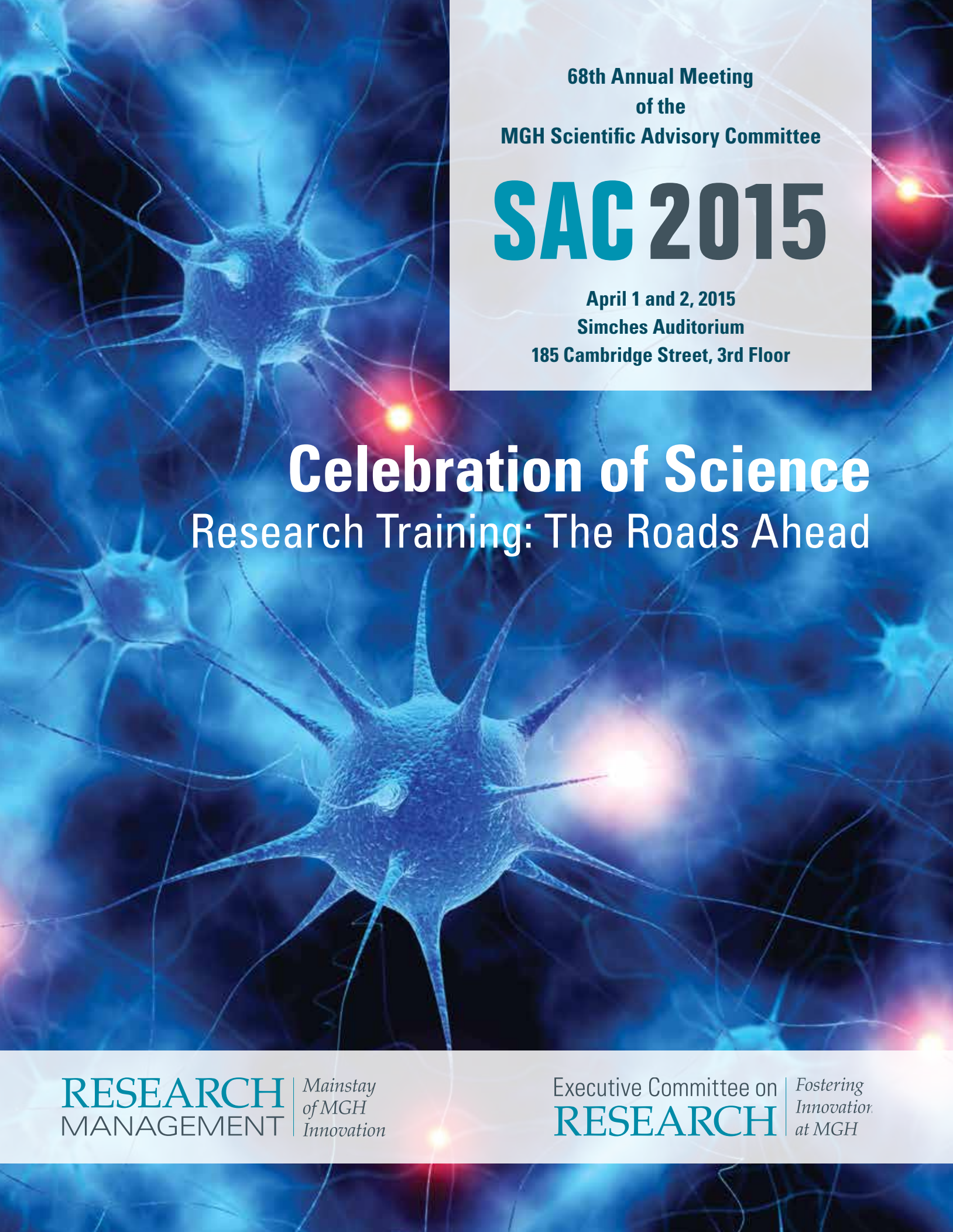


68th Annual Meeting
of the
MGH Scientific Advisory Committee

SAC 2015

April 1 and 2, 2015
Simches Auditorium
185 Cambridge Street, 3rd Floor

Celebration of Science

Research Training: The Roads Ahead

RESEARCH MANAGEMENT | *Mainstay of MGH Innovation*

Executive Committee on RESEARCH | *Fostering Innovation at MGH*



Welcome

Welcome to the 68th Annual Meeting of the MGH Scientific Advisory Committee (SAC) on April 1st and 2nd, 2015.

As in past years, we will begin our two-day SAC meeting with a Celebration of Science at MGH. Our poster session begins at 11:00 am on Wednesday, April 1, 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 2015 Howard Goodman Award recipient Alexander Soukas, MD, PhD and the 2015 Martin Basic and Clinical Research Prize recipients, Shyamala Maheswaran, PhD, and Sekar Kathiresan, MD. We are honored to have as our keynote speaker, Constance L. Cepko, PhD, from HMS. We will close the first day with a reception and dinner for invited guests at the Liberty Hotel.

On Thursday, April 2, Dr. Kingston will open the SAC meeting with an ECOR Report. After this report, Anne Klibanski, MD, Partners Chief Academic Officer, will give a presentation on the "Integration of MGH Research to the Partners Enterprise". We will next turn our attention to department presentations by the Directors of the Ragon Institute of MGH, MIT and Harvard (Bruce Walker, MD) and the MGH Cancer Center (Daniel A. Haber, MD, PhD), who will describe some of the remarkable research being conducted across MGH.

Training biomedical scientists in the current funding climate has numerous well appreciated challenges. This year seems an appropriate time to focus on how we meet those challenges and create opportunities for the various types of trainees we have at MGH.

Our afternoon session will include three focused panel discussions on training at MGH including:

Graduate Students–moderated by Thilo Deckersbach, PhD

Basic Research Fellows–moderated by Dennis Brown, PhD

Clinical Research Fellows–moderated by Andrew A. Nierenberg, MD

Experience has reaffirmed that we get the most helpful advice and perspective from SAC via open discussion of key issues. This year we have made a concerted effort to shorten presentations to allow more time for discussion with the SAC members.

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 Administration Executive Report and Financials for FY14 will be provided in these printed materials in advance of the meeting.

Dr. Kingston 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

Robert E. Kingston, PhD
CHAIR, EXECUTIVE COMMITTEE
ON RESEARCH

Harry W. Orf, PhD
SENIOR VICE PRESIDENT
FOR RESEARCH

SAC 2015 Wednesday, April 1, 2015
Annual Celebration of Science at MGH

11:00 am–1:45 pm / Simches, Floors 2 & 3
SAC 2015 Poster Session (light lunch available)

2:00–5:00 pm / Simches 3.110
Scientific Presentations

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

Opening Comments and Introductions
Robert E. Kingston, PhD, Chair,
Executive Committee On Research (ECOR)

2015 MGH Research Scholars
Dr. Kingston

2:15–2:45 pm
2015 Martin Prize for Basic Research
Targeting Cancer Metastasis through Circulating Tumor Cells
Shyamala Maheswaran, PhD

2:45–3:15 pm
2015 Martin Prize for Clinical Research
Leveraging human 'knockouts' to understand wellness and disease
Sekar Kathiresan, MD

3:15–3:45 pm
2015 Goodman Award
Regulation of starvation survival and fat storage by thrifty metabolic pathways
Alexander A. Soukas, MD, PhD

3:45–4:00 pm
Break

4:00–5:00 pm
Keynote Address
Reflections on Research Training
Constance L. Cepko, PhD, Professor, Genetics and Ophthalmology, Harvard Medical School
Investigator, Howard Hughes Medical Institute

6:00–9:00 pm
Colloquium Dinner & Reception (for invited guests)

6:00–7:00 pm
Reception

7:00–9:00 pm
Dinner

After Dinner Remarks
The MGH Research Institute
Susan A. Slaugenhaupt, PhD
Scientific Director, MGH Research Institute

SAC 2015 Thursday, April 2, 2015
Annual Celebration of Science at MGH

8:00–9:00 am / Simches 3.120
Breakfast
SAC Members with ECOR leadership

9:00–9:15 am / Simches 3.110
Welcome and Opening Comments
Peter L. Slavin, MD, President,
Massachusetts General Hospital

9:15–9:40 am
ECOR Report
Robert E. Kingston, PhD, Chair,
Executive Committee On Research (ECOR)

9:40–10:00 am
Integration of MGH Research to the Partners Enterprise
Anne Klibanski, MD, Partners Chief Academic Officer

10:00–11:30 am
Department Reports

10:00–10:40 am
Ragon Institute of MGH, MIT and Harvard
Bruce Walker, MD

10:40–10:50 am
Break

10:50–11:30 am
MGH Cancer Center, Daniel A. Haber, MD, PhD

11:30–1:00 pm / Simches, Floor 2
Lunch
SAC Members with Faculty

1:10–4:15 pm / Simches 3.110
Research Training: The Roads Ahead

1:10–1:20 pm
Opening Summary/Overview of Issue
Robert E. Kingston, PhD

Discussion Items
Roadblocks and Speedbumps
The current challenges facing trainees
Destinations
The opportunities & possible solutions
Bridges & Highways
The resources required to reach solutions

1:20–2:00 pm
Graduate Students
Moderator: Thilo Deckersbach, PhD
Panel: David Fisher, MD, PhD; David Langenau, PhD;
Andrea McClatchey, PhD

2:00–2:40 pm
Basic Scientist Fellows
Moderator: Dennis Brown, PhD
Panel: Bradley E. Bernstein, MD, PhD;
Sylvie Breton, PhD; Robert E. Kingston, PhD

2:40–3:00 pm
Break

3:00–3:40 pm
Physician Scientist Fellows
Moderator: Andrew A. Nierenberg, MD
Panel: Marcia Goldberg, MD; Jay Rajagopal, MD;
Ravi Thadhani, MD, MPH

3:40–4:15 pm
Open discussion:
"How does MGH capitalize in times of disruption?"

4:15–4:45 pm / Simches 3.120
Executive Session (SAC members only)

4:45–5:15 pm / Simches 3.120
Debriefing (SAC members and MGH Leadership)

Goodman & Martin Award Winners

2015 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 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.

Regulation of starvation survival and fat storage by thrifty metabolic pathways

Alexander A. Soukas, MD, PhD
Assistant Professor
Endocrine, Diabetes Unit & Center for Human Genetic Research

2015 Martin Research Prize for Basic 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 Basic research and Clinical research.

Basic Research

Targeting Cancer Metastasis through Circulating Tumor Cells

Shyamala Maheswaran, PhD
Associate Professor
Surgery & Cancer Center

Clinical Research

Leveraging human 'knockouts' to understand wellness and disease

Sekar Kathiresan, MD
Associate Professor
Cardiology & Center for Human Genetic Research

Keynote Speaker

Constance L. Cepko, PhD

Dr. Cepko is the Bullard Professor of Neuroscience and Genetics, in the Departments of Genetics and Ophthalmology at Harvard Medical School, and an Investigator at the Howard Hughes Medical Institute. She was an undergraduate at the University of Maryland and a PhD student at MIT, where she worked with Phillip Sharp on the assembly of the adenovirus capsid. She remained at MIT as a postdoctoral fellow in the laboratory of Richard Mulligan, where she was involved in the development of the first retroviral vectors. Her current research is focussed on the development of the central nervous system, with an emphasis on the retina. Her laboratory employs molecular and cellular approaches to discover how the >60 cell types of the retina choose their fates during development. The Cepko laborartory also has been working to develop gene therapy for prolonging vision in individuals who inherit disease genes leading to blindness. They are using AAV viral vectors to deliver genes that prolong the survival of rod and cone photoreceptors, the cell types that degenerate in most forms of blindness. Their current approach is to use these vectors to combat oxidative stress in photoreceptor cells.

The Cepko lab is also developing viral vectors for tracing neuronal circuitry. They have adapted the vesicular stomatitis virus (VSV) to enable the definition of cells that are synaptically connected. VSV transmits from one cell to the next only via synapses and they are exploiting this property to make vectors that work across many species to define microcircuits. They are also developing methods that use the green fluorescent protein (GFP) to regulate biological activities, as well as nanobodies that regulate biological activities in cells that express particular antigens.

Dr. Cepko is the founder of the PhD Program in Biological and Biomedical Sciences at HMS and was the Program Head for 11 years. She is also the founder and Co-Director of the Leder Program in Human Biology and Translational Medicine (LHB). LHB is an enrichment program for self-selected PhD students from across all of the Harvard University Life Sciences PhD Programs. The Program has two goals. One is to provide sufficient background in the basics of human anatomy, physiology, and pathology so that students can work in areas of human biology and disease in their future careers. The second goal is to bridge the cultural gap between scientists and clinicians. This is achieved by bringing students into contact with clinicians and patients, to enable them to appreciate the challenges and culture of practicing medicine. The Program courses and activities are designed to prepare students to work as members of translational teams in their future careers.

Scientific Advisory Committee 2015

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

Alan M. Garber, MD, PhD
Provost
Harvard University
Term: SAC 2012 through SAC 2015 (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 of the Department of Genetics
Professor of 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 2015

ECOR CHAIR

Robert E. Kingston, PhD
Chief, Department of Molecular Biology
April 2012–April 2015

ECOR VICE CHAIR

David Louis, MD
Chief, Pathology
April 2012–April 2015

ECOR PAST CHAIR

Daniel Haber, MD, PhD
Director, MGH Cancer Center
April 2012–April 2015

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

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

Katrina Armstrong, MD‡
Chief, Department of Medicine
Ex-officio

Dennis A. Ausiello, MD†
Department of Medicine
April 2013–March 2019

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

Sylvie Breton, PhD
Renal Unit/Nephrology
Elected Representative
January 2015–December 2017
Co-chair, MGH Research Council

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

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

Emery N. Brown, MD, PhD†
Anesthesia, Critical Care and Pain Medicine
April 2009–March 2015

Merit Cudkowicz, MD†
Chief, Neurology Service
April 2012–March 2018

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

Maurizio Fava, MD
Director, Clinical Research
Ex-officio

David Fisher, MD, PhD†
Chief, Dermatology
April 2009–March 2015

Robert Gerszten, MD
Cardiovascular Research Center
Co-Chair, Subcommittee on Review of Research Proposals
Ex-officio

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

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

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

Kurt J. Isselbacher, MD
Honorary Member

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

Anne Klibanski, MD
Chief Academic Officer, Partners
Chief, Neuroendocrine Unit
Director, Participant and Clinical Interactions Resource (PCIR), Harvard Catalyst CTSC
Director, Center for Faculty Development
Ex-officio

Keith D. Lillemoe, MD‡
Chief, Department of Surgery
Ex-officio

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

Joren Madsen, MD, DPhil†
Co-Director, Center for Transplantation Sciences
April 2012–March 2018

† Chair Appointment, ‡ Chief's Council

Executive Committee on Research

Officers and Members 2015

Karen K. Miller, MD
Neuroendocrinology
Co-Chair, Subcommittee on Review of Research Proposals
Ex-officio

David M. Nathan, MD
Representative
Harvard Catalyst Diabetes Unit
Ex-officio

Christopher Newton-Cheh, MD, MPH
Cardiology Division/Heart Failure & Cardiac Transplantation Representative
Committee on Clinical Research (CCR)
Ex-officio

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

Bruce Rosen, MD, PhD†
Director, MGH Martinos Center
April 2009–March 2015

Jerrold F. Rosenbaum, MD‡
Chief, Psychiatry
April 2012–March 2018

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 Unit
Elected Representative
January 2015-December 2017

Alice Shaw, MD, PhD
Cancer Center
Elected Representative
January 2013–December 2015

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

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

Rudolph E. Tanzi, PhD
Neurology
Elected Representative
Chair, MGH Research Council
January 2013–December 2015

Anne Thorndike, MD
General Medicine Division
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

Jeanine P. Wiener-Kronish, MD†
Chief, Anesthesia, Critical Care and Pain Medicine
April 2009–March 2015

Warren M. Zapol, MD
Anestesia, Critical Care and Pain Medicine
Chair, Subcommittee on Research Animal Care (IACUC)
Ex-officio

NON-VOTING MEMBERS

Gaurdia Banister, RN, PhD
Executive Director, Institute for Patient Care
Contributing Member

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

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

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

Ann Clancy, PhD
Director, Animal Welfare Assurance
Ex-officio

Christopher Clark, JD
Office of the General Counsel, Partners
Contributing Member

Christopher Coburn
Vice President, Partners Innovation
Ex-officio

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

Jules Dienstag, MD
Dean of Medical Education
Harvard Medical School
Ex-officio

† Chair Appointment, ‡ Chief's Council

Executive Committee on Research

Officers and Members 2015

Dianne Finkelstein, PhD
Director, Biostatistics Unit
Ex-officio

Michael L. Fisher, LPD
Director, Research Space Mangement Group
Ex-officio

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

Kate Gutierrez
Director of Development, Research
Contributing Member

Mary Hanifin, MBA
Sr. Director, Corporate and Foundation Relations
Contributing Member

Konrad Hochedlinger, PhD
Center for Regenerative Medicine
Co-Chair, Subcommittee on Animal Resources (SAR)

Elizabeth L. Hohmann, MD
Infectious Disease Unit, Medical Service
Partners IRB Chair
Contributing Member

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

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

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

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

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

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

Mary Mitchell
Corporate Director, Partners Research Compliance
Contributing Member

Bruce Morgan, PhD
Dermatology, CBRC
Co-Chair, Subcommittee on Animal Resources (SAR)

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

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

John Parrish, MD
CEO, CIMIT
Ex-officio

Kay Ryan
Director, Clinical Research Operations
Clinical Research Program
Contributing Member

Joan Sapir, EdM, MBA
Senior 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 Management

Executive Report for SAC 2015

Harry W. Orf, PhD
Senior Vice President for Research

Getting the Research Strategic Plan Off to a Running Start

At last year's SAC meeting, we presented to the committee a detailed overview of our new research strategic plan, a plan that had been formally approved and funded by the MGH Board of Trustees just one month prior to SAC. This plan, crafted to meet the many challenges of sustaining and growing our research enterprise into the next decade, contained three cornerstone elements: 1) establishment of an MGH Research Institute within the hospital; 2) building a multi-million dollar 18-bed Translational Research Center on the main hospital campus; and 3) implementing a "life registry" biobank to directly engage our patients as partners in research. The majority of our research management efforts in 2014 were focused on launching these initiatives and implementing other important components within the strategic plan. Accordingly, in the last section of this report (MGH Research Management—Progress in 2014), I summarize our progress on each cornerstone element and describe work on related programs aimed at improving support and service to the research community. But first, let's take a closer look at the results, events, and developments that impacted MGH research this past year.

By the Number$—Down But Bouncing Back

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

The effects of the 2013 government shutdown, sequestration, discontinuation of ARRA funding, and continued reductions to the NIH budget resulted in the first ever reduction in total research spending at MGH in FY2014, with revenues declining by $26M (3.4%) from $786M to $760M. Of the $760M, $575M was direct costs and $185M was indirect cost recovery. While spending was down in FY2014, the award dollars received from NIH in FY2014 actually grew from $339M to $350M. In fact, the percentage of funding awarded to MGH from the entire NIH extramural grant pool last year grew from 1.5% to 1.6%. This is a testament to the perseverance and resilience of the MGH research faculty and a hopeful indicator that research revenues will rebound in FY2015 (and early indicators are confirming this trend).

While we did not see noticeable growth in the volume of proposals submitted, we did have 20% more submissions in the "Other Federal" category and a 15% increase in submissions for internal funding, state, and local sponsors. Regarding new award trends, MGH did receive slightly fewer awards for FY14; however we saw new award amounts increase 36% to $745M (from $520M in FY13) due to a large increase in the dollar value of DHHS awards.

Support from direct DHHS funding (which consists mostly of NIH funding), now accounts for 46% of MGH research, down 3% from last year's 49%. Total research expenditures on DHHS-sponsored research in FY14 were $337M, a decrease of 9% compared to $372M in FY13. The decrease in expenditures in this area is largely attributed to operating under reduced funding guidance for the majority of the year due to sequestration and discontinuation of ARRA funding which commenced in 2009. Again in 2014, MGH remains the largest recipient of NIH funding among independent hospitals and 13th nationally for all institutions.

Research expenditures in the "All Other" category, which includes non-profit organizations, foundations, internal, subcontracts, and miscellaneous sponsors, again showed a slight increase of 2.7%, to $338M in FY14 from $329M in FY13, as investigators have continued to turn to these sources to buffer the constraints on NIH support. "Industry/Corporate" expenditures increased 1% to $58M

in FY14; this category has experienced large swings in expenditures over the last five years. The cumulative annual growth rate for FY10-FY14 across all sponsor types was 2.2%.

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 23 departments and centers.

Awards and Recognition

This summer saw the creation of the MGH Committee on Awards and Honors, chaired by Dr. Sam Thier, previous president of the hospital from 1994-97. The committee is charged with ensuring 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, and although it has only met twice, the committee has already championed the nominations of more than a dozen outstanding MGH scientists for major awards and society memberships.

National and International Awards. In 2014, MGH and its investigators continued to receive national recognition for their major research contributions. Gary Ruvkun, PhD, of the Center for Computational and Integrative Biology and the Department of Molecular Biology, together with Victor Ambros, PhD, University of Massachusetts, received three major awards this past year for their work identifying the existence of microRNAs in animals that control the activity of other genes. They received the 2015 Breakthrough Prize in the Life Sciences (awarded in November, 2014, each receiving a $3 million award), the 2014 Wolf Prize in Medicine from the Wolf Foundation in Israel, and the 2014 Gruber Genetics Prize from the Gruber Foundation through Yale University.

Other major awards and prizes received by MGH investigators in 2014 include the following:

Election to the Institute of Medicine
Bradley Hyman, MD, PhD, Department of Neurology

Election to the National Academy of Science
Emery Brown, MD, PhD, Department of Anesthesia, Critical Care and Pain Medicine
Vamsi Mootha, MD, Departments of Molecular Biology and Medicine

American Association for the Advancement of Science (AAAS) Fellows
Jay Loeffler, MD, Department of Radiation Oncology
Rakesh Jain, PhD, Department of Radiation Oncology
Jules Dienstag, MD, Department of Medicine, Gastrointestinal Unit

American Association of Neuropathologists Matthew T. Moore Lecture
David N. Louis, MD, Department of Pathology

American College of Surgeon's (ACS) 2015 Jacobson Innovation Award
Joseph P. Vacanti, MD, Department of Surgery and Center for Regenerative Medicine

American Microcirculation Society Eugene M. Landis Award
Dai Fukumura, MD, PhD, Department of Radiation Oncology

American Neurological Association Derek Denny-Brown Young Neurological Scholar Award
Leigh Hochberg, MD, PhD, Department of Neurology

Executive Report for SAC 2015

American Society for Radiation Oncology (ASTRO) Fellow
Thomas F. DeLaney, MD, Department of Radiation Oncology

American Society for Radiation Oncology (ASTRO) Gold Medal
Nancy Tarbell, MD, Department of Radiation Oncology

American Society of Hematology (ASH) Ernest Beutler Lecture and Prize
David J. Kuter, MD, DPhil, Cancer Center

American Society of Human Genetics 2014 Curt Stern Award
Mark J. Daly, PhD, Analytic and Translational Genetics Unit

António Champalimaud Vision Award
Joan Miller, MD, Department of Ophthalmology
Patricia A. D'Amore, PhD, Department of Ophthalmology
Evangelos S. Gragoudas, MD, Department of Ophthalmology
Anthony P. Adamis, MD, Department of Ophthalmology

Association of American Medical College (AAMC) Women in Medicine Leadership Development Award
Nancy Tarbell, MD, Department of Radiation Oncology

Brain & Behavior Research Foundation Colvin Prize for Outstanding Achievement in Mood Disorders Research
Andrew Nierenberg, MD, Department of Psychiatry

Endocrine Society Roy O. Greep Lecture Award
David M. Altshuler, MD, PhD, Departments of Molecular Biology and Medicine

Genetics Society of America Thomas Hunt Morgan Medal
Frederick M. Ausubel, PhD, Department of Molecular Biology

Harold Amos Faculty Diversity Award (Harvard University)
Aaron Styer, MD, Department of Obstetrics and Gynecology
Marcela del Carmen, MD, Department of Obstetrics and Gynecology
Tracey Cho, MD, Department of Neurology

International Society of Psychiatric Genetics' Theodore Reich Young Investigator Award
Ben Neale, PhD, Analytic and Translational Genetics Unit, Ctr for Human Genetic Research

Massachusetts Psychiatric Society (MPS) Outstanding Psychiatrist Award for Research
Jerrold Rosenbaum, MD, Department of Psychiatry

Muscular Dystrophy Association (MDA) Lou Gehrig Humanitarian Award
Merit Cudkowicz, MD, Department of Neurology

NIH Biobehavioral Research Award for Innovative New Scientists (BRAINS)
Amar Sahay, PhD, Department of Psychiatry and the Center for Regenerative Medicine

NIH Early Independence Award
Yakeel Quiroz, PhD, Department of Psychiatry

NIH New Innovator Award
Robert Anthony, PhD, Department of Medicine, Center for Immunology and Inflammatory Diseases

Oswald Avery Award for Early Achievement from the Infectious Disease Society of America
Rochelle Walensky, MD, MPH, Department of Medicine, Infectious Diseases Unit

Padma Shri Award of the Republic of India
Vamsi Mootha, MD, Departments of Medicine and Molecular Biology

Radiological Society of North America's Distinguished Investigator Award
Scott Gazelle, MD, PhD, Department of Radiology
Umar Mahmood, MD, PhD, Department of Radiology
Miriam Bredella, MD, Department of Radiology
Georges El-Fakhri, PhD, Department of Radiology
Anna Moore, PhD, Department of Radiology
Khalid Shah, PhD, MS, Department of Radiology
Gordon Harris, PhD, Department of Radiology

Robert L. Moody Prize for Distinguished Initiatives in Brain Injury Research and Rehabilitation
Ross Zafonte, DO, Physical Medicine and Rehabilitation

Transplantation Society Medawar Prize for Lifetime Achievement
David H. Sachs, MD, Transplantation Biology Research Center

MGH Research Scholars. As reported previously, ECOR, in partnership with the MGH Development Office and its external Research Advisory Council (RAC), 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 basic 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 2014 event last April, we announced the fourth group of MGH Research Scholars. These eight recipients were selected from 95 applications 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 2014 MGH Research Scholars are:

- Leif Ellisen, MD, PhD, Cancer Center;
- Katia Georgopoulos, PhD, Dermatology/CBRC;
- Thorsten Mempel, MD, PhD, Rheumatology, Allergy and Immunology;
- Matthias Nahrendorf, MD, PhD, Center for Systems Biology;

- Jayaraj Rajagopal, MD, Center for Regenerative Medicine;
- Stephanie Seminara, MD, Reproductive Endocrine;
- Jordan Smoller, MD, ScD, Psychiatry/CHGR;
- Jonathan Whetstine, PhD, Cancer Center.

Martin Prizes. The Martin Basic 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 2015 recipients for a 2014 publication are Shyamala Maheswaran, PhD, (Basic Science Award) for her Cell paper entitled, "Targeting Cancer Metastasis through Circulating Tumor Cells", and Sekar Kathiresan, MD, (Clinical Science Award) for his New England Journal of Medicine paper "Loss-of-Function Mutations in APOC3, Triglycerides, and Coronary Disease".

Goodman Award. The 2015 Howard Goodman Award recipient is Alexander Soukas, MD, PhD, from the Center for Human Genetic Research. 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 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 Fellow is chosen from the MGH community to honor that legacy and to support the pursuit of excellence by young scientists of uncommon passion and ability. The award is for two years, supported at $150,000 direct costs annually.

The Final Frontier (Space!)

The Research Space Management Group (RSMG) continues to act as the primary mainstay for space management, analysis, and planning within the research community. RSMG works closely with the SVP of Research, the SVP of Operations, and the Planning and Construction Department to ensure that research space activities and goals are aligned with those of the institution. RSMG also is responsible for maintaining the database of all capital equipment purchased with research funds or situated within a research area, completing a number of physical statistical audits of the equipment throughout the year, and serving as a resource for members of the research community looking to relocate, discard, or sell equipment registered in the database. RSMG also operates a number of very successful cores, the busiest of which is a glass washing/autoclaving service available to researchers in all of the research locations on or near the main campus, Charles River Plaza, or the Navy Yard.

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 in various locations throughout Boston and Cambridge. Although the amount of on-line research space remained constant from 2013 to 2014, Indirect Cost density dropped from $167 per square foot to $163 per square foot, representing a loss of approximately $10M in income to support research.

The Research Densification Committee, formed in 2009 and reconstituted in 2014 as the Research Space Advisory Committee (RSAC), a sub-committee of ECOR, works with RSMG to develop policies designed to improve research space utilization. It also reviews and approves new space assignment and reallocation recommendations developed by the RSMG professional staff. At the beginning of this year, RSAC had validated requests from the research community for an additional 90,000 nasf of space. During the year, RSMG was able to satisfy 28,547 nasf of these requests primarily

by partnering with a number of departments, assisting them in identifying and better using underutilized space already in their portfolio and, in a few cases, arranging for transfer of space from one department to another. At present, departments are requesting an additional 72,500 nasf of new space, down 20% from last year. Of this 72,500 nasf, approximately 30,000 nasf reflect recruitment or retention commitments.

Finding suitable solutions for space requests within the hospital's confined footprint continues to be the most challenging task within RSMG. This past year, working with RSAC, a series of projects were undertaken to look critically across departmental boundaries at spaces of low density and develop reallocation scenarios to satisfy new space requests and/or relieve crowding in spaces with very high densities. Recommendations were then brought to the Research SVP and ECOR leadership for review and approval. To date, five "density rightsizing" reallocation projects have been developed; two have been completed and three are currently in process.

A significant number of the large pending requests were addressed in the design of renovations for the previous Ragon Institute space in Building 149. After Ragon's relocation to new quarters in Cambridge, we recaptured 20,000 nasf of laboratory and office space on the fourth, fifth, and sixth floors. After exhaustive discussions with key researchers, chiefs of service, and RSAC, candidates for space in these areas were selected. These included Pathology Research, the MGH Cancer Center, the Martinos Center, CIID, the FACS core, Nuclear Medicine, and the Center for Systems Biology. The fourth floor component, the fifth floor offices, and the sixth floor laboratories and offices were completed and occupied in 2014. The fifth floor portion of the project experienced a number of unexpected delays and occupancy is expected mid-February 2015. Most of the scientists who have already set-up shop in the new labs (and others who had the opportunity to tour the fifth floor) are impressed with the transformation of the physical environment and the improvements in the HVAC infrastructure. Financial results from the research occurring in these newly activated laboratories will appear in next year's report.

Construction and Renovation Projects. RSMG, which serves as the client of record for all research construction or renovation projects, is managing or overseeing ongoing projects approaching the $8M mark. These projects are located in almost all of the major research locations including 400 Tech Square, Building 149, the Simches Building, Thier, 50 Staniford, and Gray Jackson and include a major renovation on White 12 and a portion of White 13 for the Translational Research Center.

During 2014, numerous projects were completed at the cost of $1.5M. These included Phase I of a renovation in 50 Staniford for Diabetes Research, a small recruiting/blood draw room for the MGH Bio Bank, and installation of an X-ray irradiator on the main campus, among others.

This coming year looks to be a very busy one for RSMG since approved projects with an estimated cost of $16.8M will be in full swing. The largest of these involves the 10th floor and a portion of the 2nd floor in Building 149, taking advantage of the space that is coming available after the Partners data center relocates almost all of its activity to a more secure site. This major 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. The other major project that is slated to start is renovation of Warren 6 to better accommodate the needs of Psychiatry research and the department's consultation program.

Survey and Analytical Activity. During 2014, RSMG continued to survey the research laboratories to ensure that the RSMG database contained accurate data for each lab's space, personnel, grants, and equipment. However, the department's ability to finalize departmental survey reports at the end of FY14 was hampered by the fact that replacement space management application software just

placed into production is not yet fully functional. Cooperative work is ongoing with Partners IS to ensure that this new application and its accompanying report generator will be available for full use by spring of 2015.

Animal Care (CCM) and Compliance (IACUC)

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 Transplantation Biology Research Center swine production facility located in Grafton, MA, which manages a breeding herd of 450 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. Its activities include husbandry, importing and exporting mouse lines from other academic institutions, 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 140 employees, including seven staff veterinarians (six of whom are board-certified in laboratory animal medicine or veterinary clinical pathology) and a leadership team of more than 12 mid- and director-level managers, provide these services.

Over the past year, animal census has increased throughout all facilities to the highest year-end level in 5 years, with our mouse average daily census approaching 25,500. 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. This savings was passed onto researchers as a 50% lower increase in FY2015 per diem charges from what was projected and published. In addition, the CCM hosted over 35 visits in FY2014 from research and laboratory animal leaders who have expressed interest in adopting a similar lean program operations model in their vivaria. Seminars 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. Also, CCM Assistant Director of Veterinary Services, Dr. Lori Palley, was recognized for her publication involving the characterization of the human-animal bond: Stoeckel, LE, Palley, LS, Gollub, RL, Niemi, SM, Evins, EA. **Patterns of Brain Activation when Mothers View Their Own Child and Dog: An fMRI Study.** PLoS One 2014; 9(10):e107205.

The Institutional Animal Care and Use Committee (IACUC) governs the use of research animals at MGH. 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 800 active protocols being performed by over 330 Principal Investigators.

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

- Oversight of the MGH IACUC Office was assumed by Anne Clancy, PhD, who joined MGH in June 2014 replacing Steve M. Niemi, DVM, who left in 2013.
- USDA and the City of Cambridge conducted annual inspections of the MGH animal research facilities; no deficiencies were identified in the program.

- In November 2014, AAALAC International conducted an in-person review of the MGH animal research program. Over a three-day period, a team of four site visitors reviewed all housing and procedural spaces on the Boston, CNY and Cambridge campuses as well as all off-site locations. The result of the site visit was generally favorable and provided the program with opportunities for improvement to ensure excellence in the care and use of animals in research. The final outcome of the review is expected to be available in February 2015 and will be shared with the research community.
- The IACUC adopted the web-based training program, CITI, to meet regulatory training requirements, promote compliance and provide a resource to research teams. The program included standard and custom modules developed in collaboration with CCM to include MGH-specific information.
- The IACUC office worked with the Insight team to make the eIACUC system available to other Partners Institutions (Brigham and Women's Hospital and McLean Hospital). This collaboration will continue in 2015 to ensure best practices are incorporated into the protocol review process and the electronic system that supports it. Suggested improvements to the eIACUC system were collected from the researcher community and will be implemented in 2015.
- In a significant collaboration across IACUC, CCM, RSMG and MGH Investigators, a rigorous review and approval process was implemented to enhance standard facility infrastructure, husbandry and veterinary care best practices in all satellite animal housing areas, ensuring these areas meet requirements of the Guide for environment, housing, and management of research animals in laboratory housing areas.
- The IACUC established a new review process for its policies and procedures to ensure its policies reflect current regulatory standards; policies are reviewed on a rolling basis and made available on approval as a reference to the research community.
- A team from CCM and the IACUC represented MGH at the AALAS meeting in San Antonio, Texas. Donna Jarrell, Gerry Cronin, and Anne Clancy presented in a Panel Session on innovative operational management entitled "Building a Culture of Continuous Improvement: Sharing Experiences"
- The IACUC, along with representatives from the research community and CCM, have taken a leadership role in co-chairing the Continuous Research Operations Improvement (CROI) Animal Care and Use Working Group who has worked to resolve ~50% of the suggestions received over the past 2 years 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, 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.

Over the past year, PRM completed several projects that improve the experience for the research community and focus on efficiency and transparency. New processes were implemented for the key research operational transactions. New reporting tools were designed that provide granular transparency into these key transactions, allowing for more effective management and

accountability. PRM also consolidated fourteen research support offices websites into a new centralized research site—the Research Navigator. In addition to creating a single site for information, the Research Navigator has functionality that allows investigators to manage their action items and monitor the status of the administrative requirements on their awards.

These initiatives help manage an increasingly complex research administrative operation and provide investigators and hospital grant administrators with precise, real-time information on their research portfolios. With this increased transparency, the administrative challenges faced by MGH Departments and Divisions have become more evident. The MGH SVP of Research, with the support of PRM, will use this information to work with specific research groups to adopt institutional best practices.

An additional challenge is the time required to review and approve award terms and conditions. Process improvements made by PRM to improve turnaround times have been hindered by an environment that has trended towards awards with more unacceptable terms and complicated collaborations. Foundations and other private sponsors are making more claims on the investigator's intellectual property as a condition of the award. Sponsors and collaborators are increasingly requiring intensive backup to demonstrate scientific progress and justify project expenses. These new challenges further complicate the already highly regulated federal funding environment and have slowed down the execution of agreements. This is a key area of concern, and PRM has engaged local research institutions to find ways to mitigate these challenges and reduce the time it takes to execute these agreements.

Distilling feedback from the MGH research community on the research administrative systems has been a priority over the past year for PRM. Improving the functionality, usability, and look and feel of the systems based on this feedback is a primary focus area for PRM over the next year.

Partners Innovation

Partners Innovation is MGH's commercialization arm. It recently re-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 have been recruited with senior investment, product development, R&D and supply chain experience. Discrete plans, deliverables and service objectives are set for each sector. Leaders are also expected to mentor junior staff who may not have been in industry or had high-level responsibilities.

Partners Innovation had a number of substantial outcomes, including the first acquisition of one of its portfolio companies, CoStim, by Novartis, which will return all funds invested to that point. The recent acquisition of Annovation, based on a new anesthetic drug developed in MGH Anesthesia, by the Medicines Company further validates the model and brings its IRR to more than 20%. MGH provided half the total investment to capitalize the Partners Innovation Fund. Additionally, Sunquest conditionally acquired GeneInsight, the path-breaking Partners personalized medicine company managed by Innovation. A comprehensive HIT commercialization strategy has been developed and is being implemented.

Finally, the first inaugural World Medical Innovation Forum will be held April 27-29, 2015. More than 1000 senior decision makers from the worldwide medical industry and investment community will join many of Partners most recognized faculty to explore breakthroughs in the neurosciences and the state of healthcare innovation. The focus this year is neurosciences, in 2016 it will be cancer and cardiovascular in 2017.

MGH OUTCOMES	FY13	FY14
Licensing Activity * *(exclusive and non-exclusive licenses, options (amendments with $ or IPP added)*	131	113
Material Transfer Agreements	908	1,073
New Disclosures *(with material inventions)*	383	408
Patents Filed (US)	218	253
Patents Filed (Int'l)	558	644
Patents Issued (US)	77	86
Patents Issued (Int'l)	237	172
Royalty and Licensing Income	$75.5M	$68.9M

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

Partners Office for Interactions with Industry (OII)

In 2014, OII 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 industry relationships.

