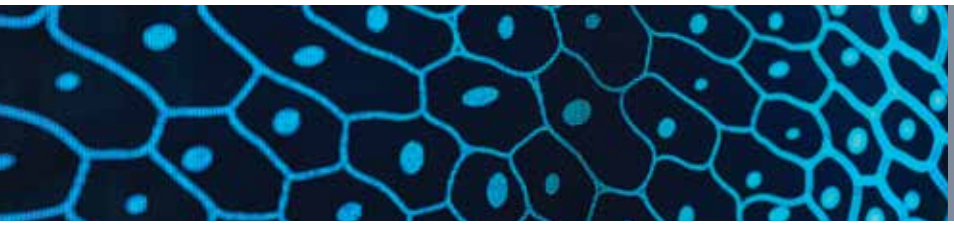
Executive Committee on RESEARCH | *Fostering Innovation at MGH*

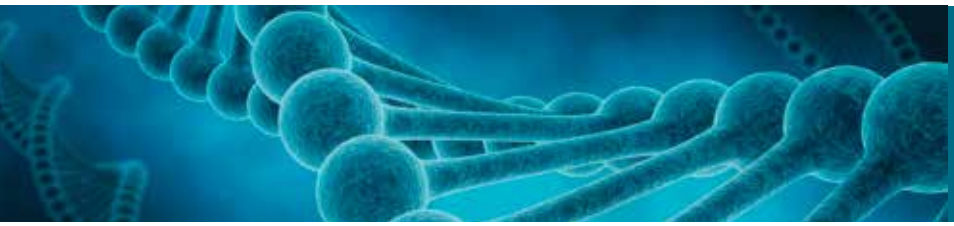
67th Annual Meeting of the
MGH Scientific Advisory Committee

SAC 2014

Celebration of Science

The MGH Research Institute: Meeting the Challenges that Lie Ahead





April 2 & 3, 2014
Simches Auditorium
185 Cambridge Street, 3rd Floor

MGH 1811 RESEARCH Management | *Mainstay of MGH Innovation*

Welcome

Welcome to the 67th Annual Meeting of the MGH Scientific Advisory Committee (SAC) on April 2nd and 3rd, 2014. Dr. Richard Lifton has graciously agreed to chair our SAC meeting again this year.

As in past years, we will begin our two-day SAC meeting with a Celebration of Science at MGH. Our poster session begins at 11:00 am on Wednesday, April 2, 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 2014 Howard Goodman Award recipient Filip Swirski, PhD and the 2014 Martin Basic and Clinical Research Prize recipients, Jayaraj Rajagopal, MD, and Stephanie Seminara, MD. We are honored to have as our keynote speaker, Richard O. Hynes, PhD, from MIT. We will close the first day with a Reception for invited guests at the Russell Museum.

On Thursday, April 3, 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 Chiefs of Neurology (Merit E. Cudkowicz, MD, MSc) and Surgery (Keith Lillemoe, MD), who will describe some of the remarkable research being conducted across MGH.

Over the past year and a half, the hospital has conducted a rigorous Strategic Planning Initiative. Harry W. Orf, PhD, Senior VP for Research will close the morning session with an overview of the Research Strategic Plan with his presentation on the MGH Research Institute.

Our afternoon sessions will include three focused discussions on the main components of the Research Institute. The initiatives we will explore are:

1. Clinical Research Reorganization—presented by Jerrold F. Rosenbaum, MD
2. Translational Research Center—presented by Mason W. Freeman, MD
3. Life Registry—presented by Susan A. Slaugenhaupt, PhD

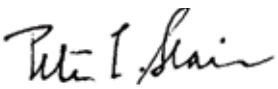
Experience has reaffirmed that we get the most helpful advice and perspective from SAC via open discussion of key issues. This year we have made a concerted effort to shorten presentations to allow more time for discussion with the SAC members.

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

To maximize the time for discussion during the day, the annual MGH Research Administration Executive Report and Financials for FY13 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 2014

Agenda: Day One, Wednesday, April 2, 2014
Annual Celebration of Science at MGH

11:00 am–1:45 pm
Wyndham, 15th Floor

SAC 2014 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)

2014 MGH RESEARCH SCHOLARS
Robert E. Kingston, PhD

2:15–2:45 pm

2014 Martin Prize for Basic Research
Dedifferentiation of Committed Epithelial Cells Into Stem Cells in Vivo

Jayaraj Rajagopal, MD

2:45–3:15 pm

2014 Martin Prize for Clinical Research
Ataxia, Dementia, and Hypogonadotropism Caused by Disordered Ubiquitination
Stephanie B. Seminara, MD

3:15–3:45 pm

2014 Goodman Award
The Role of IRA B Cells in Sepsis
Filip K. Swirski, PhD

3:45–4:00 pm

Break

4:00–5:00 pm

Keynote
INTRODUCTION
Peter L. Slavin, MD

Platelets and Extracellular Matrix—Under-appreciated Key Players in Metastasis
Richard O. Hynes, PhD, Daniel K. Ludwig Professor for Cancer Research
Investigator, Howard Hughes Medical Institute
Massachusetts Institute of Technology

5:00–7:00 pm
Russell Museum

Reception (for invited guests)

SAC 2014

Agenda: Day Two, Thursday, April 3, 2014
Annual Celebration of Science at MGH

8:00–9:00 am *SERI 2nd Floor*	**BREAKFAST** SAC Members with small groups of MGH Faculty
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 2013** **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	Neurology, **Merit E. Cudkowicz, MD, MSc**
10:40–10:50 am	Break
10:50–11:30 am	Surgery, **Keith D. Lillemoe, MD**
	The MGH Research Institute: Meeting the Challenges that Lie Ahead
11:30 am–12:00 pm	**OVERALL ORGANIZATION: THE RESEARCH INSTITUTE** **Harry W. Orf, PhD, Sr. Vice President for Research**
12:00–1:30 pm *SERI 2nd Floor* *Simches 3.120*	Lunch SAC Members with ECOR and Hospital Leadership ECOR Members & Speakers
1:30–1:40pm *Simches 3.110*	**CLINICAL RESEARCH REORGANIZATION**, **Jerrold F. Rosenbaum, MD**
1:40–2:00 pm	Discussion
2:00–2:10 pm	**TRANSLATIONAL RESEARCH CENTER**, **Mason W. Freeman, MD**
2:10–2:30 pm	Discussion
2:30–2:40 pm	**LIFE REGISTRY**, **Susan A. Slaugenhaupt, PhD**
2:40–3:00 pm	Discussion
3:00–3:15 pm	Break
3:15–3:45 pm *Simches 3.120*	**EXECUTIVE SESSION** (SAC members only)
3:45–4:15 pm *Simches 3.120*	**DEBRIEFING** (SAC members and MGH Leadership)

Goodman & Martin Award Winners

Howard M. Goodman Fellowship 2014

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.

The Role of IRA B Cells in Sepsis

Filip Swirski, PhD
Assistant Professor
Center for Systems Biology

Martin Research Prize 2014 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

Dedifferentiation of Committed Epithelial Cells Into Stem Cells in Vivo

Jayaraj Rajagopal, MD
Assistant Professor
Center for Regenerative Medicine

CLINICAL RESEARCH

Ataxia, Dementia, and Hypogonadotropism Caused by Disordered Ubiquitination

Stephanie Seminara, MD
Associate Professor
Reproductive Endocrine

Keynote Speaker

Richard O. Hynes, PhD, FRS

Richard Hynes was educated at Cambridge University (BA, MA) and MIT (PhD). He is the Daniel K. Ludwig Professor for Cancer Research at the Koch Institute and Department of Biology at MIT, Investigator of the Howard Hughes Medical Institute and Senior Associate Member of the Broad Institute. He was formerly Associate Head and then Head of the Biology Department and was Director of the MIT Cancer Center for 10 years. He is a Fellow of the Royal Society (FRS) of London and a Member of the US National Academy of Sciences, the Institute of Medicine and the American Academy of Arts and Sciences.

Dr. Hynes was born in Nairobi, Kenya and grew up in Liverpool, England. He did his undergraduate work at Trinity College in Cambridge, UK, and his PhD at MIT with Paul Gross, separating different cell types from early sea urchin embryos and studying the complexity of their RNA sequences. He then returned to the UK as a postdoctoral fellow at the Imperial Cancer Research Fund in London. By investigating the molecular changes on cell surfaces that distinguish cancer cells from normal cells, he discovered fibronectin, a cell adhesion protein present on normal cells that was noticeably absent on cancer cells. Dr. Hynes then went back to become an Assistant Professor in the Cancer Center and Biology Department at MIT in 1975, where he continued to work out the biology of fibronectin, the discovery of which set into motion a string of studies that has helped to establish cell adhesion as its own field of investigation. He showed that the extracellular matrix was connected across the membrane to the actin cytoskeleton. Dr. Hynes's studies also contributed to the discovery and subsequent cloning of integrins, a family of protein receptors that gives cells their stickiness by binding with fibronectin and other cell adhesion molecules. By forming a physical link between the extracellular environment and the cell's interior, integrins help to control cell shape and movement as well as accurate cell adhesion and control cell behavior through the transmission of signals into and out of cells.

