaxel-resistant cells showed high expression and activity of the Pgp, whereas paclitaxel-NSC23925-treated cells did not express Pgp. No changes in IC50 and Pgp expression and activity were observed in cells grown with NSC23925 alone. Our findings suggest that NSC23925 may prevent the development of MDR by specifically impeding the over-expression of Pgp. Given the significant incidence of MDR in osteosarcoma and lack of effective agents to prevent it, NSC23925 and derivatives offer great potential to improve the outcome of cancer patients with poor prognosis due to drug resistance.

Otolaryngology

Department Report

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.

We had a successful year in 2015. Investigators throughout the Department worked together and with colleagues in the field to advance our knowledge through numerous publications, including many in high impact journals. Through the generosity of the Lauer family, we launched the Lauer Tinnitus Research Center with the goal of advancing research and developing treatments for the poorly understood condition of tinnitus. As a Department, we continue to strive for better knowledge and treatments for the full spectrum of otolaryngology diseases and conditions.

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 2015–2016 hospital survey.

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

Researchers in the Department of Otolaryngology at Massachusetts Eye and Ear/Harvard Medical School engage in a range of basic science, translational and clinical research projects aimed at solving clinical problems across all subspecialties in our field. In 2015, a number of research achievements demonstrate our dedication to tackling clinically relevant issues through a variety of approaches. Highlights of the year include the following advancements:

Researchers develop techniques to bypass blood-brain barrier, deliver drugs to brain and nervous system

A team of researchers led by rhinologist Benjamin S. Bleier, MD, successfully showed neuroprotection in a Parkinson's mouse model using new techniques to deliver drugs across the naturally impenetrable blood-brain barrier. Their findings, published in Neurosurgery, lend hope to patients around the world with neurological conditions that are difficult to treat due to a barrier mechanism that prevents approximately 98 percent of drugs from reaching the brain and central nervous system.

Bleier BS, Kohman RE, Guerra K, Nocera AL, Ramanlal S, Kocharyan AH, Curry WT, Han X. Heterotopic Mucosal Grafting Enables the Delivery of Therapeutic Neuropeptides Across the Blood Brain Barrier. Neurosurgery. 2015 Sep 8. [Epub ahead of print]

Advances in vestibular schwannoma research

A team of researchers including Konstantina Stankovic, MD, PhD, FACS, have been working to better understand vestibular schwannoma, a sometimes-lethal tumor that can occur sporadically or in association with neurofibromatosis 2 (NF2).

In one paper, they demonstrated that salicylates, a class of non-steroidal inflammatory drugs (NSAIDs), reduced the proliferation and viability of cultured vestibular schwannoma cells that cause a sometimes-lethal intracranial tumor that typically causes hearing loss and tinnitus.

Dilwali S, Kao SY, Fujita T, Landegger LD, Stankovic KM. Nonsteroidal anti-inflammatory medications are cytostatic against human vestibular schwannomas. Transl Res. 2015 Jan 7.

In a second paper, the researchers showed that in some cases of vestibular schwannoma, secretions from the tumor contain toxic molecules that damage the inner ear. The findings explain why some vestibular schwannomas cause hearing loss even though they are not large enough to compress nearby structures that control hearing.

S Dilwali, LD Landegger, VY Soares, DG Deschler, KM Stankovic. Secreted Factors from Human Vestibular Schwannomas Can Cause Cochlear Damage. Sci Rep. 2015 Dec 22;5:18599.

A non-canonical pathway from the cochlea to brain signals tissue-damaging noise
A team of researchers, including M. Charles Liberman, PhD, published a paper showing that the unmyelinated fibers in the cochlear nerve, whose function has remained unknown, respond to hair cell damage in the inner ear and thus likely constitute the nonciceptive pathway of the auditory periphery responsible for signaling auditory pain. This discovery could help lead to the development of therapies for hyperacusis, a poorly understood condition of hypersensitivity to moderate level sounds that sometimes occurs following acoustic injury.

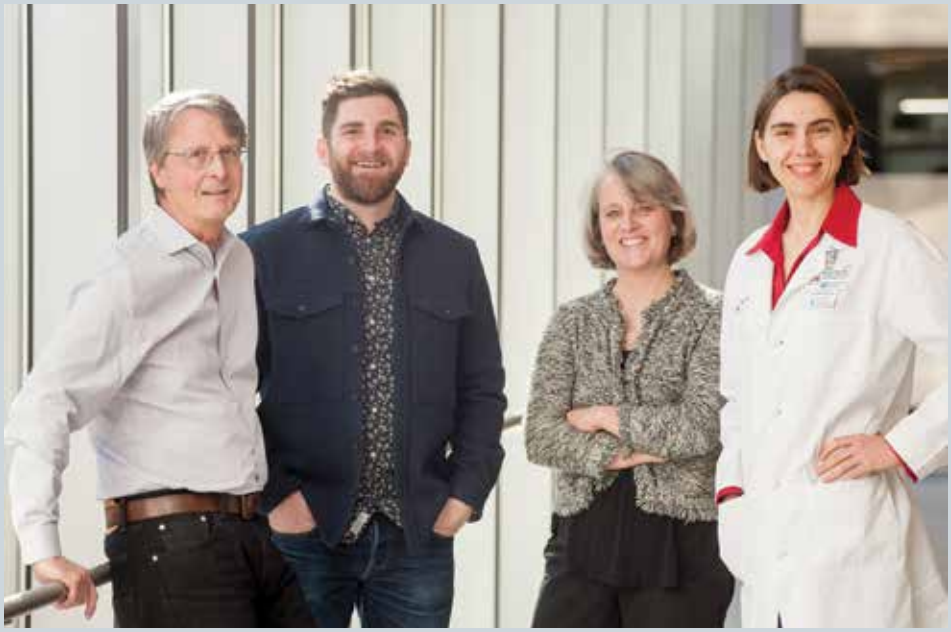
Flores EN, Duggan A, Madathany T, Hogan AK, Márquez FG, Kumar G, Seal RP, Edwards RH, Liberman MC, García-Añoveros J. A Non-canonical Pathway from Cochlea to Brain Signals Tissue-Damaging Noise. Curr Biol. 2015 Mar 2;25(5):606-12

New system could be used to treat deafness, other genetic conditions
A team of researchers including Zheng-Yi Chen, PhD, developed a system that uses commercially available molecules, cationic lipids, to efficiently deliver genome-editing proteins into cells, and have even demonstrated that the technology can be used to perform genome editing in living animals. They believe that delivering genome-editing proteins into cells could offer hope to patients suffering from a host of conditions, including certain diseases of the eye, ear, liver, muscles and blood. Dr. Chen's team will use the newly developed system to modify genes in specialized hair cells in the inner ears of mice to pursue new protein-based therapies for hearing loss.

Zuris JA, Thompson DB, Shu Y, Guilinger JP, Bessen JL, Hu JH, Maeder ML, Joung JK, Chen ZY, Liu DR. Cationic lipid-mediated delivery of proteins enables efficient protein-based genome editing in vitro and in vivo. Nat Biotechnol. 2015 Jan;33(1):73-80.

New techniques to restore eye protection in acute facial paralysis investigated
A team of investigators led by Tessa Hadlock, MD, reported upon the parameters necessary to restore the blink function of the eyelid in 40 patients with acute facial paralysis. Coverage of the cornea by the blink mechanism is essential to protection and lubrication of the delicate cornea. In this human feasibility study, the zygomatic branch of the facial nerve was stimulated transcutaneously and the blink response measured with high-speed video cameras. Complete eye closure was achieved in 55 percent of participants using stimulation, which was reported as tolerable. Artificial stimulation of eye blink may be a very useful tool in the management of patients with acute facial paralysis.

Frigerio A, Heaton JT, Cavallari P, Knox C, Hohman MH, Hadlock TA. Electrical Stimulation of Eye Blink in Individuals with Acute Facial Palsy: Progress toward a Bionic Blink.



L-R: M. Charles Liberman, PhD, Daniel B. Polley, PhD, Jennifer Melcher, PhD, and Konstantina Stankovic, MD, PhD, of the Lauer Tinnitus Research Center. Photo by John Earle.

Rhinology surgeon Benjamin S. Bleier, MD, is exploring the use of nasal mucosal grafts placed through endoscopic sinus surgery techniques to act as a "screen door" to deliver drugs to the brain and central nervous system. Photo by Garyfallia Pagonis.