This year, OII has rolled out several *process improvements* that reduce burdens on investigators and their relationships with industry and/or that address potential conflicts with more precision. OII has established a more efficient and comprehensive conflict of interest (COI) review process for IRB protocols by integrating the disclosure process for human subject research into the Partners electronic disclosure system and by working with the IRB to revise disclosure criteria and to integrate OII review of COI disclosures for IRB protocols. In addition OII, in collaboration with Research IS and Research Management, has completed a multi-year project to develop an electronic system for tracking and comprehensively capturing all individual investigators who are "responsible for the design, conduct or reporting" of Public Health Service-funded research and thus covered by federal regulations.

In terms of workload in FY14, approximately 9,000 Partners Individuals participated in the annual disclosure process. OII reviewed over 18,000 financial interests disclosed to Partners, evaluated 286 cases involving possible COIs in human subjects research, handled 1,400 consulting agreements, and processed over 3,300 user questions relating to consulting, COI disclosures, gifts, meals, speaking engagements, Sunshine reporting, research, and other topics.

In terms of *policy improvements* during 2014, OII conducted a broad review of policies on interactions with industry with the goal of making sure that they are no more restrictive than necessary to preserve the integrity of Partners research, clinical care, teaching, and service activities. This process led to the revision of several COI policies that further enable Partners and its staff to engage in a

wider range of appropriately overseen industry relationships. A key change has been the revision of policy regarding compensation of senior institutional officials in connection with outside Board positions. Moreover, OII has been collaborating with HMS on making significant changes to HMS research-related COI rules, and several of the changes that have been made were initiated by OII/COA. These changes substantially narrow the situations where the HMS "hard-stop" rules come into play and therefore substantially increase the extent to which Partners investigators can continue to participate in company-related research while having principled and adequately overseen company relationships. In addition, and in part as a consequence of OII's efforts to assure that various Partners and HMS policies that govern research are appropriately calibrated, HMS has undertaken a comprehensive review of their policies, with special attention to HMS 1(a) and 1(b).

Finally, as a matter of both *policy* and *process* improvement, OII has worked with the Chief Academic Officer and CEOs of major Partners institutions to substantially update the membership of the committee that oversees most COI-related matters and to include members that hold leadership positions within Partners, and has also worked on a succession plan for both committee chairs.

MGH Research Management—Progress in 2014

Clinical Research Program (CRP) Begins a New Chapter

An important component of the new strategic plan for research at MGH includes expanding and reorganizing the Clinical Research Program (CRP) to play a more integral and comprehensive role in bringing together the clinical and research enterprises within the hospital. Accordingly, under the leadership of its newly appointed (April 2014) Director, Dr. Maurizio Fava, the CRP will become the Division of Clinical Research (DCR) within the MGH Research Institute when the Institute formally launches later in 2015. This transition will be marked by the addition of new and modified support units within the DCR and by additional voting representation by the clinical research community on the Executive Committee on Research (ECOR). An executive summary of the goals and near term objectives for the new DCR are presented in Dr. Fava's inaugural Programmatic Report on the CRP in the section that follows this report.

Clinical Research Day continues as an important venue to celebrate clinical research at MGH. It showcases the CRP's efforts to build and support a viable community of clinical investigators and study staff across the institution. It is a platform for clinical investigators to present and receive recognition from the institution's leadership for their work, as well as a venue for interactions and collaborations amongst investigators. Participation in the 2014 Clinical Research Day was the largest ever, with an unprecedented 386 abstracts submitted, 65 team nominations, and a vibrant and well-attended poster presentation session. The day is also used to highlight issues at the forefront of clinical research on a national level and to discuss these in terms of their impact at MGH. The 2014, theme was integrating patient-centered research and patient care. Katrina Armstrong, MD, MSCE, Physician-in-Chief, MGH, and Jackson Professor of Clinical Medicine, HMS, served as the keynote speaker. Following Dr. Armstrong's keynote address, a panel discussion, moderated by Maurizio Fava, MD, focused on bridging the clinical research gap through patient engagement and translational initiatives. Leaders in patient-centered research provided their insight and suggestions on this topic to a diverse audience of clinical investigators.

The MGH Research Institute—Building Infrastructure, Preparing to Launch

As stated at the beginning of my report, we presented to last year's SAC committee a detailed overview of our new research strategic plan, a plan that had been formally approved and funded by the MGH Board of Trustees just one month prior to SAC. This plan, crafted to meet the many

challenges of sustaining and growing our research enterprise into the next decade, contained as its preeminent element the establishment of an MGH Research Institute, with the mission to "promote, support, and guide the diverse MGH research enterprise to better the human condition." Externally, the Institute is fashioned to become the "front door" through which we will engage federal and foundation funding sources, collaborators, and the industrial, venture capital, and philanthropic communities. Internally, it will become the vehicle for investment in translational research to fill the gap between our pre-eminent basic and clinical programs, and for engaging our patients directly to partner with us in research. It will also improve the support infrastructure and internal communication by establishing a formal program for continuous process improvement, leveraging technology, and increasing the efficiency of research spending by facilitating collaborative efforts and improving the effectiveness of our core facilities.

Immediately upon approval of the research strategic plan, a search committee was formed to hire a Scientific Director for the Institute. After a thorough internal search, Susan Slaugenhaupt, PhD, geneticist the Molecular Neurogenetics Unit in the MGH Center for Human Genetic Research and Professor of Neurology at HMS, was selected as the Institute's inaugural Director, beginning her duties as of September 2014. Dr. Slaugenhaupt's primary areas of responsibilities include developing closer relations with industry, broadening the philanthropic support base for research, training our investigators to think more "translationally" about their research programs, and reviewing scientific support (research cores, inter-departmental programs, etc.) within the research enterprise.

In the short time since Dr. Slaugenhaupt has come on board, she has already developed a number of initiatives. Working with our Development Department, Dr. Slaugenhaupt is engaging members of our Research Advisory Council (RAC) to devise strategies to broaden philanthropic support for basic research. In February 2015, Dr. Slaugenhaupt and Dr. Orf traveled to Palm Beach to speak at the first fund-raiser event for the Institute. In January 2015, working with Dr. Mason Freeman (see next section) and other members of research leadership, Dr. Slaugenhaupt hired Dr. Gabriela Apiou to become the Institute's first Director of Translational Research Training. Another initiative getting underway under Dr. Slaugenhaupt's direction is formulation of a plan to review scientific cores at MGH and across Partners, with an eye toward eliminating redundancies and improving efficiencies and cost effectiveness. Dr. Slaugenhaupt is also leading a committee planning formal launches of the Institute, internally and externally, later this year.

The MGH Translational Research Center (TRC)—Planning Underway

Shortly after the Trustees and senior hospital management approved the research strategic plan in March of 2014, Mason Freeman, MD, was named to be 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, together with Dr. David Nathan, Director of the Clinical Research Center (CRC), were both named by Dr. Maurizio Fava, as Associate Directors of what will become 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.

While all three of the cornerstone initiatives that comprise the research strategic plan require new infrastructure and personnel resources, the Translational Research Center (TRC) is the only one that also requires a major investment in new space. Before programmatic planning could begin on the TRC, the hospital faced the formidable task of identifying space with the capacity to house a self-sufficient, 18-bed clinical trial facility capable of taking industry or internally developed prospects in therapeutics, diagnostics, and/or devices from a pre-clinical stage into "first in human" studies and through phase 2b clinical trials. After an exhaustive search of both external and internal locations, we identified (and

senior hospital management approved) an option that will co-locate the TRC with our existing Catalyst-sponsored 5-bed Clinical Research Center, which is directed by Dr. Nathan and runs investigator-initiated trials on White 13. The co-located facilities will expand to 18 beds by encompassing the entire 12th floor of White, keeping the TRC within the heart of the main campus in-patient complex. When completed, the new facility will occupy over 10,000 net square feet of space between the two floors. Co-location with the CRC will also allow both programs to leverage excess bed capacities when available, and share common prep and analytical facilities as well as supervisory personnel.

Funding for the $10 million combined TRC-CRC facility was recently approved in the FY15 capital budget, and planning is well underway and now entering the design development phase. Because completion of the new facility will take over 18 months, plans are being developed now to make operational a smaller capacity version of the TRC within the existing CRC facility and to hire and house new project management and business development personnel nearby. The objective of the near-term plan is to demonstrate proof-of-concept to local pharmaceutical and biotech companies by successfully piloting small-scale studies within the existing CRC space.

Partners Biobank at MGH (Life Registry)—Exceeding Targets

The Life Registry 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. With the concurrent expansion of a similar effort this past year at Partners, the Life Registry program became a fully integrated component of the Partners Biobank and was renamed the Partners Biobank at MGH. 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 this past year, including the initiation of online consent, we have seen a dramatic increase in patient recruitment (to over 20,000), and our goal across Partners is to grow the Biobank to over 100,000 patient samples within the next five years.

Through the dedicated efforts of MGH Biobank co-directors, Susan Slaugenhaupt, PhD, and Jordan Smoller, MD, Biobank manager Alison Hoffnagle, MS, and their staff, the MGH program has enjoyed great success since starting operations this past summer. Infrastructure work already completed includes a new, dedicated Biobank consent/collection room in Wang 2, consenting space renovations on Wang 1 and Simches 2, and implementation of a training program for patient recruitment in Central Phlebotomy. Construction of an additional consent/collection room in Yawkey was recently approved, and design is underway for an electronic Biobank “kiosk” in the Wang lobby. The MGH team is looking to hire a marketing and education associate and web content manager, efforts to increase active on-line recruitment via Patient Gateway are underway, and a new Community Advisory Panel, consisting of patients and Biobank staff, will hold its first meeting in March 2015. Most recently, Partners approved additional funding to genotype the first 25,000 Biobank samples, and we anticipate 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 2014, consented subjects have exceeded 21,000 (with a monthly consent rate now exceeding 1,000), and actual sample collection is approaching 18,000. At MGH, face-to-face recruitment has tripled, with samples now being collected in both inpatient and outpatient settings, and the MGH team is consistently exceeding their monthly recruitment targets. Goals for this coming year include completion of the remaining

infrastructure projects described above, 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.

Getting Our Message Out (within MGH)! SAC-Inspired Research 'Road Shows'

Over the past three years, MGH Research Management has implemented numerous initiatives to improve support processes and give our researchers (our 'customers') a variety of ways to get their concerns heard and make the resources we offer more readily available. Included among these initiatives are a Continuous Research Operations Improvement (CROI) program, installation of a more user-friendly research intranet and ECOR websites (including a page containing over 60 'help-and-how-to' links), a 24 hour Research Administrator On-Call Line, faculty happy hours, a revised and streamlined weekly Research Newsletter, and more research senior management participation in public forum meetings such as ECOR, Research Council, Clinical Research Council, and RADG (Research Administrator's Discussion Group).

In spite of these efforts, feedback from last year's SAC lunch (where faculty members meet privately without research leadership present to discuss issues on their mind) informed us that important messages 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, this past summer, we developed a 'road show 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. In fact, as word has spread about them, demand for them has also increased. In the past eight months since the program began (June, 2014–January, 2015), we have held 14 road shows, have 5 more scheduled, and have already directly reached over 300 researchers on their 'home turf'. Feedback has been universally positive, with the most frequent comments being acknowledgements that researchers never knew about most of the resources or that they could be found so easily in one place (our research intranet). An added benefit of the road shows for our staff has been to raise their visibility to members of the research community and lower the barriers to those members asking for help when needed. We plan to continue the program, updating the content as warranted, and hope to visit every department annually.

Another project underway to increase visibility of the research enterprise within MGH is a plan to construct a permanent research exhibit in the main lobby of the hospital, an audio-visually active display where content will be changed every quarter. Approval was received to move forward with the exhibit in November and design plans are underway with the hope of 'unveiling' the first exhibit this summer. As an interim step, a static, "Eye of the Researcher" display, featuring photos and stories from our 28 MGH Research Scholars, is now featured on the public corridor connecting Yawkey to the main hospital complex.

Getting Our Message Out (outside MGH)! Using Social Media and the Web

In 2014, the research and marketing teams at MGH made a dedicated effort to increase the promotion of research-related news stories on the hospital's social media platforms. The result is an increased awareness of the role that research plays at the hospital, and better overall engagement with the hospital's social media followers. Research-related posts on the Mass General Facebook page have

proven to be some of the most popular, and have generated a lot of positive feedback from our followers, as illustrated by these representative research-related comments:

- "Simply amazing!!!
- "Awesome research...makes you think there is a cure for everything....somewhere, sometime."
- "Great research"
- "This is top notch research!"
- Thank you MGH for all the research"
- Thank you! Amazing research work as always!!!
- "MGH—my family will forever be grateful for research like this. Thank you for all your hard work and expertise. We are lucky to be so close to such a great hospital."

Our Facebook research posts now routinely reach over 12,000 people, with our most popular ones reaching over 30,000.

Research-related stories on Twitter have been promoted through the Public Affairs Office (@MGHNews) and Development Office (@MassGeneral) accounts as part of their regular content rotations. Together, they reach almost 25,000 regular followers.

Our external research web page (http://www.massgeneral.org/research), which was completely reconfigured last year and re-launched in January, is now much clearer, more interactive, and easier to navigate than the previous version, especially for the lay audience. This has resulted in a significant (ca. 20%) increase in usage. In 2014, page views hit 938,000, and sessions are now averaging over 1,200 daily, with 55% of the visitors being new to the site.

CROI Reaches Its Two-Year Anniversary and Prepares for an Upgrade

As described in my report last year, 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. Suggestions received are directed to Working Groups that meet regularly to address the issues presented and work on solutions. They are organized around 16 specific support areas (animal care and compliance, clinical research, materials management, etc.) and, in most instances, are co-led by a faculty and a professional staff member.

Two years after launching the program, almost 500 suggestions have been received and over 200 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. Recent suggestions that have significantly improved communication and visibility include one to organize Research Core Days at MGH, where all 50 of the MGH research cores display their offerings, and one to institute a Research Staff Appreciation Day for our non-PhD research staff. Both suggestions were implemented this past year and were very well received by the research community. In fact, the Research Core Day program is now conducted twice a year with sites alternating between Charlestown and the main campus.

This past October, as CROI turned two, we stepped back to examine the program by calling in an external consultant, Alan Robinson, PhD. Dr. Robinson is a professor at the Isenberg School of Management at UMass Amherst, an expert in corporate creativity and managing ideas within an

organization, and co-author of the books, "Ideas are Free" and "The Idea-Driven Organization". Dr. Robinson spent several days examining our program and interviewing those involved with it as well as researchers who had offered suggestions. Dr. Robinson's review identified three major areas of improvement needed to optimize the program: 1) Improve organizational alignment and buy-in by integrating the program throughout Partners; 2) Provide more formal training and a more intuitive toolset for those involved in triaging and managing suggestions; 3) refine the decision process and bring it in line with business owners who control resources needed to implement suggested changes. Following Dr. Robinson's visit, we held an all-day retreat to work on these and other ideas for process improvement. The result of these efforts is an emerging plan to implement a significantly refined program (CROI 2.0) across all of Partners starting this summer. Senior management at both MGH and Partners have endorsed this plan.

Research Institute Training and Education (RITE) Committee

Mandatory and recommended training offerings for members of the MGH research community currently reside in several departments—Environmental Health and Safety, Compliance, the Center for Faculty Development, the Clinical Research Program, and the Center for Comparative Medicine. While each department continues to develop and administer excellent courses, there has been no coordination among the offerings; each uses different programs to offer and track results and no uniform notification system exists. Accordingly, researchers must go to several different places to update training and must keep their own records to ensure they remain current.

In order to address these issues and provide a more coordinated and efficient experience for our researchers, the strategic plan called for the formation of a new Training and Education Committee. After an internal search, Andrew Nierenberg, MD, was named in November 2014 to chair the committee, members from each department offering courses were asked to join the committee, and Drs. Fava, Orf, and Slaugenhaupt were named as *ex officio* members from senior research management. The committee held its first meeting in January 2015 and has set out the following objectives to accomplish in its inaugural year:

- Develop a central catalogue of training requirements and courses
- Coordinate the rich array of teaching available both within MGH and across the Partners and Catalyst systems to improve the quality of offerings and reduce redundancy
- Develop a common toolset for use with online training offerings; provide the same 'look and feel' across different training courses
- Develop a training dashboard for each researcher so they can have one place to go to check and update all their training obligations
- Implement a training notification system that alerts researchers when mandatory training deadlines are approaching
- Begin an education campaign to explain to researchers the requirements for specific trainings and better prepare them to comply with the regulations

Overall, significant progress has been made in 2014 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,

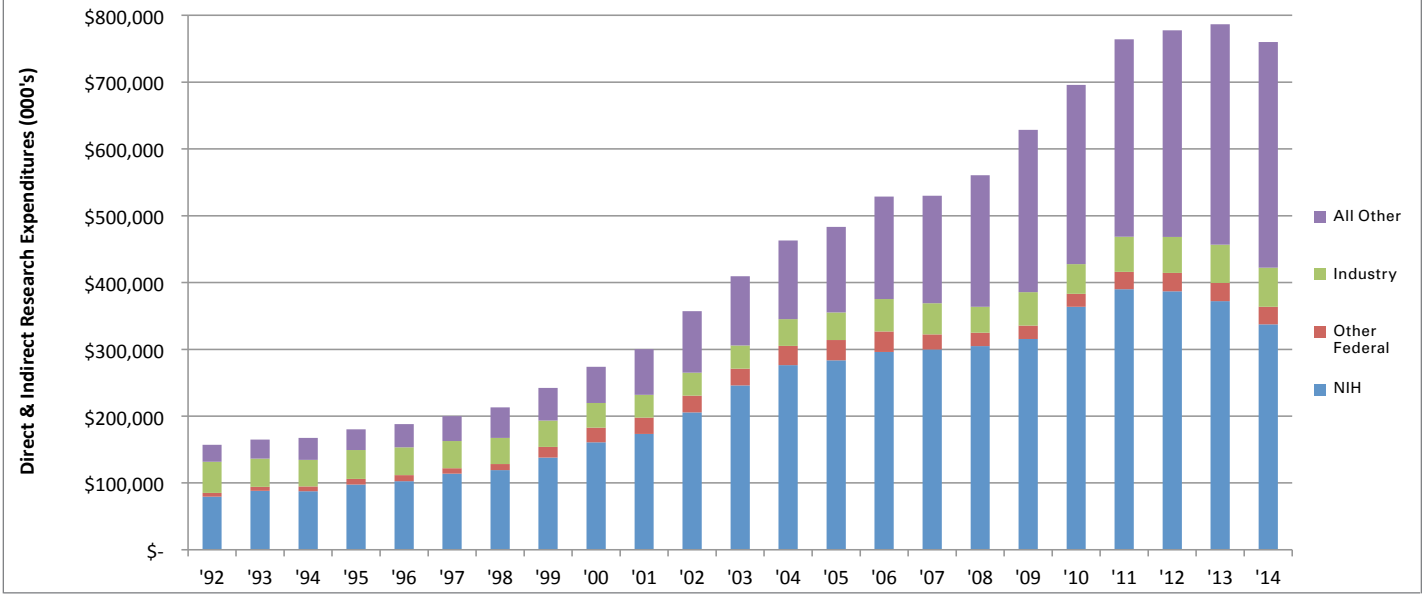
Harry W. Orf, PhD

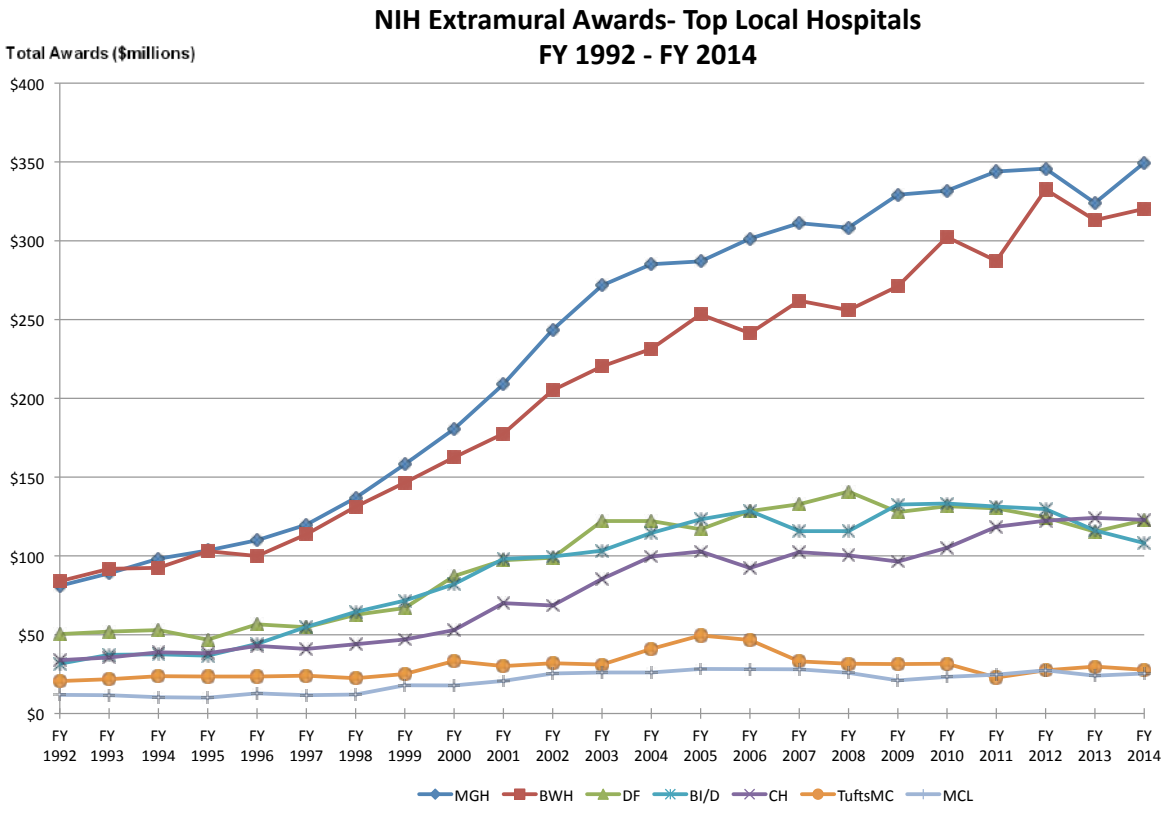
MGH Research Management

Executive Report for SAC 2015

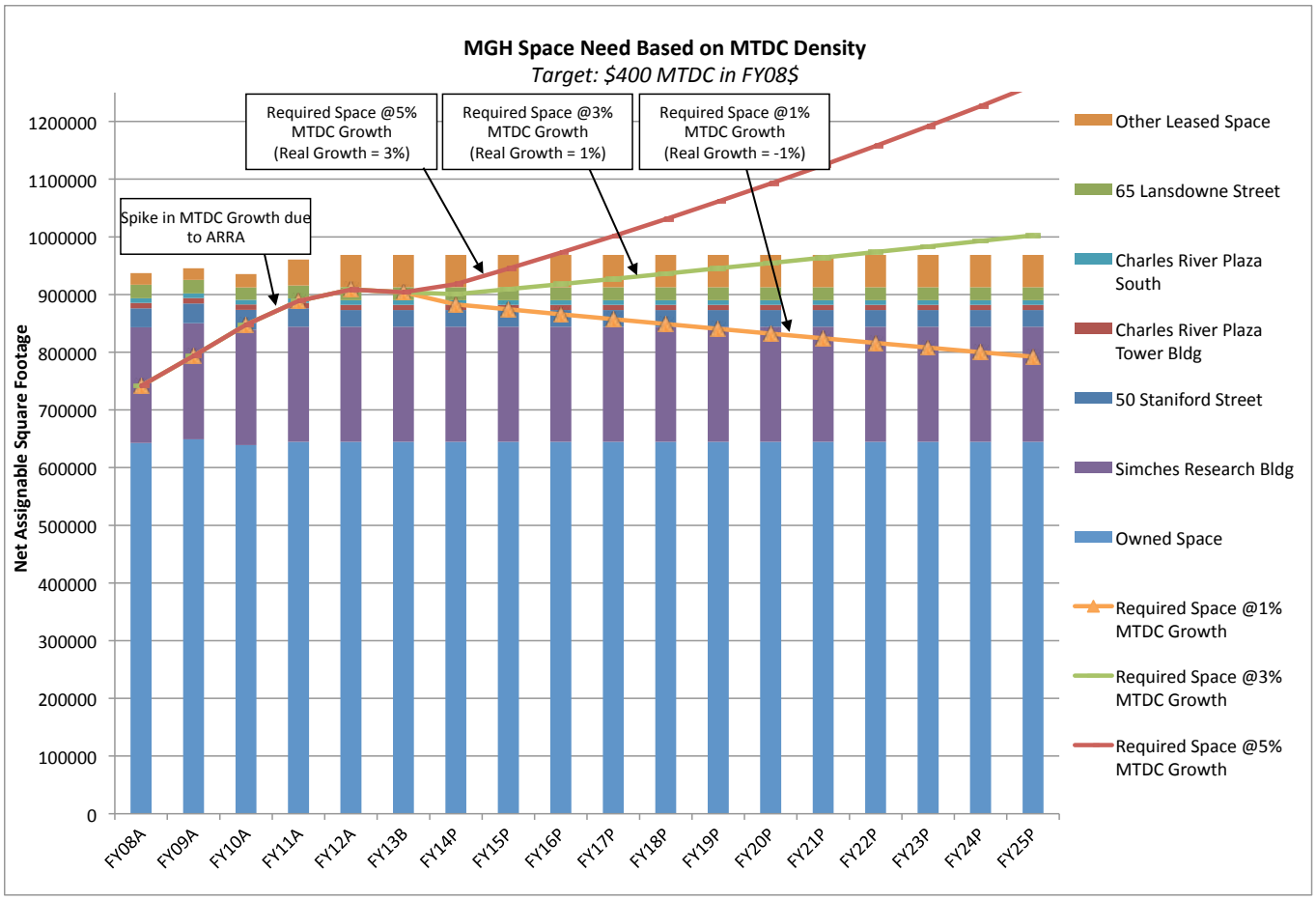
MGH Research has grown 354% over 20 years to $760M

MGH combined research has grown at a compounded annual growth rate of 7.9% between FY99 and FY14. The 5-year moving average annual growth has decreased from 7.5% in FY09 to 5.4% in FY14; the FY13-FY14 growth was (-3.4%) due to Sequestration and discontinuation of ARRA funding.

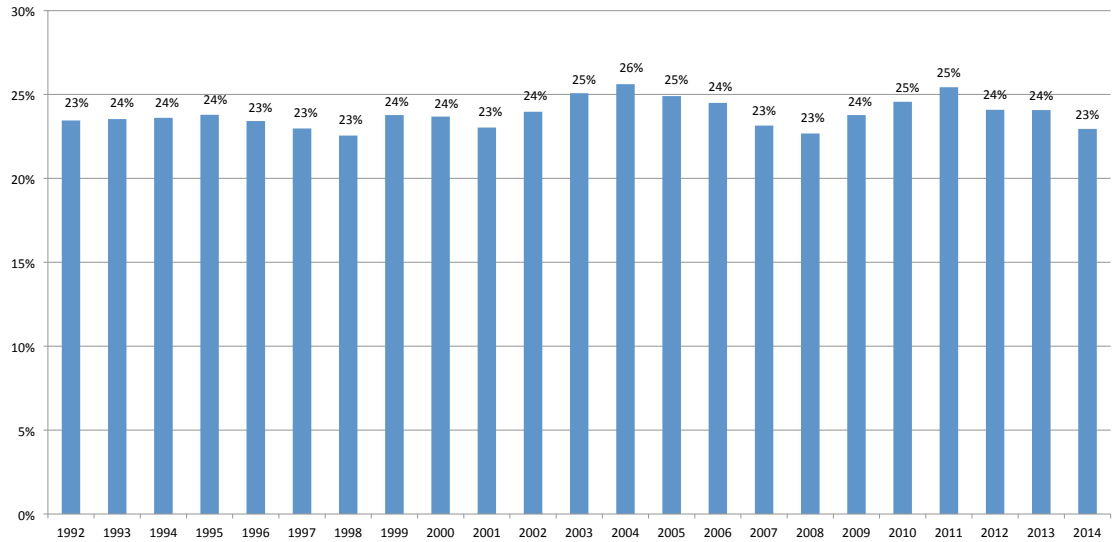




Executive Report for SAC 2015



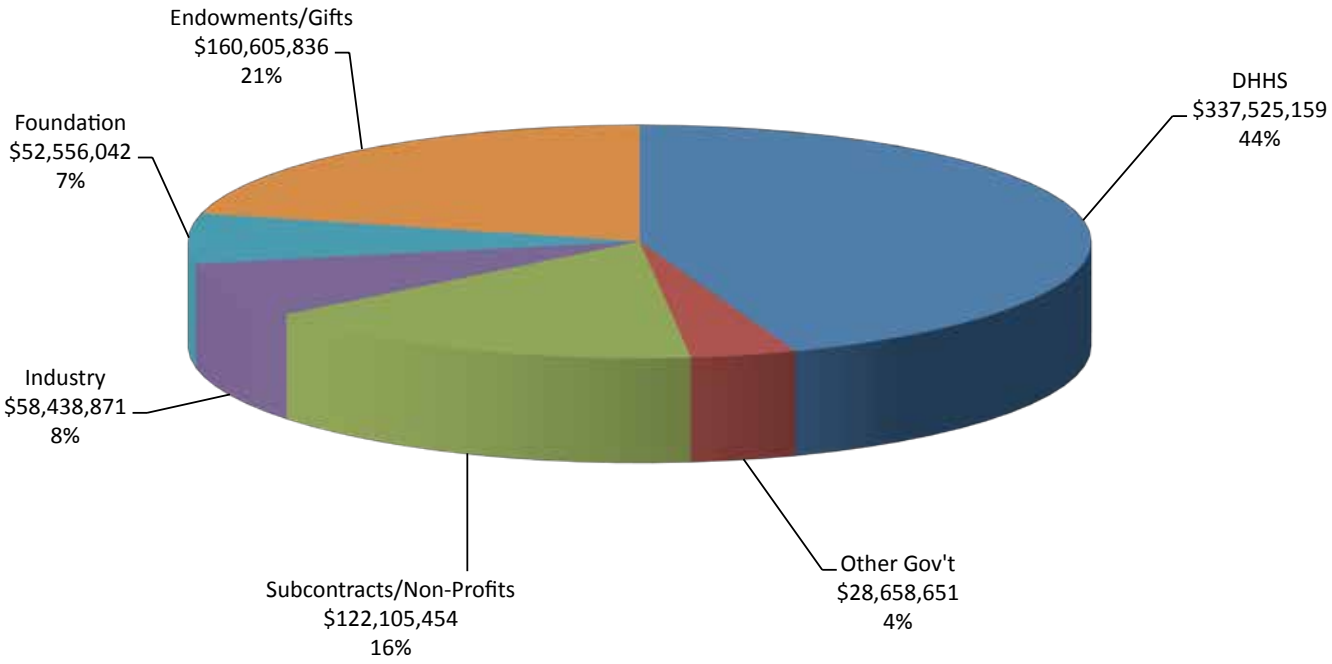
MGH Research Revenue as a Percentage of Total MGH Operating Revenue
FY1992 - FY2014 Actual



MGH Research Management

Executive Report for SAC 2015

Massachusetts General Hospital
Total Research Expenditures FY 2014
$759,926,321



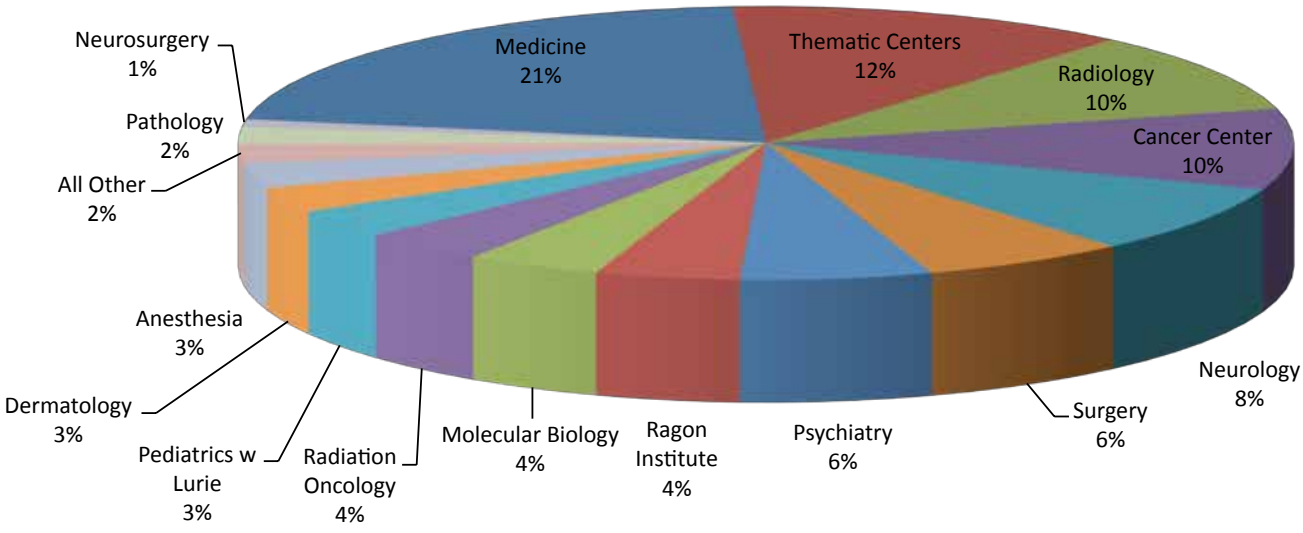
Notes:

1- DHHS includes ARRA funding

2- Other Gov't includes Other Federal and State/Local

Executive Report for SAC 2015

FY 2014 MGH Research Expenditures by Department Direct & Indirect Expenditures $760M



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

MGH Research Management

Executive Report for SAC 2015

MASSACHUSETTS GENERAL HOSPITAL
Science Activity by Sponsor

	Fiscal Year 10/01/13-09/30/14		
Type of Activity	**Direct**	**Indirect**	**Total**
Federal & State	251,896,888	114,293,913	366,190,801
Non-Federal	322,962,229	70,773,291	393,735,520
Total Expenses FY 14	574,859,117	185,067,204	759,926,321
Analysis of:			
Federal Activity by Sponsor			
DHHS	231,173,903	105,369,528	336,543,430
ARRA	987,937	783	988,720
DOD	15,732,241	7,825,201	23,557,442
USAID	518,608	84,297	602,905
NSF	449,752	295,286	745,038
DOE	550,921	45,169	596,090
Other Federal	459,117	175,535	634,652
Total Other Federal Activity	17,710,639	8,425,488	26,136,127
Subtotal Federal	249,872,479	113,795,798	363,668,278
State	2,024,409	498,115	2,522,524
Total State Activity	2,024,409	498,115	2,522,524
Total Federal and State	251,896,888	114,293,913	366,190,801
Non-Federal Activity by Sponsor			
Industry	43,312,464	15,126,407	58,438,871
Foundations	48,960,639	4,529,401	53,490,040
Subcontracts/Other Nonprofit	95,692,125	31,226,635	126,918,760
MGH Endowment & Gifts	133,443,847	19,890,847	153,334,694
Total Non-Federal Activity	321,409,075	70,773,291	392,182,366
Total Expenses	573,305,963	185,067,204	758,373,167
Harvard Medical School	1,553,154	-	1,553,154
Grand Total	574,859,117	185,067,204	759,926,321

Executive Report for SAC 2015

MASSACHUSETTS GENERAL HOSPITAL
SUMMARY OF DIRECT AND INDIRECT COST SCIENCE ACTIVITY
FY 1989 - FY 2014
(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
Government Grants & Contracts	$415,951	$415,114	$400,740	$366,191
Industry	$52,497	$53,864	$57,223	$58,439
Foundations	$64,620	$56,385	$59,487	$53,490
HMS Grants & Endowments	$1,258	$919	$1,553	$1,280
MGH Endowments & Gifts, Subcontracts /Other Nonprofit*	$229,719	$250,024	$267,509	$280,526
Total Direct & Indirect Costs	**$764,045**	**$776,307**	**$786,512**	**$759,926**

**2007 data was restated*

**2008 forward data includes Animal Facility*

Executive Report for SAC 2015

MASSACHUSETTS GENERAL HOSPITAL
SUMMARY OF ALL DIRECT COST SCIENCE ACTIVITY
FY 1983 - FY 2014
(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**

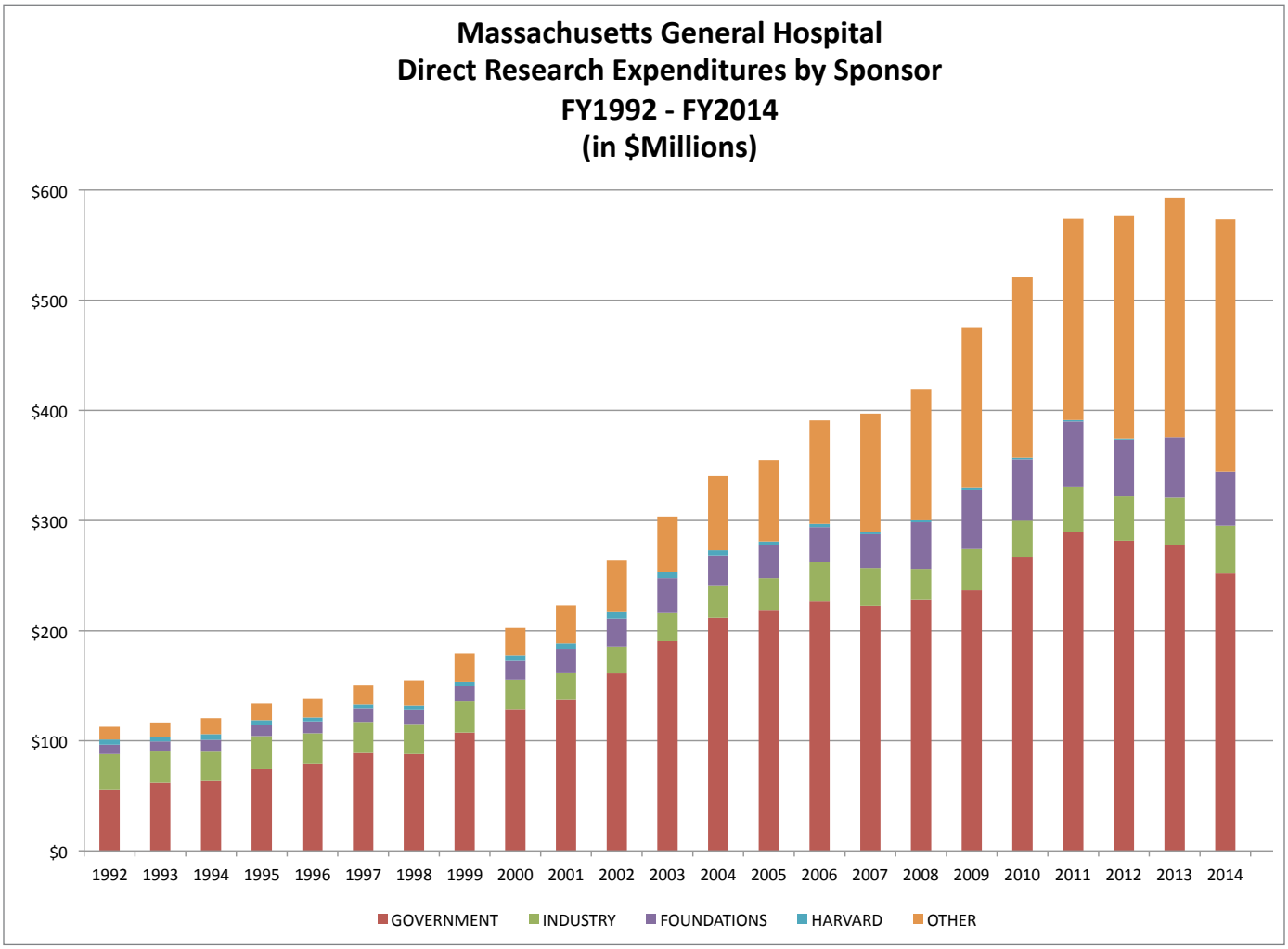
Sponsor	Actual 1997	Actual 1998	Actual 1999	Actual 2000	Actual 2001	Actual 2002	Actual 2003	Actual 2004	Actual 2005	Actual 2006	Actual 2007	Actual 2008	Actual 2009	Actual 2010
Government Grants & Contracts	$89,031	$88,035	$107,445	$128,693	$137,045	$160,990	$190,583	$211,802	$218,199	$226,609	$222,759	$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
Government Grants & Contracts	$289,838	$281,588	$277,899	$251,897
Industry	$40,643	$40,244	$42,927	$43,312
Foundations	$59,462	$51,670	$54,787	$48,961
HMS Grants & Endowments	$1,258	$919	$1,553	$1,280
MGH Endowments & Gifts, Subcontracts /Other Nonprofit*	$182,911	$202,196	$217,574	$229,409
Total Direct Costs	**$574,112**	**$576,616**	**$594,739**	**$574,859**

**2007 MTDC is restated*

**2008 MTDC includes Animal Facility and adjustments*

Executive Report for SAC 2015



Center for Faculty Development (CFD)

Programmatic Report

CFD

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

Mission

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

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

Focus

The 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 2014 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 ***108 professional development programs with ~ 3,250 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, ***259 individuals*** (72% faculty, 28% fellows, graduate students, residents and other staff) ***visited one of the offices this past year***, with the vast majority of the visits was for promotion and career advice.