The Hynes laboratory continues to study actively the molecular and cellular basis of cell adhesion and its involvement in embryonic development, physiology and pathology (inflammation, thrombosis and cancer). Particular interests focus on cell-matrix adhesion and on the adhesion of cells in the vasculature, both involving integrin adhesion receptors and their ligands. Current emphases are on vascular development and cancer metastasis with a focus on the contributions of platelets and extracellular matrix. The laboratory uses mouse models of human diseases and applies cellular and molecular approaches to decipher the mechanisms underlying phenomena revealed in those mouse models. By studying the way cells stick together and migrate in both healthy and disease states, Dr. Hynes hopes his research will lay the foundation for scientists to develop new therapies for adhesion-related disorders.

Dr. Hynes has received numerous awards in recognition of his research on extracellular matrix, integrins and cell adhesion, including the Gairdner International Award, the Pasarow Award and the E.B. Wilson medal, the highest award given by the American Society for Cell Biology. He has served as President of the American Society for Cell Biology, chaired the NAS committees that established Guidelines for Human Embryonic Stem Cell Research and is currently a Governor of the Wellcome Trust, UK.

Scientific Advisory Committee (SAC) 2014

Joan S. Brugge, PhD
Professor of Cell Biology
Head of the Department of Cell Biology
Harvard Medical School
Term: SAC 2011 through SAC 2014 (2nd term)

Alan M. Garber, MD, PhD
Provost
Harvard University
Term: SAC 2012 through SAC 2015 (1st term)

Susan J. Hockfield, PhD
Past President
Massachusetts Institute of Technology
Term: SAC 2011 through SAC 2014 (2nd 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 A. Kaiser, PhD
Professor of Biology
MacVicar Faculty Fellow
Massachusetts Institute of Technology
Term: SAC 2013 through SAC 2016 (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 2014

ECOR CHAIR

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

ECOR VICE CHAIR

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

ECOR PAST CHAIR

Daniel Haber, MD, PhD
Director, MGH Cancer Center
April 2012–March 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 2012–December 2014

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

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

Emery N. Brown, MD, PhD†
Anesthesia
April 2009–March 2015

William F, Crowley, Jr., MD
Director, Clinical Research Program
Ex-officio

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†
Executive Vice Chair, Psychiatry Department
April 2012–March 2018

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

Henry Kronenberg, MD
Chief, Endocrine Unit
Elected Representative
January 2012–December 2014
Chair, MGH Research Council

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

† Chair Appointment, ‡ Chief's Council

Executive Committee on Research

Officers and Members 2014

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†
Director, Transplant Center
April 2012–March 2018

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

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

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

Peter L. Slavin, MD
President, Massachusetts General Hospital
Ex-officio

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

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

David F. Torchiana, MD
CEO & Chairman, Massachusetts General Physicians Organization
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
Chair, Subcommittee on Research Animal Care (IACUC)
Ex-officio

NON-VOTING MEMBERS

Irene Abrams, MA
Director, Partners Research Ventures & Licensing
Contributing Member

David Altshuler, MD, PhD
Director, The Broad Institute Program in Medical and Population Genetics
Contributing Member

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

Julia Bateman
Associate Director of Development, Research
Contributing Member

Ryan Boisselle
Assistant Director, ECOR
Contributing Member

Deverie Bongard, MBA
Administrative Manager, Molecular Biology
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

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

Christopher Coburn
Vice President, Partners Innovation
Ex-officio

† Chair Appointment, ‡ Chief's Council

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

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

Deborah Farr
Director, Development for Research
Contributing Member

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

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
Director, Partners Research Compliance
Contributing Member

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

Elena Olson, JD
Executive Director, Multicultural Affairs Office
Contributing Member

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

John Parrish, MD
Director, CIMIT
Ex-officio

Mark Randolph
Interim Director, Animal Welfare Assurance, MGH
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

Frances Toneguzzo, PhD
Executive Director, Partners Research Ventures & Licensing
Contributing Member

Bruce Walker, MD
Director, Ragon Institute
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, Multicultural Affairs Office Advisory Board
Contributing Member

MGH Research Management

Executive Report for SAC 2014

Harry W. Orf, PhD
SENIOR VICE PRESIDENT FOR RESEARCH

Weathering a Stormy 2013

In 2013, the inability of our federal government to deal in a timely manner with our country's fiscal challenges placed enormous stress on sponsored research programs across the nation. A government shutdown, sequestration, and continued reductions to the NIH budget dealt a heavy blow to both fledgling and long-established biomedical research programs. MGH was no exception, with federal research expenditures dropping by 6% this past year. In spite of this drop and a slowing in growth of industry-sponsored revenue, overall research expenditures at MGH actually grew in 2013 to $786M (an increase of $10M over 2012) due to increases in foundation, philanthropic, and internally-sponsored programs. While this shift in funder mix got us through a difficult year, using a higher proportion of internal resources and relying on external funders that do not provide full indirect cost recovery is not a workable model to sustain our research enterprise.

The Challenges and Opportunities Ahead—A New Strategic Plan for Research

To sustain and grow the MGH research enterprise into the next decade, we have to deal with the harsh realities that federal funding for research is both diminishing and diluting its traditional focus on basic discovery. Concurrently, however, new opportunities to fund biomedical research are emerging. NIH NCATS programs are promoting multi-center grants focused on translational research, an area well suited to the strengths of academic medical centers like MGH. The Medicare and Medicaid Electronic Healthcare Record Incentive ("Meaningful Use") Program has catalyzed the growth of healthcare informatics, leading to new opportunities to link genetic/genomic and other 'omic' information to medical records on an individual basis. The establishment and growth of PCORI (the Patient-Centered Outcomes Research Institute funded by the Affordable Healthcare Act) has given rise to a new $700M pool of research funding for outcomes, community, qualitative, and patient-based research, and is ushering in a new era of personalized medicine. The paucity of new therapeutic candidates in the pharma industry's pipelines, coupled with recent losses of patent protection of many of their big income-producing therapeutics, will provide renewed incentives for industry to collaborate more frequently and closely with academia.

To meet these challenges and take advantages of emerging opportunities, Research Management and ECOR leadership at MGH began work in the summer of 2012 to develop a new strategic plan for research. The plan encompasses major initiatives to expand our philanthropic base, our collaborative relationships with neighboring academic research centers, our interactions with industry and the venture community, our efforts to improve infrastructure and internal communication, and the engagement of our patients as partners in biomedical discovery. We will present at this year's SAC program an overview of the strategic plan and look for guidance and feedback as we begin its implementation. Accordingly, in the last section of this report (The New Research Strategic Plan Moves Toward Implementation), I provide some background on the thought processes and approach that led to development of the plan and describe its key components. But first, let's take a closer look at this past year.

By the Number$

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

MGH total research expenditures for FY13 were $786M, of which $594M were direct costs and $192M were indirect cost recovery. This represents a 1.3% increase in total research expenditures compared to $776M for the same period in FY12. Submitted proposals increased 3% to 4,045 from 3,524 in FY12 and new awards were down 5% to 1,475 from 1,684. New award amounts have decreased 7%

to $520M in FY13 from $568M in FY12. Support from direct DHHS funding (which consists mostly of NIH funding), now accounts for 46% of MGH research, down 4% from last year's 50%. Total research expenditures on DHHS-sponsored research in FY13 were $364M, a decrease of 6% compared to $387M in FY12. Again in 2013, MGH remains the largest recipient of NIH funding among independent hospitals and 13th nationally for all institutions, down from 12th place in 2012.

ARRA expenditures contributed $9M to total research in FY13. From FY09 through FY13, MGH investigators received $152M in ARRA funding across 315 grants. This success has meant the continued recovery of indirect revenues from ARRA awards, moderating concern about research funding increasing without associated full indirect revenues. Although this positive indirect revenue benefit from ARRA funding will be phasing out, it has been a welcome bridge that has reduced pressure on institutional resources. We are mindful that the end of ARRA funds in FY13 will have an impact on both investigators and the institution, and are continuing to look for approaches to mitigate this impact.

Research expenditures in the "All Other" category, which includes non-profit organizations, foundations, internal, subcontracts, and miscellaneous sponsors, again showed a moderate increase of 6.7%, to $327M in FY13 from $307M in FY12, as investigators have continued to turn to these sources to buffer the constraints on NIH support. "Industry/Corporate" expenditures increased 5% to $57M in FY13; this category has experienced large swings in expenditures over the last five years. The cumulative annual growth rate for FY09-FY13 across all sponsor types was 5.9%.

In aggregate, research activity (direct + indirect dollars) continues to comprise approximately one-quarter (24%) of the total MGH annual operating budget and is distributed across 23 departments and centers.