Pathology

Department Report

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 10 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 personnel and infrastructure to accelerate the development of the novel discipline of Computational Pathology, and growing collaborations and interactions throughout the hospital with our Center for Integrated Diagnostics. We also continue to recruit additional basic science principal investigators and to develop new research space. 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.

Flavahan WA, Drier Y, Liau BB, Gillespie SM, Venteicher AS, **Stemmer-Rachamimov AO**, **Suvà ML**, **Bernstein BE**. Insulator dysfunction and oncogene activation in IDH mutant gliomas. ***Nature***. 2016 Jan 7; 529(7584): 110-4. Epub 2015 Dec 23.

This paper identified a novel epigenetic mechanism for oncogene activation and tumor formation. IDH1 mutation, known to drive a hypermethylator state in glioma, was shown to disrupt binding of the CTCF insulator protein and alter the three-dimensional looping of genomic DNA. Loss of oncogene-protecting insulation allows a constitutive housekeeping enhancer to aberrantly interact with and activate PDGFRA, a canonical glioma oncogene.

Kleinstiver BP, Prew MS, Tsai SQ, Topkar VV, Nguyen NT, Zheng Z, Gonzales AP, Li Z, Peterson RT, Yeh JR, **Aryee MJ**, **Joung JK**. Engineered CRISPR-Cas9 nucleases with altered PAM specificities. ***Nature***. 2015 Jul 23;523(7561):481-5.

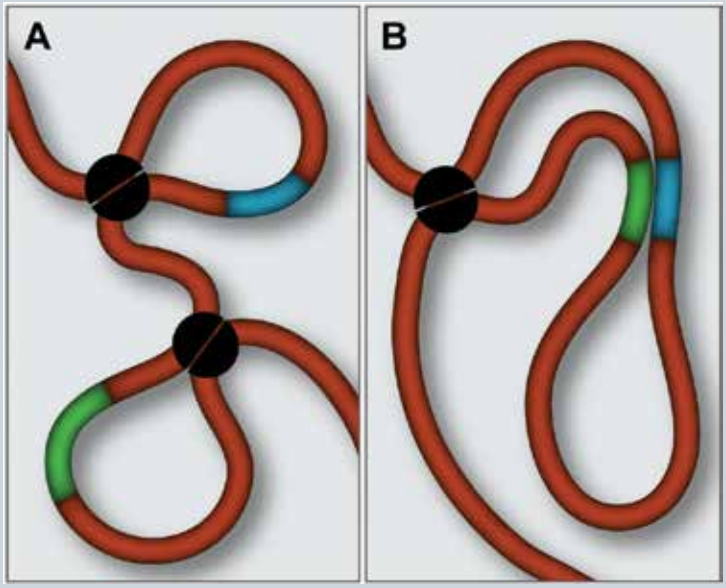
This report described the molecular evolution of CRISPR-Cas9 nucleases with altered and improved PAM recognition specificities. These variants were generated using a combination of structural information, bacterial selection-based directed evolution, and combinatorial design and enable robust editing of endogenous gene sites in zebrafish and human cells not currently targetable by wild-type SpCas9. In addition, the genome-wide specificities of these variants are comparable to wild-type SpCas9 as judged by an unbiased, comprehensive method determining Cas9 off-target mutations.

Patel H, Patel H, **Higgins JM**. Modulation of Red Blood Cell Population Dynamics is a Fundamental Homeostatic Response to Disease. ***Am J Hematol***. 2015 Feb 18.

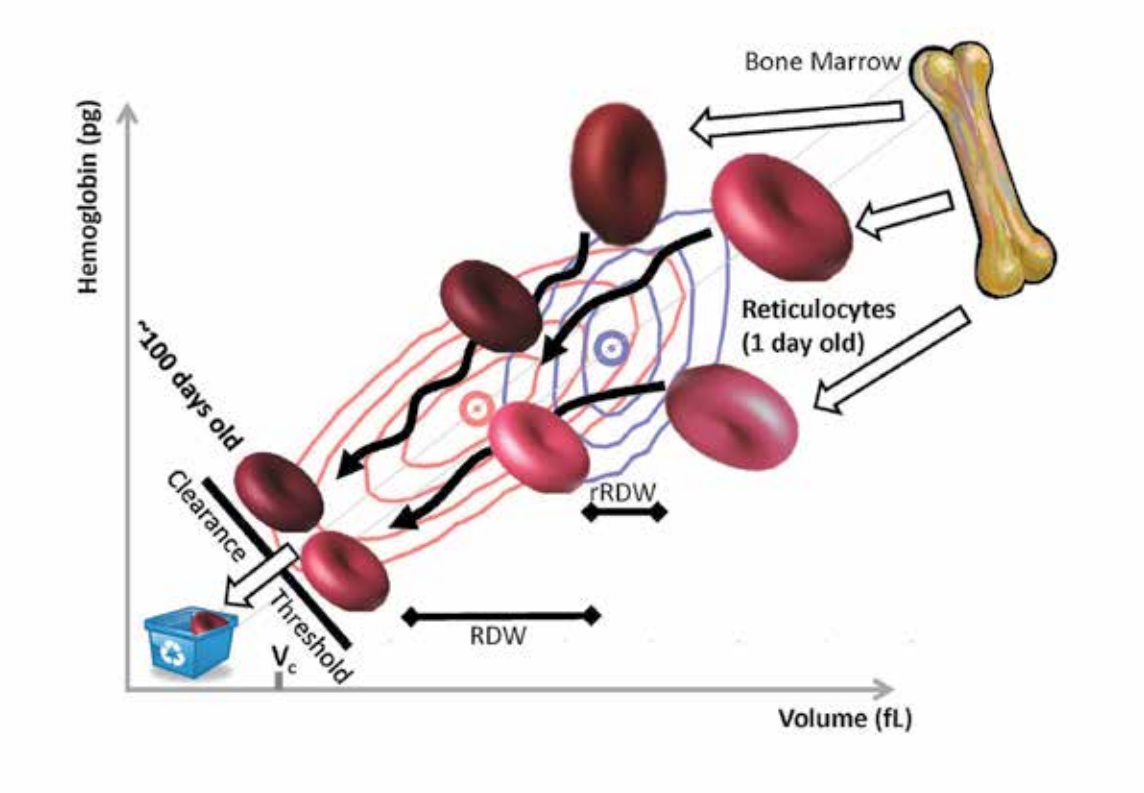
A healthy human adult produces 2,000,000 new red blood cells per second and recycles old ones at the same staggering rate. This paper used a mathematical model of the red blood cell lifecycle to estimate a patient's personalized recycling rate and found that these massive recycling (and production) rates are slightly decreased in the very early stages of a very wide range of diseases —enabling the body to devote fewer resources to building new cells and more resources to compensating for or combatting a developing disease. Measuring these recycling rates for individual patients may enable earlier detection for many important diseases, including heart disease, cancer, infection, and more.

Tang Q, Moore JC, Ignatius MS, Tenente IM, Hayes MN, Garcia EG, Yordan NT, Bourque C, He S, Blackburn JS, Look AT, Houvras Y, **Langenau DM**. Imaging the dynamics of tumour cell heterogeneity following cell transplantation into optically clear immune-deficient zebrafish. ***Nat Comm***., in press.

Imaging tumour cell heterogeneity and the hallmarks of cancer has been a technical and biological challenge. This report describes the development optically clear immune compromised zebrafish for optimized cell transplantation and direct visualisation of fluorescently labelled cancer cells at single cell resolution. Tumour engraftment permitted dynamic imaging of neovascularization, niche partitioning of tumour-propagating cells in embryonal rhabdomyosarcoma, emergence of clonal dominance in T-cell acute lymphoblastic leukaemia, and tumour evolution resulting in elevated growth and metastasis in BRAFV600E-driven melanoma. This work provides a universal platform to dynamically visualize the hallmarks of cancer at single cell resolution *in vivo*.



Insulator dysfunction leads to oncogene activation in IDH mutant gliomas. (A) Under normal conditions, *PDGFRA* (blue) and a nearby housekeeping enhancer (green) are spatially separated by the activity of genomic insulators (black). (B) In *IDH1*-mutant glioma, DNA hypermethylation causes loss of insulator function, allowing an interaction which drives *PDGFRA* expression and tumorigenesis. Image courtesy of Lauren Solomon, Broad Institute.