Strategic Priorities

- Provide professional development programs, workshops that meet the needs of our faculty, as well as to continue to provide networking opportunities for the faculty.
- Continue to review the Annual Career Conference (ACC) statistics and work with departmental liaisons on the quality of the data. Review results from the ACC quality survey to gain a better understanding of the quality of ACCs from both faculty who receive an ACC, as well as those who conduct the ACC and ultimately enhance the ACC experience.
- Continue to facilitate the annual New Faculty Orientation to familiarize new faculty with MGH/MGPO senior leadership and available resources to enhance their MGH experience.
- Continue to recognize and celebrate outstanding mentorship by sponsoring the annual John T. Potts, Jr., MD Faculty Mentoring Award.
- Sponsoring and administering 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 which is directly related to his/her academic advancement.
- Enhance the MGH Faculty Involvement Opportunities (FIO) Initiative, which fills a gap in understanding how faculty can get involved to get ahead, which is critical to the academic advancement process.

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 to help locate appropriate funding mechanisms.

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 as well, including administering the MGH Guidelines for Research Fellows and advising the Mass General Postdoctoral Association (MGPA). In 2014, 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 faculty and research fellows in individual meetings aimed at career advice and troubleshooting.
- Collaborated with the MGH development office to offer individual consultations on identifying research funding opportunities.
- Continued to offer a six session seminar series on the **Responsible Conduct of Research (RCR)** open to NIH trainees and were 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.
- The six Session **New Investigator Advancement Initiative (NIAI)** continued for MGH faculty who currently hold their first NIH R-level grant.
- Sponsored the 8th annual **Research Fellows Poster Celebration**, to recognize the excellent research conducted by MGH postdoctoral fellows. Approximately 100 posters on display highlighted their research activity.
- 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.
- Expanded the **Career Explorations Series**, with panel discussions on academic job interviews, consulting careers and industry careers in 2014.

Center for Faculty Development (CFD)

Programmatic Report

CFD

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:
    - Support and advocacy for 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)
- Offer programming for research trainees, in particular career exploration programs, and seminars to prepare them for future success in the changing research environment, such as the MGPA Industry Careers Exposure (ICE) Club.
- Enhance the process for granting extensions on the 5-year term limit on the research fellow position, (e.g. by reviewing the CVs of postdocs requesting extensions beyond 6 years, and strongly encouraging a discussion between the ORCD director and PI in these cases, and a career advice meeting at the ORCD for the postdoc.
- Facilitate collaborations between the Graduate Student Division and the MGH postdoc community to help form mentoring relationships between postdoc mentors and graduate student mentees. This initiative will begin using a "mentored lunch" format that has been very successful in our Career Exploration series. If resources allow, the ORCD will also initiate a pilot mentoring program to match postdocs and graduate students for extended 1-on-1 mentoring experiences.
- Pilot an internship program to provide research fellows and interested junior faculty with opportunities to explore different career paths outside the research lab environment. The ORCD is researching and developing potential internships on (a) career development program management, and (b) scientific writing. Internships would be short-term (e.g. 3 months) and designed to allow the intern to work on a project approximately 4 hours per week.

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.

Focus

The GSD serves greater than 350 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 develop collaborations with relevant offices at MGH, Harvard and other graduate schools, establish communication and relationships with graduate schools administration, and to generate interest in recruiting more graduate students to MGH by raising awareness on how to apply as graduate program faculty. The office continued to offer educational seminars designed to help graduate students build professional and communication skills.

CFD

Achievements

In the past year the GSD provided 14 programs to help graduate students in the following areas: job search strategy, resume building, interview skills, fellowship applications, and funding opportunities. The GSD expanded efforts to provide individual career counseling and networking opportunities for graduate students here at MGH. The office collaborated with the GSD Committee and started to build graduate student sub communities at the CNY and Simches locations to help promote a feeling of "connectedness." The GSD connected with ten graduate programs (Harvard University and Boston University) on both the administrative and faculty leadership levels to establish relationships with area schools. The GSD developed content for its website, such as: MGH faculty listing by Harvard University graduate program, cost and tuition information, and new graduate student orientation materials. The GSD collaborated with ECOR to enhance MGH Find a researcher website to help graduate students to connect with Principal Investigators. The office revised the MGH graduate student registration process and created a database of current PhD students at MGH who register with the GSD.

Strategic Priorities

- *Programming:* Develop mentorship relationships between MGH postdoctoral fellow mentors and graduate student mentees.
- *Communication:* Develop a better understanding of the international students and their needs.
- *Community building:* Create a student sub community for international students.
- *Networking and Education:* Work with the GSD committee to enhance networking and exposure to industry.
- *Knowledge:* Facilitate in person orientation for new graduate students.

In addition, the GSD will continue to:

- Provide educational seminars, social events, and career consultations for MGH graduate students.
- Enhance and strengthen 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 graduate schools.

OWC—Nancy Rigotti, MD, Director

Mission

The OWC, Office for Women's Careers, 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 Office for Women's Careers (OWC) at MGH is a branch of the Center for Faculty Development (CFD) and 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

CFD

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. Highlights of OWC activity:

- Counseled women faculty in individual meetings aimed at career advice and supporting gender equity.
- Fostered networking and highlighted female leaders as role models with the "**Meet and Greet Networking Series**."
- Supported the growing community of **Claflin Distinguished Scholars** with a *panel discussion* for applicants, the *Claflin Consultation Initiative* to provide individual assistance to applicants, and the annual *Claflin Luncheon* to welcome the newest Scholars.
- Fostered outreach and support of female research fellows by women faculty with a **Mentored Lunch** event, which allowed small groups of postdocs to speak with faculty outside their departments about career advancement and work-life balance.
- Sponsored the 4th annual **Leadership Workshop for Women Faculty** to help faculty develop and achieve leadership goals.
- Sponsored the **Faculty Parents Group** with seminars and discussions aimed at providing information and peer support to faculty and research fellows with childrearing responsibilities.
- Sponsored panel discussions in the **Managing Parenthood and Your Career** series, aimed at helping faculty and trainees learn skills to keep their career on track during the childrearing years.
- Continued to offer the annual day-long **Business of Life** workshop, to help faculty develop strategic plans to advance their career and personal life.

Strategic Priorities

- Expand professional development programs and workshops that meet the needs of women faculty, addressing in particular the challenges of career and parenting, leadership issues for women.
- Encourage more women faculty to become involved in fundraising for their research and clinical careers with a workshop on communicating with donors, in collaboration with the MGH development office.
- Advocate for women faculty—especially women seeking flexibility in the work environment.
- Offer the Claflin Consultation Initiative and the 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.
- Continue to collaborate with MGH Center for Diversity and Inclusion, Department of Medicine Women in Medicine Committee and the HMS Joint Committee on the Status of Women.
- Offer the successful Leadership Workshop for women faculty which will cover 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.

CFD

OCC—Theodore A. Stern, MD, Director

Mission

The OCC, Office for Clinical Careers, 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 more than 100 faculty from a cross section of departments in one to one consultation sessions regarding: career advancement, CV critique, and career advice
- Based on feedback from advisory committee, designed and implemented three new educational programs: *Can I/Should I Be Promoted?, Check in at 2yr-3yr mark/Where am I in my clinical career? and Transition to Practice*, all which target self reflection for clinical faculty.
- Completed The Longer Service Initiative designed to reach out to faculty at the Instructor Level for more than ten years, to encourage interest in being promoted by the HMS Longer Service Criteria. Communications were sent to ~150 faculty members and department/division chairs as part of this process.
- Sponsored 10 educational programs: CV Narrative, Drafting Your Chief's Letter, etc., 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.
- Conducted seminars for staff on "How to Turn Clinical Experience into Scientific Publications" (to give staff the skills/tools to develop scholarly materials).

Strategic Priorities

- Expand professional development programs and workshops that meet the needs of clinical faculty, stressing academic and career advancement.
- 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.

CRP

Executive Summary

Maurizio Fava, MD, Director of Clinical Research, MGH

Founded in 1996, the CRP is now entering its 19th year.
The past year marked a leadership change in the CRP. Dr. William F. Crowley, Jr., who led the CRP since its inception stepped down and, after an extensive search with many highly qualified and talented candidates, Dr. Maurizio Fava was appointed to lead the CRP effective April 1, 2014.

Over the past two decades, the CRP has become fundamental to leading MGH in thinking about not only clinical research and where we are heading, but also creating a robust infrastructure and extensive training to support and prepare our clinical research community for where we need to be in the future.

Additionally, in the past year, three major initiatives came out of the MGH Strategic Plan and CRP is involved in all of them:

1. MGH Research Institute which seeks to **promote**, **support**, and **guide** the diverse MGH research enterprise by:
   - increasing its visibility
   - managing and growing its assets (people, funding, space, infrastructure)
   - preserving its leadership in innovation
   - fully integrating it with the clinical mission to better the human condition.
2. Translational Research Center (TRC which will close the research / clinical gap by establishing a specialized center focused on first-in-human studies
3. Biobank which will engage patients as partners in research and obtaining samples for research purposes

Since its inception, the CRP 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 CRP's Mission as well as MGH Strategic Plan recommendations, the following progress has been made since April 2014:

Key Changes

- CRP is now the Division of Clinical Research of the MGH Research Institute
- Clinical Research Council expanded (held monthly and open to all)
- A new Committee on Clinical Research has been created, with representation from all departments, major divisions, and thematic centers
- A close partnership with Harvard Catalyst and MGH CRC has been established
- The new Translational Research Center (TRC): 18-bed unit on White 12 co-located with CRC is being established
- CROI continues to be a key vehicle for community feedback
- Several thematic "Think Tanks" have been initiated (via meetings with representatives from Pfizer, Merck to discuss programmatic collaboration)
- EPIC for Research (revenue cycle) rollout at MGH has been facilitated
- *New* CRP Units since April 1, 2014:

CRP

Patient-Centered Outcomes Research (PCOR)

Rationale: PCORI grant applications are rising at MGH, yet many PIs do not know how to design/implement PCOR studies.
Services: consultation on study design, identification and incorporation of PROMs into clinical research setting and linkage with other clinical datasets, as well as stakeholder engagement.
Faculty: Dr. Joshua Metlay

Electronic Health Records (EHR) Research

Rationale: Access to large population through EHR allows for critical investigations using Research Patient Data Registry (RPDR) and Informatics for Integrating Biology & the Bedside (i2b2); few investigators take advantage of such resource.
Services: consultation on study design, generation of preliminary data, linkage with other clinical datasets and identification of potential collaborators.
Faculty: Drs. Roy Perlis & Shawn Murphy (advisor)

Imaging Biomarkers

Rationale: Many investigators at MGH underutilize imaging resources and may not even be familiar with state-of-the-art technologies.
Services: consultation on study design and imaging methodologies, feedback on draft research proposals, and identification of potential collaborators.
Faculty: Drs. Brad Dickerson & Scott Gazelle

Qualitative Research (coming in January 2015)

Rationale: Grant mechanisms, such as PCORI and many NIH funding programs (K and R awards, CTSAs) increasingly require qualitative research components.
Services: consultations and training
Faculty: Dr. Elyse Park

Modified CRP Units:

Education and **IT** Units are expanded to serve the MGH Research Institute
Dr. Andrew Nierenberg is the Chair of the Education and Training Committee
Dr. Henry Chueh is the co-Chair of the IT Committee

OMICS

Rationale: New technologies such as proteomics, metabolomics and transcriptomics are often underutilized at MGH
Services: consulation on omics and genetic methodologies and study designs, human subject protection, and identification of particular resources.
Faculty: Drs. Jordan Smoller & Rob Gerszten

Biostatistics

K-Awardees
Rationale: K-award budgets do not provide for statistical support, though it's critical for successful project execution.
Services: ongoing grant/research paper preparation support and guidance throughout the duration of K-awards.
Results Reporting to www.clinicaltrials.gov
Rationale: In response to requests for support in submitting trial results to www.clinicaltrials.gov the Biostatistics Unit has developed a statistical computing support to allow investigators to retrieve the summary measures required by the website.
Faculty: Drs. Dianne Finkelstein & Hang Lee

Clinical Research Program (CRP)

Programmatic Report

CRP

New CRP Structure

- Ten Units
- Education
- Biostatistics
- IT
- Comparative Effectiveness and Survey Research
- OMICS
- Clinical Research Support
- PCOR
- EHR
- Imaging Biomarkers
- Qualitative Research
- TRC
- CRC

CRP Priorities for the Future

- Create new **Philanthropy** Unit
  - Many PIs do not how to reach out to potential prospects
- Transform **Simches 2** into a "hub for clinical research"
  - Create a CRC satellite
  - Move/consolidate bioinformatics
  - Establish IRB and Innovation office hours
  - Conduct a survey on the MGH PIs biostatistical needs
- Continue to expand CRP by working closely with leaders from key departments/centers as well as TRC, Catalyst/CRC, Biobank etc.
- Continue to transform expanded CRP into the Division of Clinical Research, once MGH Research Institute is fully established
- Continue to create new services for MGH clinical research community by working closely with internal and external partners
- Facilitate subject recruitment, capitalizing on eCARE
- Improve access to CTMS
- Enhance efficiency of central administration of clinical research
- Continue to improve interface with the central (Partners) clinical research administration
- Improve our image with industry and our overall "user friendliness"
- Create new Think Tanks

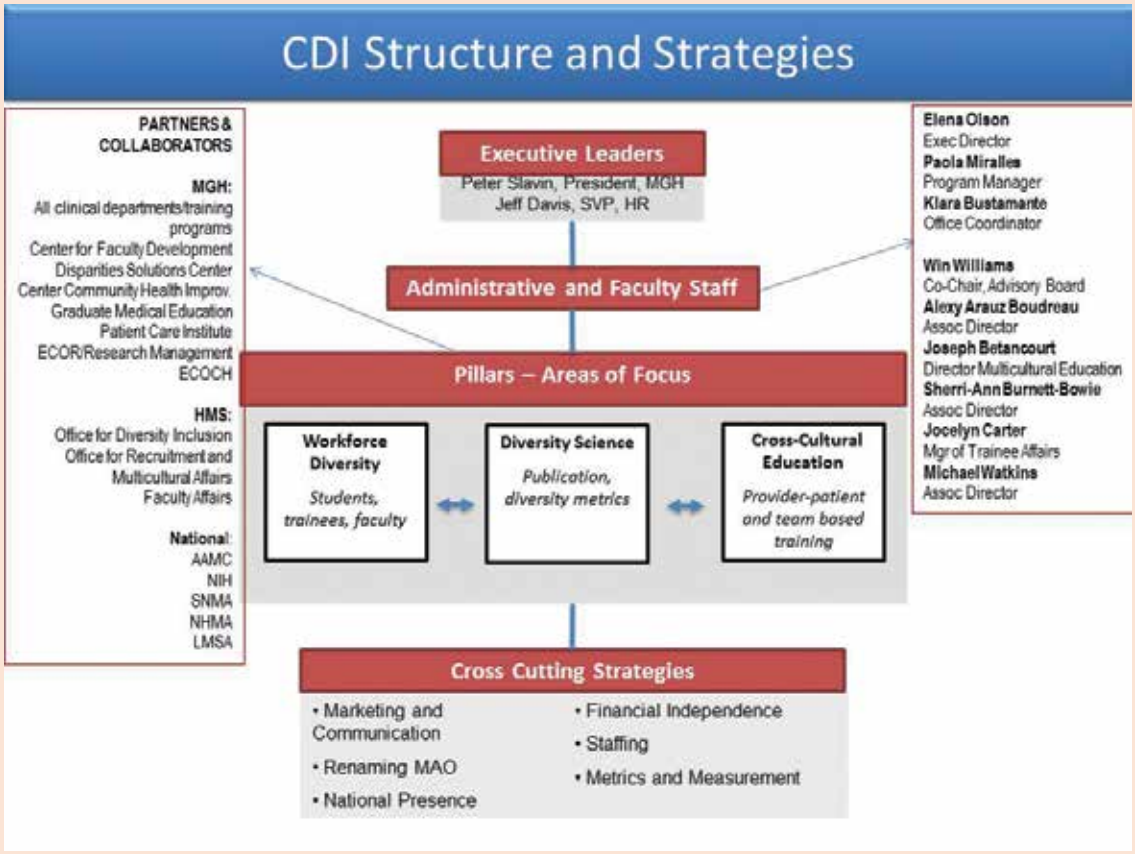
The full version of the 2014 CRP Progress Report is available online at
http://www2.massgeneral.org/crp/2014%20CRP%20Annual%20Progress%20Report.pdf

CDI

Elena B. Olson, JD, Executive Director

1. Mission

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



2. 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 dwiversity and inclusion by measuring outcomes of our programs and interventions

3. Current Strategic Priorities

- Integrating above focus areas into all MGH mission areas and the fabric of the institution
- Enhancing branding, marketing, renaming of office to center
- Advancing a new research workforce Initiative (detailed below)
- Educating workforce on cross-cultural teamwork and communication; race and social determinants of health

CDI

- Developing outcome measurement for all CDI programs
- Disseminating knowledge and innovation through publications and national presence

4. Achievements for the 2014 Year

4.1. OVERALL

Center for Diversity and Inclusion: In consideration of the multifaceted work and reach of the Multicultural Affairs Office, both MAO and MGH leadership decided this new name better reflects our contributions and value to the hospital. After extensive market research, rebranding efforts include the development of a new value statement, the creation of brochures and updates to the website, including video stories from the CDI community.

Recently, in the aftermath of the Ferguson and Staten Island cases, CDI has been involved in a number of efforts relating to discussions of race and race relations among our colleagues, residents and faculty. CDI is currently working with the MGH Diversity Committee to design an MGH community-wide race forum, the first of its kind.

4.2. PROFESSIONAL LEADERSHIP AND WORKFORCE DIVERSITY

Developing the Student Pipeline: Our student pipeline efforts start with our signature Summer Research Trainee Program, which brings in college and medical students to conduct novel research at MGH. After 22 years and over 270 students, we recently finalized a comprehensive outcomes survey to determine the impact this program has had on the careers of participants. Collaborating with the Mongan Institute for Health Policy, we are currently analyzing the data and preparing a manuscript for submission to a peer-reviewed journal.

Promoting Leadership at Harvard Medical School: CDI provides active outreach, mentorship and guidance to URM HMS students. This year, along with the President's Office and the Department of Medicine, CDI and MGH were the principal sponsors of the Student National Medical Association's Region VII annual conference at HMS. CDI's staff served as expert panelists and presenters on topics such as networking, professional development, and the benefits of physicians holding dual degrees. CDI mentors HMS students during their Primary Clinical Experience (PCE) and those doing rotations at MGH. 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, in partnership with the Lazarex-MGH Cancer Care Equity Program, CDI helped increase MGH's presence in Boston, Mattapan and Cambridge.

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 2014, for the third year in a row, we matched an overall 14% of URMs into our residency programs, with several programs exceeding 30%, well above the percentage of national graduates. What is most significant are the reasons cited by those who selected MGH: a welcoming community that values diversity and inclusion, and a place where they can see their future careers growing and flourishing. This feedback tells us we are making a difference.

During this year's recruitment season, CDI has met individually with the leadership of many residency programs to discuss URM and female recruitment and retention longitudinally since 1998. 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.

CDI

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 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.

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. Although still actively meeting, the workgroup's recommended strategies include advancing the research pipeline through marketing of NIH Diversity Supplements and focusing on the faculty who are here by helping them become successful independent investigators. The development of an extensive plan is still underway. As a direct outcome of CDI's efforts in faculty development, a second Physician/Scientist Development Award will be funded in 2015.

Promoting Clinical and Research Faculty through the Minority Faculty Development Award Program (MFDA): To date, CDI has awarded a total of 34 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 will be funding a second PSDA moving forward.

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 will be at the unit level in 2015. This program is spearheaded by CDI Associate Director Alexy Arauz Boudreau, MD, MPH, in partnership with the Institute for Patient Care and Nursing. 3) In partnership with the new Executive Committee on Community Health, Elena Olson is helping to lead an employee education campaign focused on the impact of social determinants of health.

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

CCIB carries out research that includes some of the most diverse and unusual programs at MGH, including basic scientific studies on the origin of life, on the possibility of life outside Earth, on problems in plant and microbial biology, translational medicine and host-pathogen/host-commensal interactions. 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 purview of NIH-funded single investigator awards.

CCIB houses and provides administrative support for the Translational Medicine Group at MGH, headed by Mason Freeman, MD, which designs and manages a variety of clinical research projects originating in both the academic and the private sector communities. The Translational Medicine Group has played a major role in the hospital's decision to create a Translational Research Center at MGH. Space on White 12 has been designated to house a new 18-bed clinical trial facility with capabilities to support both investigator-initiated studies as well as studies performed in conjunction with the biopharmaceutical community. The TMG is involved in designing the space and working with teams at MGH and Partners to ensure that investigators will have a usable clinical trial management system as well as appropriate data capture and analysis tools. The longest-standing drug development program has continued to proceed well with completion of a phase 1 trial of an SGLT2 inhibitor in Japan. The program held an end of phase 2 meeting with the FDA in January, 2014 and received input on the planned phase 3 development program. The first patients to be treated in the phase 3 program are expected to be enrolled by mid-year 2015.
Mitogen-Activated Protein Kinase (MAPK) cascades play central roles in innate immune signaling networks in plants and animals. In plants, however, the molecular mechanisms of how signal perception is transduced to MAPK activation remain elusive. We report that pathogen-secreted proteases activate a previously unknown signaling pathway in Arabidopsis thaliana involving the Gα, Gβ and Gγ subunits of heterotrimeric G-protein complexes, which function upstream of a MAPK cascade. In this pathway, Receptor for Activated C Kinase 1 (RACK1) functions as a novel scaffold that binds to the Gβ subunit as well as to all three tiers of the MAPK cascade, thereby linking upstream G protein signaling to downstream activation of a MAPK cascade. The protease-G protein-RACK1-MAPK cascade modules identified in these studies are distinct from previously described plant immune signaling pathways such as the one elicited by bacterial flagellin, in which G proteins function downstream of or in parallel to a MAPK cascade without the involvement of the RACK1 scaffolding protein. The discovery of the novel protease-mediated immune signaling pathway described here was facilitated by the use of the broad host range, opportunistic bacterial pathogen Pseudomonas aeruginosa. The ability of P. aeruginosa to infect both plants and animals makes it an excellent model to identify novel types of immunoregulatory strategies that account for its niche adaptation to diverse host tissues and immune systems.

Cheng, Z., Li, J.F., Niu, Y., Zhang, X.C., Woody, O.Z., Xiong, Y., Djonović, S., Millet, Y., Bush, J., McConkey, B.J., Sheen, J., Ausubel, F.M. Pathogen-secreted proteases activate a novel plant immune pathway. Nature. In press

Monomeric CRISPR-Cas9 nucleases are widely used for targeted genome editing but can induce unwanted off-target mutations with high frequencies. We have developed dimeric RNA-guided FokI nucleases (RFNs) that can recognize extended sequences and edit endogenous genes with high efficiencies in human cells. RFN cleavage activity depends strictly on the binding of two guide RNAs (gRNAs) to DNA with a defined spacing and orientation substantially reducing the likelihood that a suitable target site will occur more than once in the genome and therefore improving specificities relative to wild-type Cas9 monomers. RFNs guided by a single gRNA generally induce lower levels of unwanted mutations than matched monomeric Cas9 nickases. We have also established a simple method for expressing multiple gRNAs bearing any 5′ end nucleotide, which gives dimeric

CCIB

RFNs a broad targeting range. RFNs combine the ease of RNA-based targeting with the specificity enhancement inherent to dimerization and are likely to be useful in applications that require highly precise genome editing.

Tsai S.Q., Wyvekens N., Khayter C., Foden J.A., Thapar V., Reyon D., Goodwin M.J., Aryee M.J., Joung J.K. Dimeric CRISPR RNA-guided FokI nucleases for highly specific genome editing. Nat Biotechnol. 32:569-76. (2014)

Fu Y., Sander J.D., Reyon D., Cascio V.M., Joung J.K. Improving CRISPR-Cas nuclease specificity using truncated guide RNAs. Nat Biotechnol. 32:279-84. (2014)

Mitochondrial function is challenged by toxic by-products of metabolism as well as by pathogen attack. Caenorhabditis elegans normally responds to mitochondrial dysfunction with activation of mitochondrial-repair, drug-detoxification and pathogen-response pathways. From a genome-wide RNA interference (RNAi) screen, we identified 45 C. elegans genes that are required to upregulate detoxification, pathogen-response and mitochondrial-repair pathways after inhibition of mitochondrial function by drug-induced or genetic disruption. Animals defective in ceramide biosynthesis were deficient in mitochondrial surveillance, and addition of particular ceramides rescued the surveillance defects. Ceramide could also rescue the mitochondrial surveillance defects of other gene inactivations, mapping these gene activities upstream of ceramide. Inhibition of the mevalonate pathway, either by RNAi or statin drugs, also disrupted mitochondrial surveillance. Growth of C. elegans with a significant fraction of bacterial species from their natural habitat causes mitochondrial dysfunction. Other bacterial species inhibit C. elegans defence responses to a mitochondrial toxin, revealing bacterial countermeasures to animal defence.

Liu Y., Samuel B.S., Breen P.C., Ruvkun G. Caenorhabditis elegans pathways that surveil and defend mitochondria. Nature. 508:406-10. (2014)

Inflammatory bowel diseases (IBDs), including Crohn's disease (CD), are genetically linked to host pathways that implicate an underlying role for aberrant immune responses to intestinal microbiota. However, patterns of gut microbiome dysbiosis in IBD patients are inconsistent among published studies. Using samples from multiple gastrointestinal locations collected prior to treatment in new-onset cases, we studied the microbiome in the largest pediatric CD cohort to date. An axis defined by an increased abundance in bacteria which include Enterobacteriaceae, Pasteurellacaea, Veillonellaceae, and Fusobacteriaceae, and decreased abundance in Erysipelotrichales, Bacteroidales, and Clostridiales, was found to correlate strongly with disease status. Microbiome comparison between CD patients with and without antibiotic exposure indicated that antibiotic use amplifies the microbial dysbiosis associated with CD. Comparing the microbial signatures between the ileum, the rectum, and fecal samples showed that at this early stage of disease, assessing the rectal mucosal-associated microbiome represents a promising approach for convenient and early diagnosis of CD.

Gevers D., Kugathasan S., Denson L.A., Vazquez-Baeza Y., Van Treuren W., Ren B., Schwager E., Knights D., Song S.J., Yassour M., Morgan X.C., Kostic A.D., Luo C., Gonzalez A., McDonald D., Haberman Y., Walters T., Baker S., Rosh J., Stephens M., Heyman M., Markowitz J., Baldassano R., Griffiths A., Sylvester F., Mack D., Kim S., Crandall W., Hyams J., Huttenhower C., Knight R., Xavier R.J. The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe. 15:382-92. (2014)

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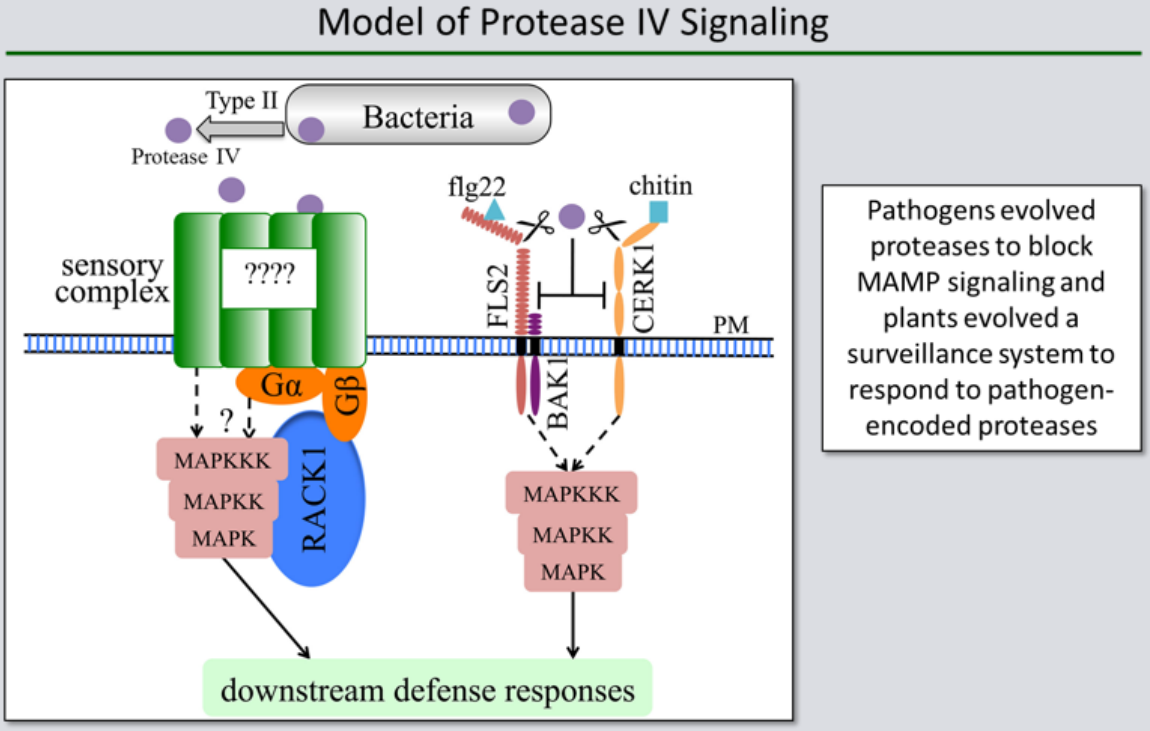
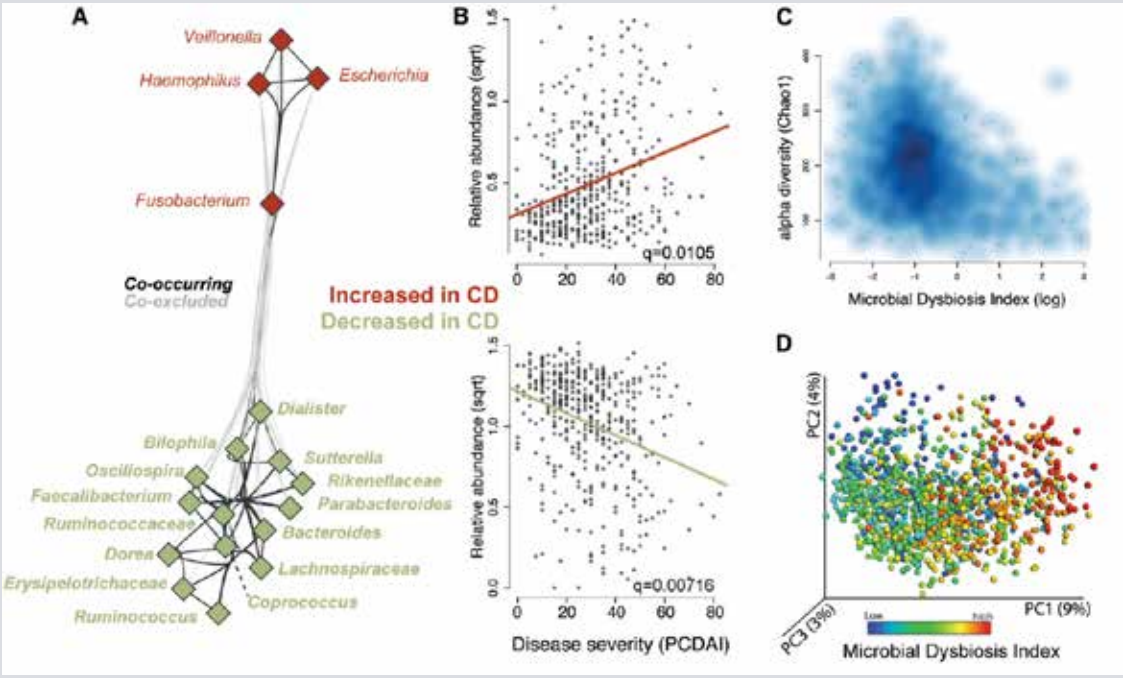


Microbial Proteases and Plant Responses



Microbial Populations in New-Onset Crohn's Disease

James F. Gusella, PhD, Director

CHGR

The mission of the MGH Center for Human Genetic Research (CHGR) is to promote the application of the powerful tool set that genetics provides to investigate fundamental mechanisms involved in all areas of human disease. The central mandate of the CHGR is the promulgation of the Genetic Research Cycle, a paradigm for disease research that begins by comparing human phenotypes and genetic variation to identify genes of importance in human disease, then 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 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 aims to pursue this mission through individual and collaborative faculty investigations at each stage of the genetic research cycle paradigm. Our current strategic priorities are to characterize variation in the human genome and interpret its meaning with respect to health and disease, to facilitate the translation of such genetic interpretation into clinical practice, and to pursue genetics-driven understanding of disease processes and intervention in humans and human cells and in genetics-based model systems ("Systems Genetics") in order to fulfill the promise of disease-modifying treatments.
Schizophrenia Working Group of the Psychiatric Genomics Consortium. Biological insights from 108 schizophrenia-associated genetic loci. Nature. 2014; 511:421-7.

Schizophrenia is devastating psychiatric disorder whose causes has remained largely an enigma, except for the knowledge that genetics is involved, as evidenced by a high degree of heritability that appears to be due to a large number of factors of small effect. In the latest example of CHGR's partnering approach to accelerate the discovery of genetic risk factors in human disease researchers in our Psychiatric and Neurodevelopmental Genetics Unit and our Analytic and Translational Genetics Unit collaborated with others in the Psychiatric Genomics Consortium to define 108 distinct genetic loci contributing to schizophrenia. In a multi-stage schizophrenia genome-wide association study of up to 36,989 cases and 113,075 controls, they identified 128 independent associations spanning 108 conservatively defined loci that meet genome-wide significance, 83 of which had never been previously reported. Associations were enriched among genes expressed in brain, providing biological plausibility for the findings. Many findings have the potential to provide entirely new insights into etiology, but associations at DRD2 and several genes involved in glutamatergic neurotransmission highlight molecules of known and potential therapeutic relevance to schizophrenia, and are consistent with leading pathophysiological hypotheses. Independent of genes expressed in brain, associations were enriched among genes expressed in tissues that have important roles in immunity, providing support for the speculated link between the immune system and schizophrenia.

Myocardial Infarction Genetics Consortium Investigators. Inactivating mutations in NPC1L1 and protection from coronary heart disease. N Engl J Med. 2014; 371:2072-82.

In a clear demonstration of the value that genetic analysis can provide in evaluating the potential for therapeutic interventions, Sek Kathiresan and his colleagues in the Myocardial Infarction Genetics Consortium reported strong evidence that a drug capable of reducing low-density lipoprotein (LDL) cholesterol can be expected to reduce the risk of coronary heart disease. Ezetimibe lowers plasma levels of LDL cholesterol by inhibiting the activity of the Niemann-Pick C1-like 1 (NPC1L1) protein. However, whether such inhibition reduces the risk of coronary heart disease was not known. Since human mutations that inactivate a gene encoding a drug target can mimic the action of an inhibitory drug, genetic analysis can be used to infer potential effects of that drug. The Consortium sequenced the exons of NPC1L1 in 7364 patients with coronary heart disease and in 14,728 controls without such disease who were of European, African, or South Asian ancestry. They identified carriers of inactivating mutations (nonsense, splice-site, or frameshift mutations) and also genotyped a

CHGR

specific inactivating mutation (p.Arg406X) in 22,590 patients with coronary heart disease and in 68,412 controls. Heterozygous carriers of NPC1L1 inactivating mutations had a mean LDL cholesterol level that was 12 mg per deciliter (0.31 mmol per liter) lower than that in noncarriers (P=0.04) and carrier status was associated with a relative reduction of 53% in the risk of coronary heart disease (odds ratio for carriers, 0.47; 95% confidence interval, 0.25 to 0.87; P=0.008). In total, only 11 of 29,954 patients with coronary heart disease had an inactivating mutation (carrier frequency, 0.04%) in contrast to 71 of 83,140 controls (carrier frequency, 0.09%). The fact that naturally occurring mutations that disrupt NPC1L1 function are associated with both reduced plasma LDL cholesterol levels and a reduced risk of coronary heart disease suggests that ezetimibe can be used to reduce the risk of this common disease.