Awards and Recognition: *National*

In 2013, MGH and its investigators continued to receive national recognition for their major research contributions. Anupam B. Jenda, MD, PhD, received an NIH Director's Early Independence Award. Jen Sheen, PhD, received a Martin Gibbs Medal for her pioneering advances in the plant sciences. David Kuter, MD, DPhil, was honored with the American Society of Hematology's Ernest Beutler Lecture and Prize. Jack Szostak, PhD, was included in the first class of Fellows of the American Association for Cancer Research. David Altshuler, MD, PhD, Xandra Breakefield, PhD, and John Parrish, MD, were all elected to the American Academy of the Arts and Sciences.

Awards and Recognition: *Hospital*

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.

In May 2013, the third group of MGH Research Scholars was announced at the hospital's Research Advisory Council (RAC) annual meeting. These seven recipients were selected from 81 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 2013 MGH Research Scholars are:

- Todd Allen, PhD, the Ragon Institute;
- Sydney Cash, MD, PhD, Neurology,—the Elizabeth Riley and Daniel Smith MGH Research Scholar;
- Raymond Chung, MD, PhD, GI Unit;
- Jose Florez, MD, PhD, Diabetes Unit/Center for Human Genetic Research;
- Robert Gerszten, MD, Cardiovascular Research Center;
- Sekar Kathiresan, MD, Center for Human Genetic Research;
- Susan Slaugenhaupt, PhD, Center for Human Genetic Research.

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 2014 recipients for a 2013 publication are Jayaraj Rajagopal, MD (Basic Science Award) for his Nature paper entitled, "Dedifferentiation of Committed Luminal Epithelial Cells into Functional Stem Cells in Vivo", and Stephanie Seminara, PhD, (Clinical Science Award) for her New England Journal of Medicine paper entitled, "Ataxia, Dementia, and Hypogonadotropism Caused by Disordered Ubiquitination".

Goodman Award. The 2014 Howard Goodman Award recipient is Filip Swirski, PhD, from the Center for Systems Biology. 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.

Clinical Research Day

The tradition of Clinical Research Day is to highlight issues at the forefront of clinical research at the national level and to discuss these in terms of the MGH clinical research community. The 2013 theme was The Role of Translational Research in Academic Medical Centers. **Elias Zerhouni, MD**, President, Global R&D, Sanofi France, served as the keynote speaker. He captivated the audience with his presentation on the future of collaborations between academic health centers and industry. Following Dr. Zerhouni's keynote address, a panel discussion, led by Mason Freeman, MD, focused on the critical role of translational medicine capabilities in academic health centers and implications for research at MGH. Leaders in translational research provided their insight and suggestions on this topic to a diverse audience of clinical investigators. Participation remained high with **263 abstracts** submitted, **21 team nominations**, and a vibrant and well-attended Poster Presentation session.

The Final Frontier (Space!)

While a detailed accounting of research space and equipment utilization is provided in the Research Space Management Group (RSMG) report, it is worth summarizing here some of the major trends and initiatives that are underway.

Demand and Densities. MGH has over 1 million square feet (nearly 23 acres) of owned and leased research space, of which 43% is in the Charlestown Navy Yard, 28% on the MGH Main Campus, 24% in the Simches Research Building, and the remainder in various locations in Boston and Cambridge. The Research Densification Committee, formed in FY09 and now renamed as the Research Space Advisory Committee (RSAC), a sub-committee of ECOR, monitors and guides research space policy and practices, with a mandate to maximize opportunities to accommodate research growth and improve recovery of indirect costs. Though IC density grew over the last four years, in FY13 MGH onsite research IC density decreased by 10% from the FY12 density to $167/nasf. The challenging funding environment and the addition of new research space were both contributing factors in the decreased density. Significant space additions included 50,300 nasf of onsite research space at 400 Tech Square for the new Philip T. and Susan M. Ragon Institute and 16,900 nasf of leased space at the Shriners Burn Institute.

In FY13 RSMG, working in conjunction with RSAC and the Planning Office, was able to finalize and document the plans for the 20,000 nasf of research space allocations made possible through the Ragon backfill process. Allocation amounts approved by RSAC ranged from 600 nasf to 6,000 nasf. Additionally, RSMG was able to negotiate and implement the allocation of existing space to several groups by reallocating some under-utilized space. On the main campus, the Surgery and Neurology Departments, as well as the Wellman Center, added small amounts of space that positively impacted their research. In Building 149, an investigator in the Wellman Center secured laboratory space for his program and gained the opportunity to work closely with collaborative scientists in the CBRC. Total space allocations of approximately 3,000 nasf were modest but critically important to support this growing program.

In FY14 RSMG has documented space requests totaling 90,000 nasf. Space requests continue to increase with a growing number of new initiatives from multiple departments. Though it is possible approximately 10,000 nasf may become available on 149-10 for dry research purposes sometime in FY15, it is clear that at least for now many of these space requests can only be resolved in a timely manner from considering existing space utilization and looking for opportunities to “right size” groups. Encouraging groups to share equipment and better utilize Core Facilities may also help to alleviate some of the space needs. The consolidation of several groups on the CNY campus in particular could also create better space efficiencies and lead to some available space.

New Projects. RSMG initiated and coordinated numerous projects during the year that helped to further densify MGH research space. In total, RSMG completed 41 construction and renovation projects totaling over $31 million and involving more than 90,000 nasf. RSMG currently has 33 projects in process totaling over $11M and covering over 100,000 nasf.

The design/development process on the CNY Backfill Project created by the relocation of the Ragon Group to Cambridge continued in FY13. During the year, numerous design/development and furniture meetings were held with the various groups to ensure the renovated laboratory space would meet a majority of their requirements while, at the same time, provide much needed upgrades to aging building infrastructure. After many meetings and detailed reviews of programs and equipment, construction documentation was completed this past summer. As a result of this work in FY13, Phase I which involved renovations to the dry office areas on the 4th and 5th floors of 149 was completed in January of this year. The lab renovations on the 6th floor (Phase II), currently stalled due to an unexpected delay involving the receipt of final permits, will resume shortly and should be completed this summer. The 5th floor (Phase III) laboratory renovation is expected to be complete by late fall if everything goes according to plan.

MGH Research Management

Executive Report for SAC 2013

Partners Research Management

The Partners Research Management (PRM) team is led by Peter Markell, Executive Vice President of Administration, CFO, and Treasurer of Partners HealthCare, and Andrew Chase, Vice President of Research Management and Research Finance. They work in close collaboration with the Senior Vice Presidents of Research, Harry Orf, PhD, at MGH and Barbara Bierer, MD, at BWH, as well as Anne Klibanski, MD, Chief Academic Officer of Partners HealthCare, and Chris Coburn, Vice President of Innovation (formerly Research Ventures and Licensing).

The team is focused on improving usability for the end user, including improvements for efficiency and transparency to the research community. Primary focus areas within Research Management are enhancing system functionality and improving business processes to allow for more granular tracking and reporting for PRM and Hospital Departments of increasingly complex day to day operations. Given feedback from the research community, the team is also reviewing existing systems to make improvements to their look and feel in order to facilitate ease of use for investigators and administrators.

Improvements continue to be challenged by the heightened regulatory burden imposed upon investigators by sponsors, and real pressure on federal funding for research. However, despite the increase in regulations, surveys conducted by the MGH Research Management Advisory Committee (established in 2009), continue to show increased satisfaction by both investigators and administrators in improvements to services and systems of PRM over the course of the last four years.

The PRM team will continue to strengthen overall performance and service to the Partners research community by streamlining administrative processes, continuously improving the efficiency of operations, and providing exceptional customer service to the research community.

Partners Innovation (formerly RVL—Research Ventures and Licensing)

Under the new leadership of Chris Coburn, Partners VP for Innovation, who joined us at the end of 2013 from Cleveland Clinic, Partners Innovation has undergone a number of organizational and operational changes to both expand and improve its support of the research enterprise. Examples include: 1) establishment of a Commercialization Council, consisting of entrepreneurial faculty members across Partners institutions to advise on policy and new initiatives and promote cross-hospital collaborations; 2) establishment of an Innovation Advisory Council consisting of CEO's and partners in the pharma, biotech, and venture communities to advise on improving relationships with private sector companies and serve as a sounding board for new models of public-private collaboration; 3) establishment of a $1M fund to award $50,000 seed grants for innovative proposals from Partners faculty and staff; 4) location of IP managers and support personnel on site at MGH and BWH to promote more direct interaction with faculty; 5) new management controls and streamlined process flow to improve turn around time on agreements, and use of performance metrics to asset opportunities for improvement.

For MGH specifically, our patent, licensing, venture activity, and associated income for FY13 is as follows:

- Licensing Activity = 153 (-6 – 159 in 2012)
- Material Transfer Agreements = 908 (-11 – 919 in 2012)
- New Disclosures = 383 (+61 – 322 in 2012)
- Patents Filed = 218 (+72 – 146 in 2012)

- Patents Issued = 74 (*16 – 90 in 2012)
- Royalty and Licensing Income = $75.5 (-$24.1 - $99.6 in 2012)

Royalty income decreased as expected due to the expiration of certain major patents.