RBC population dynamics altered in response to disease. Mathematical models can be used to infer how quickly red blood cells are maturing, starting in the top right when they are born in the bone marrow, and ending approximately 100 days later in the bottom left when they are removed from the circulation and recycled. After inferring the duration of each phase of maturation, patient-specific recycling rate can be estimated and tell-tale changes that often precede the appearance of a wide range of important diseases can be identified.

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.

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:

Discussion of the Research Mission, Focus, and Strategic Priorities of the Divisions in the Department of Pediatrics

Allergy & Immunology

The research focus for the Division of Allergy & Immunology at MGHfC is on the mechanisms of immune-mediated hypersensitivity diseases including IgE-mediated food allergy, chronic gastrointestinal inflammatory diseases related to food allergy such as eosinophilic esophagitis and allergic proctocolitis, and asthma. The scope of the division's research activity ranges from clinical trials to epidemiology to cellular immunology. Dr. Shreffler directs the multidisciplinary Food Allergy Center at MGH—a highly collaborative effort inclusive of clinical investigators in the adult allergy unit, adult and pediatric GI, nutrition and psychology as well as basic and translational scientists within MGH and at HMS, MIT, BWH, and others. Dr. Shreffler is also a principal investigator at the Center for Immunology and Inflammatory Diseases. His team leads several investigator-initiated clinical trials and complimentary immune profiling studies, sponsored by NIH, foundations and industry, aimed at achieving greater insight into the mechanisms of food allergies in the context of clinical interventions. Another major effort, in collaboration with Drs. Yuan (Peds GI) and Hundal (Peds GI) is on the mechanisms of non-IgE-mediated food allergies and the role of the microbiome in disease development and resolution. Dr. Virkud is a recently recruited clinical investigator with a primary interest in food allergen reactivity/sensitivity and a focus on adverse events during allergen exposure trials (immunotherapy). Dr. Permaul's research focus is on asthma, its association with obesity and mechanisms of obesity-associated inflammation.

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. 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 enterocyte in 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. We also look at how the enterocyte functions both as a barrier to antigen trafficking and as a site for the beneficial effects of probiotics in intestinal inflammation. Our researchers examine strategies used by gut microbiota to affect the host and how these interactions lead to intestinal inflammation and autoimmunity in the Mucosal Immunology and Biology Research Center. In addition, active clinical and translational research 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
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. Our services impact every field of pediatric and adult medicine.

Global Health
The primary goal of the Division is to build and foster international partnerships for interdisciplinary research, education and service to reduce health disparities and achieve optimal health for children and adolescents in resource-limited settings. Our faculty focus on developing innovative solutions to prematurity, birth asphyxia, neonatal sepsis, childhood pneumonia, diarrhea, and HIV in Africa, Asia, Central and South America by conducting high quality community based and facility based randomized trials, as well as developing and testing innovative technology to improve the quality of care provided to the world's children. 2015 was our most successful year to date—with a record number of publications in high impact open access journals and presentations at Global Health Forums all over the world. The Powis team focusing in Botswana is studying how the microbiome influences outcomes in HIV positive and exposed children and clinical trials and is working hand-in-hand with Ministries of Health to modify public health policies to optimize the health and survival of infants and children. The Moschovis team focusing in Uganda is studying the effect of anemia on the outcomes of children with pneumonia in Uganda and Dr Moschovis is a lead collaborator on the recently launched Gates/WHO study to evaluate the ability of Community Health Workers to treat young children with pneumonia. The Hibberd team focusing in India, Bangladesh, Pakistan and Malawi has made major strides forward in the development of a novel imaging technology for a point of care diagnostic for pneumonia that has been funded by USAID and the Gates Foundation.

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 MGH*f*C 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 estabish 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 of the Lurie Center. Translational research projects, including those involving neuroimaging, genetics, animal models of autism and neuroimmunology, allow us to explore and develop novel treatment approaches that will ultimately be paired with individual patients. Additionally, the Lurie Center is collaborating with research groups across Boston, the nation and the world, capitalizing on modern informatics approaches.

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

We will continue our efforts to define rare genetic disorders affecting the regulation of mineral ion homeostasis with a particular focus on the different forms of pseudohypoparathyroidism type Ib (PHP1B) and hypoparathyroidism. In addition, a main focus will be studying the regulation of NPT2c, one of two sodium-dependent phosphate co-transporters, which is mutated in hereditary hypophosphatemic rickets with hypercalciuria (HHRH); this disorder that was recently shown to be associated with a considerable risk of nephrocalcinosis and nephrolithiasis. We will furthermore continue our search for genetic mutations that cause structural abnormalities of the kidney and the urinary tract, and through studies in humans and genetically modified mice we will further define the role of FGF23 in patients with chronic kidney disease, in particularly the contribution of this phosphaturic hormone to kidney disease progression and left ventricular hypertrophy.

Pulmonary

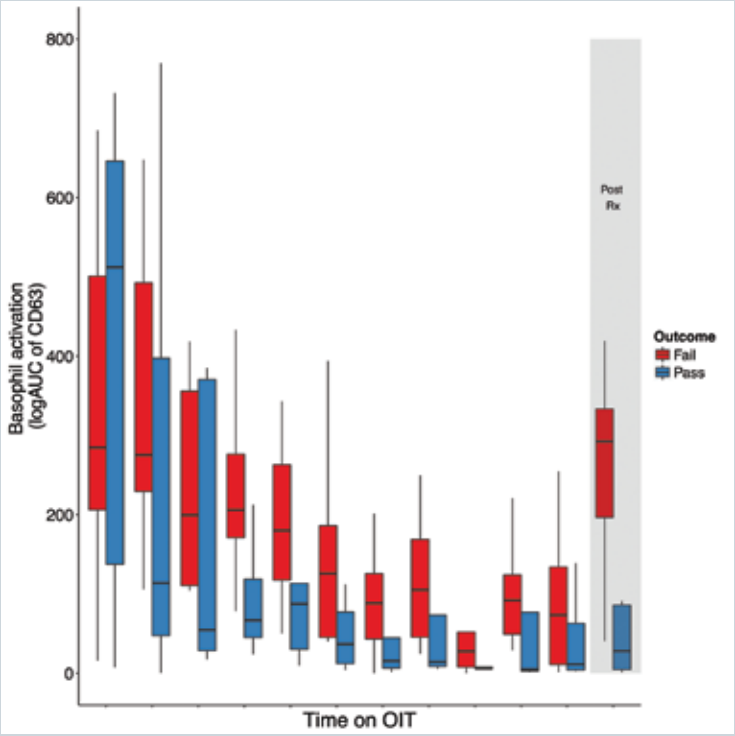
The research focus of the Pulmonary Division encompasses 3 areas. The first, led by Dr. Bernard Kinane, is the genetic basis of lung disease, including interstitial lung disease and non-cystic fibrosis bronchiectasis. In collaboration with the Partners Center for Personalized Medicine, we have developed genetic panels, which allow for rapid and multiple gene analysis. We are also developing a large birth cohort to define the predisposition to pulmonary 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 will be the identification of the mechanisms by which neutrophils control Pseudomonas infections. The third 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.

Notable Achievements 2015

Allergy & Immunology

The nature of immune suppression during oral immunotherapy (OIT) for food allergy is ill-defined. We found as a result of a three-year study of children with peanut allergy treated with OIT, that different mechanisms appear to account for the previously observed transient clinical suppression termed 'desensitization' versus longer term clinical remission. 'Desensitization' without remission was associated with reversible suppression of key IgE-responsive immune cells, basophils, and the lack of functionally suppressive antibody production. This may be key in designing more effective OIT or other forms of immunotherapy for peanut and perhaps other food allergies.