Aarathi Sugathan, Marta Biagioli, Christelle Golzio, Serkan Erdin, Ian Blumenthal, Poornima Manavalan, Ashok Ragavendran, Harrison Brand, Diane Lucente, Judith Miles, Steven D. Sheridan, Alexei Stortchevoi, Manolis Kellis, Stephen J. Haggarty, Nicholas Katsanis, James F. Gusella, and Michael E. Talkowski. CHD8 regulates neurodevelopmental pathways associated with autism spectrum disorder in neural progenitors. Proc Natl Acad Sci U S A. 2014; 111:E4468-77.

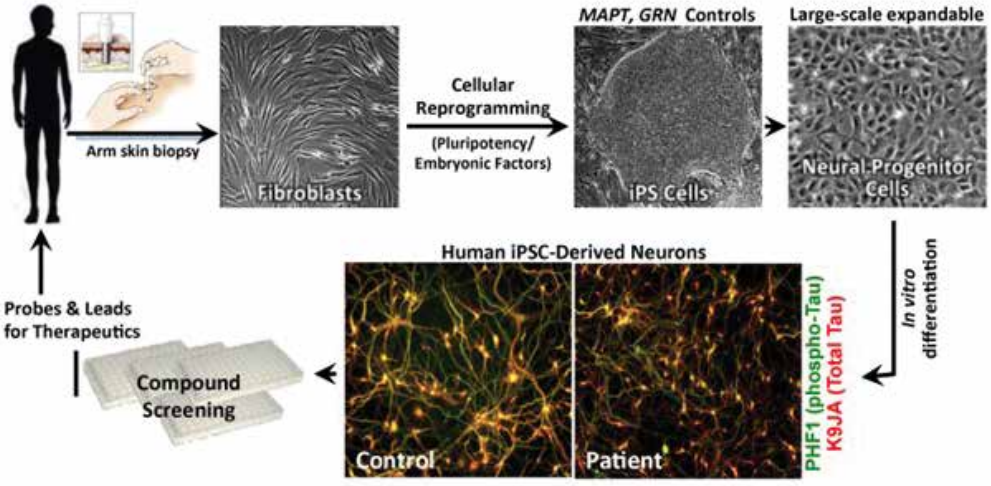
From sequencing of balanced translocations, Mike Talkowski previously discovered CHD8, the gene encoding chromodomain helicase DNA-binding protein 8 as an important strong-effect autism susceptibility gene, a finding supported by whole exome sequencing studies from the Analytic and Translational Genetics Unit of the CHGR. In this functional genomics follow-up, Mike and his collaborators explored the transcriptional networks that CHD8 regulates in neural progenitor cells (NPCs) by reducing its expression and then integrating transcriptome sequencing (RNA sequencing) with genome-wide CHD8 binding (ChIP sequencing). Suppressing CHD8 to levels comparable with the loss of a single allele caused altered expression of 1,756 genes, 65% of which were up-regulated. CHD8 showed widespread binding to chromatin, with 7,324 replicated sites that marked 5,658 genes. Integration of these data suggested that a limited array of direct regulatory effects of CHD8 produces a much larger network of secondary expression changes. Genes indirectly down-regulated (i.e., without CHD8-binding sites) reflect pathways involved in brain development, including synapse formation, neuron differentiation, cell adhesion, and axon guidance, whereas CHD8-bound genes are strongly associated with chromatin modification and transcriptional regulation. Genes associated with ASD are strongly enriched among indirectly down-regulated loci ($P < 10(-8)$) and CHD8-bound genes ($P = 0.0043$), which align with previously identified co-expression modules during fetal development. Intriguingly, there is also a strong enrichment of cancer-related gene sets among CHD8-bound genes ($P < 10(-10)$). These experiments, in which heterozygous disruption of CHD8 precipitates a network of gene-expression changes in neurodevelopmental pathways containing many other ASD-associated genes, support the notion that different autism susceptibility genes may converge on shared mechanisms of pathogenesis.

SIGMA Type 2 Diabetes Consortium. Association of a low-frequency variant in HNF1A with type 2 diabetes in a Latino population. JAMA 2014; 311:2305-2314.

Latino populations have one of the highest prevalences of type 2 diabetes worldwide. CHGR investigators Daniel MacArthur and Jose Florez led a SIGMA Type 2 Diabetes Consortium study to investigate the basis for this high prevalence using the largest whole exome sequencing effort to date in diabetes. They investigated DNA samples from 3756 Mexican and US Latino individuals (1794 with type 2 diabetes and 1962 without diabetes) and discovered a critical sequence variant whose allele frequency and association with type 2 diabetes was further tested in large multiethnic data sets of 14276 participants. This missense variant, (c.1522G>A [p.E508K]) in hepatocyte nuclear factor 1-α (HNF1A), the gene responsible for maturity onset diabetes of the young type 3 (MODY3), was associated with type 2 diabetes prevalence (odds ratio [OR], 5.48; 95% CI, 2.83-10.61; $P = 4.4 \times 10{-}7$) being observed in 0.36% of participants without type 2 diabetes and 2.1% of participants with it. In multiethnic replication data sets, the p.E508K variant was seen only in Latino patients (n = 1443

CHGR

with type 2 diabetes and 1673 without it) and was again associated with type 2 diabetes (OR, 4.16; 95% CI, 1.75-9.92; P=.0013). In experimental assays, HNF-1A protein encoding the p.E508K mutant demonstrated reduced transactivation activity of its target promoter compared with a wild-type protein. Thus, this single DNA variant in HNF1A confers a 5-fold increased risk of diabetes, and explains 20% of the ethnic differences in diabetes incidence.



Patient-specific and CRISPR/Cas modified iPSCs are being used by multiple faculty members in CHGR investigators as an extensible platform for biological & therapeutic discovery in many disorders, enabling the identification of early markers of disease pathogenesis as well as efforts using chemical genomics to identify targets to prevent or modify disease progression.

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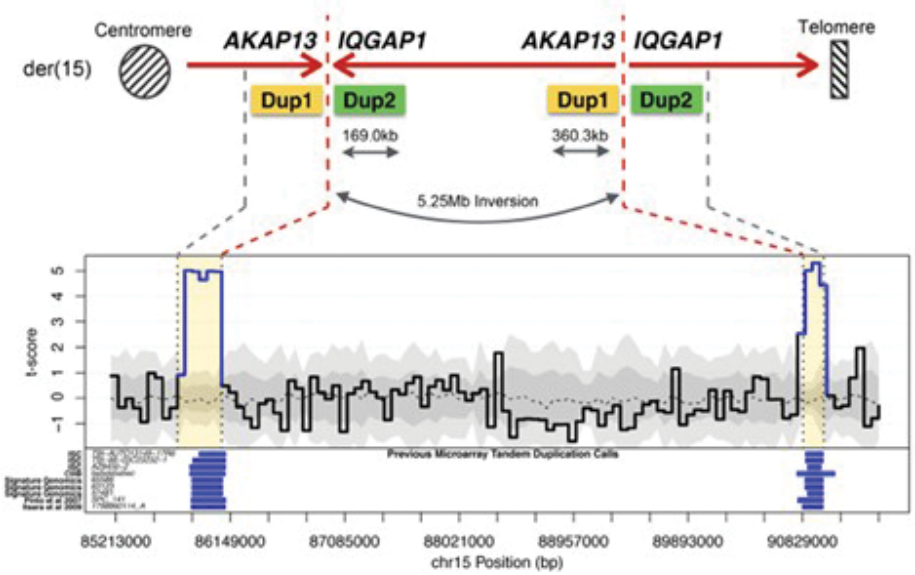

Sequencing pipelines optimized for structural variation in the genome are identifying new pathogenic lesions missed by microarray analysis and exome sequencing, including paired duplications flanking an inversion, a common mutational variant missed by clinical diagnostic arrays.

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Center for Regenerative Medicine

Thematic Center Report

CRM

David Scadden, MD, Director

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.

In a partnership with the hospital and with Drs. Charles Lin and Joel Spencer of the Wellman Center, the Center for Regenerative Medicine (CRM) has laid the groundwork for a stem cell imaging center through the purchase of a multi-photon microscope system. This instrument will push the limits of our imaging capabilities for our investigators within many different disease and organ disciplines. This dedicated high-efficiency multiphoton system will allow us to continuously image new multi-colored cell culture models (e.g. multi-colored air-liquid interface lung cell cultures) and multi-colored animal models (e.g. Confetti mice or Zebrafish Brainbow) over hours to days with simultaneous multiphoton excitation at more than one wavelength.

Junior faculty members of the CRM continue to grow their research programs. Dr. Amar Sahay, Assistant Professor of Psychiatry, was awarded an NIH Brains R01 to explore how the brain curbs fear, with the goal of developing new therapeutic strategies to help people with generalized anxiety disorder or post-traumatic stress disorder. Additionally, Dr. Sahay was one of ten scientists to receive the first DECODE (Deciphering Circuit Basis of Disease) grants, awarded by Inscopix, Inc, to accelerate the discovery of neural circuit based signatures of brain disease. Other notable faculty achievements include Dr. Jayaraj Rajagopal's promotion to Associate Professor of Medicine and the award of an endowed chair to Dr. Konrad Hochedlinger.

Investigators within the Center, including Drs. David Scadden (Medicine), Andrew Brack (Medicine) and Jenna Galloway (Orthopedics), have teamed with investigators from the MGH Department of Orthopedics and Division of Sports Medicine and the MGH Endocrine Unit to form a group called the Muskuloskeletal Research Consortium (MRC). This group meets monthly to discuss their current research and significant issues within the musculoskeletal field, drawing upon the group's expertise and multidisciplinary nature. Additional speakers such as Mehmet Toner, a leader in the field of biomedical engineering, and Louis Gerstenfeld, an expert on bone injury from Boston University, have been invited to present their work. Topics discussed include bone development and metabolism, fracture healing, tendon repair, and stem cells. The group is pioneering an integrated approach to studying the musculoskeletal system with the goal of applying this knowledge to develop therapeutic solutions for improving injury outcomes.

Scientifically, the CRM is continuing to drive discovery. As reported in the journal Cell, Dr. David Scadden and his lab compared how blood stem cells and leukemia cells consume nutrients and found that cancer cells are far less tolerant to shifts in their energy supply than their normal counterparts. The results suggest that there could be ways to target leukemia metabolism so that cancer cells die but other cell types are undisturbed. This study can open the door to industry partnerships and the generation of new treatments. Dr. Rajagopal discovered that the Yap signaling pathway regulates airway epithelial size through the maintenance of stem cells (Developmentall Cell, 2014) and Dr. Hochedlinger's lab reported on the identification of small molecules that promote cellular reprogramming of somatic cells into induced pluripotent stem cells within 48 hours (Nature Methods, 2014). The latter two discoveries may facilitate the use of adult and pluripotent stem cells in regenerative medicine.

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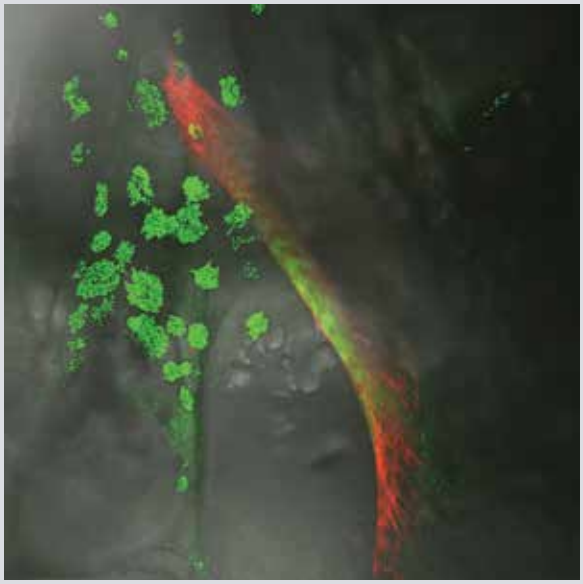

Image 1: A multiphoton image of a zebrafish tendon: red is mcherry fluorescent protein expressed in tendon cells and green is second harmonic imaging of the collagen fibers (Credit: Galloway Lab)

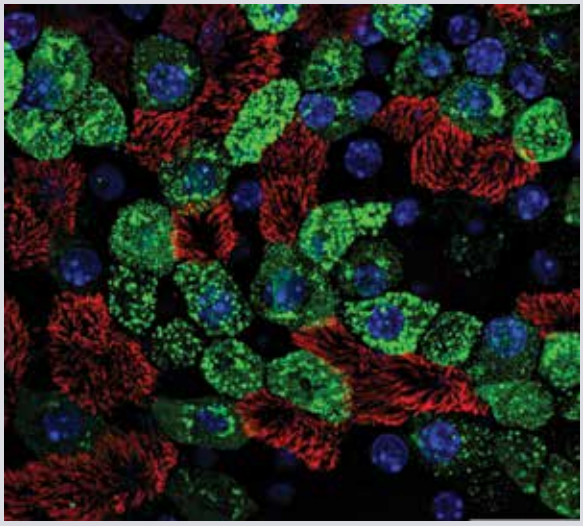

Image 2: a mature airway epithelium derived from a single dedifferentiated secretory cell that has been expanded ex vivo as a stem cell and then subsequently differentiated on an air-liquid interface. Cilia are stained for acetylated tubulin (red) and secretory cells are stained with SCGB1A1 (green) and nuclei are blue (DAPI). (Credit: Rajagopal Lab)

Center for Systems Biology

Thematic Center Report

CSB

Ralph Weissleder, MD, PhD, Director

The mission of the Center for Systems Biology (CSB) is to analyze how small molecules, proteins and cells interact at the systems level, in both healthy and diseased states. Through a multidisciplinary approach that combines clinical insight with powerful technologies, CSB 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, chemical biology, nanotechnology, cell biology, physiology, genomics, bioengineering and mathematical modeling. The Center is a major node within the Harvard-wide Systems Biology Program, and its faculty maintain joint appointments or affiliations with the HMS Department of Systems Biology, 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 186 employees, including 38 faculty. Our strategic priorities are to develop technologies and models for measurement and analysis of biological systems that 1) help reveal new biological insights and 2) provide high-yield translational opportunities.

Stem cells get stressed out (Nature Medicine 2014;20:754-758)

For decades, doctors knew that chronic stress is bad for you. Atherosclerosis has been nicknamed a "manager's disease" for this reason. Previously, we thought this is because of heightened blood pressure, and its direct actions on the blood vessel wall. In a recent study from CSB (Nahrendorf lab) it was found that psychosocial stress activates bone marrow stem cells, which in turn triggers overproduction of inflammatory leukocytes, including neutrophils and monocytes. These leukocytes are more numerous in blood and accumulate in atherosclerotic lesions, putting the individual at higher risk for myocardial infarction and stroke. Hematopoietic stem cells are very rare (only 1 in 10,000 cells in the marrow), and 95% are silent, or "hibernating" in healthy individuals until they are needed. The other 5% are cycling and produce our blood cells, billions of them every day. In case of infection or injury, more stem cells are "woken up" and produce additional cells to defend the body. In diseases that involve chronic inflammation such as atherosclerosis, more stem cells are active, overproducing inflammatory macrophages that migrate to the arterial wall. Once in plaque, macrophages accelerate plaque growth and increase the likelihood of myocardial infarction. This study discovered that stress activates the sympathetic nerve, which is a part of the autonomous nervous system. This is useful in dangerous situations, to ready the organism for fight and flight. Possibly, increased production of leukocytes prepares the stressed human for a potential injury, to better heal any resulting wounds. Chronic stress leads to chronic firing of the sympathetic nerve, which changes the microenvironment in the bone marrow. To put it simply, the nervous signals remove the "brake" from stem cells, or awaken them to produce more leukocytes. A key factor is CXCL12, which is produced by bone marrow niche cells connected via a synapse-like connection to sympathetic nerve fibers.

Heidt T, Sager HB, Courties G, Dutta P, Iwamoto Y, Zaltsman A, von Zur Muhlen C, Bode C, Fricchione GL, Denninger J, Lin CP, Vinegoni C, Libby P, Swirski FK, Weissleder R, Nahrendorf M. Chronic variable stress activates hematopoietic stem cells. Nature Med. 2014;20(7):754-758 - PMID: 24952646 - PMCID: PMC4087061

CSB

Air supply for hematopoietic stem cells (Nature 2014;508:269-73)

Another major accomplishment from CSB (Charles Lin lab) this past year was the first direct measurement of local oxygen concentration in the bone marrow of live animals by two-photon phosphorescence lifetime microscopy. As described above, only 5% of hematopoietic stem cells (HSCs) in the bone marrow are actively cycling while 95% are quiescent under homeostatic conditions, but this can change when the body is under stress. What molecular signals tell HSCs when to remain quiescent and when to wake up? The availability of oxygen in the local microenvironment is thought to be a key factor regulating HSC metabolism. In particular, quiescent HSCs are thought to reside in oxygen-deprived microenvironments call hypoxic niches. However, the local oxygen distribution within the bone marrow has never been measured directly. Oddly, the concept of hypoxia seems incongruent with the observation that bone marrow is highly perfused. Approximately 25% of the bone marrow volume is occupied by blood vessels. How can such a highly vascularized tissue be hypoxic? The Lin Lab resolved this puzzle by measuring local oxygen concentration in the bone marrow with high spatial resolution using a custom microscope developed in their own laboratory, together with a novel metalloporphyrin-based oxygen sensor decorated with antenna molecules to facilitate two-photon excitation (for precise spatial localization). The measurements show that the bone marrow is indeed hypoxic despite very high vascular density (oxygen supply), due to the simultaneous presence of high cellularity (oxygen consumption). The measurements further uncovered local gradients in oxygen tension consistent with the local blood flow profile. Notably, the balance between oxygen supply and consumption can be altered drastically following treatments such as radiation and chemotherapy. As a result, in the setting of HSC transplantation, engrafting cells sense a microenvironment that is very different from the steady state, and the biology of the HSC niche need to take into account differences in homeostatic vs. stressed conditions.

Spencer JA, Ferraro F, Roussakis E, Klein A, Wu J, Runnels JM, Zaher W, Mortensen LJ, Alt C, Turcotte R, Yusuf R, Côté D, Vinogradov SA, Scadden DT, Lin CP. Direct measurement of local oxygen concentration in the bone marrow of live animals. Nature. 2014;508(7495):269-73 - PMID: 24590072 - PMCID: PMC3984353

Tiny holes enable big measurements (Nature Biotechnology 2014;32(5):490-5)

A new technology developed at CSB (Weissleder lab) allows profiling of small subcellular structures such as exosomes. Exosomes show potential for cancer diagnostics because they transport molecular contents of the cells from which they originate. Detection and molecular profiling of exosomes is technically challenging and often requires extensive sample purification and labeling. Here we describe a label-free, high-throughput approach for quantitative analysis of exosomes. The nano-plasmonic exosome (nPLEX) assay is based on transmission surface plasmon resonance through periodic nanohole arrays. Each array is functionalized with antibodies to enable profiling of exosome surface proteins and proteins present in exosome lysates. We show that this approach offers massively improved sensitivity over previous methods, enables portable operation when integrated with miniaturized optics and allows retrieval of exosomes for further study. Using nPLEX to analyze ascites samples from ovarian cancer patients, we find that exosomes derived from ovarian cancer cells can be identified by their expression of CD24 and EpCAM, suggesting the potential of exosomes for diagnostics. This technology will allow high-throughput analysis of a number of clinically important biomarkers.

Im H*, Shao H*, Park YI, Peterson VM, Castro CM, Weissleder R*, Lee H*. Label-free detection and molecular profiling of exosomes with a nano-plasmonic sensor. Nat Biotechnol. 2014;32(5):490-5 - PMID: 24752081

CSB

Intratumoral heterogeneity in GBM (Science. 2014;344:1396-401)

Human cancers are complex ecosystems composed of cells with distinct phenotypes, genotypes, and epigenetic states, but current models do not adequately reflect tumor composition in patients. We used single-cell RNA sequencing (RNA-seq) to profile 430 cells from five primary glioblastomas, which we found to be inherently variable in their expression of diverse transcriptional programs related to oncogenic signaling, proliferation, complement/immune response, and hypoxia. We also observed a continuum of stemness-related expression states that enabled us to identify putative regulators of stemness in vivo. Finally, we show that established glioblastoma subtype classifiers are variably expressed across individual cells within a tumor and demonstrate the potential prognostic implications of such intratumoral heterogeneity. Thus, we reveal previously unappreciated heterogeneity in diverse regulatory programs central to glioblastoma biology, prognosis, and therapy.

Patel AP, Tirosh I, Trombetta JJ, Shalek AK, Gillespie SM, Wakimoto H, Cahill DP, Nahed BV, Curry WT, Martuza RL, Louis DN, Rozenblatt-Rosen O, Suvà ML, Regev A, Bernstein BE. Single-cell RNA-seq highlights intratumoral heterogeneity in primary glioblastoma. Science. 2014;344(6190):1396-401 - PMID: 24925914 - PMCID: PMC4123637

For a complete list of > 150 publications from CSB in 2014, please see here: https://csb.mgh.harvard.edu/publications?year=2014

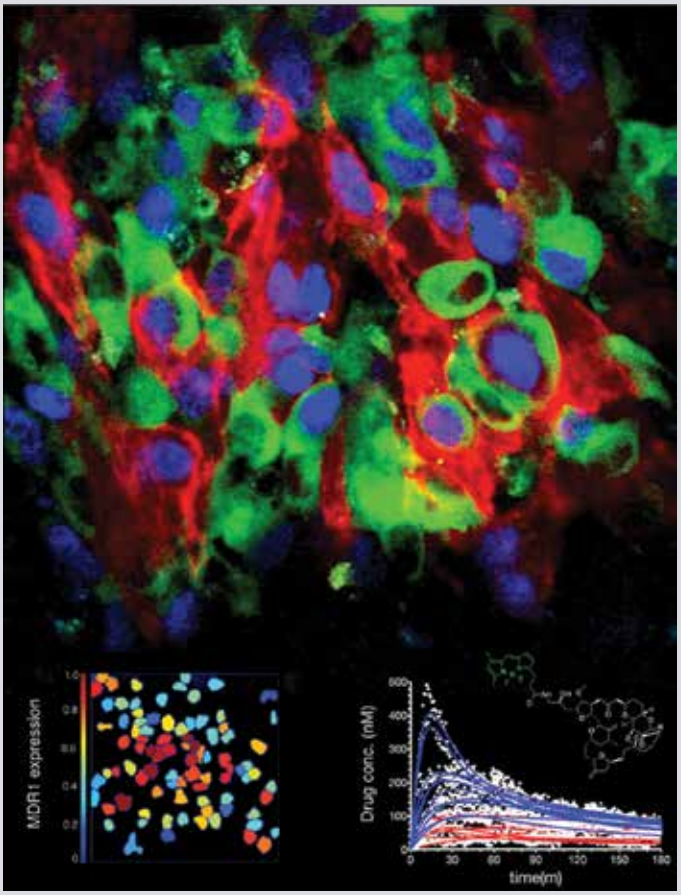

Fig. 1: Extracting maximal information from minimal, easily acquired samples is the holy grail for patient screening and monitoring in clinical practice and in clinical trials. Until now, invasive or expensive procedures have been the only means of gaining accurate information regarding disease status and treatment response. Now, a new technology developed at the CSB, holds promise for revolutionizing clinical monitoring by allowing simultaneous analysis of hundreds of cancer-related protein markers from minute, minimally invasive patient samples. Left: cells are harvested from cancer patients by fine needle aspirate. In this case, a heterogeneous population of EpCAM-positive cancer cells (green) is displayed alongside mesothelial cells (red) with nuclei shown in blue (Hoechst) from an abdominal fine needle cancer aspirate. Cancer cells are enriched and isolated via magnetic separation in PDMS microfluidic devices using both positive (e.g. Ep-

CSB

CAM+/CK+) and negative (e.g. CD45-) selection modes. Middle: Cells of interest are incubated with a cocktail of DNA-conjugated antibodies containing a photo-cleavable linker to allow DNA release after exposure to ultraviolet light. Right: DNA-antibody conjugates released from lysed cells are isolated via size-separation and IgG pull down. Released "alien" DNA barcodes are processed with a fluorescent DNA barcoding platform (NanoString). This new technology, uses antibodies linked to unique DNA barcodes to detect a wide range of target proteins, is both highly robust and exquisitely sensitive. From: Ullal AV, Peterson V, Agasti SS, Tuang S, Juric D, Castro CM, Weissleder R. Cancer Cell Profiling by Barcoding Allows Multiplexed Protein Analysis in Fine-Needle Aspirates. Sci Transl Med. 2014;6(219):219ra9 – PMID: 24431113

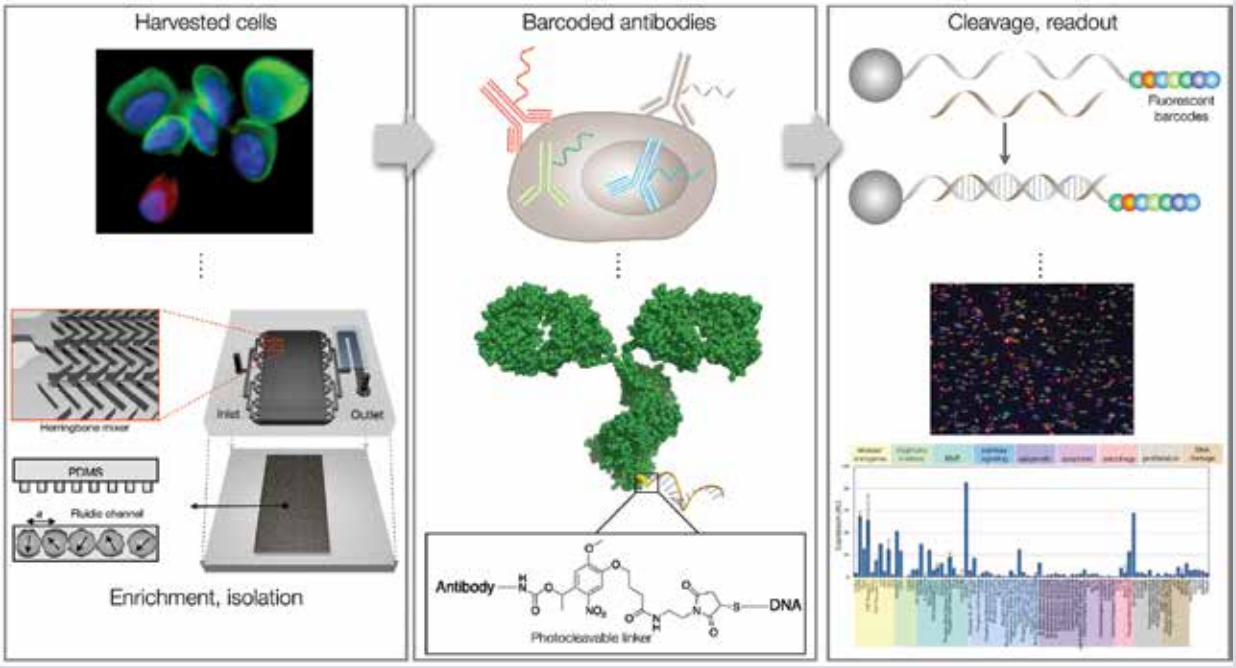

Fig. 2: Eribulin was developed as a potent anticancer agent, but it fails in many patients for unknown reasons. In a recent study, CSB researchers used in vivo single cell imaging in tumors to show that resistance is primarily due to MDR1-mediated drug efflux. In the image above, the green drug (eribulin) accumulates in some but not all cancer cells (red) because of stochastic MDR overexpression. It was discovered that a new nano-encapsulated MDR1 inhibitor was able to restore drug efficacy. These studies indicated that in vivo imaging is a powerful strategy for elucidating mechanisms of drug resistance in heterogeneous tumors and for evaluating strategies to overcome this resistance. From: Laughney AM, Kim E, Sprachman MM, Miller MA, Kohler RH, Yang KS, Orth JD, Mitchison TJ, Weissleder R. Single-cell pharmacokinetic imaging reveals a therapeutic strategy to overcome drug resistance to the microtubule inhibitor eribulin. Sci Transl Med. 2014;6 (261):261ra152 - PMID: 25378644

Wellman Center for Photomedicine

Thematic Center Report

WCP

R. Rox Anderson, MD, Director

Overview

Our mission is to improve people's lives through research, education, innovation and development. The field of Photomedicine encompasses all of light's beneficial, harmful, diagnostic, therapeutic, surgical, medical and technological aspects in biology and medicine. The Wellman Center is intellectually diverse, and is the world's largest laboratory in this field. Cancer, coronary artery disease, infection, trauma, wound healing, immunization and pain management are prevalent themes. We are a world leader for *in vivo* microscopy; tissue imaging and spectroscopy; light-activated drug treatments; novel optical diagnostics; laser surgery; and integration of these with other technologies. We are part of the MIT-Harvard H.S.T. program, teach related graduate courses, work with many other universities, and host an undergraduate summer school.

Strategic priorities

The Wellman Center "translates" its discoveries and innovations all the way to commercialization, and into practice. Being successful in this regard, we supplement the annual research budget of about $25M from NIH and DOD, with royalty income to provide core services including experimental pathology, chemistry, computation and translational research facilitation. Wellman Center recently inspired the creation of an investment fund aimed at streamlining translational research and licensing. Another priority is simply to foster the excellent research and clinical communities of MGH. There are >50 active collaborations with various MGH laboratories and departments, including project grants spearheaded by the Wellman Center. For 2015 we plan to host unsolved-problem-oriented seminars aimed at sparking new collaborations. Finally, Wellman can, and needs to grow as it leads the dynamic field of photomedicine. Growth should come both from expansion of existing programs, and from recruiting new faculty. Our laboratories are currently spread among 10 floors in 7 buildings, in Boston, Charlestown and Cambridge—it is difficult to find the center of the Wellman Center! The benefits of membership, level of excellence, and collaborative spirit are largely what hold the Wellman Center together.

Key Achievements during 2014 (samples of work from more than 200 WCP scientists).

Cancer: Prof. Hensin Tsao's laboratory discovered that EphA2, a receptor tyrosine kinase, is an important oncogene that can mediate resistance to Vemurafenib therapy for melanoma. Furthermore, EphA2 can be targeted with small molecule inhibitors that lead to profound melanoma growth suppression. (Miao B, et al Cancer Discov. 2014 Dec 26.) Ben Vakoc's laboratory began first-in-man clinical studies with high-resolution in vivo imaging of tumor vasculature; Gary Tearney's laboratory performed first-in-man, wide-field confocal microscopy of the esophagus. Separately, Prof. Tayyaba Hasan's laboratory demonstrated a novel targeted molecular strategy for simultaneous optical detection and treatment of ovarian cancer (Spring BQ, et al Proc Natl Acad Sci 2014;111(10):E933-42. doi: 10.1073/pnas.1319493111). They synthesized molecules with a fluorescent, phototoxic dye and a potent quencher, connected by a cleavable linkage susceptible to tumor cell activation. Until taken up by tumor cells, there is neither fluorescence nor cell killing. After uptake, which was mediated through a tumor-selective antibody carrier, ovarian cancer tumors become fluorescent, and are preferentially killed upon light exposure.

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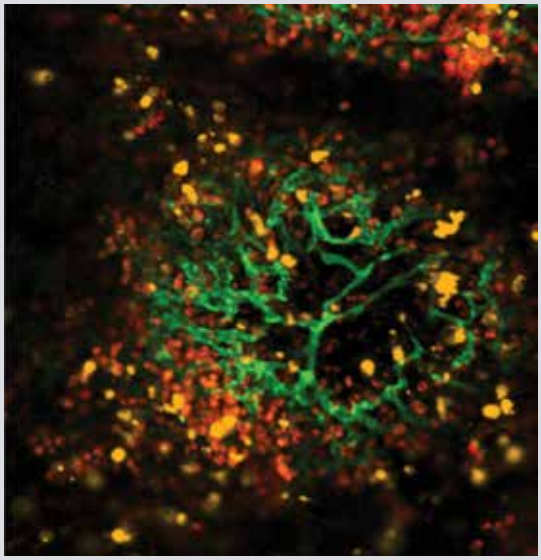
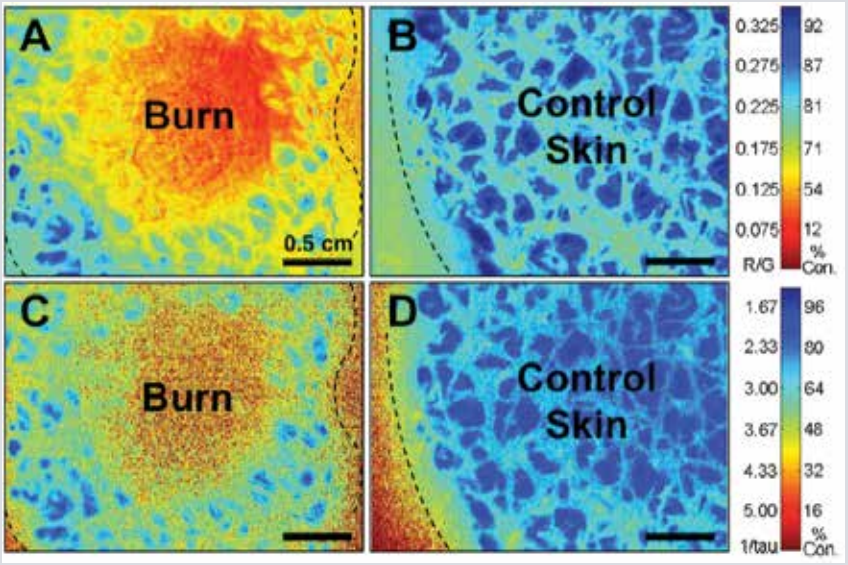


Pictured is a micrometastasis with cancer cells shown in orange, microvessels in green and tumor-targeted, activatable immunoconjugates in red. Spring et al. developed selective destruction and imaging of cancer micrometastases using the activatable immunoconjugate. With this strategy, microscopic tumors presently invisible in practice can potentially be monitored and selectively destroyed.

Mapping Oxygen:

Charles Lin's laboratory pursues advanced microscopy in complex tissue microenvironments. In collaboration with the MGH Center for Regenerative Medicine, they succeeded to measure and image local oxygen concentration in the bone marrow of live animals, using two-photon phosphorescence lifetime microscopy. (Spencer et al Nature 2014;508:269-73). They found that bone marrow is hypoxic despite very high vascular density, and uncovered the local gradients in oxygen tension thought to be an important factor regulating hematopoietic stem cell (HSC) quiescence. Following radiation and chemotherapy, a very different oxygenation microenvironment exists, affecting HSC engraftment in the setting of transplantation. On the larger scale of wounds, Conor Evans' lab invented an oxygen-sensing bandage that maps the pO2 of underlying tissue. Stable oxygen-sensing phosphors were synthesized, incorporated into dressings, calibrated and tested in various wounds (burn, ischemia, transplantation). The "SMART" dressing sensor is so bright, that it can be seen directly or recorded with a smartphone camera. This DOD-supported project is promising for translation to clinical practice. Also related to wound care, Rox Anderson's laboratory developed and reported a novel epidermal grafting device, which received FDA approval for wound treatment.

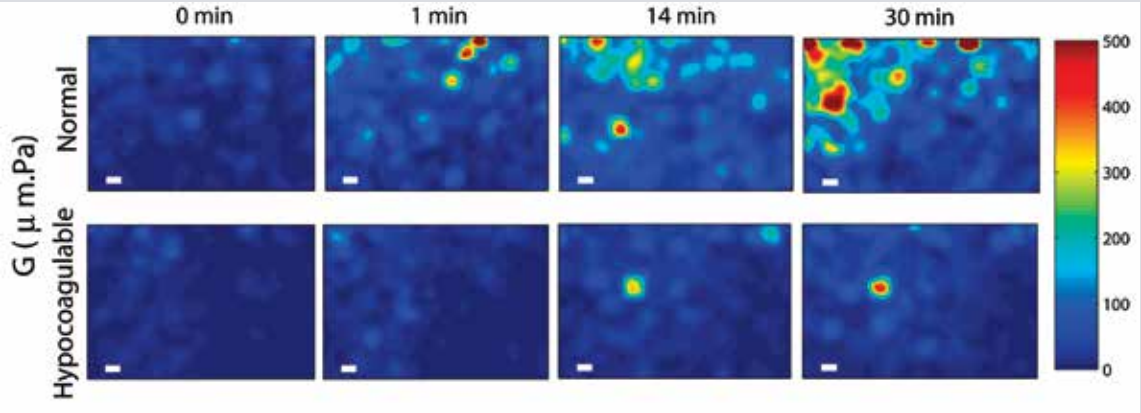


The depth of skin burns is difficult to determine by inspection, and greatly affects outcome. The SMART dressing maps pO2, which strongly correlates with burn severity. Oxygenation under the dressing can be mapped using a smartphone camera.

WCP

Immunization: Unfortunately, annual flu vaccines are much less effective in elderly people, and often provide little or no protection against different influenza virus strains. Mei Wu, MD PhD and colleagues discovered that "fractional" laser-induced thermal micro-injury of the skin, can potently increase response to intradermally-delivered vaccines, including flu vaccines. Fractional laser treatment was invented and developed at the Wellman Center a decade ago, and is now widely used worldwide for treatment of aging and scars. Micro-injury of the skin activates antigen presenting cells, stimulates innate immunity and other pathways. Wu's laboratory found that a simple over-the-counter non-ablative fractional laser (NAFL) designed for consumer use, significantly enhances the efficacy of intradermally-delivered influenza vaccines (Wang J, et al. Nature Communications 2014;5: 4447. doi:10.1038/ncomms5447; also selected as a feature article in Popular Science, July 29, 2014). Furthermore, Wu's laboratory tested intradermal micro-injection of influenza vaccines in a fractional pattern in elderly mice. There was an increased systemic response to influenza virus vaccine, with decreased local inflammation, compared with conventional intradermal vaccination. When NAFL and fractional intradermal injection were combined, there was synergy. Notably, a broader spectrum of cross-protective immunity was induced, suggesting that this approach can not only increase response to the flu vaccine but broaden the protection against viral strains. She plans next to conduct studies in people receiving flu vaccines. Old mice intradermally immunized with NAFL, then challenged, retained body weight, lived longer, achieved higher antibody titers and remained afebrile compared with conventional immunizations.

Coagulation: The status of blood clotting is a critical issue for many patients, and one of the most commonly performed routine and emergency blood tests. Is it possible to determine coagulation status rapidly, at the bedside, from a single drop of blood? Seemantini Nadkarni's laboratory is using dynamic laser light scattering to determine coagulation status. The property of coherence causes an interference pattern called "speckle" to occur in scattered laser light. In blood, Brownian motion of erythrocytes predictably modulates the speckle pattern. As blood clots, erythrocyte motion decreases, such that speckle modulation can rapidly detect blood coagulation. Nadkarni's group built, validated and is optimizing small, practical speckle modulation devices for rapid coagulation testing (Tripathi MM, et al Biomed Opt Express. 2014 Feb 24;5(3):817-31).