Office for Interactions with Industry (OII)

OII continued in 2013 to refine and improve Partners policies and processes relating to the complex relationship between academic medicine and the for-profit biomedical sector. While our focus continues to be on ensuring that such relationships do not bias Partners charitable activities, we are also committed to fostering these relationships as essential to Partners ability to carry out its missions. Consistent with those two values, OII constantly re-evaluates Partners policies to ensure that they assure integrity while avoiding unnecessary impediments to healthy industry relationships. In addition, OII constantly seeks to improve processes to make the navigation of complex policies easier for Partners staff.

Thus, in the past year OII has rolled out several process improvements plus key policy recommendations that reduce burdens on investigators and their relationships with industry and/or that address potential conflicts with more precision. In terms of process, a key development that resulted from OII working with Harvard Medical School was the elimination of the need for Partners staff to fill out both a Partners and an HMS annual COI disclosure form. In addition, and in furtherance of implementation of federal regulations that went into effect in 2012, OII has enhanced the systems for obtaining needed disclosures from Partners investigators, improving how we conduct the regulatory-required conflict of interest (COI) analysis, implementing management plans where conflicts may exist, providing extensive COI training for investigators, and monitoring and auditing federally-funded research on an on-going basis.

Key policy improvements over the past year resulted in a reduction in administrative burden on Partners individuals, a broadening of conditions under which research is permitted to move forward, with effective management, where it was previously not permitted to be undertaken at all, and the closing of a significant gap in policy coverage in measured, narrowly-focused ways. Specifically, these changes include: (1) collaboration with HMS to substantially narrow the reach of the HMS I(a) "clinical research rule" prohibitions; (2) enabling certain clinical research to be undertaken at Partners when Partners owns equity in the company, where formerly it was prohibited; and (3) completion of a Task Force process leading to recommendations for more comprehensively addressing financial interests in clinical care, but in ways that represent minimal intrusion on the clinical care setting.

MGH Research Management—Progress in 2013

CROI Reaches Its One-Year Anniversary. 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.

MGH Research Management

Executive Report for SAC 2013

Over a year after launching the program, more than 300 suggestions have been received and more than a hundred have been resolved. A sampling of these include: 1) establishment of a dedicated 'Help Line', new email inbox, and website to help investigators with IRB-related questions and issues; 2) placing the weekly new animal user orientation on-line via a webinar to eliminate the need for researchers to travel to CNY; 3) a major change in software and hardware purchasing policy making academic discount pricing the new default for research purchases [n.b., very significant savings have already been achieved as a result of changing this policy]; Other software improvements consist of Windows 7 upgrades and the ability to purchase Adobe Enterprise licenses; 4) the creation of a new Research Safety Committee for the hospital; 5) a new pilot email system with dramatically expanded mailbox capacity through automatic archiving and retrieval; 6.) the creation of a Research Personnel Database to better manage training and communication with our researcher base.

At the one-year anniversary of the program in October, 2013, RMAC (the committee that oversees the CROI program) awarded ten $50 prizes for the best suggestions of the year and gave everyone who offered a suggestion during the first year of the program a $5 gift certificate to the MGH Cafeteria. The program remains vibrant, with 3-5 new suggestions received every week.

Research Safety Committee Approaches Its One-Year Anniversary. A concern recognized by Research Management in FY12 was the need to develop a comprehensive safety program for the research community. As described in my report last year, a research safety task force worked throughout 2012 to form an MGH Research Safety Committee and it inaugural meeting was held in April 2013.

Today, as the committee approaches its one-year anniversary, we are pleased to report that much has been done to improve research safety throughout the Hospital. The Committee has over 70 active members and meets quarterly. Every research department is represented and a series of departmental, unit, site, and lab safety coordinators provide coverage for literally every person and square foot of space associated with the research enterprise. Five safety working groups have been formed and are currently active—Documentation, Training, Chemical Hygiene, Lab Surveys, and Communications. Each meets monthly to address safety issues, establish/refine research safety policies and programs, and promote safety across the Hospital. Important progress made this first year includes the assembly and complete update of all research safety policies and procedures, the development of new and streamlined on-line safety training modules, a new schedule for annual survey round visits to include all research laboratories, and a new research safety website providing direct and clear access to important safety resources and programs.

The New Research Strategic Plan Moves Toward Implementation. As reported last year, a major effort was undertaken to formulate a strategic plan for research as part of a greater hospital-wide initiative to develop an overall strategic plan for MGH for the next decade. The research plan has been vetted, reviewed, and approved by both senior management and the MGH Board of Trustees. Work on implementing key components of the plan are beginning in 2014 and will continue over the next several years. In the remainder of this section, I provide some background on the thought processes and approach that led to development of the research plan and describe its key components—the MGH Research Institute, the Translational Research Center, and the Life Registry.

The Challenges that Lie Ahead

The MGH research community has always been counted on to improve the lives of patients through medical discovery. Today, MGH is a leader in healthcare innovation and home to one of the largest and most successful research enterprises in the nation. In FY13, research revenue exceeded $780

million, almost 25% of the entire hospital revenue stream. We remain the #1 NIH funded institution among independent hospitals and rank 13th nationally among all funded institutions. Unfortunately, the very foundation upon which our research enterprise has been built is now being threatened by sea changes in federal funding, policy, and regulations. To sustain and grow the MGH research enterprise into the next decade, we must devise strategies that will allow us to address these challenges. Specifically, we must:

1. ***Adjust to a shrinking and shifting federal funding base.*** There are fewer grant dollars available. In 2013, NIH suffered an 8% reduction in grant funding, issuing 640 fewer grants. Since, 2003, it has suffered an effective 22% loss in grant support. Also, grants are becoming increasingly harder to get. Success rates have dropped to an average of 17%, with many centers funding in the single digits. To quote Frances Collins, NIH Director, in the 9 November 2013 issue of the WSJ, "When grant rates drop below 20%, the process becomes almost like a lottery." Finally, funding is being redirected away from basic discovery toward translational and outcomes research. In 2011, NIH established NCATS, the National Center for Advancing Translational Sciences, by shifting over $700 million out of traditional grant funding sources. In 2012, PCORI, the Patient-Centered Outcomes Research Institute, was established. This year alone, PCORI will issue grants in excess of $500 million.

   These funding changes threaten the research programs of our established investigators and discourage our younger physician-scientists from starting research programs of their own. We must teach our investigators to think and do more about the potential applications of their discoveries, and we must engage our patients as partners in the research process to more effectively complete in the emerging fields of outcomes research and personalized medicine.

2. ***Overcome the relative anonymity of our research enterprise.*** Associated Press, 5 October 2009, "Jack Szostak of Harvard wins the Nobel Prize….. London-born Szostak, 56, has been at Harvard Medical School since 1979 and is currently professor of genetics. He is also affiliated with the Howard Hughes Medical Institute." Dr. Szostak has actually been at MGH for over thirty years, yet we are not acknowledged. This headline is sadly indicative of the fact that MGH research is one of the best-kept secrets in Boston. While this lack of recognition has not limited the success of our traditionally funded research programs to date, it will severely handicap our efforts to secure new funding streams to replace those lost from the shrinking and shifting federal base.

   We must become more visible to these potential sources—industry, the venture community, potential donors, and the public—and develop the means to more effectively engage them to partner with us and support our research enterprise.

3. ***Minimize the time our researchers spend 'away from the bench' dealing with policy and regulatory obligations.*** Elias Zerhouni, former NIH Director, stated during his keynote address at the 2013 MGH Clinical Research Day that the federal government now spends more money to regulate clinical research than it does to fund clinical research. According to a national survey taken by the Federal Demonstration Partnership in 2012, researchers now spend an astonishing 42% of their time on administrative tasks. This increasing burden of regulatory obligations can lead to frustration with the institutional programs and staff that must enforce these regulations, making our researchers anxious and lowering their productivity. The situation is often exacerbated when institutions, faced with decreasing indirect cost recoveries, reduce support staff or fail to invest in modern technologies and

"best practice" support programs. This can lead (and indeed has led!) to an environment ripe for finger pointing between investigators and support staff, missed opportunities for economies/cost savings, suboptimal support for researchers, a jaded research community, and an overall loss of trust in the research support system.

To address these concerns, we must ensure that our support services are continuously reviewed and optimized by leveraging technology. We must assure that channels of communication are opened among investigators, support staff, and senior leadership. Doing so will foster an environment of accountability, promote transparency, and begin to rebuild trust between our researchers and those who support them.

4. ***Devise new approaches to bridge the translational research "valley of death."*** At a time when therapeutic pipelines are diminishing and many high income-producing pharmaceuticals are coming off patent, industry is actively seeking partners to develop new products. Our investigators possess the creativity to make important discoveries in biomedical research but often lack the incentives, financial resources, and practical understanding required to turn their discoveries into products. If we can overcome these shortcomings, it will afford us an opportunity to establish new models for partnerships that can more effectively bridge the translational research gap between discovery and product development.