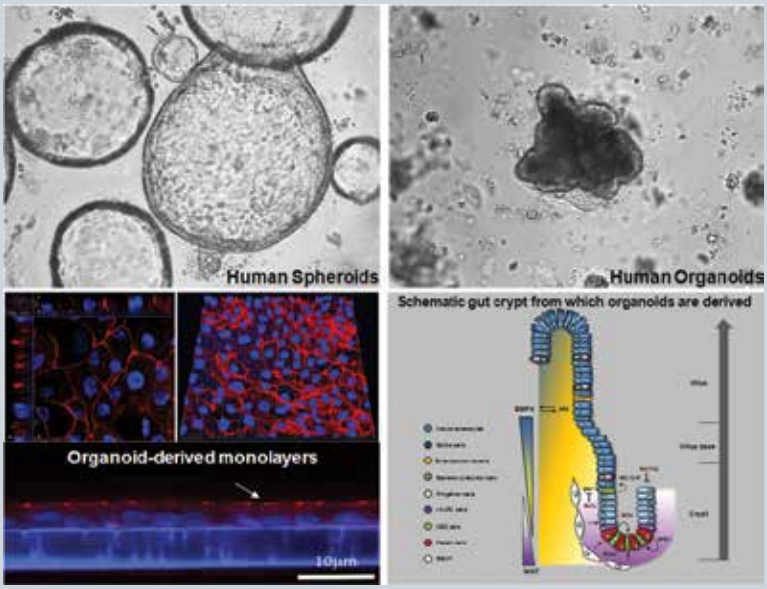
General Academic Pediatrics

Raising the tobacco sales age to 21 was a particular focus in 2015 for the Winickoff research group. Their work was a critical factor in the successful spread of legislative action to restrict the sales age to 21. More than 90 cities and towns in Massachusetts, including Boston, have adopted tobacco 21 sales laws from 2013–6 with the support of Dr. Winickoff's research and testimony. New York City recently became the largest city to date to adopt this legislation. In June 2015,Hawaii passed state-level legislation and legislation is currently pending in Massachusetts and other states. At the Federal level, the "Tobacco to 21 Act" were introduced in both the US Senate and the US House of Representatives in September 2015. Dr. Winickoff's research was also cited in the 2015 Institute of Medicine report, *Public Health Implications of Raising the Minimum Age of Legal Access to Tobacco Products*.

Obesity prevention is a major focus of the Taveras research group and the results of their STAR trial published this year showed that children enrolled in the intervention group that included electronic clinician decision support for clinicians and self-guided behavior change support for families showed significant improvements in their BMI., thus establishing this methodology as an important component of obesity prevention in childhood. STAR was a cluster-randomized controlled trial to improve childhood obesity. Children in the trial were recruited from 14 pediatric practices in the greater Boston area and randomized to one of three arms: 1) computerized point-of-care decision support (alerts) to pediatric primary care providers; 2) computerized alerts plus direct-to-parent outreach and support relating to their child's BMI, screening and management; and 3) usual care (control)

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

Dr. Fasano's research group has developed new technologies that will change the way we will approach pre-clinical studies. The major limitation to performing pre-clinical studies pertinent to human gastrointestinal diseases is the recent appreciation that animal models do not realistically recapitulate the complexity of host-microbiota interactions that can influence early gut mucosal functional and immune responses dictating tolerance/immune response balance. Although the functional outcomes appear to be similar between humans and mice, the molecular mechanisms leading to human disease might be dissimilar. We have developed and validated human gut organoid tissues from both fetal and adult intestine. Adult organoids are generated from intestinal biopsies obtained during clinically indicated endoscopies performed on both non-diseased subjects and subjects affected by intestinal inflammatory diseases (celiac disease and IBD). These integrated models provide robust and reliable high throughput pre-clinical tools directly applicable to the developmental biology and pathophysiology of specific diseases. Ultimately, these innovative tools can not only assist with the development of novel treatments relevant to human intestinal diseases but also minimize the use of research animals.



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 17 of the past 20 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 FY15, the Department had more than $55 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 50,000 psychiatrists, non-psychiatric physicians and other health professionals through the MGH 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.
- **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. This year, 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.

- **Development and Evaluation of Novel Therapeutics.** Dr. Darin Dougherty and colleagues published the first controlled clinical trial of deep brain stimulation (DBS) for a psychiatric indication, in this case treatment resistant depression (TRD). All previously published clinical data of DBS for psychiatric illness (including obsessive compulsive disorder and TRD) have been open label data and the results have been encouraging. However, this controlled trial of DBS at the ventral capsule/ventral striatum for TRD was negative. Since publication of this manuscript, another controlled trial of DBS (at area 25 target) for TRD was halted due to a failed interim futility analysis. Currently, the field is evaluating whether open loop (continuous stimulation) DBS, while effective for movement disorders, may not be adequate for treating psychiatric illness. Efforts are now under way to develop closed loop (intermittent, responsive) DBS for psychiatric indications. One such initiative is the $30 million DARPA-funded SUBNETS project (part of the White House Brain Initiative) where Dr. Emad Eskandar (neurosurgery) and Dr. Dougherty serve as principal investigators

  Dougherty DD, Rezai AR, Carpenter LL, Howland RH, Bhati MT, O'Reardon JP, Eskandar EN, Baltuch GH, Machado AD, Kondziolka D, Cusin C, Evans KC, Price LH, Jacobs K, Pandya M, Denko T, Tyrka AR, Brelje T, Deckersbach T, Kubu C, Malone DA Jr. A Randomized Sham-Controlled Trial of Deep Brain Stimulation of the Ventral Capsule/Ventral Striatum for Chronic Treatment-Resistant Depression. Biol Psychiatry. 2015 Aug 15;78(4):240-8. doi: 10.1016/j.biopsych.2014.11.023. Epub 2014 Dec 13. PubMed PMID: 25726497.

- **Very early clues to Alzheimer's Disease:** To glean clues to the question of how early Alzheimer's Disease begins, Dr. Yakeel Quiroz and colleagues studied the brains of Columbian preteens and teenagers who carry the presenilin-1 "Paisa" mutation. As reported in the June 29 JAMA Neurology, they found that young cognitively normal carriers displayed the same functional brain abnormalities seen in older carriers. As expected, they also overproduced Aβ42. Unexpectedly, however, some abnormalities went in the opposite direction from those in older carriers. The brains of young carriers contained more gray matter in several regions than non-carriers had, and had stronger functional connections. Overall, the results indicate that the brains of carriers display detectable differences from non-carriers even by nine years of age. It is unclear whether these changes reflect different trajectories of brain development or early neurodegeneration. Future studies will be needed to determine whether similar early changes occur with other early-onset AD mutations or those who are on their way to developing late-onset AD.

  Quiroz YT, Schultz AP, Chen K, Protas HD, Brickhouse M, Fleisher AS, Langbaum JB, Thiyyagura P, Fagan AM, Shah AR, Muniz M, Arboleda-Velasquez JF, Munoz C, Garcia G, Acosta-Baena N, Giraldo M, Tirado V, Ramírez DL, Tariot PN, Dickerson BC, Sperling RA, Lopera F, Reiman EM. Brain Imaging and Blood Biomarker Abnormalities in Children With Autosomal Dominant Alzheimer Disease: A Cross-Sectional Study.JAMA Neurol. 2015 Aug;72(8):912-9. doi: 10.1001/jamaneurol.2015.1099.

- **Estimating Heritability of Brain Imaging and Other High-Dimensional Phenotypes.** Practical tools for high-dimensional heritability-based screening are invaluable for prioritizing phenotypes for genetic studies with the dramatic expansion of available phenotypic data. Classical estimates of heritability require twin or pedigree data, which can be costly and difficult to acquire. Alternative methods based on whole-genome data from unrelated individuals exist but are computationally intensive. Ge and colleagues present a novel, fast, and accurate statistical method for massively expedited genome-wide heritability analysis (MEGHA), and making heritability-based prioritization of millions of phenotypes based on data from unrelated

individuals tractable. The method was applied to large-scale heritability analyses of brain imaging measurements to demonstrate its potential for facilitating phenome-wide analyses and characterizing the genetic architecture of complex traits. Heritability was computed on global and local morphometric measurements derived from brain structural MRI scans, using genome-wide SNP data from 1,320 unrelated young healthy adults of non-Hispanic European ancestry. In addition, surface maps of heritability were computed for cortical thickness measures and empirically localized cortical regions where thickness measures were significantly heritable. These analyses demonstrate the unique capability of MEGHA for large- scale heritability-based screening and high-dimensional heritability profile construction. In addition to neuroimaging applications, the method is now being applied to screen for heritable phenotypes captured in the vast phenotypic repositories in electronic health record systems and population-based biobanks.

Ge T, Nichols TE, Lee PH, Holmes AJ, Roffman JL, Buckner RL, Sabuncu MR, Smoller JW. Massively expedited genome-wide heritability analysis (MEGHA). Proc Natl Acad Sci U S A. 2015 Feb 24;112(8):2479-84. doi: 10.1073/pnas.1415603112. Epub 2015 Feb 9. PMID: 25675487.