The colormap shows clot stiffness variations measured optically in 100μL blood sample from a normal patient (top row) and a patient with defective coagulation (bottom row). As early as 1 minute, incipient microclots can be detected, demonstrating the capability for rapid coagulation sensing within minutes at the point of care.

Living Lasers

Andy Yun's laboratory group, who conceived and demonstrated the world's first living laser, greatly increased its efficiency by using solid state fluorescent proteins as the gain medium.

Jeanine Wiener-Kronish, MD; Chief

1. 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 of this Department occupy over 30,000 sq. ft. and are 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 about 80 grants per year including over 30 NIH grants.

(5) The DACCPM faculty publishes annually over 150 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 salary support and mentoring to T32/K08 trainees, gap funding for MD and/or PhD principal 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 recently implemented several initiatives to support clinical and comparative outcome research including competitive intra-departmental clinical research funds and establishment of a clinical research core.

(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.

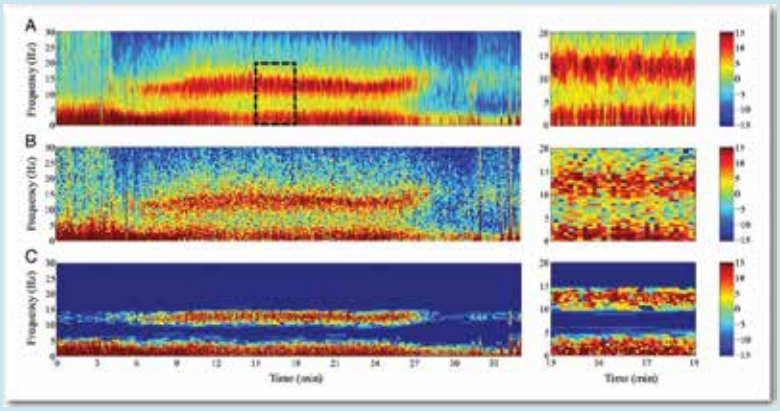
2. In 2014, the DACCPM faculty published over 230 journal articles as first authors, senior authors, or co-authors. The following are four representative achievements from our research faculty.

(1) **Stem cell research:** Dr. Brian Wainger developed and used stem cell technology to model diseases affecting sensory and motor neurons. He defined a technique to derive nociceptor neurons from fibroblasts using transcription factor lineage reprogramming. Using existing approaches to differentiate motor neurons from induced pluripotent stem cells, Dr. Wainger demonstrated that motor neurons derived from patients with amyotrophic lateral sclerosis (ALS) were hyperexcitable compared to motor neurons derived from healthy controls. Using the FDA-approved antiepileptic retigabine, which increases potassium currents, he showed that treatment with the drug both reduced the hyperexcitability and increased the in vitro survival of the ALS motor neurons. These findings were published in *Nature Neuroscience*, *Stem Cell*, etc.

(2) **Signal transduction research:** Dr. Masao Kaneki's lab demonstrated that S-nitrosylation inactivates SIRT1 by interfering with the protein's ability to bind zinc, which, in turn, increases the activity of p53 and NF-kB in cultured cells and rodent models of systemic inflammation, Parkinson's disease and age-related muscle atrophy. Since different pathological mechanisms have been identified for aging-related diseases, it has been assumed that therapeutic strategies for those conditions should also differ. Dr. Kaneki's findings identified NO-mediated inactivation of SIRT1—proposed to be a longevity gene—as a hub of the inflammatory spiral common to many human diseases, which clarifies a new potential preventive molecular target. These findings were reported in *Science Signaling*.

(3) **Comparative outcome and genetic research:** Dr. Brian Bateman, in collaboration with colleagues from the Division of Pharmacoepidemiology and Pharmacoeconomics at BWH, the Department of Obstetrics and Gynecology at MGH, the Harvard School of Public Health, and the Karolinska Institute completed a study examining the familial aggregation of postpartum hemorrhage (PPH) in the Swedish population. This study showed, for the first time, that family history is an important risk factor for PPH, which is the leading cause of maternal mortality worldwide. The study suggested that both maternal and fetal genetic factors play a role in conferring risk. The writer of the editorial accompanying the article stated "the authors' findings make it imperative for caregivers of women to take a targeted family history, along with details of the other risk factors for postpartum haemorrhage, to help to stratify their risk for excessive bleeding in childbirth". The study also motivates future work examining the genetic basis for PPH risk. These findings were published in *BMJ*.

(4) **Research on medical device interoperability:** Dr. Julian Goldman founded the Medical Device Plug-and-Play Interoperability Program (MD PnP) in 2004, which is now funded by three awards from DoD, two from NSF, one from NIH/NIBIB, and one from CIMIT, totaling over $4M ($2.7M direct). The Program is contributing to the development of international standards to support contextually rich data acquisition for research and advance device capabilities for closed loop control. This Program co-led the Presidential Innovation Fellows' SmartAmerica challenge on "Closed Loop Healthcare". In response to a Federal request to support Ebola response, this Program convened 20 groups from government, academia, and industry and demonstrated remote control of ventilators and infusion pumps, and real-time remote data access to improve patient and caregiver safety.



The research group led by Drs. Emory Brown and Patrick Purdon has focused on studying the mechanisms of general anesthesia through a system neuroscience approach. The figures illustrate spectral estimates of real EEG data from a subject undergoing propofol-induced general anesthesia. (A) Multitaper with 2-s temporal resolution, (B) multitaper with 0.5-Hz frequency resolution, and (C) robust spectral estimate. (Right) Respective zoomed-in views from t=15 min to t=18 min (Ba et al., PNAS 2014).

In the spring of 2014, clinical trials began on a novel intravenous sedative-hypnotic/general anesthetic agent (ABP-700) that was invented by Dr. Douglas Raines and his colleagues at the MGH Department of Anesthesia, Critical and Pain Medicine. This drug shares etomidate's unusually high therapeutic index and is also ultra-short acting and devoid of etomidate's dangerous effects on adrenal function. This technology is supported by four patent applications and forms the basis of the start-up company Annovation BioPharma, which has attracted more than $10M of venture funding. At the end of 2014 and on the basis of highly positive results from ABP-700's clinical trials, the Medicines Company exercised its option to acquire Annovation BioPharma.

Cancer Center

Department Report

Daniel Haber, MD, PhD; Director

MISSION: The mission of the Massachusetts General Hospital Cancer Center is to provide innovative treatments, comprehensive and compassionate care to both adults and children, and to make fundamental advances in our understanding of cancer diagnosis, treatment, and prevention. Through multidisciplinary collaborations and a synergy between laboratory scientists and clinicians, the Cancer Center seeks to foster innovation in all phases of cancer research.

BACKGROUND AND SCOPE: The MGH Cancer Center **Clinical Services** comprise 24 fully integrated, multidisciplinary disease centers and a comprehensive array of support and educational services, along with a network of affiliations around Boston and throughout New England. In 2014, the Cancer Center handled 123,600 patient visits (7,000 new patients), entering 1,263 patients onto ~500 therapeutic clinical trials, with 535 (42%) of patients on early phase I/II trials. The **Center for Cancer Research (CCR)** is the engine for basic and translational science discovery, with a dedicated faculty of 40 primary and affiliated investigators spanning fields from genetics and developmental biology to proteomics and computational biology. In addition, strong cancer research programs exist within MGH departments, including Radiation Oncology, Surgery and Surgical Specialties, Pathology, Dermatology and Radiology among others. The MGH is also a founding member of the Harvard-wide NCI-designated comprehensive cancer center (DF/HCC).

For the purposes of this review, research highlights are presented for the CCR and the Division of Hematology Oncology (Department of Medicine), which are jointly administered through the Cancer Center. Dr. David Ryan is Chief of Hematology/Oncology and Clinical Director of the Cancer Center and Dr. Nick Dyson serves as Scientific Director (CCR). **Total annual research expenditures** for CCR and Heme/Onc is 72M total (15M NIH, 32M industry, 25M non-profit).

STRATEGIC PRIORITIES: The MGH Cancer Center supports a number of **specialized facilities** to enhance research activities for laboratory-based Principal Investigators, clinical investigators, as well as to facilitate translational interactions. These are briefly described below:

The Center for Molecular Therapeutics (CMT) is dedicated to high throughput screens (1,000 cancer cell lines) to correlate sensitivity to targeted agents (alone or in combination) with underlying genotypes. A major multi-year collaborative program with the Sanger Center is supported by the Wellcome Trust, and recent studies have focused on the generation of patient-derived in vitro cell cultures to overcome acquired resistance to targeted therapeutics.

The Translational Research Laboratory (TRL) is a partnership with the Department of Pathology, providing CLIA-certified tumor genotyping (35 genes) as part of standard clinical care, as well as more advanced next generation sequencing research platforms for large cancer panels (1,000 genes), novel translocations, and applications to minimal template material. A recent Protein Biomarker Lab is being launched, with the goal of transitioning both RNA and protein-based markers from the research lab to clinical trials platforms.

The Center for Excellence in Circulating Tumor Cell (CTCs) Technologies is a collaboration between bioengineers, clinicians, and molecular biologists to create, develop and validate advanced micro-fluidic technologies to isolate and characterize cancer cells circulating in the bloodstream. The project has been funded by a major NIH grant, a Stand-Up-To-Cancer Dream Team Award, and a Center for Excellence grant from Johnson & Johnson (Veridex).

Additional resources available to laboratory investigators include the ***Molecular Profiling Lab (MPL)*** providing shRNA constructs and next generation sequencing; the **Center for Computational Discovery** which provides consulting services to support large data analyses; the ***Mass Spectrometry*** laboratory which has advanced instrumentation for whole cell proteome analysis; the ***Confocal Microscopy*** shared resource; and the ***Tissue Histopathology Core*** supported by the Dept of Pathology.

The Henri and BelindaTermeer Center for Targeted Therapies conducts over 500 Phase I and II clinical trials annually, providing a centralized resource, with dedicated physicians, nursing and data management staff. The 10-bed outpatient unit is tightly linked to clinical sample processing and translational laboratory support, pharma partnerships and interactions with each of the Cancer Center's disease centers.

The Cancer Center Research Protocol Office oversees 535 therapeutic "risk" and 83 observational "non-risk" cancer research protocols, providing data management, clinical research coordinators and centralized oversight from initiation of protocol review through to FDA inspections. The 15M budget is supported through a combination of research grants, industry contracts, charges to individual cancer disease centers and a partial institutional subsidy.

KEY ACHIEVEMENTS: Highlighted 2014 accomplishments for the Cancer Center are grouped into four thematic areas:

1. Clinical Trials of Targeted Therapies: In a seminal phase I study, Dr. Alice Shaw and coworkers reported that the "next–generation" ALK inhibitor ceritinib is highly active in most patients with EML4-ALK translocated non-small cell lung cancer that have acquired resistance to the first generation ALK inhibitor crizotinib (1). Based on these results, ceritinib was granted accelerated approval by the FDA. In a major phase III clinical trial, Dr. Keith Flaherty and colleagues demonstrated that combined BRAF and MEK inhibition is more effective than BRAF inhibition alone in patients with metastatic melanoma harboring the common BRAF V600E mutation (2). This combination therapy is now considered standard-of-care.

(1) Shaw AT, et al. Ceritinib in ALK-rearranged non-small-cell lung cancer. NEJM *370:1189-97, 2014.*

(2) Long GV, et al., Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. NEJM *371: 1877-88, 2014.*

2. Tackling Acquired Resistance to Cancer Targeted Therapies: The highly specific molecular targeting of oncogenic drivers in cancer is associated with equally specific mechanisms of acquired resistance, which can be defined molecularly and targeted using combinations of second line agents. In a major proof of principle study, Drs. Jeff Engelman and Cyril Benes established in vitro cultured cell lines from a cohort of patients whose lung cancer had become resistant to EGFR or ALK inhibitors. High throughput testing of single and combination inhibitors identified therapies potentially capable of overcoming acquired drug resistance, establishing a new paradigm for predictive preclinical testing (3). In additional studies, Dr. Engelman et al showed that CDK 4/6 inhibitors sensitize PIK3CA mutant breast cancer to PI3K inhibitors (4), and Dr. Dejan Juric and coworkers showed that multiple independent metastatic lesions in a patient with PIK3CA mutant breast cancer acquired resistance to PI3K inhibitors through a variety of distinct mechanisms all leading to inactivation of the PTEN tumor suppressor (5).

(3) Crystal AS, et al., Patient-derived models of acquired resistance can identify effective drug combinations for cancer. Science. *Nov 13. pii: 1254721, 2014*

(4) Vora SR, et al., CDK 4/6 inhibitors sensitize PIK3CA mutant breast cancer to PI3k inhibitors. Cancer Cell *26:136-49, 2014*

(5) Juric D, et al., Convergent loss of PTEN leads to clinical resistance to a PI(3)Kα inhibitor. Nature *Nov 17. doi: 10.1038/nature13948, 2014*

3. Characterizing Circulating Tumor Cells: Blood borne metastases are the leading cause of death from cancer, yet the unique properties of Circulating Tumor Cells (CTCs) are poorly understood. Using a unique microfluidic CTC isolation strategy followed by single cell RNA sequencing, a team led by Drs. Daniel Haber, Mehmet Toner, Shyamala Maheswaran and colleagues demonstrated that rare CTC-clusters in the circulation, held together by the cell junction protein Plakoglobin, are far more potent initiators of distant metastasis than are single CTCs in the bloodstream (6). They went on compare a comprehensive single cell transcriptional profile of pancreatic cancer CTCs, describing their aberrant expression of ECM proteins (7). Finally, in breast cancer, they achieved the in vitro culture of CTCs, expanding them into cell lines to enable detailed genotyping and drug sensitivity profiling (8).

(6) Aceto N,et al., Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis. Cell *345:216-20, 2014*

(7) Yu M, et al., Ex vivo culture of circulating breast tumor cells for individualized testing of drug susceptibility. Science *345:216-20, 2014*

(8) Ting DT, et al., Single-cell RNA sequencing identifies extracellular matrix gene expression by pancreatic circulating tumor cells Cell Rep. *8:1905-18, 2014*

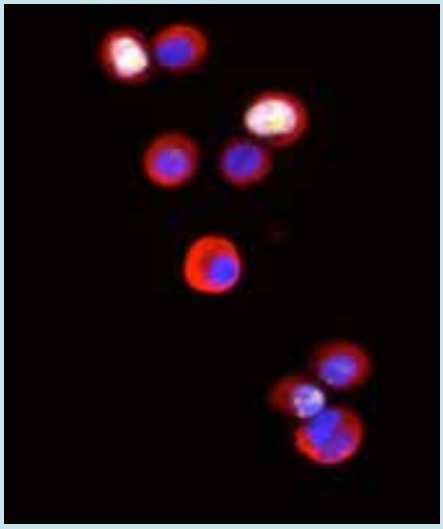
4. Genetic causes of cancer: Collaborative research between Dr. John Iafrate's molecular pathology team and cancer center scientists identified frequent mutations in isocitrate dehydrogenase (IDH) genes in cases of intrahepatic cholangiocarcinoma. Following up on these studies, Drs. Nabeel Bardeesy, Sridhar Ramaswamy and colleagues reported that mutant IDH blocks liver progenitor cells from undergoing hepatocyte differentiation through production of 2HG and suppression of HNF-4α, a master regulator of hepatocyte identity and quiescence (9). These mechanistic studies underlie future therapeutic opportunities. In a genome-wide screen for chromatin alterations, Drs. Miguel Rivera and Brad Bernstein defined specific targets of the EWS-FLI1 translocation product in the pediatric cancer Ewings Sarcoma (10), while Drs. Bernstein and Mario Suva identified reprogramming factors that modulate tumorigenic properties in Glioblastomas (11). In addition, in a Broad Institute-led collaboration, Dr. Gaddy Getz analyzed the frequency of mutations in "cancer drivers" across all histological types analyzed to date, establishing computational criteria for classifying rare variants as potential cancer genes and setting parameters for the comprehensive annotation of rare mutant alleles across all human cancers (12).

(9) Saha SK, et al., Mutant IDH inhibits HNF4a to block hepatocyte differentiation and promote biliary cancer. Nature *513:110-4, 2014.*

(10) Riggi N, et al., EWS-FLI1 utilizes divergent chromatin remodeling mechanisms to directly activate or repress enhance elements in Ewing Sarcoma. Cancer Cell *26: 668-81, 2014*

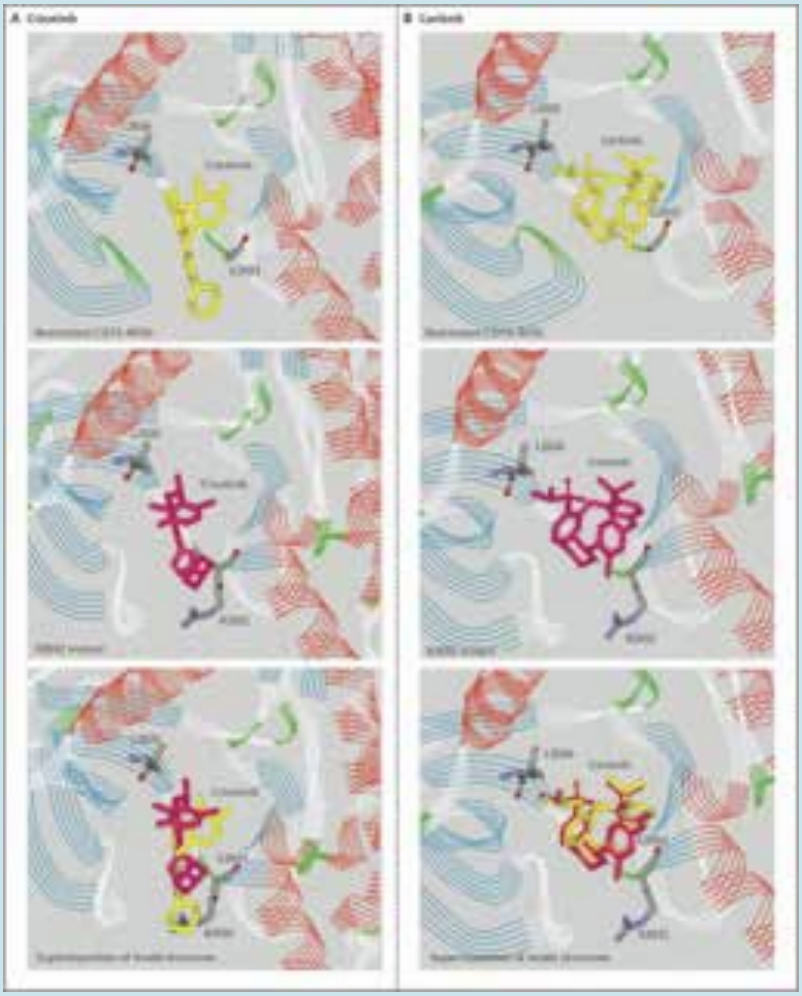
(11) Suva M, et al., Reconstructing and reprogramming the tumor-propagating potential of glioblastoma stem-like cells. Cell *157: 580-94, 2014*

(12) Lawrence MS, et al., Discovery and saturation analysis of cancer genes across 21 tumour types. Nature *505:495-501, 2014*



Ex vivo cultures of circulating tumor cells from breast cancer patients stained with cytokeratin (Red) and the proliferation marker Ki67 (White). Nuclei are stained with DAPI (Blue).

Yu M, Bardia A, Aceto N, Bersani F, Madden MW, Donaldson MC, Desai R, Zhu H, Comaills V, Zheng Z, Wittner BS, Stojanov P, Brachtel E, Sgroi D, Kapur R, Shioda T, Ting DT, Ramaswamy S, Getz G, Iafrate AJ, Benes C, Toner M, Maheswaran S, Haber DA. Ex vivo culture of circulating breast tumor cells for individualized testing of drug susceptibility.
***Science*. 345:216-20, 2014. PMID: 25013076**



Docking conformations of crizotinib and ceritinib with CD74–ROS1 protein
Shaw AT, Engelman JA. Ceritinib in ALK-rearranged non-small-cell lung cancer. *N Engl J Med*. 370:2537-9, 2014. PMID: 24963575.

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 Boston's world-class MedTech communities (Figure).

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 2014, 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.

Key achievements in 2014

Joint Warfighter Program funding to CIMIT provided $2.1M of direct costs towards the research of seven MGH investigators in cutting-edge, commercializable projects: Jerome Ackerman, Tianhong Dai, Julian Goldman, Raj Gupta, Michael Lev, Marc de Moya, 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 serves on its Technology Assessment and Development Group. In that capacity, Paul provides coaching to investigators on commercialization of translational research and in preparing B-BIC grant applications. Paul coached one of the first two B-BIC grant recipients, Seemantini Nadkarni, PhD, MGH Wellman Center for Photomedicine, who was initially funded through CIMIT's NIBIB grant and whose B-BIC grant will enable continued development of a low-cost, bed-side blood sensor that rapidly will identify patients with an elevated risk of life-threatening bleeding or thrombosis.

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 allow the team to bid on a second-phase, $8M contract. A company is being formed to further commercialize these innovations and discussions are underway with multiple outside investment groups.

Consortia for Improving Medicine Through Innovation and Technology (CIMIT)

Department Report

John Parrish, CIMIT CEO, receiving the Distinguished Service Award at the 2014 Military Health System Research Symposium from Rear Admiral Bruce Doll in Ft. Lauderdale, Florida. Rear Adm. Doll is Director, Research, Development and Acquisition, Defense Health Agency and Deputy Commander, US Army Medical Research and Material Command. The plaque reads, "Presented in recognition of your unequaled 47+ years of contributions to the success of the military health system. You established two highly successful centers for translational medicine at the Harvard Medical School and the Massachusetts General Hospital. The Department of Defense is forever indebted to you."

MGH was a founding member of CIMIT in 1998. The CIMIT network has grown significantly since then.

David E. Fisher MD, PhD; Chief

The primary mission of the Department of Dermatology at MGH is the delivery of world-class care to patients from around the globe and around the corner. This core mission is coupled with a commitment to contribute cutting edge discoveries in a diverse set of research laboratories, and to translate laboratory-based discoveries into improvements in clinical care. To achieve these goals the Department maintains a busy clinic that cares for >1000 patients per week, and includes subspecialty clinics in numerous areas spanning high risk skin cancers and melanoma, to cosmetic dermatology. In addition, the Department houses a vibrant Clinical Trials Unit which has maintained a portfolio of 15-20 active clinical trials in dermatology. Outside of the clinic, the Department houses the Cutaneous Biology Research Center (CBRC), home to 13 Principal Investigators who run independent research laboratories. The topics investigated at CBRC span diverse research areas, including molecular/cellular biology of skin, stem cells, epigenetics, immunobiology, chemical biology/screening, topical drug delivery, itch, UV-protection, metabolism, cancer biology, inflammation, pigmentation, hair follicle biology, and laser applications. Additional research faculty based in Dermatology include numerous researchers housed in the Wellman Center for Photomedicine, an MGH Thematic Center that has made seminal contributions to the current practice of dermatology.

During 2014, Dermatology research and clinical faculty have contributed 285 publications, presented at 309 speaking engagements, and expended ~$25.5M of funding. These publications include works in very high profile journals (e.g. *Nature*, *Science*, *Cell*), speaking engagements at top Dermatology and Cross-specialty meetings (e.g. American Academy of Dermatology, Society for Investigative Dermatology) and include funding from NIH, Department of Defense, numerous foundations, industry partners, royalties, and philanthropy. Collectively, these efforts continue to drive an engine of outstanding academic and clinical productivity, leading to discoveries that become Textbook standards as well as practice-changers for the field of Dermatology. MGH Dermatology is also extremely proud of its Community Service and Educational missions, both of which are robustly represented by daily activities in the department, and range from free skin cancer screenings and care for the homeless, to teaching of local and international trainees who include high school, college, and medical school students, as well as clinical and research fellows from nearby and abroad. Finally, the Dermatology Department is proud of numerous cross disciplinary activities from the lab bench to the clinic, which bring together skin expertise with specialists in other fields, such as Oncology, Pathology, Internal Medicine, Anesthesia, Plastic Surgery, Immunology, Radiation Oncology, Psychiatry, and others.

Notch1 and its control by estrogen receptor β. Notch1 expression is downregulated or mutated in multiple malignancies of squamous epithelium. Paolo Dotto and colleagues had previously demonstrated that Notch1 plays a central role in normal epithelial differentiation, and now studied which factors modulate its expression in keratinocyte epithelial cells. His group identified several factors including DLX5, EGR3, and estrogen receptor b, that play key roles in controlling Notch1 expression. ERβ was also found to be deficient in expression within skin, lung, and head and neck cancers. Moreover re-expression of ERβ or treatment with estrogen agonists inhibited proliferation of Squamous Cell Carcinomas in vitro and in murine models. These studies combined a key mechanistic insight to common cancer types with a therapeutic strategy for these malignancies.

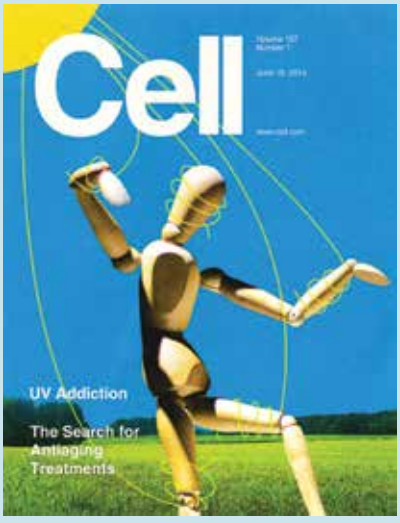
Brooks,Y., Ostano, P., Jo, S.-H., Dai, J., Getsios, S., Dziunycz, P., Hofbauer, G.F.L. Chiorino, G., Lefort, K. and Dotto G.P. Multifactorial ERß and Notch1 Control of Squamous Differentiation and Cancer. J *Clin Invest.* 2014 May 1;124(5):2260-76

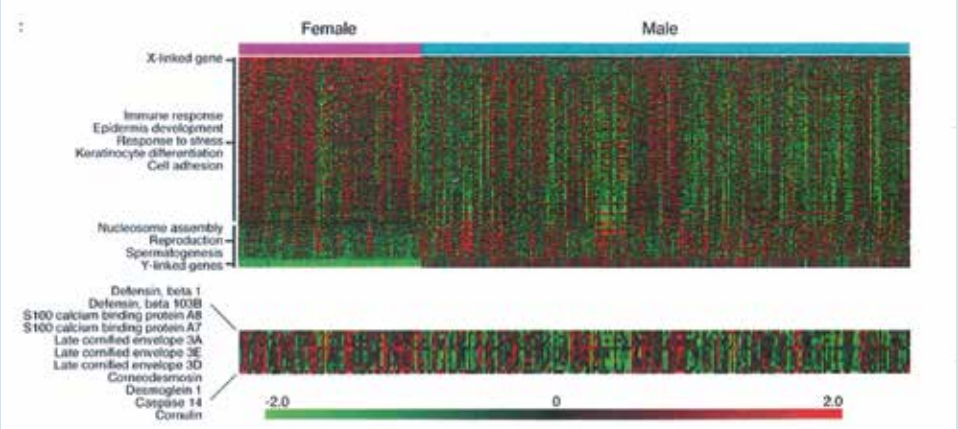
β-endorphin and UV-seeking behavior. The lab of David Fisher presented the elucidation of a cutaneous pathway in which UV radiation triggers production of the endogenous opiate β-endorphin. The work utilized a collection of genetically defined mice (including β-endorphin knockouts) to show that UV-induced β-endorphin is sufficiently potent to elevate blood levels, alter pain/nociceptive thresholds, produce opiate "dependency," and produce behavioral conditioning consistent with "UV-seeking." This pathway is mediated by p53-dependent "sensing" of DNA damage in keratinocytes, and was suggested to potentially represent a primordial addiction, pertinent to evolution of terrestrial species. Due to its potential impact on public awareness and tanning bed legislation, the work was reported widely in the public media, and further discussed in a review on Melanoma from the same laboratory.

Fell et al. Skin β-endorphin mediates addiction to UV light. *Cell.* 2014 157(7):1527-34. Lo JA & Fisher DE. The melanoma revolution: from UV carcinogenesis to a new era in therapeutics. *Science.* 2014 Nov 21;346(6212):945-9.

Pseudo-cellulitis: the common "misdiagnosis" of cellulitis. Dr. Daniela Kroshinsky, director of the Dermatology Consult Service, carried out a multi-center, prospective, randomized study to assess the frequency of diagnostic accuracy in cellulitis diagnosis at outpatient internal medicine offices. The study also assessed antibiotic usage. The findings indicated 67-90% incorrect cellulitis diagnosis by Internists relative to Dermatologists, and also indicated remarkable concordance at distinct geographic locations. The study—suggesting a high frequency of inaccurate cellulitis diagnosis as well as antibiotic usage and hospitalization—carries major implications for population health management as well as resource utilization.

Arakaki RY, Strazzula L, Woo E, Kroshinsky D. The impact of dermatology consultation on diagnostic accuracy and antibiotic use among patients with suspected cellulitis seen at outpatient internal medicine offices: a randomized clinical trial. *JAMA Dermatol.* 2014 Oct 1; 150(10):1056-61.





Gene expression differences in female vs. male Squamous Cell Carcinomas highlight differential expression of epithelial differentiation factors.
Taken from Brooks et al *J Clin Invest*. 2014;124(5):2260-2276

David F. M. Brown, MD; Chief

Mission

To perform innovative research that improves the diagnosis and treatment of patients seeking emergency care. This research spans the spectrum from basic science to individual patient care to care of populations.

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 the possibility of new emergency care delivery systems. Areas under active investigation include: cardiovascular and thrombotic emergencies, respiratory/allergic emergencies, acute neurologic emergencies, infectious disease emergencies, trauma care and injury prevention, global health problems, emergency systems engineering, ultrasound, simulation in medical education, disaster preparedness, physiologic monitoring, pediatric emergencies and emergency care access, workforce, and policy.

Strategic priorities for the past year included:

A. Expanding our portfolio and broadening it to include basic science, pediatrics, geriatrics, disaster preparedness, trauma care and injury prevention.
B. Continuing to form networks with other MGH departments, Partners Health Care, Harvard Medical School and other institutions.
C. Expanding the size of our clinical research coordinator pool to enable us to perform more studies.
D. Increasing our research space and research storage capacity.

1. ProCESS Investigators, Yealy DM, Kellum JA, Huang DT, Barnato AE, Weissfeld LA, Pike F, Terndrup T, Wang HE, Hou PC, LoVecchio F, ***Filbin MR****, Shapiro NI, Angus DC. A Randomized Trial of Protocol-Based Care for Early Septic Shock.* N Engl J Med. *2014 May 1; 370(18):1683-93. PMID: 24635773.*

The ProCESS study (Protocolized Care for Early Septic Shock) was a multicenter randomized, controlled trial that compared a stylized versus a standard care intervention for early sepsis. The results of this trial redefined the priorities of early septic shock management and shifted the focus of early sepsis care from invasive resuscitative techniques to methods of optimizing initial disease recognition and prompt basic therapies. These results have already impacted both emergency medicine and critical care guidelines.

2. Smith-Bindman R, Aubin C, Bailitz J, Bengiamin RN, ***Camargo CA Jr****, Corbo J, Dean AJ, Goldstein RB, Griffey RT, Jay GD, Kang TL, Kriesel DR, Ma OJ, Mallin M, Manson W, Melnikow J, Miglioretti DL, Miller SK, Mills LD, Miner JR, Moghadassi M,* ***Noble VE****, Press GM, Stoller ML, Valencia VE, Wang J, Wang RC, Cummings SR. Ultrasonography versus computed tomography for suspected nephrolithiasis.* N Engl J Med. *2014 Sep 18; 371(12):1100-10. PMID: 25229916.*

This was a randomized, controlled trial funded by the AHRQ as part of the stimulus grant initiative. The results showed that complications and alternate diagnoses for patients suspected of renal colic are the same (and quite low) for both an US first or CT first diagnostic approach. Decreasing CT utilization in renal colic ED patients is one of the top five choose wisely initiatives for American College of Emergency Physicians (ACEP) for 2015 as a result.

3. ***Macias Konstantopoulos WL****, Dreifuss JA, McDermott KA,* ***Parry BA****,* ***Howell ML****, Mandler RN, Fitzmaurice GM, Bogenschutz MP, Weiss RD. Identifying patients with problematic drug use in the emergency department: results of a multisite study.* Ann Emerg Med. *2014 Nov; 64(5):516-25. Epub 2014 Jul 3. PMID: 24999283.*

Using data from a large multicenter randomized prospective trial that prescreened over 15,000 ED patients for possible problematic drug use, self-reported variables related to demographics, substance use habits, and ED visit were examined to determine their correlative value for problematic drug use. This secondary analysis proposes a simple clinical decision rule to assist in identifying ED patients who may benefit from more comprehensive drug screening, intervention, and referral to treatment.

4. ***Hasegawa K****,* ***Sullivan AF****, Tsugawa Y, Turner SJ, Massaro S, Clark S,* ***Tsai CL****,* ***Camargo CA Jr****, on behalf of the MARC-36 Investigators. Comparison of U.S. emergency department acute asthma care quality, 1997-2001 and 2011-2012.* J Allergy Clin Immunol. *2014 Sep 26. [Epub ahead of print]. PMID 25263233.*

In this 48-center analysis based on 3 observational studies of 4039 adults with asthma exacerbation between 1997 and 2012, we observed changes in the quality of emergency asthma care that differed by level of the NIH guideline recommendation. Although emergency care became highly concordant with level A guideline recommendations, the concordance with non–level A recommendations (i.e., use of peak expiratory flow measurement and timeliness measures) decreased. Additionally, the variations in these measures became larger across the emergency departments, with significant regional differences. Our data also demonstrated a strong association between quality of care and patient outcomes. More specifically, complete concordance with the NIH asthma guidelines was associated with a significantly reduced risk of hospitalization.

MGH EMERGENCY MEDICINE FACULTY

Back (L-R): Christopher Kabrhel, MD, MPH, Murtaza Akhter, MD, Renee Salas, MD, MS, Kohei Hasegawa, MD, MPH, Andrew Reisner, MD, Elizabeth Temin, MD, MPH, Leslie Milne, MD, James Kimo Takayesu, MD, MSc *Front (L-R):* Ali Raja, MD, MBA, MPH (Vice Chair), David F. M. Brown, MD (Chair), John T. Nagurney, MD, MPH, N. Stuart Harris, MD, MFA, Joshua Goldstein, MD, PhD

MGH EMERGENCY MEDICINE RESEARCH STAFF

Back (L-R): Tyler Rubin, Chris Wisnik *Middle (L-R):* Rebecca Lee, Jacqui Matczak, Shane Donnelly, Tayla Parker, Jill Thorsen, Greg Tirrell, Savanah Harshbarger, Emily Douglass, Jaci Gassaway *Front (L-R):* Praveen Hariharan, MD, MPH, Blair Alden Parry, CCRC, BA (Clinical Research Program Manager), John T. Nagurney, MD, MPH (Research Director), Ryan Callahan, Susann Jarhult, MD

Medicine

Department Report

Katrina Armstrong, MD; Chief

As the largest of the MGH Departments, the Department of Medicine is integral to the MGH mission and 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. The five cross cutting goals identified in the Roadmap for the Next Decade are to *(1) bring transformational discovery to patients and populations, (2) advance models of high quality patient care that foster inquiry and learning, (3) transform training to advance innovation, leadership and educational excellence, (4) build community to incubate innovation, and (5)invest in diverse human capital across the career spectrum.* In line with these goals, we have highlighted accomplishments across the Department of Medicine and its ten clinical divisions and 5 research units in 2014 in four key thematic areas: genomic science, innate immunology and immune tolerance, therapeutic interventions, and population health.

Achievement in ***genomic science*** included work where Christopher Newton-Cheh from the Cardiology Division and colleagues identified 35 loci related to electrocardiographic QT interval variation, 22 of which are novel and 11 of which he previously reported in an earlier paper at *Nature Genetics*. They went on to demonstrate that several of these genes are associated with cardiac function. Two genes were identified as potential novel LQTS genes because of coding variants in congenital LQTS. (1) SAME HERE Also in the Cardiology Division, Sek Kathiresan led a large-scale analysis to find gene mutations that protected against disease, finding that 1 in 150 in the U.S. carried a mutation in the apolipoprotein C3 (APOC3) gene and had lower triglyceride levels as well as reduced risk for coronary heart disease.(2) This discovery suggest that beyond LDL cholesterol, triglyceride-rich lipoproteins are causal factors for coronary heart disease, and provides a roadmap for developing medicines that block APOC3 and mimic this natural success of the genome.

Additional accomplishments were made in the area of ***innate immunity and immune tolerance***. Using an unbiased genome-scale pooled shRNA screen, Terry Means from the Division of Rheumatology, Allergy and Immunology and colleagues identified a novel positive regulator of TLR7 signaling called Triggering Receptor Expressed on Myeloid cells-Like 4 (Treml4). Toll-like receptors (TLRs) play a critical role in innate immunity by recognizing conserved pathogen associated molecular patterns (PAMPs) found in bacteria, viruses and fungi, and then activating innate immune cells to initiate an immune response.(3) These results show for the first time that TREML4 is an important positive regulator of TLR7 signaling and a novel therapeutic target for the development of new immunosuppressive or anti-inflammatory drugs. Also in the Division of Rheumatology, Allergy and Immunology, Thorsten Mempel and his research group have used intravital microscopy to reveal that regulatory T cells (Treg) interact with dendritic cells (DC) in tumor tissue in an antigen-specific manner. (4) This interaction enables Tregs to deplete DCs of the co-stimulatory molecules necessary to sustain the anti-tumor activity of cytotoxic effector T cells in the tumor microenvironment. Such approaches of targeted local modulation of tumor immune tolerance have the potential to maximize effectiveness while avoiding systemic autoimmune toxicity. The international collaborative team (MGH-Boston and Bangladesh) led by Ed Ryan from the Infectious Diseases Division has leveraged

the transient migration of lymphoblasts during the acute febrile stage of typhoid fever to identify a subset of antigenic targets from the proteome of Salmonella typhi that are targeted by the immunoglobulins associated with these lymphocytes. Typhoid affects over 20 million people and kills over 100,000 people annually. (5) This approach will enable the development of an improved diagnostic assay.