   To advance our translational research enterprise and compete with similar efforts underway at virtually all of the other major academic medical centers in the US, we need to educate our own investigators about the translational process. We must help them select the most promising ideas for advancement, organize the resources required for development activities, remove the barriers that inhibit this work, and facilitate access to needed resources

5. ***Actively engage our patient population and make them partners in research.*** MGH has the ability to create a world-renowned biobank that, when linked with existing large stores of data in the electronic medical record, will enable us to revolutionize the way we translate research discoveries into new medical treatments, and to evaluate the clinical effectiveness and outcomes of new diagnostics and interventions. Biomedical research enterprises that do not invest in biorepositories and patient partnerships will eventually not be able compete for funding in the rapidly growing fields of genomics, personalized medicine, and patient-based outcomes research.

Meeting the Challenges

Our plan to meet these formidable challenges is built around the concept of establishing a formal Research Institute within MGH. The master plan to establish the Institute is comprised of three major initiatives, each with a fully developed business plan. These are:

- The MGH Research Institute—the overarching matrix for structure and operations
- The Translational Research Center—the bridge to close the research/clinical care gap and the means to more effectively collaborate with industry
- The MGH Life Registry—the base for engaging our patients as partners in research and the platform for the emerging fields of outcomes research and personalized medicine

The MGH Research Institute. The formal mission of the Institute—to promote, support, and guide the diverse MGH research enterprise to better the human condition—will be accomplished by:

Increasing visibility of the research enterprise

Managing and growing research assets (people, funding, space, infrastructure)

Preserving our leadership in biomedical innovation

Fully integrating the research enterprise with the clinical mission of the hospital

Externally, the Institute will become the "front door" through which we 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.

Top priorities and needs for the Research Institute are:

- #1: Build the organization and brand the institute—hire an Executive Scientific Director (immediate)
- #2: Solidify funding base—hire business development and development staff (year 1) and develop major gift strategy to name the Institute (year 2)
- #3: Optimize space—develop space metrics and plan (immediate), relocate programs to optimize adjacencies (years 2-3), and build new research space at the main campus (years 4-5)
- In Process: Improve infrastructure—continue operations improvement, develop research personnel database and support metrics, and review cores (immediate-year 1), hire IT programmer (year 2)

The Translational Research Center. Biotechnology, med-tech device, and pharmaceutical companies have traditionally played key roles in advancing translational research by leveraging insights generated in academic medical centers. However, recent reductions in research and development budgets, additional regulatory requirements, and an increased understanding about complexity of human biology itself have significantly impaired industry's ability to advance novel treatments. MGH investigators possess the creativity to develop new treatments but often lack incentives, financial resources, and the practical understanding required to turn their discoveries into products. Overall, MGH is extraordinarily well positioned to succeed in this arena because of our proximity to industry, outstanding clinical investigative staff, thriving basic research community, enormous technical clinical infrastructure, and large, well-characterized patient population. However, all these assets, without the appropriate coordination and administrative structures, cannot spontaneously cohere into a translational research enterprise. The Research Strategy Implementation Plan therefore proposes to develop a Translational Research Center to help investigators select the most promising ideas for advancement, organize the resources required for development activities, remove the barriers that inhibit this work, and facilitate access to needed resources.

Executive Report for SAC 2013

The TRC will have the capacity and infrastructure to support investigators at any stage of the translational research process—from study idea to product development. It will be a "one-stop shop" that supports translational research in its various stages. This support will either be provided directly by TRC staff, or through existing resources that the TRC staff would bring to the investigator. Organized around five functional areas—business development, project feasibility, project management, clinical testing, and leadership—the TRC will facilitate our ability to effectively conduct translational research and expand the use of existing resources.

Patients demand access to the latest technology and medicines, and ultimately we believe that if MGH can provide the most advanced therapies, it will help to sustain our clinical enterprise. In addition, the TRC will offer not only a mechanism for stimulating the development of new therapeutics but also has the potential to bolster research, philanthropic, and royalty funding at a time when NIH funding is declining.

Top priorities and needs for the Translational Research Center are:

- #1: Appoint leadership team and cultivate industry partnerships (years 1-2)
- #2: Implement project feasibility and management functions (years 1-3)
- #3: Renovate (year 1) and phase opening of clinical testing facility (years 2-4)

The Life Registry. The MGH Life Registry will be a collaborative effort among patients, clinicians, and scientists to understand disease better, identify targets for therapy, and enable personalized medicine. This will ultimately lead to improved patient care and improved cost effectiveness. The infrastructure will be built upon the existing Partners Biobank currently in place for recruitment, storage, processing, and distribution of biological samples.

Over the past five years, the Partners Biobank has collected approximately 8,500 patient samples. Our goal, however, is to grow this to over 50,000 within the next five years. To be successful, we must move beyond the clinic recruitment model and integrate fully into the clinical mission at MGH. Online consent has been approved by the Partners IRB and is set to go live in early 2014 via Patient Gateway. Our vision is to significantly increase the visibility of the Life Registry (whose name will soon become the Partners Biobank at MGH), by increasing patient engagement and communication. To do this, we will hire a Patient Outreach Coordinator to engage our clinicians through the efforts of the Life Registry Directors, and help integrate directly into clinical phlebotomy those patients who are scheduled for clinical blood draws. We will create centralized Biobank locations at MGH that are staffed by study coordinators who can answer questions, draw research blood samples, and engage patients during their visits to MGH. We will actively educate our clinical staff so patients get positive input about the initiative from their caregivers and understand that research is an important part of the MGH mission. Lastly, we will provide continuous patient outreach to those already enrolled in the Biobank to ensure that they remain our partners in research.

An integral part of this work will be creating the infrastructure to link Biobank specimen, genetic, and patient-reported data to the clinical and operational data contained in the Research Patient Data Registry. This integrated healthcare system will allow researchers to identify the genetic, biological, and behavioral features of study populations in one place. This will enhance the number, speed,

cost-effectiveness, and predictive power of clinical trials and basic science, as well as creating an infrastructure for constant improvement and innovation. The resulting ability to create sets of ubiquitous experimental results across multiple projects and disciplines will be a huge step toward the goal of having research embedded into routine care delivery, with results that are fed back to the system to inform both research and practice.

Top priorities and needs for the Life Registry are:

- #1: Patient identification, consent, and sample collection—identify space and hire study coordinators (immediate)
- #2: Making patients our partners in research—hire patient outreach coordinator and web developer to begin marketing effort (year 1)
- #3: Initiate genotyping effort—buy server and hire IT data manager (immediate)

Overall, the strategic plan for research at MGH will keep the hospital at the forefront of biomedical progress for the next decade by providing the operational resources to carry out cutting-edge research and to translate that work into improved health care for our patients.

Respectfully submitted,

Harry W. Orf, PhD

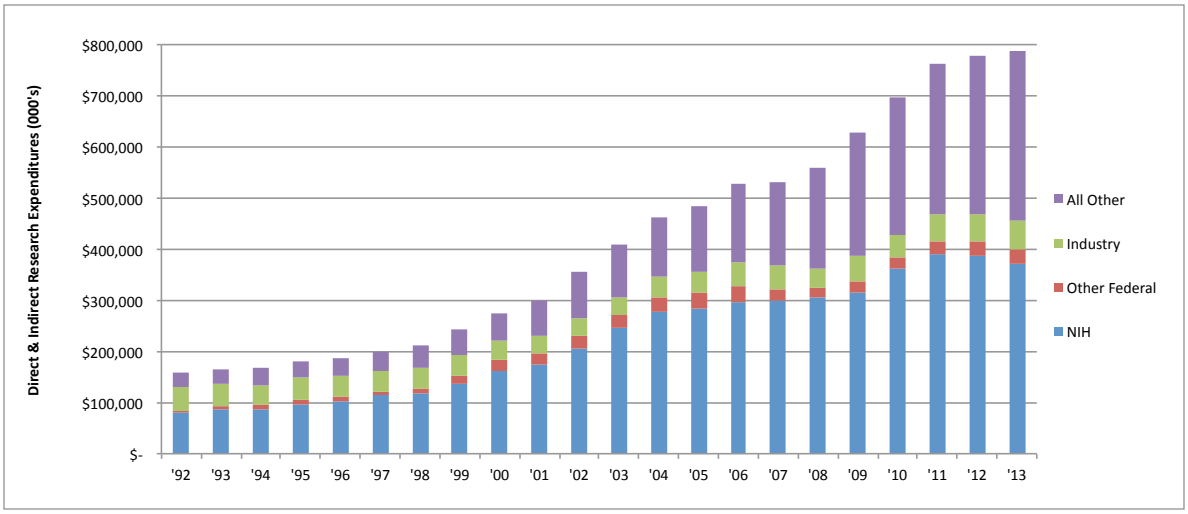
MGH 1811 RESEARCH Management | *Mainstay of MGH Innovation*