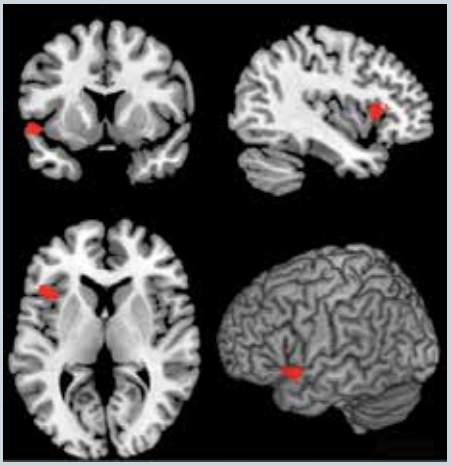
- **A New Resource for Assessing the Safety of Antipsychotics in Pregnancy.** In October of 2015, the first release of data from the National Pregnancy Registry of Atypical Antipsychotics was published in the American Journal of Psychiatry. The National Pregnancy Registry for Atypical Antipsychotics was established in 2008 to provide rigorous, prospective information regarding the reproductive safety of atypical antipsychotics. Based on the 214 cases of first-trimester exposure to atypical antipsychotics, it is reasonable to conclude that the use of an atypical antipsychotic during the first trimester does not substantively increase the risk of major malformations. Treatment decisions regarding discontinuation or maintenance of treatment with atypical antipsychotics during pregnancy are complex, and clinicians and patients must balance the potential risks of pharmacologic treatment with the risks of untreated psychiatric illness. Only through rigorously collected reproductive safety data can clinicians and patients make risk-benefit decisions tailored to individual clinical situations and patient wishes.
- **Identifying structural and functional brain signatures of smoking behavior.** Although nicotine addiction is characterized by both structural and functional abnormalities in brain networks involved in salience and cognitive control, few studies have integrated these data to understand how these abnormalities may support addiction. A recent MGH study found lower gray matter density and functional connectivity in the anterior insula in smokers compared with never smokers. Grey matter density in the anterior insula was inversely correlated with cigarettes smoked per day. Smokers also exhibited negative functional connectivity between the anterior insula and regions involved in cognitive control and semantic processing/emotion regulation. Additionally, there were differences in the anterior insula, a central region in the brain's salience network. Deficits in the lateral temporal cortex and prefrontal cortex (executive control) may contribute to the difficulty those with addiction have modifying pathological emotional responses that contribute to maintenance of addictive behaviors. This research has created a foundation to examining an understudied region in the context of addiction and an important area of future research focus. Future studies should examine the role of lateral temporal cortex functioning in nicotine addiction. Disruptions in these functions may protocol addictive behaviors and interfere with treatment success.

  Stoeckel LE, Chai XJ, Zhang J, Whitfield-Gabrieli S, Evins AE. Lower gray matter density and functional connectivity in the anterior insula in smokers compared with never smokers. Addict Biol. 2015 May 20. doi: 10.1111/adb.12262. [Epub ahead of print]

Psychiatry

Department Report

DEPARTMENT OF PSYCHIATRY FACULTY PUBLICATIONS 2015	
Journals Articles:	600
Books & Books Chapters:	85
Newsletters & Other:	7
Clinical Guidelines:	1
Patents:	1
Conference Proceedings:	6
TOTAL:	**700**



Lower grey matter density in left anterior insula, extending into the inferior frontal gyrus and lateral temporal cortex (red) in smokers versus controls (family-wise error corrected, cluster level, P,0.05, cluster extent = 768)

Jay S. Loeffler, MD, Chief

The mission of the Department of Radiation Oncology is to provide excellence in patient care by administering the highest level of quality in a safe and compassionate environment. We strive to excite, educate, encourage, train and mentor a diverse team of physicians, physicists, radiation therapists, and dosimetrists to become excellent caregivers, to develop methods to improve outcomes for patients with a wide variety of malignancies, to use their expertise to benefit their community, and to become future leaders in academic medicine and/or healthcare delivery. We are active participants, not bystanders, in the revolution of life science discoveries that will distinguish the first part of this century as reducing human suffering.

The four main areas of research focus within the Department of Radiation Oncology are:

1. **Cellular and Molecular Radiation Oncology Laboratory**—Working primarily at the cellular and molecular levels, but also at the whole organism level, our studies cover a range of radiation-related topics, including mechanisms of cell death, DNA damage induction and repair processes, intra- and inter-cellular communications, cancer genetics, radiation sensitization, radiation mitigation, particle radiations, and screening approaches for efficacy of drug-radiation interactions in various tumor types.
2. **The Edwin Steele Laboratory**—The Steele Laboratories include a highly interactive and multidisciplinary team of PI's directed by Professor Rakesh K. Jain. There are four main goals in the Edwin Steele Laboratory which include: 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. Development of new strategies to overcome these barriers in animal models, to translate these insights into the clinic to improve treatment of human patients, and to educate basic scientists, bioengineers, and oncologists in the integrative biology of cancer.
3. **Medical Physics Research Group**—The focus of physics research is considered translational in nature rather than basic research. Thus, physics research in radiation oncology is not only aimed at long-term goals where research results only find their way into the clinic via translation by vendors, but is also aimed at developments together with the clinical staff that changes treatment delivery and planning for our patients in the short-term, sometimes even while the patient is undergoing treatment.
4. **Proton Research Group**—The proton clinical research program has grown rapidly over the last five years. Our investigators are leading clinical trials of proton therapy in every radiation oncology subspecialty, we will continue to optimize the physical delivery of proton therapy with the adoption of a smaller proton spot size beam scanning and the incorporation of apertures and range compensators to facilitate delivery of highly conformal IMPT.

Notable Achievements in 2015

- Rakesh Jain, PhD, director of the Edwin L. Steele Laboratory for Tumor Biology wins the National Medal of Science. This prestigious honor is awarded by the President of the United States to individuals in science and engineering who have made an important contribution to the advancement of knowledge in the fields of behavior and social science, biology, chemistry, engineering, mathematics and physics.
- Thomas Bortfeld, PhD, Professor, received the Breit Preis award from the German Society for Radiation Oncology, DEGRO, at their annual meeting in June 2015 in Hamburg. This honor recognizes Dr. Bortfeld's for his outstanding international scientific contributions over the past 20 years that led to significant clinical improvements of radiation therapy. The Breit Preis is the most prestigious award of the DEGRO and Dr. Bortfeld will be the first physicist to receive this honor.

- Dan G. Duda, DMD, PhD, Associate Professor, became the Secretary General of the International Association of Surgeons, Gastroenterologists, and Oncologists (IASGO), and received the Capussotti Award from IASGO. He also became a 2015 Honoree of the One Hundred, Mass General Cancer Center, and a Warshaw Institute Fellow in Pancreatic Cancer Research. He delivered Keynote Lectures at the 14th International Wolfsberg/ESTRO Meeting on Molecular Radiation Biology/Oncology.

Dr. Rakesh Jain

Dr. Thomas Bortfeld (center) receiving the Breit Preis award

Steele Lab, including Dr. Jain in the front row and Dr. Duda three over to the right (gray sweater).

James A. Brink, MD, Chief

Tom Brady, MD, Director, Radiology Research

The Department of Radiology Research Mission is to advance the frontiers of medical imaging science through collaboration with physicists, chemists, engineers, mathematicians and clinical experts to develop and validate novel imaging approaches for scientific and clinical applications.

The approaches include: 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, grid structure of the brain, *in vivo* membrane potential measurements; 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; 5) development and application of analytic tools to support economically-based assessment of medical imaging technologies and outcomes research including machine learning to enhance patient care.

The Department is recognized as the national leader in Radiology research based on its scientific output and NIH funding. For the past 15 years MGH has held the #1 ranking in NIH funding among all academic Radiology departments. Through its major programs (below) and Core Facilities (PET Core, MRI Core and Tumor Metric Core), the department has significantly enabled the research efforts of many investigators in Anesthesiology, Cardiology, Emergency Medicine, Neurology, Oncology, Psychiatry, Radiation Medicine, Surgery and other MGH Departments.