Therapeutic interventions were at the forefront of departmental achievements in 2014. Steven Russell, MD from the Diabetes Unit has led the clinical testing of a novel bionic pancreas device, which combines a minimally invasive continuous glucose monitor, a control algorithm to determine dosing, and two infusion pumps that deliver insulin and glucagon into the subcutaneous tissue. The bionic pancreas dramatically reduces the effort associated with diabetes management and was demonstrated to achieve clinically meaningful improvements in mean glucose levels—a step that is critically needed to reduce the morbidity and mortality that is associated with type 1 and insulin-dependent type 2 diabetes.(6) Also in the Endocrine Division, Steve Grinspoon from the Neuroendocrine Unit led a placebo-controlled trial demonstrating that augmentation of endogenous growth hormone with tesamorelin, a growth hormone releasing hormone analogue, reduces liver fat in individuals with HIV-infection and visceral adiposity. (7) In the pulmonary division, Andrew Tager has identified new molecular pathways involved in the pathogenesis of idiopathic pulmonary fibrosis (IPF) and scleroderma that are now being targeted in patients. Based on his identification of lysophosphatidic acid (LPA) as a critical mediator of fibrosis in these diseases, antagonists of its receptor, LPA1, are being evaluated in clinical trials in both areas. A Phase 2 trial of an LPA1 receptor antagonist in scleroderma just reported statistically significant and clinically meaningful improvements in fibrosis and symptom efficacy endpoints in patients receiving this treatment. (8-9) Peter The Nephrology Division, Peter Mundel demonstrated that abatacept induced partial or complete remissions of proteinuria in five patients who had focal segmental glomerulosclerosis and B7-1 immunostaining of podocytes, potentially by stabilizing β1-integrin activation in podocytes. (10) And in an area of tremendous growth for the Department, Ramnik Xavier and his team from the Gastroenterology Division are investigating patterns of gut microbiome dysbiosis in Crohn's Disease- an avenue that offers opportunities for early diagnosis, new treatment strategies and a reevaluation of the role of antibiotic therapy in Crohn's disease treatment. (11)

A continued commitment to ***population health*** can be seen in the works of the research team of Nancy Rigotti from the General Internal Medicine Division who performed a randomized clinical trial showing that among hospitalized adult smokers who wanted to quit smoking, a postdischarge intervention providing automated telephone calls and free medication resulted in higher rates of smoking cessation at 6 months compared with a standard recommendation to use counseling and medication after discharge. These findings, if replicated, suggest an approach to help achieve sustained smoking cessation after a hospital stay.(12) Andrew Chan from the Gastroenterology Division and his research team found that the association of aspirin use with lower risk of colorectal cancer was predominantly observed among individuals with an intact level of expression of 15-hydroxyprostaglandin dehydrogenase (15-PGDH), the principal enzyme involved in prostaglandin catabolism. These results suggest that the effect of aspirin on colorectal cancer risk is dependent on cooperation with the 15-PGDH pathway, which supports the use of this biomarker to risk-stratify patients with colorectal polyps for aspirin chemoprevention. (13) And finally, in the Nephrology Unit, Ravi Thadhani demonstrated that the low levels of vitamin D previously found among black Americans are attributable to lower levels of vitamin D-binding protein, resulting in similar concentrations of estimated bioavailable 25-hydroxyvitamin D across the groups. They also demonstrated that racial differences in the prevalence of vitamin D binding protein polymorphisms are likely to explain this observation. (14)

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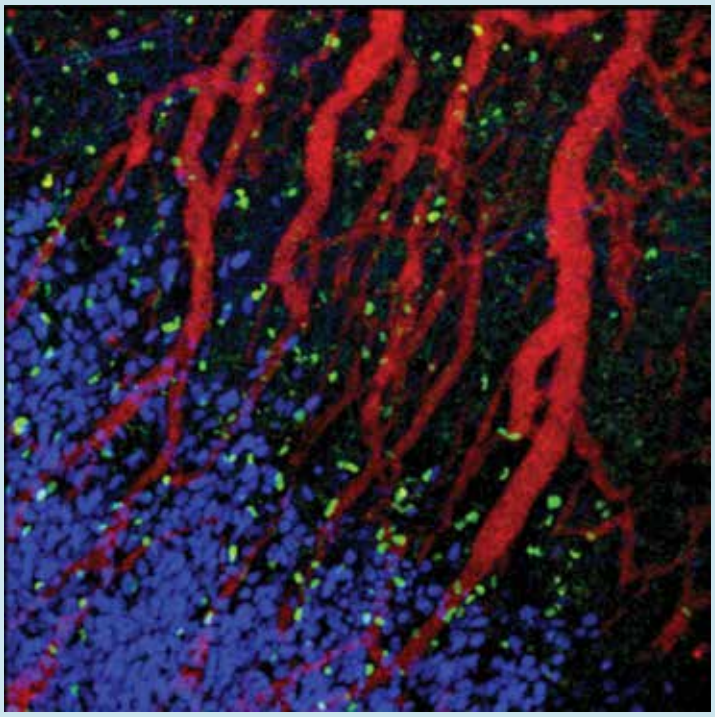


Cytotoxic T cells (green) infiltrate and destroy colon carcinoma cells (blue nuclei) in the tumor microenvironment as visualized by multiphoton intravital microscopy. Blood was visualized by intravenous injection of quantum dots (red).

Molecular Biology

Department Report

Bob 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 200 people, including 14 faculty and over 85 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, epigenetics, long noncoding RNA, and X-chromosome inactivation (Kingston, Lee).
- Human/population genetics, (Altshuler, Mootha), pathophysiology of type 2 diabetes (Altshuler), 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).

This has been a remarkable year for the Department of Molecular Biology, in which members our faculty won four of the most prestigious honors recognized in the sciences.

The Genetics Society of America's 2014 Thomas Hunt Morgan Medal was awarded to Frederick Ausubel, whose 40-year career has centered on host–microbe interactions and host innate immunity. Fred's contributions to genetics, to numerous to list fully, include an understanding of the evolution and regulation of Rhizobium genes, symbiotic nitrogen fixation, and innate immunity in plants and C. elegans. Fred also helped to establish Arabidopsis thaliana as a model organism.

Gary Ruvkun was the recipient of two prizes widely regarded to be a step removed from the Nobel Prize. Together with Victor Ambros, his longtime collaborator and friend, Gary was awarded the 2014 Wolf Prize in Medicine, for the discovery of microRNAs and the demonstration of their relevance in human physiology. Later in 2014, Gary and Victor were recognized for their work a second time: they were awarded the Breakthrough Prize in the Life Sciences. These two awards are the most recent in a series of prestigious honors bestowed on Gary and Victor, whose work led to a paradigm shift in our understanding of post-transcriptional regulation of gene expression across all domains of life.

Vamsi Mootha was elected to the National Academy of Sciences in 2014, a mere ten years after his first faculty appointment. Vamsi is a leader in the field of mitochondrial physiology and disease. His research group consists of clinicians, computer scientists, and biologists, who work collaboratively to elucidate the network properties of mitochondria, and how these properties go awry in human disease. His work has led to the discovery of over one dozen Mendelian mitochondrial disease genes, to the discovery that mitochondrial dysfunction is associated with the common form of type 2 diabetes mellitus, and to the identification of the molecular component of the mitochondrial calcium uniporter.

Our faculty published several important papers in 2014. Some highlights include:

1. Rare variants in PPARG with decreased activity in adipocyte differentiation are associated with increased risk of type 2 diabetes.
Majithia AR, Flannick J, Shahinian P, Guo M, Bray MA, Fontanillas P, Gabriel SB; GoT2D Consortium; NHGRI JHS/FHS Allelic Spectrum Project; SIGMA T2D Consortium; T2D-GENES Consortium, Rosen ED, Altshuler D
Proc Natl Acad Sci U S A. 2014 Sep 9;111(36):13127-32. doi: 10.1073/pnas.1410428111. Epub 2014 Aug 25. PMID: 25157153 [PubMed - in process]

Interpretation of rare variant sequencing data requires improved ability to distinguish functional mutations from those that are benign. This paper describes development of high throughput functional assays in human adipocytes as a means to identify deleterious missense variants in PPARG, and shows that loss of function mutations in this gene contribute to T2D outside the context of classical lipodystrophy.

2.RNA stimulates Aurora B kinase activity during mitosis.
Jambhekar A, Emerman AB, Schweidenback CT, Blower MD
PLoS One. 2014 Jun 26;9(6):e100748

This paper demonstrates that the mitotic kinase Aurora-B is a RNA binding protein that interacts directly with RNA. We also show that Aurora-B is directly activated by RNA and that this activation is important for proper mitotic spindle assembly. This paper is important because it demonstrates a novel mode of activation of a well-studied mitotic kinase and provides a molecular mechanism by which RNA promotes mitosis in a translation-independent manner. This work is likely relevant to the recent observation that repetitive centromeric DNA is transcribed during mitosis and that this transcription is upregulated in cancer.

3.Identification of new small RNA pathway genes from correlated patterns of phylogenetic retention and loss.
Tabach Y, A Billi, G Hayes, O Zuk, H Gabel, R Kamath, M Newman, K Yacoby, B Chapman, M Borowsky, J Kim, and G Ruvkun 2013.
Nature Jan 31;493(7434):694-8. doi: 10.1038/nature11779. Epub 2012 Dec 23.

This paper uses comprehensive comparative genomics across the eukaryotic tree of life, 86 genomes, to reveal correlated loss and retention of RNAi and miRNA components. We used tested the genes that emerged from the analysis for defects in RNAi to reveal that the predictions from the informatic analysis are highly enriched for gene inactivations that disrupt small RNA pathways. Most importantly, we describe the striking phylogenetic correlation between intron number and competence for RNA interference and prove that the splicesome is intimately integrated into the process of RNAi. This is unexpected. We also describe an amazing correlated loss and retention of the glycolysis pathway component cofactor independent phosphoglycerate mutase with the production of secondary siRNAs.

4. Structural insights into the effects of 2′-5′ linkages on the RNA duplex.
Sheng J, Li L, Engelhart A, Gan J, Wang J and Szostak JW.
Proc. Natl. Acad. Sci. USA, 2014; 111:3050-3055.

Last year we showed that aptamers and ribozymes were surprisingly tolerant of 2′-5′ linkages in the RNA phosphodiester backbone. In order to understand this better, we obtained crystal structures of RNA duplexes containing zero, one or three such linkages per strand. The structural changes were largely localized to the 'incorrect' linkage, and were compensated by opposing changes in the flanking base-pairs. This paper, the first crystal structure from my lab, explains in part the minimal disruption of folded RNA structures by backbone heterogeneity.

5. ATRX promotes binding of PRC2 to Xist RNA and Polycomb targets.
Sarma, K., Cifuentes-Rojas, C., Ergun, A., del Rosario, A., Jeon, Y., White, F. Sadreyev, R., and Lee, J.T. 2014.
Cell 159: 869-883.

Along with an accompanying paper (Cifuentes-Rojas, C., Hernandez, A.J., Sarma, K., and Lee, J.T. 2014. Regulatory interactions between RNA and Polycomb repressive complex 2. Mol Cell. 55: 171-185), this paper demonstrate that Polycomb repressive complex 2 (PRC2) interacts with RNA specifically both in vitro (Cifuentes-Rojas et al.) and in vivo (Sarma et al.). In Sarma et al., we identified a new factor, ATRX, that interacts with Xist RNA and is required for Xist to bind to PRC2. Without ATRX, PRC2 cannot load onto Xist or onto other Polycomb targets in cells.

6. Expansion of biological pathways based on evolutionary inference.
Li Y, Calvo SE, Gutman R, Liu JS, Mootha VK. 2014.
Cell: 158(1):213-25.

In this paper, we report a new statistical algorithm (called CLIME, for 'clustering by inferred models of evolution'), for clustering genes based on models of inferred evolution, and then expanding the clusters with new members. It's a powerful new bioinformatic strategy for inferring gene function. We also released a web-based version of the tool, www.gene-clime.org, to make the tool broadly available to the community.

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.

In 2014 the Department of Neurology embarked on a strategic planning effort resulting in six Strategic Research Priorities for the Department of Neurology:

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

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 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's NIH success rate is 26.5% (2013 data), while the average for NIH's NINDS applications is 19.8 %. Last year, the Department of Neurology brought in $78M in research revenue.

The Case for Urate

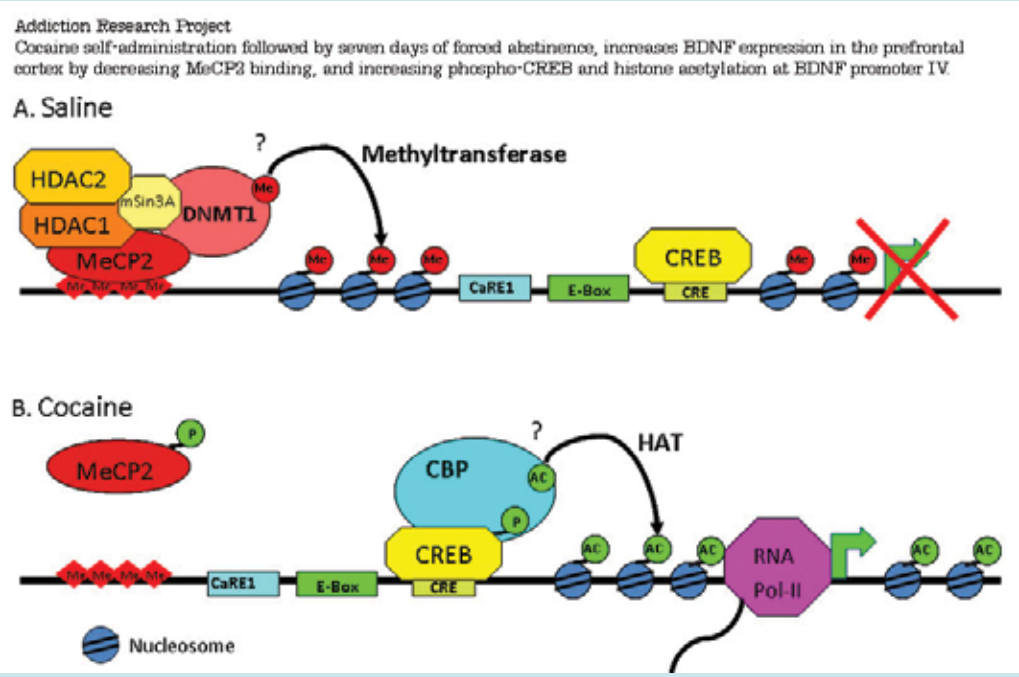
The Molecular Neurobiology Laboratory at the MassGeneral Institute for Neurodegenerative Disease, under the direction of Michael Schwarzschild, MD PhD, investigates molecular mechanisms in mouse models of Parkinson's disease in an effort to develop improved therapies for Parkinson's and related neurodegenerative diseases. Over the past year the case for urate as promising target for slowing progression of Parkinson¹s and other neurodegenerative diseases has been strengthened by our convergent laboratory and clinical research findings. We have identified a novel mechanism of neuroprotection by urate in our bench studies at the MassGeneral Institute for Neurodegenerative Disease. In parallel we have reported human genetic and positive phase 2 trial data that support advancing of a full efficacy trial of the urate precursor inosine as a disease-modifying treatment for Parkinson¹s. Accordingly we developed a phase 3 trial protocol, which has been submitted for review to the FDA and NIH.

http://archneur.jamanetwork.com/article.aspx?articleid=1790169#Abstract

Basic research leading to better understanding of addiction

In a study led by Dr. Ghaz Sadri-Vakili lab, the investigators find evidence that changing one amino acid in a subunit of the glutamate AMPA receptor alters whether cocaine-experienced animals will resume drug seeking after a period of cocaine abstinence. Furthermore, increasing expression of the enzyme responsible for that change within the GluA2 subunit of AMPA receptors reduced cocaine seeking in animals allowed to self-administer the drug. AMPA receptors consist of four subunits, GluA1 through GluA4. The GluA2 subunit determines whether the receptor is permeable to calcium, which enhances the strength of signals transmitted through the receptor. In the normal adult brain, 99 percent of GluA2 subunits are edited at the RNA processing stage into a form that is impermeable to calcium. Disruptions in GluA2 editing that create a calcium-permeable receptor have been associated with disorders including depression, epilepsy and amyotrophic lateral sclerosis. Since chronic cocaine exposure produces major changes in glutamate transmission in the brain, including the nucleus accumbens, a brain region known to be involved in reward and addiction, the research team investigated the relationship of GluA2 editing to cocaine seeking in the accumbens of rats that self-administered cocaine. Examination of the animals' brains after 7 days of drug abstinence indicated that both edited GluA2 and ADAR2, the enzyme responsible for editing were reduced in the nucleus accumbens of animals that were exposed to cocaine. These findings suggest that activation of AMPA receptors containing unedited GluA2 could potentially stimulate cocaine craving. In addition, overexpression of ADAR2 in the nucleus accumbens both increased the presence of edited GluA2 in AMPA receptors and reduced the resumption of cocaine seeking in habituated animals. These findings support the novel hypothesis that calcium-permeable AMPA receptors containing unedited GluA2 subunits contribute to cocaine seeking. Importantly, repairing the deficient editing of GluA2 via regulation of ADAR2 expression, could be a potential treatment strategy for cocaine addiction.

ADAR2-dependent GluA2 editing regulates cocaine seeking. H D Schmidt, K N McFarland, S B Darnell, M N Huizenga, G R Sangrey, J-H J Cha, R C Pierce and G Sadri-Vakili. Molecular Psychiatry: 2014;

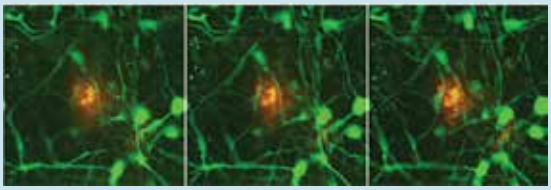


Alzheimer's in a dish

Doo Yeon Kim, PhD, working in the Tanzi lab in Neurology's Genetics and Aging Research Unit succeeded, for the first time, in reproducing the full course of events underlying the development of Alzheimer's disease. By adding a third dimension to a cell culture model of Alzheimer's disease, they have reproduced the two key features of the disease: amyloid-β plaques and neurofibrillary tangles.

The amyloid hypothesis of Alzheimer's disease suggests that the accumulation of amyloid-β into plaques drives the aggregation of hyperphosphorylated tau into neurofibrillary tangles. However, two-dimensional human cell culture models of Alzheimer's disease have failed to produce both plaques and tangles in the same culture, making it difficult to test this hypothesis. Doo Yeon Kim's three-dimensional culture system culture system is the first to reproduce both amyloid-β accumulation and neurofibrillary tangles in human cells. It may provide a system to further investigate the links between these two aspects of Alzheimer's pathology, as well as a potential tool for the screening of drugs designed to modulate these processes.

A three-dimensional human neural cell culture model of Alzheimer's disease. Choi S H, Kim H K, Hebisch M, Sliwinski C, Lee S, D'Avanzo C, Chen H, Hooli B, Asselin C, Muffat J, Klee J, Zhang C, Wainger B, Peitz M, Kovacs D, Woolf C J., Wagner S, Tanzi R, Kim DY. Nature 2014;515:274–278



Characterizing the functional genomic consequences of a new autism gene

The Talkowski lab, led by Michael Talkowski, PhD, winner of the 2013 Joseph B. Martin Research Award previously published a paper that described the discovery of many new genes contributing to autism and neurodevelopment (Talkowski et al., 2012, Cell). Among these loci was a series of genes involved in chromatin modification and transcriptional regulation, which proposed a new pathway of genes involved in autism and neurodevelopment. Most prominent among those genes was CHD8, a chromodomain helicase that was also implicated in ASD by multiple exam sequencing studies that same year. This year, we completed a long-term study to evaluate the impact of editing the genome in iPS-derived neural progenitor cells to be deficient for this gene, mimicking the effect in patients with loss-of-function mutations. We integrated multiple functional genomic measures to determine the consequences of CHD8 deficiency in NPCs, and the results of this study were striking. Through ChIP-sequencing, we discovered that this genes binds pervasively throughout the genome, and through RNA-sequencing we uncovered a series of pathways and genes associated with neural development that are regulated by CHD8. Moreover, we discovered that CHD8 influences the expression of genes involved in transcriptional regulation that are highly expressed early in neural development, as well as genes involved in synapse formation and development that are expressed later in prenatal and early postnatal development. We also found strong connections between this locus and genes associated with cancer. Based upon these findings, many groups are actively pursuing this new avenue of research into the pleiotropic effects of strong effect chromatin modifiers.

Sugathan A*, Biagioli M*, Golzio C*, Erdin S, Blumenthal I, Manavalan P, Ragavendran A, Brand H, Lucente D, Miles J, Sheridan SD, Stortchevoi A, Kellis M, Haggarty SJ, Katsanis N, Gusella JF, Talkowski ME. CHD8 regulates neurodevelopmental pathways associated with autism spectrum disorder in neural progenitors. Proc Natl Acad Sci U S A. 2014 Oct 21;111(42):E4468-77. PMID:25294932

Neurosurgery

Department Report

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 development of oncolytic viruses and vaccines for the treatment of nervous system tumors.

Oncolytic virus therapy for tumors. The use of genetically engineered viruses to treat brain tumors was initially pioneered in the Department of Neurosurgery at the MGH. Dr. Robert L. Martuza, Dr. Samuel Rabkin and colleagues are studying the use of oncolytic herpes simplex virus (oHSV) as a mechanism for cancer therapy. This area of study has led to several clinical trials world-wide for brain tumors and other cancers including prostate cancer and melanoma. This group is now studying interactions of oncolytic virus with other modes of therapy. For example, anti-angiogenic therapy is a promising therapeutic strategy for the highly vascular and malignant brain tumor, glioblastoma (GBM). The small molecule tyrosine kinase inhibitor axitinib targets vascular endothelial growth factor receptor, potently inhibits angiogenesis and has single-agent clinical activity in non-small cell lung, thyroid, and advanced renal cell cancer. In the following study *(Lu L, Saha D, Martuza RL, Rabkin SD, Wakimoto H. Single agent efficacy of the VEGFR kinase inhibitor axitinib in preclinical models of glioblastoma. Journal of Neuro-oncology 2014 Sept 12; DOI: 10.1007: 1-10)* the authors demonstrate that axitinib exerts direct cytotoxic activity against a number of patient-derived GBM stem cell (GSCs) and an endothelial cell line, and inhibits endothelial tube formation in vitro. Axitinib treatment of mice bearing hypervascular intracranial tumors generated from human U87 glioma cells, MGG4 GSCs and mouse 005 GSCs significantly extended survival and was associated with decreases in tumor-associated vascularity. They thus show for the first time the anti-angiogenic effect and survival prolongation provided by systemic single agent treatment with axitinib in preclinical orthotopic GBM models including clinically relevant GSC models. These results support further investigation of axitinib as an anti-angiogenic agent for GBM. This forms the basis for encouraging studies that are now underway combining axitinib with oncolytic viruses to advance to clinical trial.

Defining genetic underpinnings of brain tumors: Neurosurgery residents actively participate in research during two years of dedicated research time. The following study is by Dr. A.P. Patel, one of our mid-level neurosurgery residents *(Patel AP, Tirosh T, Trombetta JJ, Shalek AK, Gillespie SM, Wakimoto H, Cahill DP, Nahed BV, Curry WT, Martuza RL, Louis DN, Rozenblatt-Rosen O, Suvà ML, Aviv R, and Bernstein BE. Single-cell rna-seq highlights intratumoral heterogeneity in primary glioblastoma. Science 2014, DOI: 10.1126: 1-9).* Human cancers are complex ecosystems composed of cells with distinct phenotypes, genotypes, and epigenetic states, but current models do not adequately reflect tumor composition in patients. The authors used single-cell RNA sequencing (RNA-seq) to profile 430 cells from five primary glioblastomas, which were found to be inherently variable in their expression of diverse transcriptional programs related to oncogenic signaling, proliferation, complement/immune response, and hypoxia. They also observed a continuum of stemness-related expression states that enabled them to identify putative regulators of stemness in vivo. Finally, they showed that established glioblastoma subtype classifiers are variably expressed across individual cells within a tumor and demonstrate the potential prognostic implications of such

intratumoral heterogeneity. Thus, they revealed previously unappreciated heterogeneity in diverse regulatory programs central to glioblastoma biology, prognosis, and therapy.

Using genetics to guide brain tumor therapy: Dr. Daniel Cahill is studying genes that are involved in brain tumor formation. In the following study (IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection.

Beiko J1, Suki D, Hess KR, Fox BD, Cheung V, Cabral M, Shonka N, Gilbert MR, Sawaya R, Prabhu SS, Weinberg J, Lang FF, Aldape KD, Sulman EP, Rao G, McCutcheon IE, Cahill DP. Neuro Oncol 2014 Jan;16(1):81-91. doi: 10.1093/neuonc/not159. Epub 2013 Dec 4.) the authors sought to determine the impact of surgical resection on survival after controlling for IDH1 status in malignant astrocytomas-WHO grade III anaplastic astrocytomas and grade IV glioblastoma. Clinical parameters including volumetric assessment of preoperative and postoperative MRI were recorded prospectively on 335 malignant astrocytoma patients: n = 128 anaplastic astrocytomas and n = 207 glioblastoma. IDH1 status was assessed by sequencing and immunohistochemistry. IDH1 mutation was independently associated with complete resection of enhancing disease (93% complete resections among mutants vs 67% among wild-type, P < .001), indicating IDH1 mutant gliomas were more amenable to resection. The impact of residual tumor on survival differed between IDH1 wild-type and mutant tumors. Complete resection of enhancing disease among IDH1 wild-type tumors was associated with a median survival of 19.6 months versus 10.7 months for incomplete resection; however, no survival benefit was observed in association with further resection of nonenhancing disease (minimization of total tumor volume). In contrast, IDH1 mutants displayed an additional survival benefit associated with maximal resection of total tumor volume (median survival 9.75 y for >5 cc residual vs not reached for <5 cc, P = .025). Therefore, the survival benefit associated with surgical resection differs based on IDH1 genotype in malignant astrocytic gliomas. Therapeutic benefit from maximal surgical resection, including both enhancing and nonenhancing tumor, may contribute to the better prognosis observed in the IDH1 mutant subgroup. Thus, individualized surgical strategies for malignant astrocytoma may be considered based on IDH1 status.

Transferring information within the nervous system. Dr. Ziv Williams and colleagues have devised ways to detect and decode information from the brain and transfer it via computerized systems to the spinal cord and peripheral nerves *(A cortical-spinal prosthesis for targeted limb movement in paralysed primate avatars. Shanechi, M. M.,Hu, R. C.,Williams, Z. M.; Nature Commun. 2014 Feb 20).* In this study, the authors created a functional cortical to spinal bypass where they were able to record neural signals in the brain of a subhuman primate, extract information about what the animal is intending on doing and then use this information in real-time through a computerized algorithm to stimulate the spinal cord of a second animal that was anesthetized to produce movements in its paralysed limb to those same intended target locations. Indeed, in some cases the first monkey just needed to think about what it wanted to do and then the other monkey would make the movement. The connection was basically a computational link which basically detected the movement that the master monkey was thinking about and then matched that with movements produced in the avatar. While this is experimental at present, its applications include nervous system re-wiring for stroke and paralysis due to spinal cord injury.

Obstetrics and Gynecology

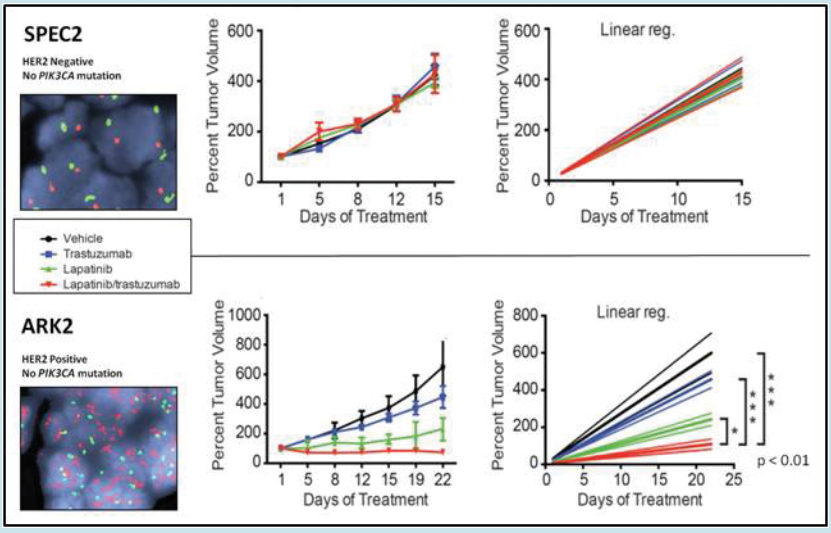
Department Report

Isaac Schiff, MD; Chief

Our departmental 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.

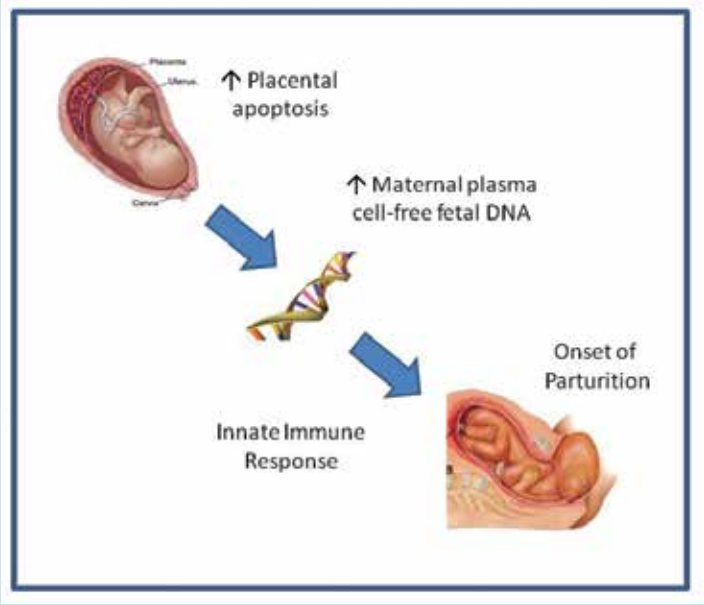
Management and outcomes for elderly women with vulvar cancer over time: Utilizing a grant from the Deborah Kelly Center for outcomes research, Dr. Rauh-Hain, the senior gynecologic oncology fellow in the Vincent Department of Obstetrics and Gynecology, worked with a programming team to analyze the experience of over 8,000 women with vulvar carcinoma. This data set was made available through the Surveillance, Epidemiology, and End Results (SEER) Program database. In 2014, Dr. Rauh-Hain and Dr. Marcela Del Carmen published one of the first comprehensive investigations of how age significantly impacts morbidity and mortality in vulvar cancer in the *British Journal of Obstetrics and Gynecology*. He found that across all eras of time between 1988 and 2009, increasing age was associated with a linear elevation in cancer specific mortality with those women >80 years of age having the most guarded survival with a hazard ratio of 6.98. Importantly, this study revealed that older patients, even when controlling for stage, grade and patient characteristics, were less likely to undergo surgery and more likely to undergo radiation alone, suggesting a national bias that may account for this age disparity. *Rauh-Hain JA et al: BJOG. 2014 May;121(6):719-27*

Dual HER2 Targeting Inhibits HER2-Amplified Uterine Serous Carcinoma: Recently highlighted by the ASCO Post was Dr. Growdon's study in *Clinical Cancer Research* utilized patient derived xenografts to model trastuzumab resistance in serous endometrial cancer, and demonstrate how dual anti-*HER2* therapies can overcome this resistance. In this investigation, the lead author, Dr. Groeneweg and colleagues tested single-agent trastuzumab and showed little effect in all models with and without *HER2* gene amplification. Lapatinib, a dual EGFR/HER2 inhibitor, reduced proliferation in all cell lines and inhibited growth of *HER2*-amplified in specific cell lines and xenografts. Dual therapy with trastuzumab and lapatinib, however, produced synergistic antitumor activity in the *HER2* gene amplified tumors in association with alteration of downstream MAPK and PI3K pathway mediators. These results suggested *HER2* amplification can be a biomarker of response in serous tumors of the uterus, as well as suggesting that dual *HER2* inhibition with agents that inhibit the receptor in different ways can overcome trastuzumab resistance. The authors concluded that while single agent anti-HER2 therapy has proven an ineffective strategy in clinical trial, dual HER2 blockade may be a promising avenue for future investigation." *Groeneweg JW, et al: Clin Cancer Res 20:1-12, 2014.*



Cell-free fetal DNA (cffDNA) functions as a fetal/placental signal to trigger the spontaneous onset of labor: The exciting research being performed in the Vincent Center for Reproductive Biology by Dr. Phillippe seeks to test the novel hypothesis that cell-free fetal DNA (cffDNA) functions as a fetal/placental signal to trigger the spontaneous onset of labor (parturition) at the end of pregnancy. As described in a recent New England Journal of Medicine publication (NEJM 2014;370:2534-36), Dr. Phillippe has proposed that cffDNA is released into maternal plasma as a result of placental apoptosis which peaks at term, and that cffDNA activates the innate immune system through stimulation of TLR9 (a DNA-sensing pattern recognition receptor). This sequence of events would lead to activation of the proinflammatory signaling events that have been demonstrated by him and other investigators in this field to result in spontaneous parturition. Thus this new research seeks to identify the missing link that triggers these inflammatory events leading to parturition in the absence of microbial invasion and intrauterine infection. The mechanistic knowledge gained from these studies will lay the foundation for novel tests and medical interventions in the future to more effectively manage parturition and its potential complications, especially preterm delivery.

Comprehensive recommendations for clinical care of midlife women: Dr. Jan Shifren served as Editor-in Chief for the publication, *The North American Menopause Society Recommendations for Clinical Care of Midlife Women*, the first comprehensive set of evidence-based recommendations for the care of women at menopause and beyond. In addition to publication in the Society's journal, Menopause, this resource is available on the NAMS website as a free resource for clinicians and women to allow for a better understanding of the health concerns of midlife women and options for evaluation and treatment. These key points and recommendations on more than 50 topics cover the management of everything related to midlife women's health, from hot flashes, genitourinary syndrome of menopause, and osteoporosis to depression, cardiovascular disease, and thyroid dysfunction. For each topic, the key points and recommendations were written by an expert in the field and graded for level of evidence. Dr. Shifren carefully reviewed and edited each topic, with the assistance of an editorial panel of experts.



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 now constitutes one of the largest vision research groups in the world. Today, we are well-positioned to bring rapid and intense efforts toward accelerating knowledge, diagnosis, treatment, management and rehabilitation of vision-threatening disorders. The Department pursues a programmatic research strategy focused on areas of greatest unmet medical need, including retinal degenerations and diabetic eye disease, and optic neuropathies, particularly glaucoma.

Our current research structure crosses traditional laboratory boundaries and is based around nine HMS-wide Centers of Excellence and Institutes, each of which is directed toward a specific class of eye disorder (AMD, cornea, glaucoma, diabetic eye disease, ocular oncology, mobility enhancement and vision rehabilitation) or scientific approach (Ocular Genomics Institute, Ocular Regenerative Medicine Institute, Infectious Disease Institute). Centers and Institutes bring together clinicians, principal investigators, trainees and laboratories, and provide thematic direction for research while emphasizing clinical care and training. Their goal is to provide premier clinical care, conduct transformational research, and offer world-class training for future leaders. The Centers and Institutes are led by the top researchers in the HMS Department of Ophthalmology who exemplify the scientific and collaborative leadership characteristics critical to the achievement of our mission. Notably, leadership has been appointed to equally represent basic scientists with clinician scientists resulting in great synergy. To complement our COEs and Institutes, several research programs are advancing the understanding of ocular structure and function—from basic neurobiology to functional assessment and clinical intervention. These programs include: Imaging, pediatric ophthalmology and strabismus, neuro-ophthalmology, oculoplastics, proliferative vitreoretinopathy, uveitis and ocular inflammation, and visual perception.

Mass. Eye and Ear Faculty among recipients of the most prestigious honor in ophthalmology

Joan W. Miller, MD, FARVO, Evangelos Gragoudas, MD, and Patricia D'Amore, PhD, MBA, FARVO were among the recipients honored with the 2014 António Champalimaud Vision Award, the highest distinction in ophthalmology and visual science. The award was given for efforts in the development of anti-angiogenic therapy for retinal disease. This series of translational breakthroughs led to a new class of ophthalmic anti-VEGF drugs, which have revolutionized care for neovascular age-related macular degeneration, diabetic macular edema and macular edema following retinal vein occlusion. Prior to these developments, neovascular AMD caused 90 percent of AMD-related blindness. With today's treatments, vision loss now can be avoided in 90 percent of patients with up to one-third of patients experiencing significant improvements in vision. The laureates shared the award with Lloyd Paul Aiello, MD, PhD of Joslin Diabetes Center/ Beetham Eye Institute, George King, MD of the Joslin Diabetes Center, Anthony Adamis, MD (of Genentech, affiliated with Mass. Eye and Ear) and Napoleone Ferrara, MD of the University of California, San Diego School of Medicine and Moores Cancer Center. Established by The Champalimaud Foundation in 2006, the António

Champalimaud Vision Award honors outstanding contributions to the preservation and understanding of sight, and is often referred to as the "Nobel Prize for Vision." With its €1 million purse, it is among the world's largest scientific and humanitarian prizes. The awardees were honored during a ceremony held at the Champalimaud Centre for the Unknown in Lisbon, Portugal on Sept. 10, 2014.

Mass. Eye and Ear Launches the Grousbeck Center for Gene Therapy

Mass. Eye and Ear launched the Grousbeck Center for Gene Therapy in 2014 supported by a generous donation from the Grousbeck Family Foundation. Directed by Luk Vandenberghe, PhD the Grousbeck Center aims to develop sight-restoring treatments for people with inherited blindness. Dr. Vandenberghe is a leading scientist who has invented, developed and translated many enabling technologies for gene therapy. At the Grousbeck Center he is leading an ambitious research program focused on the discovery of improved and novel vectors to replace diseased genes with new healthy genes to restore vision. The Grousbeck Center comprises the Vandenberghe Laboratory and the Gene Transfer Vector Core (GTVC), which is co-directed by Dr. Vandenberghe and Ru Xiao, MD. The GTVC provides research-grade inventory and custom-made vector reagents and offers expert advice to researchers regarding the design and execution phase of their vector and experimental plans.

The Grousbeck Center is a key component of Ocular Genomics Institute [directed by Eric Pierce, MD, PhD and for which Dr. Vandenberghe serves as an Associate Director], which has the primary goal of translating the promise of personalized genomic medicine into clinical care for patients with ophthalmic disorders. Institute members are working to achieve this goal via a combination of laboratory-based translational research to identify the genetic causes of inherited eye disorders and to develop gene therapies for these diseases, clinical research focused on clinical trials of novel genetic therapies, and provision of state-of-the-art clinical care for patients with hereditary ophthalmic disorders.

Differentiation potential of limbal fibroblasts and bone marrow mesenchymal stem cells to corneal epithelial cells. Katikireddy KR, **Dana R, Jurkunas UV. Stem Cells. 2014 Mar;32(3):717-29. PMID: 24022965**

Published in the key journal of the stem cell field (Impact Factor 7.133), the authors demonstrate a subset of limbal fibroblasts that have the capacity to be reprogrammed to maintain epithelial regenerative potential when placed into a limbal stem cell niche. The cells express the SSEA4 antigen and also show similarities to bone marrow mesenchymal cells that also have regenerative potential or 'stemness'. Delineating the molecular characteristics of these cells is essential to permit their purification for their use in stem cell therapies.