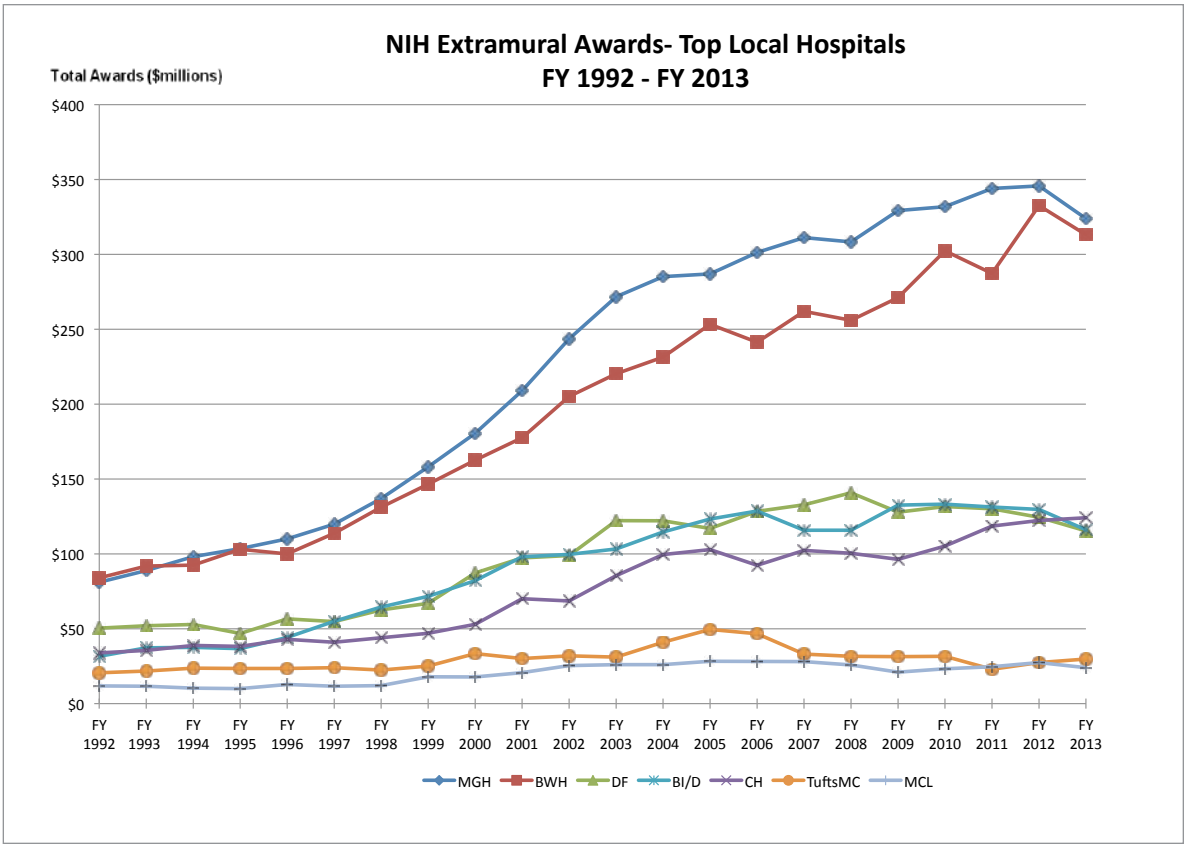
MGH Research Management

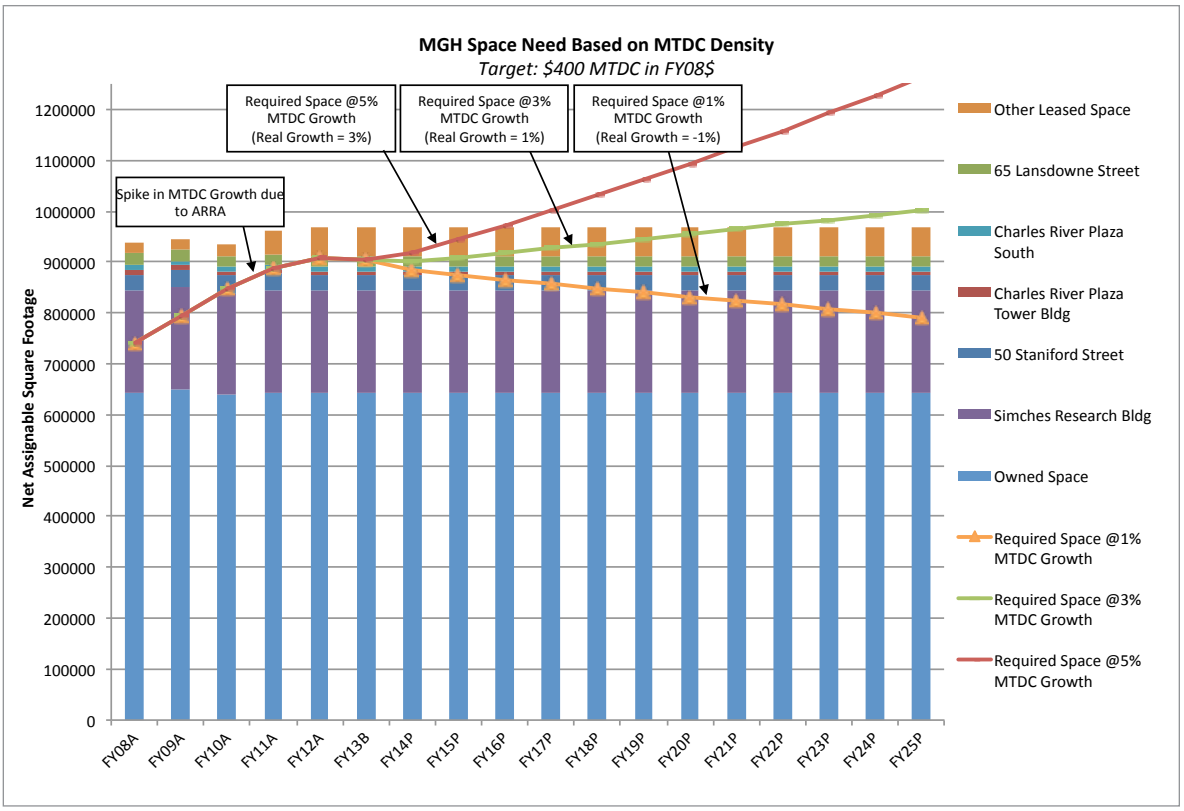
Executive Report for SAC 2013

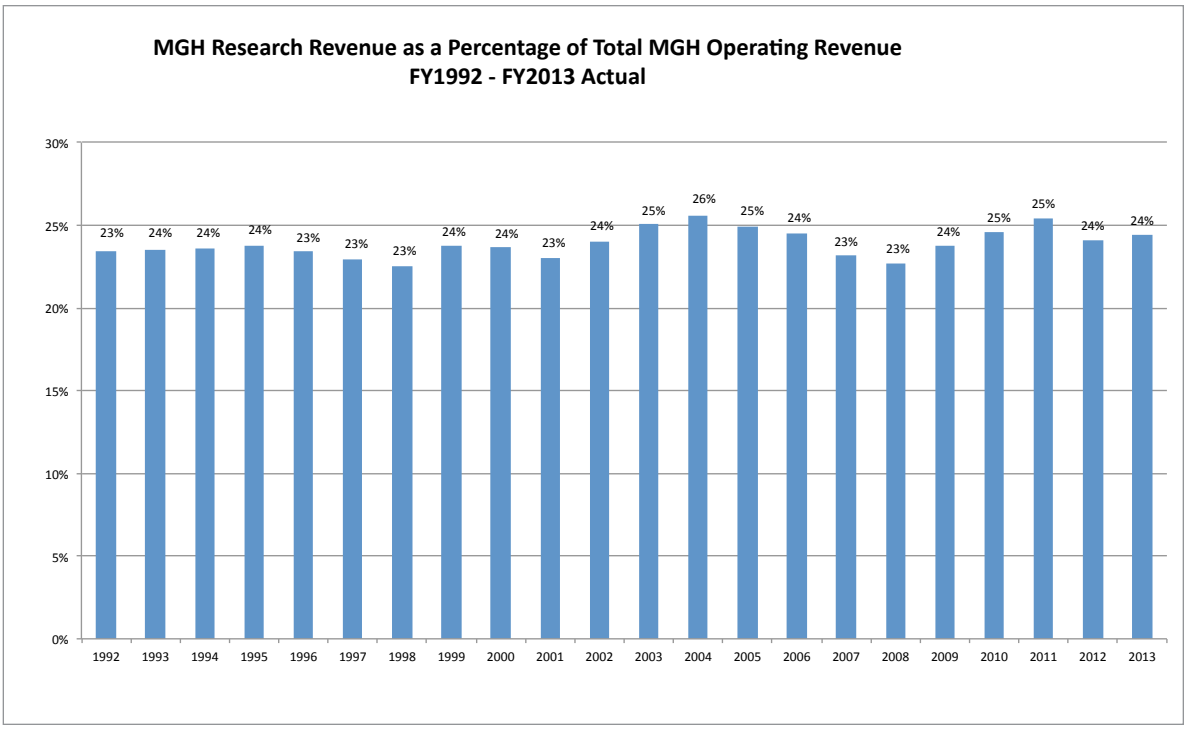
MGH RESEARCH HAS GROWN 377% OVER 20 YEARS TO $786.5 M

MGH combined research has grown at a compounded annual growth rate of 9.5% between FY98 and FY13. The 5-year moving average annual growth has decreased from 8.3% in FY07 to 6.9% in FY13; the FY12-FY13 growth was 1.1%.