Cardiac MR PET CT Program
Director: Udo Hoffmann, MD, MPH
Based on large longitudinal cohort studies published in **JAMA** by A. Pursnani and colleagues and a randomized trial reported ***N Engl J Med*** by P. Douglas and colleagues, the program reported in these general medicine journals on imaging results and cardiovascular outcomes in the community. Both studies served to educate physicians as to the benefits and limitations of diagnostic testing and emphasize a nuanced approach to judicious use of cardiac imaging as the clinical standard with implications for medical and interventional treatment.

In addition, the group has performed innovative translational research providing unique insights into the association between coronary atherosclerosis and inflammation, both by demonstrating the effect of medical therapy in high risk HIV patients by J. Lo and colleagues in **Lancet HIV** and by raising the provocative hypothesis that our field of view for imaging of atherosclerosis in the clinical setting should be expanded to include hematopoietic and extramedullary sites upstream from the atherosclerotic plaque by H. Emami and colleagues in **JACC Cardiovasc Imaging**.

The Gordon Center
Director: Georges El Fakhri, PhD
This was a pivotal year for the Gordon Center for Medical Imaging that received an endowment in perpetuity from the Bernard and Sophia Gordon Foundation resulting, over the next 10 years, in the creation of Gordon fellowships and Innovation Awards, Gordon faculty as well as an Endowed Gordon Professorship. The breadth and depth of scientific innovation and productivity is best characterized by the significant papers published ranging from instrumentation, biochemistry and radiochemistry to image quantitation and reconstruction.

Our push for improved understanding of pathophysiology through molecular imaging has been rewarded with several seminal publications: In a key work published in ***Angewandte Chemie,*** Normandin and colleagues described a novel approach to radiolabeling an approved nanoparticle drug and demonstrated its utility for noninvasive imaging of immune cell trafficking, a first in

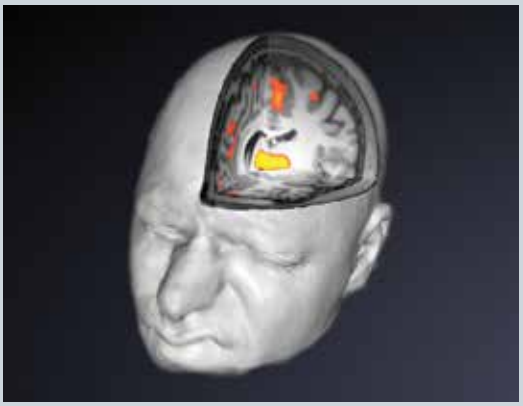
non invasive *in vivo* imaging. Rotstein and colleagues reported in **Nature Communications** on overcoming a major challenge to radiofluorinate non-activated aromatic rings that opens the way to major advances in the radiochemistry of PET radiotracers. The efforts to make PET instrumentation more accessible has also been rewarded with a groundbreaking fabrication process of scintillator crystals, reported by Sabet and colleagues in ***Medical Physics***, that uses laser-induced optical barriers that provide 3-fold improvement in spatial resolution and identical sensitivity while substantially reduction manufacturing costs. Imaging time is also being shortened significantly while compensating for the main factors affecting image quality such as patient voluntary and cardiac and respiratory motion. Huang and colleagues reported in **Medical Physics** on accelerated tMR images obtained with more than 4 times acceleration that can provide accurate motion fields and yield tMR-based motion corrected PET images with similar image quality as those reconstructed using fully sampled tMR data. Detection of focal brain tau deposition during life could greatly facilitate accurate diagnosis of Alzheimer disease (AD), staging and monitoring of disease progression, and development of disease-modifying therapies. In a seminal paper in the ***Annals of Neurology,*** Johnson and colleagues reported abnormally high cortical 18F-T807 binding in patients with mild cognitive impairment and AD dementia compared to clinically normal controls. Consistent with the neuropathology literature, the presence of elevated neocortical 18F-T807 binding was associated with clinical impairment. These findings suggest that 18F-T807 PET has great potential as a biomarker that reflects both the progression of AD tauopathy and the emergence of clinical impairment.

MGH Institute for Technology Assessment (ITA)
Director: Pari Pandharipande, MD, MPH
The ITA continued its history of productive, policy-relevant contributions in health outcomes research. In 2015 Pari Pandharipande, Chung Yin Kong, and Chin Hur developed one of the first mathematical models of pancreatic cancer that is capable of projecting screening benefits according to patient risk. They published a paper in ***Radiology*** that projects a potential life expectancy benefit when MRI screening is offered to high-risk populations. These populations include patients with multiple affected relatives, or who are known carriers of specific genetic mutations (e.g. STK11/LKB1 (Peutz-Jeghers)). This model will be important for identifying optimal paths to early detection, particularly as new screening platforms emerge.

With the goal of shaping national policies to address the high expense of new antiviral therapies for hepatitis C, Jagpreet Chhatwal and colleagues published a key paper in ***Annals of Internal Medicine*** in which they evaluated the cost-effectiveness of sofosbuvir and ledipasvir in U.S. populations. They found that use of these agents together was cost-effective for most patients, but that their use would cost payers up to $136 billion over the next five years, raising concerns about the affordability of these agents when applied on a national scale. Bridging science and policy directly, Amy Knudsen was part of a five-member, NCI-funded team that published a ***Technical Report for the Agency for Healthcare Research and Quality*** in which they used mathematical models of colorectal cancer to project the long-term benefits and drawbacks of a spectrum of colorectal cancer screening strategies. The results were used to inform the U.S. Preventive Services Task Force's preliminary recommendations for colorectal cancer screening in the United States.

Martinos Center
Director: Bruce Rosen, MD, PhD
The Martinos Center for Biomedical Imaging saw another year of significant accomplishments in developing and applying imaging technologies for the advancement of healthcare. Among the many examples: In an important study published in ***Cancer Research*** where Anna Moore and colleagues showed lasting regression of metastatic breast cancer in a mouse model using image-guided RNA-based therapies. This represents a substantial step toward the overall goal of the project: clinical translation of the therapies for patients with currently untreatable metastatic disease. In addition, in a ***Nature Scientific Reports*** paper, Matt Rosen and colleagues reported an ultra-low-field MRI

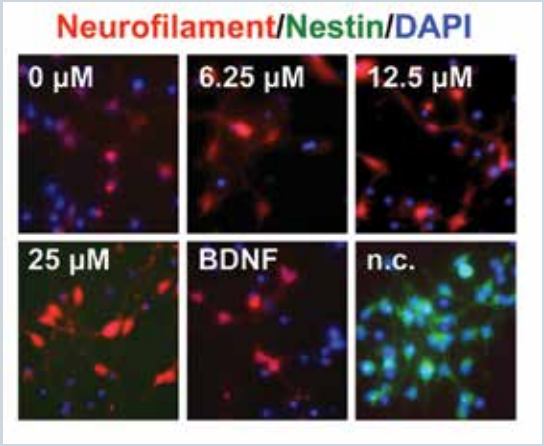
technique that could greatly expand the reach of the modality. Operating at a magnetic field strength of 6.5 millitesla—more than 450 times lower than with clinical MRI scanners—the technology could enable MR imaging in situations where MRI systems are not traditionally available: for instance, with mobile standalone scanners used during military conflicts, natural disasters or sports events. Also, we continue to see meaningful results from our PET and PET/MR research programs. In an ***Arteriosclerosis, Thrombosis and Vascular Biology*** paper, Peter Caravan and colleagues described a PET probe that could find blood clots anywhere with the body in a single PET scan. The probe could prove integral in identifying and treating secondary clots in the wake of a stroke. Further, in a PET/MR study reported in ***Brain***, Marco Loggia and colleagues found, for the first time, evidence of neuroinflammation in key regions of the brains of chronic pain patients see Figure below. This significant work paves the way for exploration of new treatment strategies while also suggesting a means to address a major limitation in the study and in the treatment of chronic brain patients—the lack of an objective means of measuring the presence or intensity of pain.



PET images from a chronic pain patient demonstrates evidence of higher levels of inflammation-associated translocator protein (orange/red) in the thalamus (Marco Loggia, PhD, Martinos Center)

Program in Neuroprotection Research
Director: Eng H. Lo, PhD

Our unit 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. We collaborate widely within and outside of MGH in order to dissect mechanisms of injury and repair in the CNS. In collaboration with Glaxo-Smith-Kline and the Harvard Stem Cell Institute, we established a platform to screen drugs in neural, glial and endothelial stem cells (Koh *et al*, **PLOS One** 2015). We have also collaborated with the MGH Center for Bio-MicroElectroMechanical Systems to initiate a microfluidic system to model the blood-brain barrier (Cho *et al*, **Sci Reports** 2015).