ABCB5 is a limbal stem cell gene required for corneal development and repair.

Ksander BR, Kolovou PE, Wilson BJ, Saab KR, Guo Q, Ma J, McGuire SP, Gregory MS, Vincent WJ, Perez VL, Cruz-Guilloty F, Kao WW, Call MK, Tucker BA, Zhan Q, Murphy GF, Lathrop KL, Alt C, Mortensen LJ, Lin CP, **Zieske JD**, Frank MH, Frank NY. Nature. 2014 Jul 17;511(7509):353-7. PMID: 25030174

Published in one of the two top journals in the life sciences (Impact Factor 42.351) this team of predominantly Harvard scientists identify a critical marker for limbal stem cells and show through a series of in-depth studies that the function of this gene is essential for corneal development and repair. Corneal limbal stem cells are responsible for the formation and continual regeneration of the corneal epithelium and this life-long balance is required to maintain vision and their loss results in blindness. This advance will lead to the ability to purify and expand limbal cell populations permitting the development of limbal stem cell therapies which will allow the recovery of vision for those with corneal blindness due to limbal stem cell loss.

Leonard B. Kaban, DMD, MD; Chief

The mission of the Department of Oral and Maxillofacial Surgery (OMFS) is:

1) To be recognized as the leading clinical and academic OMFS center in the world.
2) To provide the highest level of patient care, research and teaching in OMFS.
3) To provide efficient, timely and high quality service to MGH patients (inpatient, outpatient and emergency/trauma).
4) To be on the cutting edge of novel research and diagnostic and treatment techniques in OMFS.
5) To provide residents and students with faculty role models who are nationally and internationally recognized as leaders in OMFS research, teaching and patient care.

The focus of our research is a thematically driven translational research program intimately integrated with our clinical program and organized into two Centers: Skeletal Biology Research Center and Center for Advanced Clinical Investigation. Research has been funded by a combination of internal grants (MGH/Partners Center for Innovation and Minimally Invasive Technology in Medicine-CIMIT; OMFS Education and Research Fund-(ERF); Foundations (AO Foundation, Berne, Switzerland; Hanson Foundation, Boston, MA; Oral and Maxillofacial Surgery Foundation, Rosemont IL); Industry (Theric Corporation; Synthes, CMF) and NIH.

Skeletal Biology Research Center (SBRC) is located in a laboratory (1500 sq feet) in the Thier building and focuses on Distraction Osteogenesis, Tissue Engineering, Giant Cell Tumors, Minimally Invasive Surgery. We developed a standard minipig model for the study of the biology of mandibular distraction osteogenesis. This has become a standard model throughout the world to study distraction. We have also developed a similar animal model for midface 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 device placement. Projects in surgical navigation, development of a totally buried, miniature, automated distraction device, bone tissue engineering and scaffold design, sialendoscopy and the molecular biology of giant cell 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. The Center offers a Clinical Research Methods Fellowship, a 2 year program which includes an MPH from the Harvard School of Public Health.

A. Peacock ZS, **Tricomi BJ**, **Lawler ME**, Faquin WC, Magill JC, Murphy BA, **Kaban LB**, Troulis MJ: *Skeletal and Soft Tissue Response to Automated, Continuous, Curvilinear Distraction Osteogenesis*. J Oral Maxillofac Surg. 2014 Sep; 72(9):1773-87. Epub 2014 Jan 16.

Our laboratory has been at the forefront of the development of novel bone distraction devices for use in craniomaxillofacial surgery. Using a minipig model of mandibular DO and a novel continuous, automated, buried, 3-dimensional distraction device designed, patented and tested at MGH we have been studying the biology of the continuous distraction wound. We are the first to successfully carry out automated, continuous distraction in a series of animals and to document the sequence of bone and soft tissue healing of this wound. The first phase of the biology project was completed and published this year.

B. Pace CG, **Hwang KG**, **Papadaki M**, **Troulis MJ**: Interventional sialoendoscopy for treatment of obstructive sialadenitis. J Oral Maxillofac Surg. 2014 Nov; 72(11):2157-66. Epub 2014 Jun 24. **Papadaki ME**, **Kaban LB**, **Troulis MJ**: Endoscopic vertical ramus osteotomy: a long-term prospective study. Int J Oral Maxillofac Surg. 2014 Mar;43(3):305-10. Epub 2013 Nov 15.

MGH OMFS has been at the forefront of the development of maxillofacial minimally invasive surgery for jaw reconstruction and for management of obstructive salivary gland disease. This project has gone from the laboratory bench to the bedside during the past 15 years. This clinical, translational research and education program has led the way to major changes in the management of certain types of jaw reconstruction and fractures and management of salivary gland disease. This year Troulis et al have published two landmark outcome studies demonstrating the efficacy of these minimally invasive techniques.

C. Geary S, **Selvi F**, **Chuang SK**, **August M**. Identifying dental panoramic radiographic features for the screening of low bone mass in postmenopausal women. Int J Oral Maxillofac Surg. 2014 Dec 2. pii: S0901-5027(14)00438-X. doi: 10.1016/j.ijom.2014.11.008. [Epub ahead of print]

Panoramic radiographs are inexpensive and produce low radiation exposure when compared to CT scans and other radiographic techniques. These x-rays are commonly done by dentists for screening purposes and they are available for many patients. We explored the possibilty of using panoramic radiographs as a cheap and low radiation dose screening tool to evaluate patients for osteopenia/osteoporosis. We evaluated panoramic radiographic features that may be predictive of osteopenia/osteoporosis in vulnerable patients. Mandibular cortical integrity was found to be a significant determinant and may be useful as a low cost efficient screening tool.

D. Lee SH, **Kaban LB**, **Lahey ET**, Skeletal Stability of Patients Undergoing Maxillomandibular Advancement for Treatment of Obstructive Sleep Apnea, Journal of Oral and Maxillofacial Surgery (2014), doi: 0.1016/j.joms.2014.10.018.

Lahey and others in the Department have been investigating the relationship of maxillofacial skeletal anatomy, upper airway characteristics and obstructive sleep apnea. In particular, we have been interested in the effects of skeletal anatomy on the supra-glottic airway and the relationship of these characteristics to the presence and severity of obstructive sleep apnea and the outcomes of surgical treatment. The above manuscript details a study completed and published this year to determine if the large advancements of the maxillofacial skeleton completed to treat obstructive sleep apnea remain stable. We demonstrated clinical anatomic stability of maxillo-mandibular advancement which correlated with significant clinical improvement in OSA symptoms. This is the first such study to systematically correlate anatomic stability with clinical OSA outcomes.

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, and Orhun Muratoglu, 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 formulations of highly cross-linked ultrahigh molecular weight polyethylene (UHMWPE), stabilized by re-melting or vitamin E, for large scale usage in implant manufacturing. This has since changed the landscape of joint replacement by reducing the number of wear particles and instances of osteolysis associated with total joint implants. One of the laboratory's current focus areas is advancing material development in joint repair and replacement. Under the direction of Orhun Muratoglu, PhD, the pre-clinical material research team develops novel UHMWPEs for improving the longevity of joint implants and expanding the use of joint replacement safely to younger, more active patients. 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.

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 develops local and regional implant registries in collaboration with orthopaedic surgeons in arthroplasty, spine, hand, sports medicine, trauma, and orthopaedic oncology. They also 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.

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 Y1, Sassi S, Shen JK, Yang X, Gao Y, Osaka E, Zhang J, Yang S, Yang C, Mankin HJ, Hornicek FJ, Duan Z.) 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.

The other key topic was "Prevention of multidrug resistance (MDR) in osteosarcoma by NSC23925." (Yang X1, Yang P2, Shen J2, Osaka E2, Choy E2, Cote G2, Harmon D2, Zhang Z3, Mankin H2, Hornicek FJ2, Duan Z2.) 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.

Orthopaedic Laboratory Poster Session at the Annual Department Retreat

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

The year 2014 marked the beginning of a new chapter for the Department of Otolaryngology. When Joseph B. Nadol, Jr., MD, announced that he planned to step down as chief and chair after 28 years of service, our institution faced a challenging search for his successor. A yearlong search culminated in the appointment of D. Bradley Welling, MD, PhD, FACS, as the next Chief of Otolaryngology at Massachusetts Eye and Ear and Massachusetts General Hospital and the Walter Augustus LeCompte Professor and Chair of Otology and Laryngology at Harvard Medical School. Dr. Welling joined the Department after devoting much of his career to The Ohio State University, where he served in multiple capacities from 1989 to 2014, including nine years of service as Chair of Otolaryngology.

Even in the midst of this major administrative change, Department faculty and staff have had a remarkably productive year and continue to advance otolaryngology research across the broad range of systems and disciplines of our specialty.

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

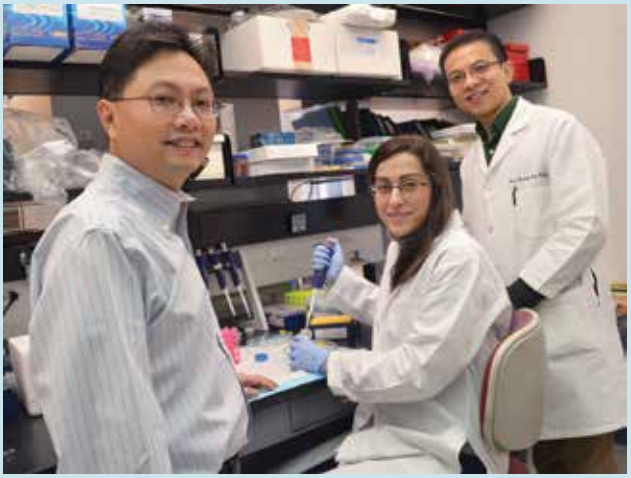
Researchers in the Department of Otolaryngology at Mass. Eye and Ear/Harvard Medical School engage in a range of basic science, translational and clinical research projects aimed at solving clinical problems across all subspecialties in our field. In 2014, a number of research achievements demonstrate our dedication to tackling clinically relevant issues through a variety of approaches.

Prosthetic Approaches to Hearing Loss

Our researchers are working to develop and refine sensory prostheses, such as the cochlear implant, for the treatment of profound deafness. In 2014, a team including **Konstantina Stankovic, MD, PhD** introduced a prototype system-on-chip (SoC) that could make possible a fully implantable cochlear implant.1 The SoC not only offers the cosmetic benefit of an invisible prosthesis, but it may also facilitate better sound localization. Because the SoC uses a sound sensor in the middle ear, as opposed to a microphone located outside the ear in the traditional cochlear implant, the user may benefit from directional cues provided straight from the ear canal. In addition, the SoC was designed to require lower power sound processing and auditory nerve stimulation to enable operation from an implantable battery that is wirelessly recharged once daily.

Bioengineering Approaches to Hearing Loss

Though sensory prostheses (like the cochlear implant) have been remarkably successful for some patients and some types of deafness, otolaryngology researchers around the world are in search of biological treatments for deafness. This year, a team including **M. Charles Liberman, PhD**, restored the hearing of mice partly deafened by noise using genetic tools to boost the production of a key protein in their inner ears.2 By demonstrating the importance of the protein NT3 in eliciting neural outgrowth and the re-establishment of synaptic connections between the sensory cells and brain, these findings pave the way for human treatments that could improve hearing loss caused by noise exposure and normal aging.



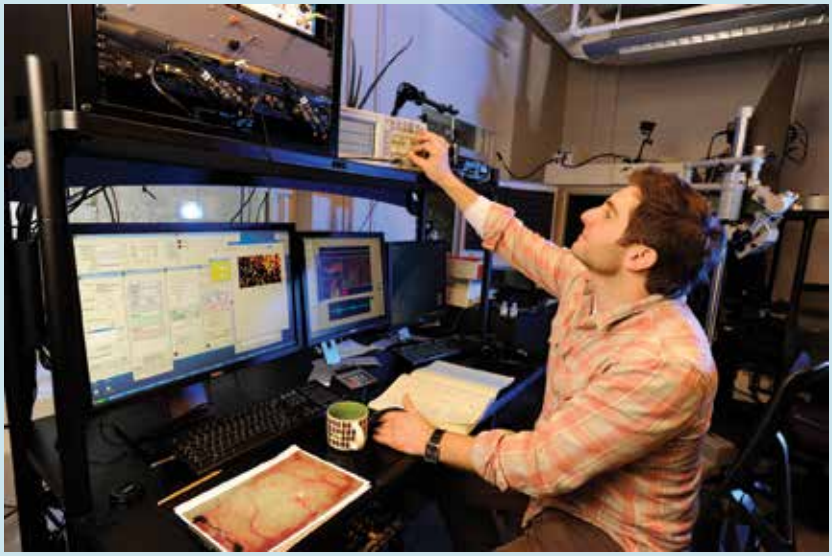
In a separate initiative, **Zheng-Yi Chen, D.Phil.**, and colleagues have shown that blocking the Notch pathway, a key modulator of hair cell development in the inner ear, can lead to partial hair cell regeneration after noise-induced damage.3 These findings further underscore the therapeutic potential of drugs targeting this signaling pathway in the ear.

Cognitive Therapies for Tinnitus

Tinnitus is a condition that pervades otology clinics, and yet, there are very few treatment options available to patients. Our researchers are working to develop and refine cognitive approaches that may offer therapeutic benefit to this large population of patients.

Daniel B. Polley, PhD, and colleagues programmed a new type of game that has trained both mice and humans to enhance their ability to discriminate soft sounds in noisy backgrounds.4 In the experiment, adult humans and mice with normal hearing were trained on a rudimentary 'audiogame' inspired by sensory foraging behavior that required them to discriminate changes in the loudness of a tone presented in a moderate level of background noise. These findings suggest new therapeutic options for clinical populations that receive little benefit from conventional sensory rehabilitation strategies.

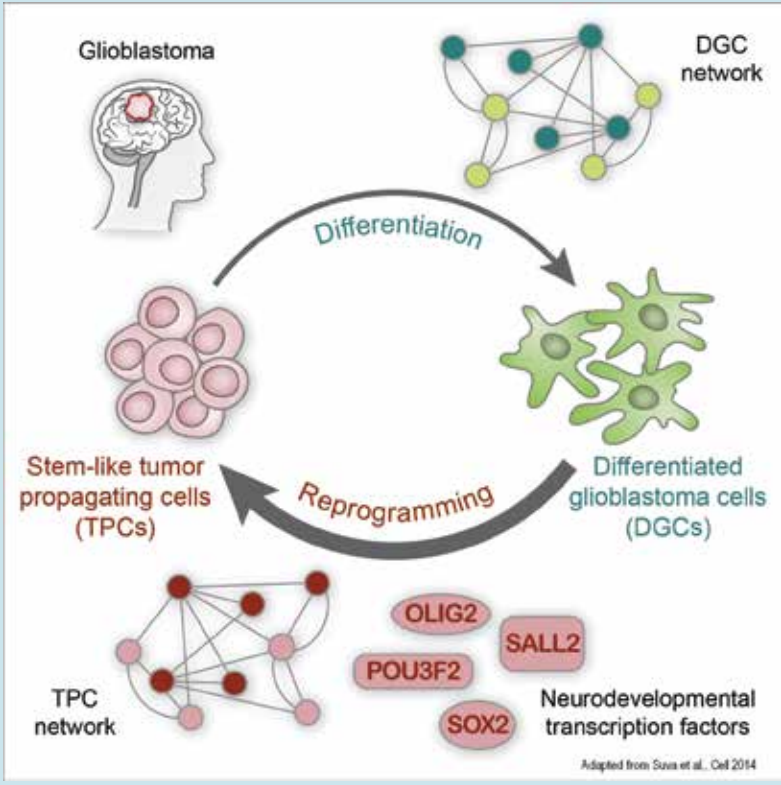
1. *Presented on Feb. 11, 2014 at the IEEE International Solid State Circuits Conference in San Francisco.*
2. *Wan G, Gómez-Casati ME, Gigliello AR, Liberman C, Corfas G. Neurotrophin-3 regulates ribbon synapse density in the cochlea and induces synapse regeneration after acoustic trauma. Elife. 2014 Oct 20;3.*
3. *Li W, Wu J, Yang J, Sun S, Chai R, Chen ZY and Li H. Notch inhibition induces mitotically-generated hair cells in mammalian cochleae via activating the Wnt pathway. Proc Natl Acad Sci U S A 2014, 2015 Jan 6;112(1):166-71.*
4. *Whitton JP, Hancock KE, Polley DB. Immersive audiomotor game play enhances neural and perceptual salience of weak signals in noise. Proc Natl Acad Sci USA. 2014 Jun 24;111(25):E2606-15.*



David N. Louis, MD; Chief

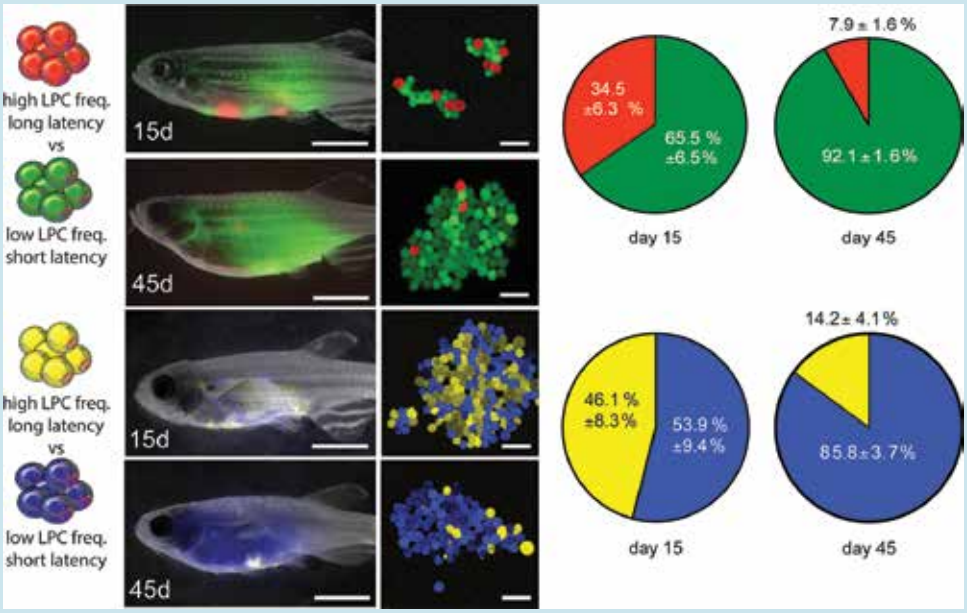
Pathology plays a key role in academic medicine, as a natural bridge between the study of human disease and experimental biological investigation. Major advances in molecular pathology and in pathology informatics are accelerating the pace of this translational research. In turn, the rapidity and frequency of interactions between the 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. We are currently implementing initiatives identified from our recent departmental strategic planning process, which include: expanding computational biology and bioinformatics resources to enable the development of the novel discipline of Computational Pathology, growing collaborations and interactions throughout the hospital with our Center for Integrated Diagnostics, and building additional links between basic and clinical/translational researchers within the department. 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.



Suvà ML, Rheinbay E, Gillespie SM, Patel AP, Wakimoto H, Rabkin SD, Riggi N, Chi AS, Cahill DP, Nahed BV, Curry WT, Martuza RL, **Rivera MN**, Rossetti N, Kasif S, Beik S, Kadri S, Tirosh I, Wortman I, Shalek AK, Rozenblatt-Rosen O, Regev A, **Louis DN**, **Bernstein BE**. Reconstructing and reprogramming the tumor-propagating potential of glioblastoma stem-like cells. *Cell*. 2014 Apr 24;157(3):580-94.

This paper identified a neurodevelopmental transcription factor code critical for glioblastoma stem cell generation and maintenance. Specifically, four transcription factors that can convert a non-tumorigenic cell into a very aggressive stem-like cell were identified. This work highlights the importance of epigenetic programs in cancer cell properties.



Blackburn JS, Liu S, Wilder JL, Dobrinski KP, Lobbardi R, Moore FE, Martinez SA, Chen EY, Lee C, **Langenau DM**. Clonal evolution enhances leukemia propagating cell frequency in T-cell acute lymphoblastic leukemia through AKT/mTORC1 pathway activation. *Cancer Cel*l. 2014; 25(3):366-78.

This paper utilized large scale transplantation approaches to identify key functional differences between single T-ALL cells. Significant functional variation was observed within individual clones, with only a minority enhancing growth rate and leukemia propagating potential with time. AKT activation was acquired in a subset of clones, which increased the number of self-renewing leukemia propagating cells (LPCs) through activation of the mTORC1 pathway, elevated growth rate likely by stabilizing Myc protein levels, and rendered cells resistant to front-line dexamethasone treatment, which was reversed by combined treatment with an AKT inhibitor. This work provides much needed preclinical data for combination therapies that utilize dexamethasone and PI3K/AKT inhibitor to kill LPCs in a subset of human refractory and relapse T-ALL.

Riggi N*, Knoechel B*, Gillespie S*, Rheinbay E, Boulay G, **Suvà ML**, Rossetti NE, Boonseng WE, Oksuz O, Cook EB, Formey A, Patel A, Gymrek M, Thapar V, **Deshpande V**, Ting DT, Hornicek FJ, **Nielsen GP**, Stamenkovic I, **Aryee MJ**, **Bernstein BE**, **Rivera MN**. EWS-FLI1 Utilizes Divergent Chromatin Remodeling Mechanisms to Directly Activate or Repress Enhancer Elements in Ewing Sarcoma. *Cancer Cell*. 2014 Nov 10;26(5):668-81.

Ewing sarcoma, the second most common pediatric bone tumor, is driven by an EWS-FLI1 translocation who function is not well understood. This study revealed how EWS-FLI1 can either activate or repress genes. At stretches of repetitive GGAA DNA sequences, EWS-FLI1 multimers operate as pioneer factors and activate oncogenes by creating enhancer elements de novo. By contrast, at non-repeat GGAA sequences EWS-FLI1 displaces wild-type ETS transcription factors to repress enhancers that regulate tumor suppressors and differentiation pathways. The work has therapeutic implications for Ewing sarcoma because it points to specific mechanisms of chromatin remodeling that could form the basis of targeted therapies. The results of the study may also have broad implications beyond Ewing sarcoma because they suggest that non-conserved DNA repeats can become key active regulatory elements in cancer and point to competition between related transcription factors as a general mechanism for enhancer repression.

Tsai SQ, Zheng Z, Nguyen NT, Liebers M, Topkar VV, Thapar V, Wyvekens N, Khayter C, **Iafrate AJ**, Le LP, **Aryee MJ**, **Joung JK**. GUIDE-seq enables genome-wide profiling of off-target cleavage by CRISPR-Cas nucleases. *Nat Biotechnol*. 2014 Dec 16. doi: 10.1038/nbt.3117. [Epub ahead of print]

Genome-editing nucleases, such as the CRISPR-Cas system, have become widely adopted for a broad range of research applications and have promise as potential therapeutic reagents for inherited diseases. This report describes the first report of an important capability that has both eluded the field and that will be needed to characterize these reagents if they are to be used in the clinic: an unbiased, genome-wide, and highly sensitive method for identifying off-target mutations induced by CRISPR-Cas9 nucleases in human cells. This approach, which we term GUIDE-seq (for Genomewide Unbiased Identification of Double-strand breaks Enabled by sequencing), defines the most rigorous framework for genome-wide identification of CRISPR-Cas9 nuclease-induced off-target effects to date and provides a method for evaluating the safety of these nucleases before clinical use.

Pediatrics

Department Report

Ronald E. Kleinman, MD; Chief

Discussion of the Research Mission, Focus, and Strategic Priorities of the Department

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.

MUCOSAL IMMUNOLOGY / DEVELOPMENTAL GASTROENTEROLOGY

The major mission of the Mucosal Immunology and Developmental Gastroenterology Laboratories remains a multidisciplinary approach to characterize the role of the enterocyte in mucosal barrier function at the interface between microbial luminal stimuli and lymphoid effector responses. Our investigators study oral tolerance, gut inflammation and microbial-epithelial "crosstalk". Members of the Neurogastroenterology Program are actively involved in leading scientific research to understand better the causes of intestinal failure. There is much work to be done to understand the natural history and treatment outcomes of motility disorders including gastroparesis, intestinal pseudo-obstruction and intractable constipation.

All areas of the Pediatric GI program are involved in both clinical and bench research and look forward to expanding those research endeavors. Both clinical and translational research continues to grow and flourish. With the recent opening of The Center for Celiac Research, increased opportunities exist for both faculty as well as trainees.

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 Long-Term Survivor Clinic is a prime example of this effort. New subspecialists are recruited to help provide comprehensive care for these survivors and we have been implementing an electronic health record that can be queried for clinical research projects. The Long-Term Survivor Clinic is now a member of a consortium for New England childhood cancer survivors. This consortium presents an opportunity for additional collaborative research in this population of patients.

Continued collaborate across disciplines and departments at MGH and MGHfC with respect to our research initiatives remains at the forefront. Our joint research efforts with Dr. Miguel Rivera in the Department of Pathology are examples of new, collaborative and cutting edge lab projects. We are also working with our colleagues at the Broad Institute at MIT to implement a new effort in performing both germline and tumor whole exome sequencing to identify a possible germline genetic predisposition for malignancy in our youngest patients.

PULMONARY

The research focus over the next year will encompass 3 areas. Dr. Kinane's groups is focusing on the genetic basis of lung disease including interstitial lung disease and non-cystic fibrosis bronchiectasis. In collaboration with Partner's Center for Personalized Medicine, his group has developed genetic panels which allow for rapid and multiple gene analysis. Dr. Moskowitz's group focuses on developing new approaches to the treatment of Pseudomonal infections in the airway of patients with Cystic Fibrosis by understanding antibiotic resistance and by defining how the innate immune system, mainly leukocytes, modulates airway infections. A particular focus will be the

identification of the mechanisms by which neutrophils control of pseudomonal infections. Drs Yonker, Kinane and Scirica are working on the use of social media to educate teenagers about asthma therapy and lifestyle changes for the treatment of obesity; two studies in these areas are coming to completion thus providing new strategies for intervention.

ENDOCRINOLOGY

The Endocrinology division research looks to enhance the understanding of endocrine systems and endocrine disease in childhood. Areas include investigations of the biology of obesity and eating disorders utilizing state of the art neuro-imaging techniques coupled with investigations of circulating hormones important in appetite, carbohydrate metabolism, fat metabolism, and bone development, studies of the immunology of diabetes, and molecular approaches to beta cell regeneration. Collaboration with the many fine laboratories at Harvard actively engaged in these areas could create a rich and interactive reinforcing environment that would lead to changes in medical care paradigms and enhanced research direction for both clinical and bench investigators.

GENERAL ACADEMIC PEDIATRICS

Our internationally-known academic research division continues to be dedicated to improving the health of children and adolescents through: Excellence in 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. Preparing and supporting primary care pediatricians in the delivery of health care innovations and in the conduct of research that leverages clinical and community partnerships.

GENETICS

The Genetics division will continue expanding and further developing liaisons between our clinical service and researchers throughout the area. Together with Mark Daly and the Broad Institute we have initiated a large project designed to sequence the exomes of tumor and germ line samples from all Pediatric Oncology solid tumor patients. This study will identify germ line predisposition alleles important in long-term follow-up as well and family member counseling, and will also identify potential targets for therapy in the tumor. Our Down Syndrome Program is continuing clinical trials of two agents with the hope of improving cognition and behavior in Down Syndrome.

GLOBAL HEALTH

The Division of Global Health at MassGeneral Hospital for Children was founded in March 2010 and includes faculty, research fellows, postgraduate and undergraduate trainees and staff members. 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.

NEONATOLOGY AND NEWBORN MEDICINE

The research efforts in the Neonatology and Newborn Medicine Unit are multifaceted and range from basic science on investigating the role of inflammatory mediators in the disease process of necrotizing enterocolitis to working with an international neonatology collaborative to determine the scope of neonatal abstinence syndrome (NAS) and how it may be best treated. Other projects involve studying the use of near infrared spectroscopy (NIRS) to determine the extent of neonatal brain injury and developing new treatment strategies in the delivery room to decrease the incidence

of chronic lung disease in preterm infants. All of these projects are aimed towards improving the care and treatment of this very vulnerable population.

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.

ALLERGY & IMMUNOLOGY

The research focus for the Division of Allergy & Immunology at MGHfC is on the mechanisms of immune-mediated disease in the context of both type I (IgE-mediated) hypersensitivity and immune deficiency due to defects in the function of RAG in lymphocytes. Dr. Shreffler directs the multidisciplinary Food Allergy Center at MGH—a collaborative effort involving adult and pediatric A/I, adult and pediatric GI, nutrition and psychology as well as investigators at MIT, BWH, and others—which leads several investigator-initiated clinical trials and complimentary immune profiling studies aimed at achieving greater insight into the mechanisms of food allergies. Dr. Walter leads the division's research in immune deficiency using a combination of murine models and human samples to interrogate the diversity of immune pathology resulting from hylomorphic mutations of RAG.

Key Publications of the Department 2014

1. Cespedes EM, Gillman MW, Kleinman K, Rifas-Shiman SL, Redline S, Taveras EM. Television Viewing, Bedroom Television, and Sleep Duration from Infancy to Mid-Childhood. Pediatrics. 2014. PMID: 24733878

The associations of short sleep duration in children across early- to mid-childhood were examined and it was found that chronic insufficient sleep is associated with higher body mass index, greater adiposity as measured by dual x-ray absorptiometry, and increased odds of obesity.

2. Taveras EM, Gillman MW, Peña MM, Redline S, Rifas-Shiman SL. Chronic Sleep Curtailment and Adiposity. Pediatrics. 2014;133(6):1013-1022. PMID: 24843068

The risk factors for poor sleep in childhood were examined and it was found that television viewing and bedroom TVs substantially affected child sleep duration.

3. Falbe J, Davison KK, Franckle R, Ganter C, Gortmaker S, Smith L, Land T, Taveras EM. Sleep duration, restfulness, and screens in the sleep environment. Pediatrics, 2015 Jan 5. pii: peds.2014-2306

It was found that the presence of small screens, e.g. iPods, smart phones, etc. also negatively impacted sleep duration in school-age children.

4. Sharifi M, Marshall G, Goldman R, Rifas-Shiman SL, Horan CM, Koziol R, Marshall R, Sequist T, Taveras EM. Exploring Innovative Approaches and Patient-Centered Outcomes from Positive Outliers in Childhood Obesity. Acad Pediatr. 2014 Nov-Dec;14(6):646-55.

This paper was an exploration of childhood obesity positive outliers—overweight or obese children who have managed to maintain or lose weight in the context of adverse built or social environments. This study found several practices and assets of positive outlier children that we are applying in a large randomized controlled trial to reduce obesity prevalence in eastern MA.

5. **Taveras EM**, Gillman MW, Peña MM, Redline S, Rifas-Shiman SL. Chronic Sleep Curtailment and Adiposity. Pediatrics. 2014;133(6):1013-1022. PMID: 24843068

6. Chen K, Wu W, Mathew D, Zhang Y, Browne SK, Rosen LB, McManus MP, Pulsipher MA, Yandell M, Bohnsack JF, Jorde LB, Notarangelo LD, **Walter JE**. Autoimmunity due to RAG deficiency and estimated disease incidence in RAG1/2 mutations. J Allergy Clin Immunol. 2014 Mar;133(3):880-2.e10. doi: 10.1016/j.jaci.2013.11.038. Epub 2014 Jan 25. PubMed PMID: 24472623; PubMed Central PMCID: PMC4107635.

7. Weng M, Ganguli K, Zhu W, Shi, HN, and Walker, WA. "Conditioned medium from Bifidobacteria infantis protects against Cronobacter sakazakii-induced intestinal inflammation in newborn mice." Physiol Gastrointest Liver Physiol. 2014, March:306: G779–G787.

Necrotizing enterocolitis (NEC) is associated with a high morbidity and mortality in very low birth weight infants. This in vivo study tested the anti-inflammatory effect of probiotic-conditioned medium (PCM) in neonatal mice exposed to a pathogen associated with NEC. Study results suggest that an active component released into the culture medium by Bifidobacterium infantis may prevent ileal damage by a pathogen linked to NEC.

8. **Singhal V**, Lawson EA, Ackerman KE, Fazeli PK, Clarke H, Lee H, Eddy K, Marengi DA, Derrico NP, Bouxsein ML, **Misra M**. Irisin Levels are Lower in Young Amenorrheic Athletes Compared with Eumenorrheic Athletes and Non-Athletes and are Associated with Bone Density and Strength Estimates. PLoS ONE 2014;13:9(6):e100218. PMCID:PMC4057451

Irisin and FGF21 are novel hormones implicated in the "browning" of white fat, thermogenesis, and energy homeostasis. However, there are no data regarding these hormones in amenorrheic athletes (AA) (a chronic energy deficit state) compared with eumenorrheic athletes (EA) and non-athletes. In this study, we showed that irisin and FGF21 are low in AA, and irisin (but not FGF21) is independently associated with resting energy expenditure, as well as with bone density and strength in athletes

9. **Stanley TL**, Chen ML, Goodman E. The Typology of Metabolic Syndrome in the Transition to Adulthood. J Clin Endo Metab. 2014. 99:1044-1052.

Metabolic syndrome is a contentious diagnosis in adolescents and growing children. Diagnosis carries with it a set of future health risks which may not be justified. This study demonstrates that the diagnosis of "metabolic syndrome" is not stable during puberty.

10. **Lin AE**, Krikov S, Riehle-Colarusso T, Belmont J, Geva T, Anderka M, Getz K, Botto LD. 2014. Laterality Defects in the National Birth Defects Prevention Study: Am J Med Genet Part A. 164A:2581–2591.

Using data from the National Birth Defects Prevention Study, a population-based case-controlled multi-site study funded by the CDC, we reported the largest study to date of this complex. We determined the prevalence and race/ethnic differences of this disorder and investigated potential causes of the differences we found.

11. Wheat JC, Krause DS, Shin TH, Chen X, Wang J, Ding D, Yamin R, **Sweetser DA**. The Corepressor Tle4 Is a Novel Regulator of Murine Hematopoiesis and Bone Development. 2014 PLoS One 9:e105557

The is the first study to determine the wide variety of developmental effects this TLE4 tumor suppressor gene has during development. Most interesting was the determination of previously unknown, but major regulatory roles on bone development and mineralization. It's role in leukemia appears in part due to is ability to set up a permissive niche in the bone marrow.

12. Nelson B, Zhou X, White M, Hartshorn K, Takahashi K, Kinane TB, Anandaiah A, Koziel H. Recombinant human mannose-binding lectin dampens human alveolarmacrophage inflammatory responses to influenza A virus in vitro. J Leukoc Biol. 2014 Jan 7

This paper supports the concept that mannose-binding lectin may serve a protective innate host response and a critical biological response modifier function by limiting airway macrophage inflammation, oxidative injury, and airway macrophage apoptosis, which may allow effective influenza viral clearance while limiting collateral damage to vital organs, such as the lungs.

13. Yoo DG, Winn M, Pang L, Moskowitz SM, Malech HL, Leto TL, Rada B. Release of cystic fibrosis airway inflammatory markers from Pseudomonas aeruginosa-stimulated human neutrophils involves NADPH oxidase-dependent extracellular DNA trap formation. J Immunol. 2014 May 15;192(10):4728-38.

The main cystic fibrosis airway pathogen is Pseudomonas aeruginosa, This paper proposes that neutrophil net formation is a critical mechanism by which these bacteria induce inflammation.

14. Boronat S, et al. Hippocampal abnormalities in magnetic resonance imaging (MRI) of 15q duplication syndromes. Journal of Child Neurology (2014) 1-6.

A review of brain MRI studies of 11 individuals seen at the Massachusetts General Hospital Dup 15q Center was performed. Two subjects had unilateral hippocampal sclerosis and 6 had bilateral hippocampal malformations. Hypoplasia of the corpus callosum was present in 2 subjects. These findings are consistent with results from a recent neuropathologic found frequent hippocampal heterotopias and dysplasias in these disorders. The severity of the hippocampal malformation does not appear to correlate with the epileptic phenotype.

15. Wu L, Walas S, Leung W, Sykes DB, Wu J, Lo EH, **Lok J**. Neuregulin1-β decreases IL-1β-induced neutrophil adhesion to human brain microvascular endothelial cells. Transl Stroke Res. 2014 May 28. [Epub ahead of print]

16. Zash RM, Ajose-Popoola O, Stordal K, Souda S, Ogwu A, Dryden-Peterson S, **Powis K**, Lockman S, Makhema J, Essex M, Shapiro RL. Risk factors for mortality among human immunodeficiency virus-exposed and unexposed infants admitted to a neonatal intensive care unit in Botswana. J Paediatr Child Health. 2014 Mar;50(3):189-95. doi: 10.1111/jpc.12454. Epub 2013 Dec 23. PubMed PMID: 24372811.