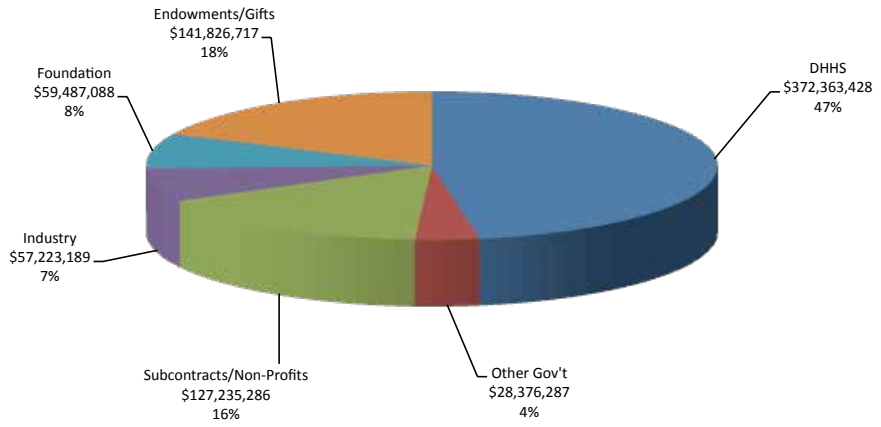

MGH Space Need Based on MTDC Density
Target: $400 MTDC in FY08$
Required Space @5% MTDC Growth (Real Growth = 3%)
Required Space @3% MTDC Growth (Real Growth = 1%)
Required Space @1% MTDC Growth (Real Growth = -1%)
Spike in MTDC Growth due to ARRA
Net Assignable Square Footage
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
FY08A
FY09A
FY10A
FY11A
FY12A
FY13B
FY14P
FY15P
FY16P
FY17P
FY18P
FY19P
FY20P
FY21P
FY22P
FY23P
FY24P
FY25P
Other Leased Space
65 Lansdowne Street
Charles River Plaza South
Charles River Plaza Tower Bldg
50 Staniford Street
Simches Research Bldg
Owned Space
Required Space @1% MTDC Growth
Required Space @3% MTDC Growth
Required Space @5% MTDC Growth


MGH Research Revenue as a Percentage of Total MGH Operating Revenue
FY1992 - FY2013 Actual
30%
25%
20%
15%
10%
5%
0%
23% 24% 24% 24% 23% 23% 23% 24% 24% 23% 24% 25% 26% 25% 24% 23% 23% 24% 25% 25% 24% 24%
1992 1993 1994 1995 1996 1997 1998 1999 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012 2013

MGH Research Management

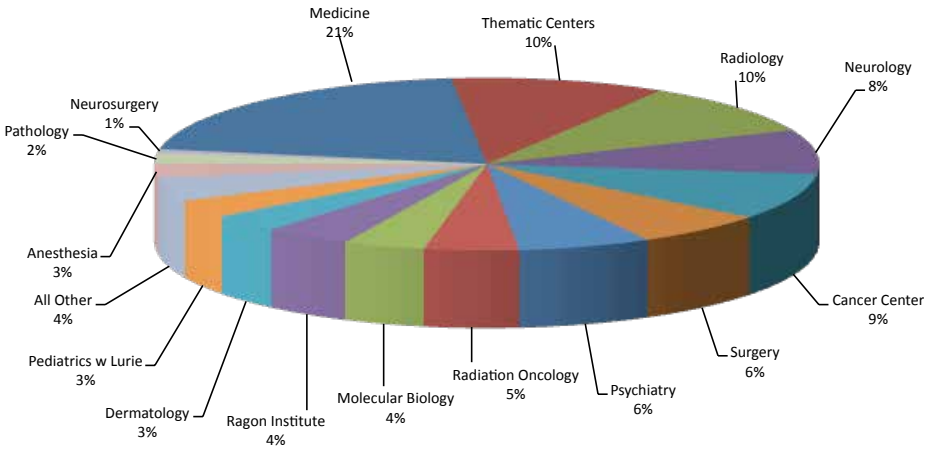
Executive Report for SAC 2013

Massachusetts General Hospital
Total Research Expenditures FY 2013
$786,512,995



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

FY 2013 MGH Research Expenditures
by Department
Direct & Indirect Expenditures $786M



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

MASSACHUSETTS GENERAL HOSPITAL
Science Activity by Sponsor

Type of Activity	Fiscal Year 10/01/12-09/30/13 Direct	Indirect	Total
Federal & State	277,898,710	122,841,005	400,739,715
Non-Federal	316,840,108	68,932,171	385,772,279
Total Expenses FY 13	594,738,818	191,773,177	786,511,995
Analysis of:			
Federal Activity by Sponsor			
DHHS	250,904,317	112,866,591	363,770,909
ARRA	6,815,146	1,777,373	8,592,520
DOD	17,768,504	7,330,864	25,099,369
NASA	180,108	131,852	311,960
NSF	322,031	220,579	542,610
DOE	347,715	27,810	375,525
Other Federal	562,543	263,344	825,887
Total Other Federal Activity	19,180,902	7,974,448	27,155,350
Subtotal Federal	276,900,365	122,618,413	399,518,778
State	998,345	222,592	1,220,937
Total State Activity	998,345	222,592	1,220,937
Total Federal and State	277,898,710	122,841,005	400,739,715
Non-Federal Activity by Sponsor			
Industry	42,926,781	14,296,408	57,223,189
Foundations	54,786,517	4,700,570	59,487,088
Subcontracts/Other Nonprofit	93,993,054	31,689,078	125,682,132
MGH Endowment & Gifts	123,580,602	18,246,114	141,826,717
Total Non-Federal Activity	315,286,954	68,932,171	384,219,125
Total Expenses	593,185,664	191,773,177	784,958,841
Harvard Medical School	1,553,154	-	1,553,154
Grand Total	594,738,818	191,773,177	786,511,995

Executive Report for SAC 2013

MASSACHUSETTS GENERAL HOSPITAL
SUMMARY OF DIRECT AND INDIRECT COST SCIENCE ACTIVITY
FY 1989 - FY 2013
(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
Government Grants & Contracts	$415,951	$415,114	$400,740
Industry	$52,497	$53,864	$57,223
Foundations	$64,620	$56,385	$59,487
HMS Grants & Endowments	$1,258	$919	$1,553
MGH Endowments & Gifts, Subcontracts /Other Nonprofit*	$229,719	$250,024	$267,509
Total Direct & Indirect Costs	**$764,045**	**$776,307**	**$786,512**

**2007 data was restated*
**2008 forward data includes Animal Facility*

MASSACHUSETTS GENERAL HOSPITAL
SUMMARY OF ALL DIRECT COST SCIENCE ACTIVITY
FY 1983 - FY 2013
(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
Government Grants & Contracts	$289,838	$281,588	$277,899
Industry	$40,643	$40,244	$42,927
Foundations	$59,462	$51,670	$54,787
HMS Grants & Endowments	$1,258	$919	$1,553
MGH Endowments & Gifts, Subcontracts /Other Nonprofit*	$182,911	$202,196	$217,574
Total Direct Costs	**$574,112**	**$576,616**	**$594,739**

**2007 MTDC is restated*

**2008 MTDC includes Animal Facility and adjustments*

Overview

Center for Faculty Development

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

The Center for Faculty Development (CFD) facilitates career development for MGH faculty. It 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 within the clinical, research and women faculty and trainees respectively. In addition, a Graduate Student Division is housed within the ORCD branch to address the needs of the graduate student community.

In 2013 the CFD 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, there were ***83 programs and close to 2,801 faculty, fellows and other professional staff in attendance*** at these programs. In addition, ***177 individuals*** (73% of which were faculty, the other 27% were research/clinical fellows, graduate student, residents and other staff) ***visited one of the offices this past year,*** the vast majority was for promotion and career advice. One hundred and forty one of these individuals (77% faculty and 23% staff) were seen by CFD Directors/staff, and the other thirty six individuals came to the office for consults with external consultants relating to difficult conversation scenarios or life coaching.