Isx-9 promoted the differentiation of neural stem/precursor cells in a dose-dependent way, increasing the mature neuron marker neurofilament, and decreasing the immature marker nestin (BDNF was used as a positive control)

Ragon Institute of MGH, MIT and Harvard

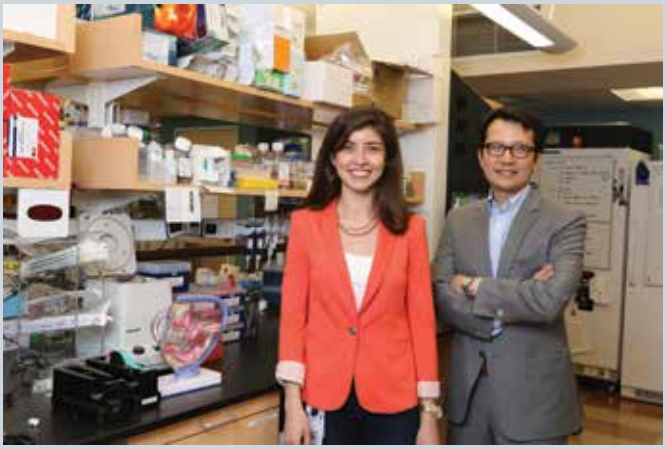
Department Report

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 a commitment of $150 million over 15 years from Mr. and Mrs. Ragon, in 2015 the Institute was given an additional $50 million to establish a new Endowment, as well as funding to establish two named Professorship Chairs at Harvard. The Ragon Institute is structured and positioned to significantly contribute to a global effort to develop an HIV/AIDS vaccine by:

- Creating non-traditional partnerships among experts with different but complementary backgrounds;
- 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 avenues of study that are unlikely to attract funding from traditional sources. Such funding will encourage innovation, compress the time it takes to conduct bench-to-bedside research and attract 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.



Anahtar MN, Byrne EH, Doherty KE, Bowman BA, Yamamoto H, Soumillon M, Padavattan N, Ismail N, Moodley A, Sabatini M, **Ghebremichael MS**, Nusbaum C, Huttenhower C, Virgin HS, **Ndung'u T**, **Dong KL, Walker BD**, Fichorova RN, and **Kwon DS**. "Cervicovaginal microbiota modulate host inflammatory responses in the female genital tract". *Immunity,* 2015 May 19; 42, 965–976. doi: 10.1016/j.immuni.2015.04.019.

Genital inflammation has long been attributed to increasing HIV acquisition risk, but the culprits of this inflammation were thought to be traditional sexually transmitted infections like chlamydia, gonorrhea, and herpes simplex virus. Anahtar *et al.* report the surprising discovery that genital inflammation is most highly associated with the billions of commensal bacteria that normally live within the female genital tract, much more so than the handful of pathogens that the field has focused on in the past. By applying cutting-edge sequencing methods to samples collected from an MGH clinical study in South Africa, they found that the majority of participants had genital communities with low lactobacillus abundance and high ecological diversity. High-diversity communities strongly correlated with genital pro-inflammatory cytokine concentrations in both cross-sectional and longitudinal analyses. They went on to perform detailed *in vitro* and *ex vivo* studies to identify the bacterial properties that elicit an inflammatory response from genital epithelial cells and antigen presenting cells. This paper has unveiled a new interventional target for the prevention of HIV acquisition in women at highest risk, while providing new insights in the role of the microbiome in health and disease.

Chung AW, Kumar MP, Arnold KB, Yu WH, Schoen MK, Dunphy LJ, **Suscovich TJ, Frahm N**, **Linde C**, Mahan AE, Hoffner M, Streeck H, Ackerman ME, McElrath MJ, Schuitemaker H, Pau MG, Baden LR, Kim JH, Michael NL, **Barouch DH,** Lauffenburger DA, **Alter G**. "Dissecting Polyclonal Vaccine-Induced Humoral Immunity against HIV Using Systems Serology." Cell. 2015 Nov 5;163(4):988-98. doi: 10.1016/j.cell.2015.10.027.

Following vaccination, waves of polyclonal antibodies are generated forming immune complexes poised to eliminate pathogens via innate immunity. With mounting evidence pointing to a role for extra-neutralizing-antibody functions in protection from HIV and other pathogens, a "systems serology" profiling approach was developed to capture the interactions between antibodies at unprecedented depths. Systems Serology revealed unique vaccine-induced "fingerprints", highlighting known-and-novel markers of protection against HIV, providing a powerful method for comparing vaccines for pathogens for which correlates of protection remain elusive.

Ndhlovu ZM, Kamya P, Mewalal N, Kløverpris HN, Nkosi T, Pretorius K, Laher F, Ogunshola F, Chopera D, Shekhar K, **Ghebremichael M**, Ismail N, Moodley A, Malik A, Leslie A, Goulder PJ, Buus S, **Chakraborty A**, **Dong K**, **Ndung'u T, Walker BD**. "Magnitude and Kinetics of CD8+ T Cell Activation during Hyperacute HIV Infection Impact Viral Set Point" Immunity. 2015 Sep 15;43(3):591-604. doi: 10.1016/j.immuni.2015.08.012. Epub 2015 Sep 8.

The ultimate goal of ending the HIV epidemic will require development of an effective and affordable HIV vaccine. By investigating how HIV attacks the body and how the body defends itself, our research seeks to identify molecular targets that can be exploited for a rationally designed HIV vaccine. This study utilized a very unique cohort of individuals identified before seroconversion to determine the earliest immune responses to HIV infection. The cohort termed FRESH, for Females Rising through Education, Support and Health is based in the Umlazi Township located in KwaZulu-Natal, South Africa, where HIV-prevalence rates in young women rise from less than 1% at age 15 to 66% at age 23. It has two interlinked objectives.1) provision of an intensive empowerment, life-skills and job readiness curriculum for young women living in poverty and at high risk of HIV infection, coupled with HIV prevention education, 2) Screening participants twice weekly by finger-prick plasma HIV RNA for evidence of acute HIV infection. The results show that the onset of plasma viremia is associated with a massive HIV-specific CD8 T cell response, the magnitude and rapidity of which are associated with set point viral control. The results also show that this period of acute infection leads to rapid immune dysregulation and failure to develop long term memory, providing key insights for understanding lack of control of chronic viremia.

Martin-Gayo E, Buzon MJ, Ouyang Z, Hickman T, Cronin J, Pimenova D, **Walker BD**, **Lichterfeld M**, **Yu XG**. "Potent Cell-Intrinsic Immune Responses in Dendritic Cells Facilitate HIV-1-Specific T Cell Immunity in HIV-1 Elite Controllers" PLoS Pathog. 2015 Jun 11;11(6):e1004930. doi: 10.1371/journal.ppat.1004930. eCollection 2015 Jun.

This study investigated cell-intrinsic immune responses against HIV-1 in dendritic cells (DC) in a small group of HIV-1 infected individuals who spontaneously control the infection in the absence of therapy, known as Elite Controllers (EC). We show that exposure of conventional DCs (cDCs) from EC to HIV-1 leads to a rapid and sustained production of type I interferons and upregulation of several interferon-stimulated effector genes, associated with an accumulation of viral reverse transcripts that were sensed by the cytosolic DNA sensor cGAS. Importantly, improved cell-intrinsic immune recognition of HIV-1 in cDCs from ECs translated into stronger abilities to stimulate and expand HIV-1-specific CD8 T cell responses. These data suggest an important role of cell-intrinsic type I interferon secretion in DC for the induction of effective HIV-1-specific CD8 T cells, and may be helpful for eliciting functional T cell immunity against HIV-1 for preventative or therapeutic clinical purposes.

Surgery

Department Report

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

Mission

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

Surgical Research Council

The Surgical Research Council (SRC), 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 itself. Serving as co-directors; Ronald Tompkins, MD, Mehmet Toner, PhD, and Martin Yarmush, MD.

Vital Organ Engineering and Tissue Regeneration

Jay 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, vascularized bone, CNS implants, and hepatic tissue for implantation or drug discovery. 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 and David Shahian, MD, serving as the associate director.