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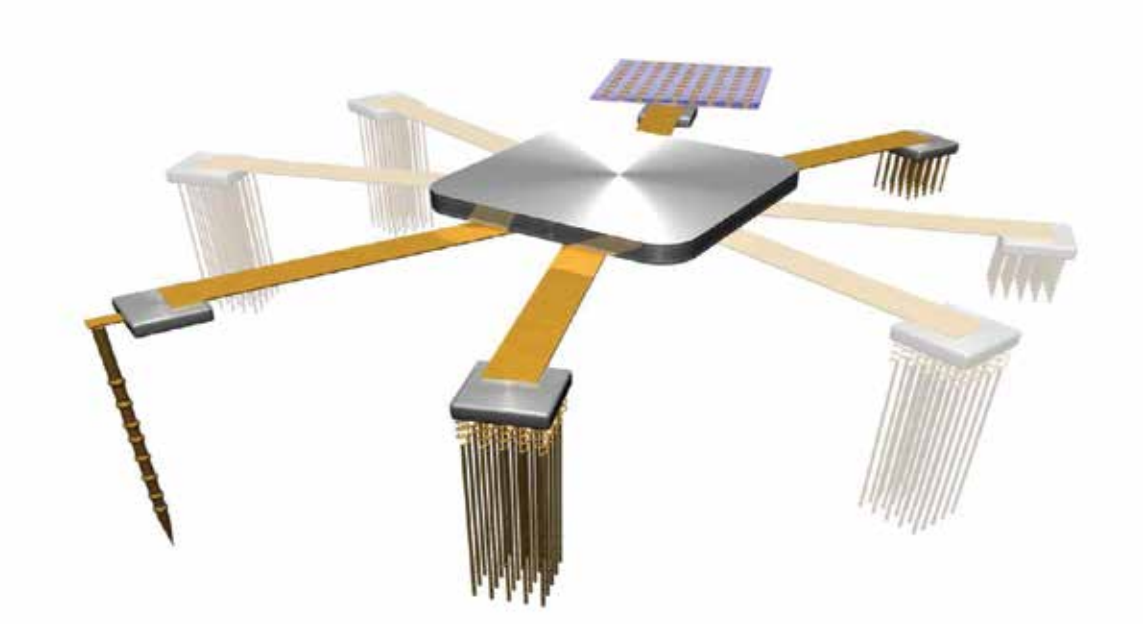
Jerrold F. Rosenbaum, MD; Chief

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

1. **Clinical Care:** The Psychiatry Department is devoted to providing the highest standard of care for our patients and their families across the full spectrum of mental health and mental illness. The department's more than 600 affiliated psychiatrists and psychologists are uniquely trained as clinicians, researchers and 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 18 years in the annual "America's Best Hospitals" survey by *US News & World Report*.
2. **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, the 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 2014, the Department had more than $70 million in research support, continuing its record of successful funding despite an increasingly challenging funding environment.
3. **Professional Education:** The Department offers a comprehensive portfolio of programs aimed at training the next generation of mental health care providers, providing postgraduate education to our colleagues at MGH and beyond, and disseminating clinical and research advances to improve the availability and quality of expert psychiatric care. Each year, the Department of Psychiatry trains 100 adult and child psychiatry residents, psychology interns, and clinical fellows to become leaders in their areas of specialization. Another 40,000 psychiatrists, non-psychiatric physicians, and other health professionals are reached through the MGH Psychiatry Academy, a comprehensive program of web-based seminars, satellite symposia, teleconferences and live symposia. In addition, the Department educates professionals in education, law, the military and the clergy, individuals who carry their enhanced understanding of the discipline of psychiatry out into their work with affected individuals and their families.
4. **Community Service:** To address the mental health needs of people who live in Mass General's neighborhoods and suffer from severe and persistent mental illness, substance use disorders, poverty, immigration challenges, homelessness and multiple traumas, the Department of Psychiatry partners with local organizations through its Division of Public and Community Psychiatry. The department also offers free patient and family education programs in Boston through its Psychiatry Academy. To serve the hospital's global neighbors, the department was the first hospital department in the United States to establish a division of global psychiatry. The Chester M. Pierce Global Psychiatry Division addresses the acute shortage of mental health professionals in developing countries through training and service opportunities.



Novel Neurotherapeutics for the Treatment of Neuropsychiatric Disorders. In a cross-departmental collaboration, Dr. Darin Dougherty (Director of the Neurotherapeutics Division of the Psychiatry Department) along with Dr. Emad Eskandar (MGH Neurosurgery) was awarded a $30 million grant from the Defense Advanced Research Projects Agency (DARPA) to establish the *Transdiagnostic Restoration of Affective Networks by System Identification and Function Oriented Real-Modeling and Deep Brain Stimulation* (TRANSFORM DBS) initiative. This initiative will design and build a first-of-its-kind implantable deep brain stimulation (DBS) device to monitor signals across multiple brain structures in real time. Based on the monitored activity, it will then deliver stimulation to key areas of the brain targeted to alleviate symptoms related to neuropsychiatric disorders such as PTSD, severe depression, drug addiction, and traumatic brain injury. This landmark project has the potential to develop novel therapeutic approaches for these devastating disorders.

Clarifying Risks of Antidepressant Use During Pregnancy. Approximately 10% of women use antidepressants during pregnancy and several studies have suggested that this exposure is associated with an increased risk of congenital cardiac defects in offspring. In a collaboration with researchers at the Brigham and Women's Hospital and the Harvard School of Public Health, Dr. Lee Cohen (Director of the MGH Center for Women's Mental Health) and colleagues (Huybrechts et al., New Engl J Med 2014;370:2397-407) examined data from the Medicaid Analytic eXtract for a nationwide cohort of nearly 950,000 women over a seven-year period to assess the risk of congenital cardiac defects after the use of specific antidepressants. Comparing offspring of 64,389 women who used antidepressants during the first trimester of pregnancy to those with unexposed mothers, there was no increased risk of cardiac malformations attributable to antidepressant use. This rigorous study, which included several methodological advances over prior work in controlling for potential confounders, provides reassuring data regarding the safety of antidepressant use during early pregnancy. Pregnancy-related antidepressant use has also been implicated in the risk of autism spectrum disorder (ASD) in several studies. Dr. Roy Perlis (Director of the Center for Experimental Drugs and Diagnostics in the Department of Psychiatry) and colleagues at MGH, Children's Hospital and the Brigham and Women's Hospital, examined the effect of prenatal antidepressant use on offspring risk of ASD and attention deficit hyperactivity disorder (ADHD) (Clements et al., Molecular Psychiatry, 2014). Data were derived from the Partners Healthcare electronic health record system

and included 1,377 children with ASD, 2243 with ADHD, and 9,653 healthy matched controls aged 2-19 over a 13-year period. After controlling for multiple potential sources of confounding and bias, they found no evidence of increased risk of ASD, but a significant increase in risk of ADHD associated with prenatal antidepressant exposure. This study finds that the risk of autism observed with prenatal antidepressant exposure is likely confounded by severity of maternal illness, although such exposure may still be associated with ADHD risk.

Elucidating the Genetic Basis of Psychiatric Disorders. Faculty in the Psychiatric and Neurodevelopmental Genetics Unit (PNGU; MGH Psychiatry and Center for Human Genetic Research) have continued to play leading roles in defining the genetic contributions to neuropsychiatric disease. In 2014, several PNGU faculty contributed to a landmark report from the international Psychiatric Genomics Consortium (Nature 2014;511:421-7) that identified more than 100 genetic loci contributing to schizophrenia and provided insights into the biological pathways through which they might exert effects on disease risk. Additional highlights from this year included research combining genetic and neuroimaging methods that identified an amygdala-expressed acid-sensing ion channel in risk for panic disorder as well as variation in amygdala structure and function (Smoller et al., Biological Psychiatry, 2014;76:902-10). Drs. Alysa Doyle, Michael Talkowski and colleagues, applying whole genome sequencing methods to a unique cohort from the MGH Psychiatry Learning and Emotional Assessment Program, found evidence for unrecognized structural variation related to early-onset, non-syndromic neuropsychiatric disorders (Brand et al., Am J Hum Genet 2014;454-61). This work suggests the potential utility of sequence-based assessment of structural variation in youth referred for neuropsychiatric evaluation and clinical diagnostic screening more broadly.

Relieving the Burden of Smoking in Patients with Serious Mental Illness. Smoking is a significant source of morbidity and mortality among patients with serious mental illness such as bipolar disorder and schizophrenia. More than half of those with serious mental illness smoke tobacco regularly. Standard courses of pharmacotherapeutic cessation aids improve short-term abstinence, but most who attain abstinence relapse rapidly after discontinuation of pharmacotherapy. To address this gap, Dr. Eden Evins (Director of the MGH Center for Addiction Medicine) and colleagues reported their findings on "Maintenance Treatment with Varenicline for Smoking Cessation in Patients with Schizophrenia and Bipolar Disorder: a Randomized Clinical Trial" in JAMA (JAMA 2014;311:145-54). Among 203 smokers with schizophrenia or bipolar disease who received 12 weeks of open-label treatment with varenicline and cognitive behavioral therapy (CBT), 87 met abstinence criteria to enter a placebo-controlled relapse prevention intervention, where all received CBT but half stayed on varenicline and half switched to placebo. Maintenance pharmacotherapy with varenicline and CBT led to significantly higher tobacco abstinence rates compared with CBT alone after 1 year of treatment and at 6 months after treatment discontinuation. These findings have tremendous public health significance, as they suggest the utility of maintenance pharmacotherapeutic cessation aids in smokers with serious mental illness.

Sexual orientation and anabolic-androgenic steroids in U.S. adolescent boys. Anabolic steroid use has become a significant public health problem, particularly among young people, with serious cardiovascular, endocrine and psychiatric complications. This year, Drs. Aaron Blashill and Steven Safren (Director of Behavioral Medicince) reported the first study to examine anabolic androgenic steroids (AAS) as a function of sexual orientation. Utilizing a large, nationally distributed sample of male adolescents (N = 17,250), gay and bisexual youth were found to have a lifetime prevalence of AAS use at 21%, compared to 4% for heterosexual youth. Elevated depression/suicidality, victimization, and substance use were significant mediators in the relationship between sexual orientation and AAS use. This study, which received substantial attention from national media, underscores the importance of prevention and intervention efforts are needed for sexual minority adolescent boys.

Radiation Oncology

Department Report

Jay Loeffler, MD; Chief

The four main areas of 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**—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, and 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 Intensity Modulated Proton Therapy (IMPT).

Dr. Nancy Tarbell honored with 2014 Gold Medal from American Society for Radiation Oncology (ASTRO)

The Gold Medal is ASTRO's highest honor bestowed on revered members who have made outstanding contributions to the field of radiation oncology. This includes research, clinical care, teaching and service. Recipients are drawn from any of the scientific disciplines represented by the members of the Society.

Dr. Jason Efstathiou serves as Principal Investigator and is currently leading an exciting multicenter proton protocol entitled "PARTIQoL: Prostate Advanced Radiation Technologies Investigating Quality of Life. A Phase III Randomized Clinical Trial of Proton Therapy vs. IMRT for Low or Intermediate Risk Prostate Cancer". This rigorous technology assessment trial which uses patient-reported outcomes has captured significant interest from patients, physicians, payers, industry, federal agencies and other stakeholders. Our robust clinical trial oversight has allowed MGH to lead the way in patient accrual and the expansion to additional sites including University of Pennsylvania, MD Anderson, Washington University in St. Louis and other centers. We will continue to enroll and are very optimistic that the trial will meet or exceed all accrual goals and anticipate that this will be the definitive study of the comparative clinical and cost effectiveness of these advanced radiation therapies for prostate cancer.

Rakesh Jain, PhD and Jay Loeffler, MD were selected as 2014 American Association for the Advancement of Science (AAAS) Fellows, honoring them for their contributions in innovation, education, and scientific leadership. The tradition of electing AAAS Fellows began in 1874 to recognize members for their scientifically or socially distinguished efforts to advance science or its application. The accomplishments of the new Fellows were celebrated at the 2015 AAAS Annual Meeting convening this year under the theme "Innovation, Information, and Imaging."

Radiology

Department Report

James A. Brink, MD; Chief

The Department of Radiology provides excellence in patient care teaching and research. The research mission of the Department includes: 1) development of novel technologies (instrumentation and algorithms) for data acquisition and analysis to discover and/or measure novel biological structures and processes e.g. fMRI, grid structure of the brain, membrane potential; 2) design and synthesis of molecular agents (PET, MR, Optical) for assessment of receptors, abnormal proteins and other biological targets of disease; 3) assessment of novel instrumentation and molecular imaging agents in preclinical disease models and in clinical research; 4) translation of these discoveries, in concert with industry, into patient care; 5) development and application of analytic tools to support economically-based assessment of medical imaging technologies and outcomes research. Our strategic priority is the continuous development of intellectual and physical resources to enable researchers within and outside of Radiology to further their goals.

The department is recognized as the national leader in radiology research based on its scientific output and NIH funding. For the past 12 years among all academic Radiology departments, MGH has held the #1 ranking in NIH funding. Approximately 200 Radiology faculty members serve as principal investigators on one or more grants, either from the NIH or other funding sources, with total funding of ~$80 million. Through its major programs (CAMIS, Cardiac MR PET CT Program, ITA and the Martinos Center) and Core Facilities (MRI Core, PET 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.

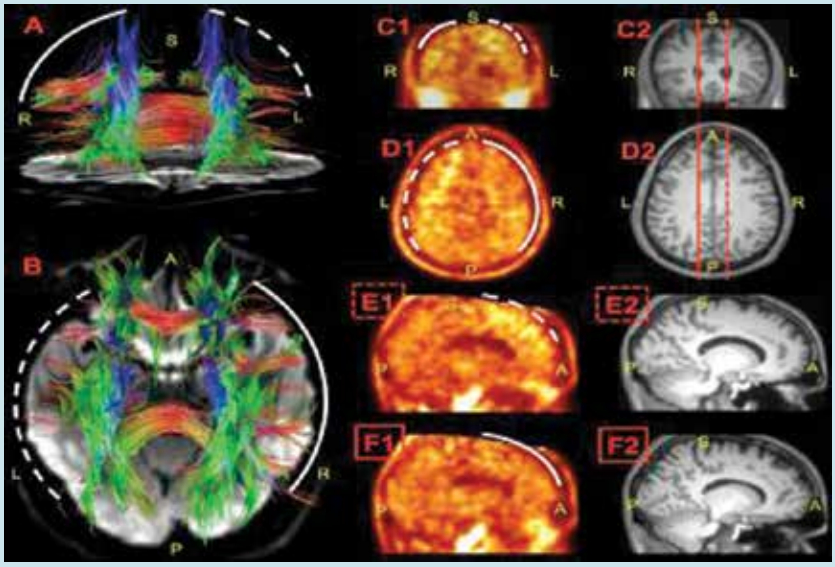
Center for Advanced Medical Imaging Sciences (CAMIS)

The mission of CAMIS, under the direction of Georges El Fakhri, PhD, is to improve patient care by bringing together clinicians, scientists, engineers and technologists to catalyze and translate developments in molecular imaging agents and advanced quantitative imaging technologies to optimize diagnosis and therapy monitoring using PET, PET/CT, PET/MR, CT, and optical imaging The Center serves as a catalyst for productive collaborations with physicians and scientists in other departments, including Anesthesiology, Cardiology, Neurology, Oncology, Psychiatry, Pulmonary Medicine, and Radiation Oncology located on the main MGH campus. One example is pioneering in-room PET imaging of subjects undergoing proton therapy and addressed the main factor affecting accuracy, namely, the biological washout of proton generated PET species (^{11}C, ^{13}N, ^{15}O) in the brain. CAMIS has rapidly grown to include ~130 faculty and staff and ~$12M funding, mainly from NIH.

Labeling with Spirocylic Iodonium Ylides: an Effective Method to make 18F-labeled Compounds Rotstein, BH, Stephenson, NA, Vasdev, N, Liang, SH. *Nature Communications.* 5 (2014) 4365.

We have developed an effective method to synthesize ^{18}F-labeled compounds that involves one-step labeling, is metal-free, regioselective, compatible with a wide variety of functional groups and can be readily translated to routine clinical use. This approach has the potential to revolutionize the production of ^{18}F radiopharmaceutical for preclinical and clinical PET studies.

Visualization of Tau pathology in Traumatic Brain Injury and correlation with reduction in white matter tracts (CAMIS, Neurology and Spaulding Rehabilitation Hospital)



(A,B) MR Diffusion Tractography, (C1-F1) First in Man [18F]T807 tau PET images, and (C2-F2) MPRAGE in a 32 year old male former NFL football player. Broken white arc annotates part of the brain having tau pathology and fiber thinning, solid white arc annotates the contralateral side of the brain for reference. Broken red line on MPRAGE corresponds to sagittal slice displayed in E panels, solid red line shows the symmetric slice displayed in F panels. Areas of increase tau uptake (C1, D1 and E1) represent aggregates of hyperphosphorylated tau protein (neurofibrils tangles) which correlate with corresponding areas of decrease in white matter tracts.

Cardiac MR PET CT Program

The Cardiac MR PET CT Program, directed by Udo Hoffmann, MD, MPH, is a combined clinical and research program of the Department of Radiology and the Division of Cardiology. The mission of the program is to perform high quality, innovative and translational clinical research. Specific research focuses include epidemiological studies, clinical trials and cost effectiveness analyses to determine the role of cardiac imaging in patient care. The program has strong collaborations with the DCRI, the Framingham Heart Study, major NIH clinical trial networks and internal collaborations with the Department of Medicine. 2014 was one of the program's most productive years with over 80 original peer-reviewed publications. Among the major trials awarded in 2014 is the NIH funded REPRIEVE (Randomized Study to Prevent Vascular Events in HIV) trial to investigate, whether treatment with a statin can reduce cardiovascular disease in HIV-infected patients and to determine the mechanism of this effect through advanced imaging and metabolic phenotyping of inflammatory pathways. The 6-year trial will enroll 6,500 participants at up to 100 sites primarily in North America, bringing over $39 million in direct support of the trial to the MGH.

High-risk plaque detected on coronary CT angiography predicts acute coronary syndromes independent of significant stenosis in acute chest pain: results from the ROMICAT-II trial. Puchner SB, Liu T, Mayrhofer T, Truong QA, Lee H, Fleg JL, Nagurney JT, Udelson JE, Hoffmann U, Ferencik M. J Am Coll Cardiol. 2014 Aug 19;64(7):684-92.

The goal of this research is to determine whether high-risk plaque features, as detected by CTA in the emergency department (ED), may improve diagnostic certainty of ACS independently and incrementally to the presence of significant CAD in patients with acute chest pain but without objective evidence of myocardial ischemia infarction (MI). The study concluded that in patients presenting to the ED with acute chest pain but negative initial electrocardiogram and troponin, presence of high-risk plaques on coronary CTA significantly increased the likelihood of ACS independent of significant CAD and clinical risk assessment.

MGH Institute for Technology Assessment (ITA)

The Institute for Technology Assessment (ITA), directed by Scott Gazelle, MD, MPH, PhD, is a multidisciplinary research program within the Department of Radiology. Its mission is to conduct health outcomes research to guide the development, evaluation, and utilization of medical technologies that improve the quality and cost-effectiveness of care. Its principal activities are centered in the innovation and application of scientific methods, including clinical epidemiology, cost-benefit and cost-effectiveness analysis, health state preference and health-related quality-of-life methods, decision analysis, economics, and risk analysis. Members engage in numerous cross-departmental collaborations across MGH, Harvard Medical School affiliates, the Harvard School of Public Health, and nationally and internationally—for example, through the NIH/NCI-funded Cancer Intervention and Surveillance Modelling Network (CISNET) consortium, in which ITA faculty serve as both coordinating center and site investigators. The ITA's accomplishments span methodologic and policy domains. For example, novel engineering methods for calibrating cancer models to epidemiologic data have been developed and applied. These methods have been used to build cancer models that have informed imaging-based cancer screening recommendations and coverage decisions at state and national levels.

Pandharipande PV, Heberle C, Dowling EC, **Kong CY**, Tramontano A, Perzan KE, Brugge W, **Hur C**. Targeted screening of individuals at high risk for pancreatic cancer: results of a simulation model. *Radiology* 2014 November 12:141282 [epub ahead of print].

The goal of this research was to identify when, from the standpoint of relative risk, MRI-based screening may be effective in patients with a known or suspected genetic predisposition to pancreatic cancer. To accomplish this, the authors developed a Markov model of pancreatic cancer that was calibrated to NCI Surveillance, Epidemiology, and End Results registry data. The authors found that life expectancy gains could be achieved if an individual's risk exceeded 2.4 (men) or 2.7 (women) times that of the general population, suggesting that those with even modestly increased risk may benefit from screening.

Martinos Center

The Martinos Center for Biomedical Imaging at MGH is one of the world's premier research centers devoted to the development and application of advanced biomedical imaging technologies. The Center's mission is to advance imaging in healthcare through technology development, translational research and education, with over $40M of funding each year. Located on the MGH Research Campus in Charlestown, the center is home to roughly 100 faculty researchers and more than 200 affiliate and visiting faculty, postdoctoral research fellows and graduate students. These investigators use imaging technologies, both separately and in concert, to investigate a broad range of biologically and medically important questions.

Major Accomplishments

- Our work with the connectome imaging and the human connectome project received considerable attention last year, especially in the wake of a late 2013 Science cover featuring a connectome image by the Center's Van Wedeen. In February, for example, *National Geographic* profiled our work in this area and featured another image by Wedeen on the cover.
- The Center's Larry Wald and Kawin Setsompop were among the recipients of the first wave of grants awarded through the Brain Research through Advancing Innovative Neurotechnologies (BRAIN) Initiative.
- October saw the official launch of the Society for Functional Near Infrared Spectroscopy, with the Center's David Boas—a pioneer of the optical imaging technique—as the founding president.

- With two publications in September, the Center's Hooker Research Group introduced the PET radiotracer [11C]Martinostat, which could provide a first look at an important family of proteins in the living human brain.
- In a paper in the journal *Circulation*, the Center's David Sosnovik and colleagues provided the first example of serial diffusion tensor magnetic resonance imaging (DTI) tractography as a monitoring tool in an animal model of heart disease as well as in healthy human volunteers.

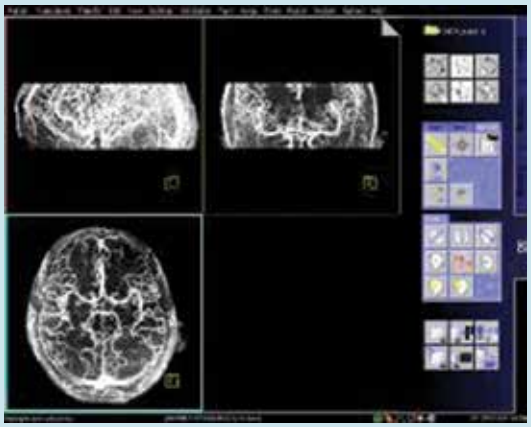
Industry Collaboration Highlights

- Canon Inc. and the Optics Group at the Martinos Center are developing a new device for monitory physiological conditions of newborns.
- Pfizer Inc. and the Martinos Center entered into a master agreement to perform pre-clinical imaging projects.
- Siemens Healthcare and the Martinos Center continued their longstanding research and development relationship by focusing on devising and validating a five-minute brain scan.

Two-Dimensional Imaging in a Lightweight Portable MRI Scanner without Gradient Coils Magnetic Resonance in Medicine 73:872–883 (2015)

Magnetic resonance imaging (MRI) is the premiere modality for imaging of the brain. As widespread as the modality is, though, its impact would be even greater if lightweight, highly portable MRI systems were available to enable imaging in unconventional locations—in intensive care units, physician offices, surgical suites, ambulances, emergency rooms, sports facilities, and rural or developing-world healthcare sites. In this paper, the Center's Larry Wald and colleagues reported both the engineering principles and the prototype results from a very novel, highly portable (<100 kg), and silent proof-of-concept MRI scanner. This has no precedent with existing MRI systems. It represents a truly revolutionary approach to conceptualizing the MR imaging process.

Ultra High Resolution MR Angiography



This example 200×200×200 μm^3 MR Angiography (MRA) data acquired with our 7-Tesla scanner represents a recent milestone for the Martinos Center. Martinos investigators were among the first in the world to produce such high-quality scans at this spatial resolution.

At 7 Tesla, MRA scans do not require administration of intravascular contrast agents, such as gadolinium, as do conventional MRA scans at lower field strengths. This can be particularly important for patient populations—some elderly patients, for example—prone to kidney problems.

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 an original commitment of $100 million from Mr. and Mrs. Ragon, and an additional commitment $50 million in 2014, the 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.

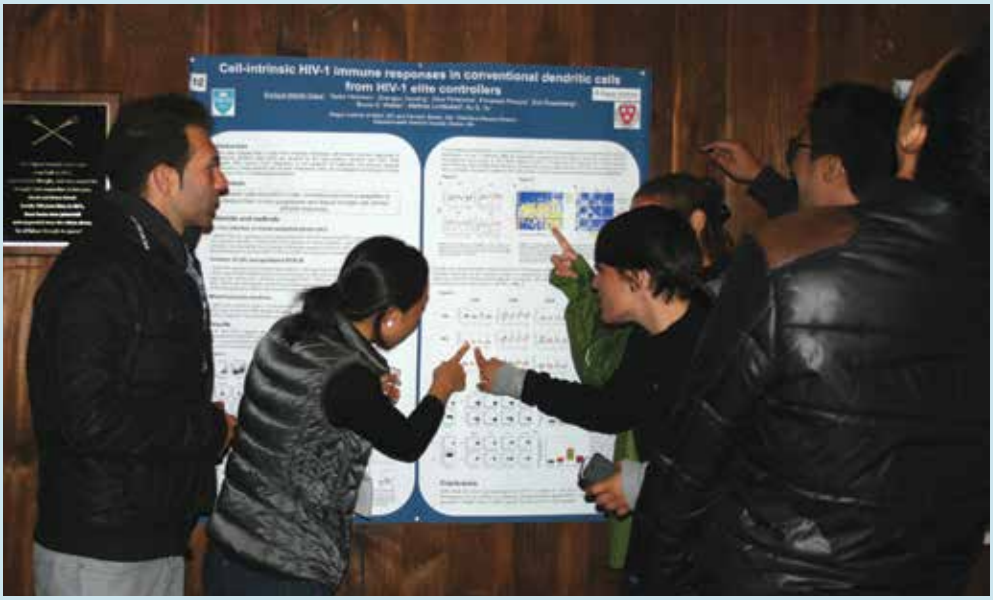
Four key achievements from the calendar year of 2014.

Buzon MJ, Sun H, Li C, Shaw A, Seiss K, Ouyang Z, Martin-Gayo E, Leng J, Henrich TJ, Li JZ, Pereyra F, Zurakowski R, **Walker BD**, Rosenberg ES, **Yu XG**, **Lichterfeld M**. HIV-1 persistence in CD4(+) T cells with stem cell-like properties. Nat Med. 2014 Jan 12. doi: 10.1038/nm.3445. [Epub ahead of print] PubMed PMID: 24412925.

Although antiviral therapy against HIV suppresses viral replication and allows infected individuals to live relatively healthy lives for many years, the virus persists in the body, and replication resumes if treatment is interrupted. The cells that harbor HIV and allow it to persist for such extended periods of time are uncertain, particularly since most human cells are short lived. This question led to the hypothesis that HIV might infect stem cells—the most long-lasting cells in the body—but traditional organ-specific stem cells, even those that give rise to all immune and blood cells, are resistant to HIV infection. This manuscripts demonstrates that a newly-defined subset of T cells with stem cell-like properties are susceptible to HIV-1 infection, and that HIV-1 can use the stem cell-like characteristics of these cells to maintain viral persistence despite suppressive antiretroviral therapy. As such, this study provides important information about cellular reservoirs for HIV-1 persistence, and identifies novel therapeutic targets for inducing a drug-free remission of HIV infection.

Porichis F, Hart MG, Griesbeck M, Everett HL, Hassan M, Baxter AE, Lindqvist M, Miller SM, Soghoian DZ, **Kavanagh DG**, Reynolds S, Norris B, Mordecai SK, Nguyen Q, Lai C, **Kaufmann DE**. High-throughput detection of miRNAs and gene-specific mRNA at the single-cell level by flow cytometry. Nat Commun. 2014 Dec 4;5:5641. doi: 10.1038/ncomms6641. PubMed PMID: 25472703; PubMed Central PMCID: PMC4256720.

Single-cell analysis is one of the most rapidly growing fields in biomedical research that is significantly expanding our understanding on the biologic characteristics of various diseases. Flow cytometry has been the gold standard for immunologists due to its high throughput characterization of hundreds of thousands of cells as they quickly pass through laser beams. However, the tool's major barrier is that the antibody-based detection of proteins is limited by the non-availability of antibodies covering all existing proteins in a cell, and also that the staining methods are currently not



compatible with transcriptional investigation of immune cells. Recent advances in molecular biology enable techniques to perform analysis of transcriptional expression at the single-cell level but these techniques follow laborious methods that involve cell sorting of individual cells and perplexing protocols for the isolation and amplification of RNA.

One of the biggest obstacles for a more comprehensive understanding of how the immune system works in physiologic and pathologic conditions is the availability of novel technologies that push the barriers of current analytical tools. Single cell analysis is a rapidly growing field in biomedical research that is expanding our understanding of biologic characteristics of human diseases. In a study recently published at Nature Communications, we describe a novel flow-FISH (Fluorescent in situ hybridization) method for high-throughput detection of mRNA and miRNA at the single-cell level with flow cytometry. This new technology developed in collaboration with Affymetrix, is based on a branched DNA technology that allows robust (up to 8,000 fold) signal amplification through a sequential hybridization of DNA branches followed by staining with labelled probes. By investigating human blood samples, we show that this novel technique enables simultaneous detection of several mRNA molecules in various leukocyte subsets identified by antibody staining for cell surface markers. Similarly, we show how this technique can be readily used for detection of small miRNA molecules that play major regulatory roles in eukaryotic cells without being translated to proteins. Finally, we prove that this technique can be used in combination with the ImageStream technology, allowing for high-throughput visualization of mRNA in combination with protein expression at the single cell level. The results further demonstrate their ability to measure expression of genes critical for immune cells, such as cytokines, in white blood cells specifically targeting the HIV or CMV viruses. In conclusion, we describe a user friendly protocol that enables immunologists to perform in depth transcriptional analysis of single cells using flow cytometry.

Gaiha G, McKim KJ, Woods M, Pertel T, Rohrbach J, Barteneva N, Chin CR, Liu D, Soghoian DZ, Cesa K, Wilton S, Waring MT, Chicoine A, Doering T, Wherry J, Kaufmann, D, Lichterfeld M, Brass AL & **Walker BD**. Dysfunctional HIV-specific CD8+ T cell proliferation is associated with increased caspase-8 activity and mediated by necroptosis Immunity in press.

Decreased HIV-specific CD8+ T cell proliferation is a hallmark of chronic HIV infection, but the molecular mechanisms that govern the decline are poorly understood. In this report, we identified caspase-8 and necroptosis as a novel correlate and key mediator, respectively, of dysfunctional

HIV-specific CD8+ T cell proliferation. While necroptosis has recently been implicated in the immunopathology of Crohn's disease and systemic inflammatory response syndrome, this report is the first demonstration of its involvement in disrupting the adaptive immune response during a chronic infection. These findings have potential implications for additional states of persistent antigenemia such as HBV and HCV infection, and malignancy. Thus, based on this work, necroptosis may now represent a new therapeutic target to enhance the proliferative potential of antigen-specific CD8+ T cells and thereby strengthen T-cell specific immunity.

Chung AW, **Ghebremichael M**, Robinson H, Brown E, Choi I, Lane S, Dugast AS, Schoen MK, Rolland M, Suscovich TJ, Mahan AE, Liao L, Streeck H, Andrews C, Rerks-Ngarm S, Nitayaphan S, de Souza MS, Kaewkungwal J, Pitisuttithum P, Francis D, Michael NL, Kim JH, Bailey-Kellogg C, Ackerman ME, Alter G. Polyfunctional Fc-effector profiles mediated by IgG subclass selection distinguish RV144 and VAX003 vaccines. Sci Transl Med. 2014 Mar 19;6(228):228ra38. doi: 10.1126/scitranslmed.3007736. PubMed PMID: 24648341.

Results for the first, and to date, only protective human HIV vaccine trial, RV144, pointed to an unexpected signature of protection, not associated with traditional mechanisms of vaccine-induced immunity such as neutralizing antibodies and/or killer T cell immunity. Instead, protection was associated with specific subpopulations of antibodies able to direct killing of HIV-infected cells. However, little is known about the properties of these antiviral antibodies. Thus, in our study, we functionally profiled antibodies induced by the protective RV144 vaccine trial and its non-protective predecessor, VAX003 trial, also conducted in Thailand. RV144 vaccination uniquely induced antibodies capable of directing multiple different antiviral functions in a coordinated manner, while VAX003 predominately induced single or un-coordinated antiviral responses.

Functional co-ordination of the RV144 antibodies was regulated by the selection of antibody responses targeted to vulnerable regions on the HIV envelope, known as the V1V2 loop, and were specifically tuned to enhanced functionality through the selection of a specific antibody subclass, IgG3, known to harbor stronger functional activity than most other antibody subclasses. Collectively, our data suggest that vaccines able to induce broader, more coordinated antibody functional profiles, through the selection of more potent antibody subclasses, that target vulnerable regions of the virus, may represent a novel means by which to achieve protection from HIV.

Keith D. Lillemoe, MD; Chief

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

To help the Chair oversee this enterprise, the Department of Surgery has established the **Surgical Research Council (SRC)** co-chaired by Laurence Turka, MD, and Richard Hodin, MD. The SRC has broad membership that includes the Department Chair, all Division Chiefs and Center Directors, and other members representative of each division and the large community of PhD and MD researchers. The SRC meets on a monthly basis and holds research town halls quarterly that bring the entire departmental research community together in a forum designed for information exchange and promotion of collaboration. Four subcommittees under the SRC umbrella perform key functions for the research community: (1) Resident Research Training and Education Committee (chair, Richard Hodin); (2) Research Faculty Mentoring Committee (chair, Ken Tanabe); (3) Research Support and Operations Committee (chair, Joren Madsen); and (4) Grants and Program Committee (chair, Laurence Turka).

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

(1) **Center for Transplantation Sciences:** co-directors, Joren Madsen, Laurence Turka and James Markmann

(2) **Center for Surgery, Innovation and Bioengineering:** co-directors, Ronald Tompkins, Mehmet Toner and Martin Yarmush

(3) **Center for Vital Organ Bioengineering:** director, Harald Ott

(4) **Codman Center for Clinical Effectiveness in Surgery:** director, Matt Hutter, MD; assoc. director, David Shahian, MD

The CTS team conducts leading research in the field of transplantation.

Surgery

Department Report

Under the leadership of Drs. Turka, Madsen and Markmann (from left to right), the CTS enables scientific synergy within the Mass General transplant research community, helping scientists to make the next scientific and clinical breakthroughs that will drive the field forward.

Center for Surgery, Innovation and Bioengineering and Division of Surgical Oncology: Shyamala Maheswaran, PhD, Associate Professor of Surgery, received the Martin Prize 2015 for outstanding basic science publication in 2014. By applying microfluidic circulating tumor cell (CTC) technologies developed in the Center together with *in vivo* cytometry and next generation RNA sequencing, Dr. Maheswaran demonstrated CTCs in both breast cancer patients and mouse models, pointing to CTC clusters as critical mediators of cancer metastasis. The ability of tumor cell clusters to detach from a primary tumor and maintain their cohesion as they survive in the bloodstream may identify a novel potential target against the dissemination of cancer.

[Aceto N, Bardia A, Miyamoto DT, Donaldson MC, Wittner BS, Spencer JA, Yu M, Pely A, Engstrom A, Zhu H, Brannigan BW, Kapur R, Stott SL, Shioda T, Ramaswamy S, Ting DT, Lin CP, Toner M, Haber DA, Maheswaran S. Circulating tumor cell clusters are oligoclonal precursors of breast cancer metastasis. *Cell*. 2014; 158: 1110-22].

Center for Transplantation Sciences: MGH was awarded a major portion (~$6 million/year for 7 years) of the NIH-funded UM1 for the Immune Tolerance Network (Laurence Turka, MD, PI), a national research consortium that conducts phase I/II clinical trials for immune tolerance in transplantation, autoimmunity and allergy. MGH will take responsibility for biomarker analysis and discovery research, and bioinformatics for the network. In addition, members of the CTS (A. Benedic Cosimi, James Markmann, David Sachs and Laurence Turka) are protocol-chairs for a number of ITN funded trials.

Division of General and Gastrointestinal Surgery: Richard Hodin, MD and colleagues made an important discovery that the gut enzyme intestinal alkaline phosphatase (IAP) can be administered orally to mice in order to prevent *Clostridium difficile* colitis. The dysbiosis caused by antibiotics was reversed by IAP, thereby protecting mice against antibiotic-associated bacterial infections, including *C. difficile*. Oral IAP supplementation would represent a novel preventive strategy against antibiotic-associated gut infections. [Alam SN, Yammine H, Moaven O, Ahmed R, Moss AK, Biswas B, Muhammad N, Biswas R, Raychowdhury A, Kaliannan K, Ghosh S, Ray M, Hamarneh S, Barua S, Malo NS, Bhan AK, Malo M, Hodin RA. Intestinal alkaline phosphatase prevents antibiotic-induced susceptibility to enteric pathogens. *Annals of Surgery* 2014 259:715-22.]

Center for Vital Organ Bioengineering and Division of Thoracic Surgery: Harald Ott, MD and his research group have continued to make strong progress toward the aim of whole organ regeneration. To that end, they published a report in Nature Protocols outlining the foundational techniques for decellularization of rodent, porcine, and human lungs, hearts, and kidneys. [Perfusion decellularization of whole organs. Guyette JP, Gilpin SE, Charest JM, Tapias LF, Ren X, Ott HC. Nat Protoc. 2014; 9:1451-68)]

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.

1. **Intra tumor hetero geneity in the evolution of prostate cancer.** In this study we're drawing on a cohort of prostate cancer patients on active surveillance to compare the cancer genomes of patients with time proven indolent prostate cancer to those with aggressive disease and failed active surveillance. We have identified and consented the patients and retrieved their archival tissue specimens for DNA extraction. After performing DNA quality/quantity assessment, we'll move forward with whole exom sequencing followed by analysis of the genomic data to identify potential mutational drivers of disease progression. This study will constitute the first analysis to our knowledge of invivo genetic evolution of individual human cancers in a treatment naive setting. For this project, Dr Keyan Salari, the principal investigator, has received the American Urologic Association Scholarship Resident Research Award as additional supplemental funding.
2. Dr Matthew Wszolek, principal investigator and one of six finalist for the V Foundation award in bladder cancer research for the project, "Enhancing non-muscle invasive bladder cancer outcomes, the novel use of patient direct cells." The proposed project is a collaborative effort between MGH and Georgetown University using conditionally reprogrammed cell technique to develop novel therapeutics for non-muscle invasive bladder cancer.
3. Along with Dr Adam Feldman and Dr Mukesh Harisinghani, Dr Matthew Wszolek has introduced a multiparametric MRI transurethral ultrasound fusion biopsy of the prostate. This is a technique analyzing the potential benefits of multiparametric MRI to more accurately identify early and aggressive prostate cancer. The fusion technique of prostate ultrasound and MRI is an office biopsy technique which can more accurately target areas of the prostate that are suspicious for high-grade prostate malignancies. Thus enhancing overall management of prostate cancer by providing a platform to appropriately stratify patients for active surveillance versus aggressive treatments for prostate malignancy. The fusion biopsy technique is an office based procedure which is comfortable for patients, represents a significant advance over "in bore" techniques which require a general anesthetic.
4. Seth Bechis, MD, Aria Olumi, MD. A project which has recently found a link between obesity, age and methylation status of the 5-Alpha reductase gene in men with symptomatic BPH. This lab is also using a global gene expression micro array to search for differential gene expression in those patients with symptomatic BPH who require surgery. This work has received 1st place Max K. Willscher Resident Research Award, New England Section American Urologic Association. Dr. Bechis has been awarded a travel scholarship for an AUA summer research conference regarding "patient phenotyping and advancing treatment of lower urinary tract dysfunction."

5. Another major achievement is the announcement of the Chair for the American Urologic Association Office of Research. After an exhaustive review and nominating process, the Office of Research and the Board of Directors for the American Urologic Association has awarded the position of "Director of the Office of Research" to Dr Aria Olumi. This will allow Dr Olumi to direct research efforts for our specialty to improve care for our patients for a defined term of at least 4 years with a possible 3 year extension after that. This reflects greatly on the traditions of research and scholarly activity of the MGH Department of Urology.