First Use of Antigen Specific Tregs in Patients

A team led by Drs. James Markmann and Laurence Turka initiated a clinical trial in which renal transplant patients receive antigen specific regulatory T cells (Tregs). Funded by a grant from the European Union, this trial, termed the ONE Study, investigates the use of cellular products as novel immunosuppressive treatments in transplantation. The MGH trial is the culmination of a collaboration with a Dr. Eva Guinan and her colleagues at the Dana-Farber Cancer Institute, and is the first ever use of antigen specific Tregs in patients. The team has received NIH funding to plan a liver transplant study in which the goal will be use antigen-specific Tregs to enable patients to reduce, and hopefully discontinue, their immunosuppressive drugs. In related work, Dr. Turka and colleagues published a landmark paper in Nature Immunology defining novel signal requirements for Treg homeostasis, and showing how inflammation can lead to loss of Treg stability. Lastly, Drs. Tatsuo Kawai and Benedict Cosimi received approval from the Immune Tolerance Network to conduct a novel renal transplant tolerance trial at MGH using a new protocol to induce mixed chimerism.

Using Patient Reported Outcome Measures (PROMs) to determine the best surgical procedure for metabolic and bariatric Surgery

Matthew M. Hutter, MD, was awarded $2.6M from the non-profit Patient Centered Outcomes Research Institute (PCORI) headquartered in Washington, DC. The study, titled Comparative Effectiveness of Metabolic and Bariatric Surgery Using Patient Reported Outcome Measures (PROMs), will be conducted over four years and will address the comparative benefits of three surgical procedures used to treat individuals with nutritional and metabolic disorders: bypass, sleeve, and band. Importantly, the study will aid patients and doctors to determine which of the three operations will deliver the best result for a particular patient based on the characteristics and natural history of the patient's disease.

The Laboratory for Organ Repair and Regeneration

Harald Ott, MD, and his research laboratory focuses on developing novel strategies to generate personalized solid organ grafts for transplantation, and to repair damaged organs *in vivo* and *ex vivo*. In early 2015, they reported a novel culture system that enables biomimetic whole organ culture of human lungs. This enables the translation of earlier work done in rodent lungs to human scale. They further reported novel non-invasive methods, to monitor cell metabolism in whole organ culture in vitro, an important improvement over current, more invasive techniques. In mid-2015, they reported engineering of a perfusable pulmonary vascular bed from adult derived induced pluripotent stem cells on native extracellular lung matrix. This was an important step towards the generation of personalized organ grafts, since blood perfusion is required immediately after transplantation, to provide nutrient and oxygen supply, and to enable higher level functions such as gas exchange. Next, they reported successful engineering of composite tissue on acellular matrix on the model of rodent and primate forearms. This study showed that tissues of high three dimensional diversity and complexity could potentially be regenerated to provide transplantable grafts in case of traumatic or surgical amputation. In late 2015, they reported the first study showing successful engineering of human stem cell derived myocardium on human whole heart matrix. Through a collaboration with the New England Organ Bank, they had the unique opportunity to perfusion decellularize human

hearts that had been declined for transplantation, and rebuilt functional myocardium on this platform. Looking ahead to 2016, they are on pace to successfully complete their first large animal transplantation studies of bioengineered lungs.

This image shows a decellularized heart matrix that has been repopulated with human iPS derived cells, and has undergone whole organ culture. Harald Ott, MD, The Laboratory for Organ Repair and Regeneration.

Collaborative Research: from hypothesis to startup

The Center for Surgery, Innovation & Bioengineering collaborative research activities have nurtured dozens of Newcos over the past decades representing productive research translation and commercialization. We are proud of the closing that took place recently for MicroMedicine, our first start-up to be financed since we became this new MGH Center. MicroMedicine is a company based upon three different applications of microfluidics technologies that have been incubating within the Hospital for many years. A non-traditional investor, the Oyak Group, which is a private pension fund management company with $18B in its portfolio, invested $35M for a 55% stake in MicroMedicine. As part of this deal, an intellectual property holding company (BostonNanoTech) has been established to fuel additional spinoffs based upon verticals of its multiple platform technologies. Also during 2015, we have had earnest discussions with Nippon Electric Corp (NEC) in four topic areas, two of which are moving forward rapidly. One spinoff, GeneralFluidics, which is a point-of-care diagnostics company, is entering into a corporate relationship with NEC for its product development, marketing, and sales worldwide. NEC is also entering into a NEC-MGH Collaboration in Big Data within our new Center. This collaboration takes advantage of NEC's data analytics systems and the very rich MGH clinical and research environment together with the Partners' database, Research Patient Data Registry. NEC represents a second, non-traditional investor opportunity for the Center.

CTC chip to isolate cancer cells. **The CTC chip, invented by Mehmet Toner, PhD, Co-Director, Center for Surgery, Innovation, and Bioengineering and co-developed jointly with Dr. Daniel Haber, Director MGH Cancer Center, has emerged as one of the most significant technological advances in the isolation of rare circulating tumor cells from the peripheral blood since its inception in 2007. The CTC-chip now requires no a priori knowledge of the tumor type to isolate the CTCs as it is based on negative depletion of billions to blood cells to find the rare CTCs.**

Urology

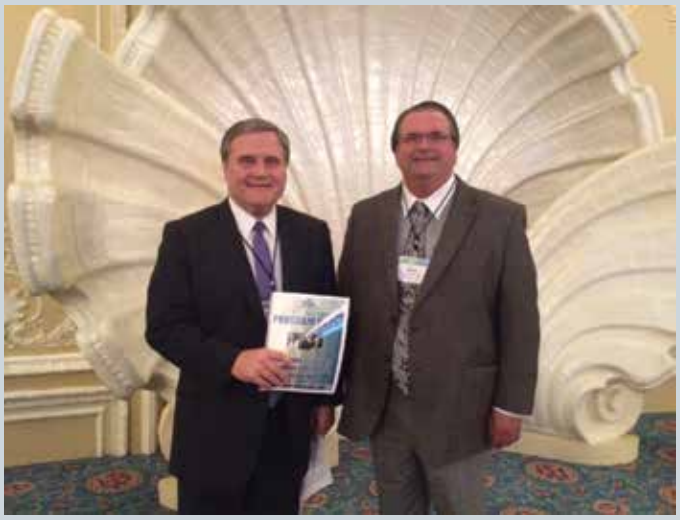
Department Report

Michael L. Blute, Sr., MD, Chief

The Department of Urology at Massachusetts General Hospital strives to integrate the missions of an academic department of urology. This includes excellence in clinical practice, education, research, and community care. We feel that the vision of the department of urology is consistent with the institutional strategic plan and will enhance the care of our patients and bring discovery and innovation to our practice. We strive to provide the platform for multiple educational opportunities for all levels to include staff, fellow, resident, medical student and paramedical personnel and promote CME activity. Finally, we work to integrate our clinical practice with research activity to expand the opportunity for translating discovery to clinical practice.

- Dr. Aria Olumi (Residency Program Directory & Director of Research) was selected from a competitive pool of applicants to serve a four-year term as the Chair of Research for the American Urological Association, the largest urologic professional society in the world. In this highly visible national position, Dr. Olumi will help shape the future direction of urologic research and research education nationally.
- With her commitment to advancing our understanding of male infertility, Dr. Cori (Cigdem) Tanrikut has been elected as president-elect for the Society of Male Reproduction and Urology.
- The Department of Urology had a record number of peer-reviewed publications in 2015. With 64 publications the Department averaged 4 publications per faculty member, which is a strong accomplishment for a clinical department.
- The Department celebrated the contributions of Dr. W. Scott McDougal, the immediate past chairman for Department of Urology at MGH. Internationally recognized faculty members were invited to a research symposium and celebratory dinner in January 2015 to honor Dr. McDougal's contributions to the field of urology.
- In an inaugural event that was held in Boston, Mass General and Johns Hopkins Departments of Urology came together for an educational CME credited event that received high praise from urologists who attended the three-day course. Given the program's success, next year's event will be held in Baltimore, and will alternate between the two cities annually.

Honor of W.Scott McDougal, MD, celebration that was held in January 2015.



Dr. Michael Blute (MGH Urology Chairman) and Dr. Alan Partin (Johns Hopkins Urology Chairman) at the joint MGH/JHH inaugural meeting.

The Massachusetts General Hospital Research Institute is a community of over 6,000 people working to find new diagnostics, devices and treatments to improve the lives of our patients—and those across the globe.

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