Mission: To facilitate the career advancement and job satisfaction of MGH faculty. Our strategies are to:

- Develop and implement programs for faculty 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 the promotion process
- Provide counseling, advice and support

The CFD enhances communication and facilitates work-life balance that is critical to improved outcomes and to faculty satisfaction. In doing what we do, we believe that our mission facilitates the retention of faculty and helps fulfill the MGH Mission: "Guided by the needs of our patients and their families, we aim to deliver the very best health care in a safe, compassionate environment; to advance that care through innovative research and education; and, to improve the health and well-being of the diverse communities we serve."

MGH Faculty Council: This group which serves as the CFD advisory board met once this year and provided insight and guidance on: Center for Faculty Development programming efforts, speakers for the Nancy J. Tarbell, MD, Lectureship Series, CFD Office feedback, formation of the Graduate Student Division, John T. Potts, MD Mentoring Award, Caring For Dependent (CFD) Awards and HMS Promotion Data. This year the CFD added additional faculty members to the Council to leverage cross-departmental experiences.

In the past year the CFD has:

- Established the **Caring for Dependents (CFD) Travel Awards**, aimed at facilitating travel to professional conferences for junior faculty (Instructors and Assistant Professors) who have dependent care obligations that might otherwise make travel difficult. Each award provides up to $500 towards additional dependent care during the travel period (e.g. hiring extra coverage of nanny or eldercare assistant, travel costs of bringing a young child to a conference, sitter costs at the conference). In 2013, 30 awards were given to faculty out of the approximately 60 applications submitted.

- Completed the *third* round of the **MGH Faculty Mentoring Program** with Claflin Distinguished Scholar Award winners with 18 mentoring participants. Senior award winners were paired with junior award winners to meet their mentoring objectives. The final session included the completion of a "Constellation of Support" exercise to help mentees enhance their mentoring network.
- Continued to work on the **Annual Career Conference (ACC) Initiative**, which helps to standardize expectations for these conferences across all hospital departments for both clinical and research faculty:
    - The CFD worked on the reporting and the quantity of ACCs, and with individual departments over the course of the year to enhance their ACC process and began to understand the quality of the Annual Career Conference discussion.).
    - Continued delivering ACC "Difficult Conversations" training program for faculty who are responsible for giving ACC's as well as other senior leaders. This year the classroom session was held on 3/13/13 with ~11 faculty members in attendance and individual follow up sessions were offered to faculty who attended the classroom session. Seven faculty members took advantage of the individual sessions and very positive feedback was received.
- This year the CFD continued to offer individual coaching sessions for faculty with Allison Rimm on a wide range of topics including personal and career advice as well as work-life balance. Sixteen faculty members who attended previous leadership sessions, attended these coaching sessions.
- Continued facilitation of the **John T. Potts, MD Faculty Mentoring Award** to celebrate good mentorship and help build a "culture of mentoring." Maurizio Fava, MD, Executive Vice Chair, Department of Psychiatry was named the 2012 award recipient and a celebration luncheon was held on 4/10/13. This luncheon was attended by John T. Potts, MD, senior hospital leadership as well as those mentees who nominated Dr. Fava. This year, **Isaac Schiff, MD** was named the 2013 winner and a celebration luncheon will be held in early 2014.
- Hosted the third annual **New Faculty Orientation** program on 10/9/13 designed to provide an overview of the MGH environment and faculty resources focusing on several key areas: MGH and MGPO Overview, Research Overview, Teaching/Education Overview, Introduction to HMS environment and the promotion process and Center for Faculty Development Overview. A sampling of session speakers included: Peter Slavin, MD, Gregory Pauly, Harry Orf, PhD, Anne Klibanski, MD and Maureen Connelly, MD to name a few. There were approximately 52 new faculty in attendance. This year breakout sessions were held to target the research versus clinician teacher audiences.
- Hosted a variety of programs and workshops to help faculty at all stages in their careers:
    - **Academic Career Development:** Sessions were held on 6/3/13, 6/5/13 and 6/10/13, to increase awareness of HMS Promotion Criteria and Areas of Excellence with more than 50 faculty members in attendance. Panels of faculty represented the HMS, Department Chairs and newly promoted faculty members' perspectives. In conjunction with HMS and ORCD, a program on HMS Foundation Funds was held on 3/7/13 for MGH faculty to hear about funding opportunities as well as the grant and funding application process, with approximately 40 attendees. A HMS CV seminar was held on 2/28/13 with approximately 35 faculty members in attendance.

- **Faculty Development Series:** Multiple sessions were held over the course of the year with more than 180 attendees. E.g. Conflict Management at Work (1/30/13), Nancy J. Tarbell, MD, Faculty Development Lectureship Series (5/1/13), Negotiation Essentials (4/9/13), Power of Presentation (1/10/13 and 10/24/13) and Making the Most of Your MGH/ MGPO Benefits (11/14/13)
- Co-sponsored with CFD Offices: A negotiation series seminar "Speaking Up" on 9/26/13 was held in conjunction with the Office for Women's Careers.

- **Outreach efforts** included meetings with new department chairs in Radiology (5/29/13) and Medicine (5/6/13) , continued professional development opportunities with Orthopedic Surgery (in developing a faculty development needs assessment survey and HMS New Faculty Orientation (10/28/13 and 11/14/13).
- Co-chaired with HMS and collaborated with Consortium of Harvard Affiliated Faculty Development and Diversity Offices (CHADD) to host: **"Strategies to Strengthen Your Mentoring Relationship"** a faculty development course for mentors that drew approximately 75 participants from across Harvard hospitals. Herbert Lin, MD, PhD, FASN from MGH facilitated a break out session on the "Best Practices to Jump Start a Successful Mentoring Relationship" at this event held 11/22/13.
- Actively participated on HMS Joint Committee on Status of Women Task Force, Multicultural Affairs Office Advisory Board, and MGH Leadership Academy Curriculum Committee.
- To continue to maximize the available infrastructure, the CFD and its associated offices continued our collaborative efforts with many groups (e.g., Multicultural Affairs Office, Consortium of Harvard Affiliated Offices for Faculty Development and Diversity, Harvard Medical School, MGPO, MGH Leadership Academy, Human Resources, Office of the General Counsel, Partners Research Office).

Future Activities:

- Continue to utilize the CFD infrastructure to best allocate all resources and maximize efficiencies.
- Continue to 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 the ACC initiative by examining the "quality" of the Annual Career Conference experience.
- Continue to offer the faculty mentoring program/trainings to enhance the culture of mentoring here at MGH. .

Office for Research Career Development (ORCD)

Center for Faculty Development

Dennis Brown, PhD, Director

As one of the original offices of the CFD, the ORCD has served the career advancement needs of the MGH research community since December 2005. Originally designed and introduced to serve the hospital's approximately 800 Faculty Investigators, the office also supports the large community of MGH Research Fellows (approximately 1000) including administering the MGH Guidelines for Research Fellows and advising the Mass General Postdoctoral Association (MGPA). In 2013, we continued to offer individual career counseling, to organize seminars designed to help all MGH researchers build professional and leadership skills, to provide networking opportunities, and to advocate on behalf of the research community.

In 2013 the ORCD continued to expand efforts to educate junior faculty and research fellows about career options, and continued to offer a six-part seminar series on the Responsible Conduct of Research (RCR) now in its third year, as part of the Partners institutional RCR education for NIH-funded trainees. The *New Investigator Advancement Initiative*, launched in October 2012, finished a very successful inaugural year, and enrolled another group of new investigators in the fall of 2013.

Mission: The ORCD addresses specific needs of the MGH research faculty and fellows that are identified by continual discussions with the research community, by the MGH Scientific Advisory Committee, and by the Executive Committee on Research (ECOR). While the general mission is enduring, the ORCD welcomes suggestions from all researchers that will enhance the specifics of the mission, and especially ideas that will further the careers of those in the MGH research community.

ORCD Advisory Council: Comprised of senior hospital administrators and faculty, the council provides advice and guidance to the ORCD in relation to career advancement issues for the research community. In 2013, the council was reconstituted, met once and provided guidance on: ORCD programming for faculty and trainees, how the ORCD can help researchers during the current funding climate (form strategies to increase our number of K awardees, help researchers identify funding beyond NIH), mentoring in the MGH research community, and expanding the ORCD's advocacy for investigators' career advancement (e.g. clarifying the promotion process across departments, and clarifying the role of Instructor).

In the past year, the ORCD has:

- Continued the **New Investigator Advancement Initiative (NIAI)** for MGH faculty who currently hold their first NIH R-level grant. The inaugural year of the NIAI concluded in June 2013 and another group of new investigators began the series in October 2013.The NIAI is designed to provide a forum for new PIs in which they can gain information to help them succeed as funded researchers, meet MGH research leadership, and develop a cohesive and supportive peer group to maximize their chances of success. Each investigator who enrolls commits to attend NIAI meetings throughout the year. The 2012-2013 group met three times in 2013 to discuss: Mentoring—For Yourself and Your Mentees (1/24/13), Developing Your Future Research and Career Goals (3/28/13) and Setting Expectations in the Lab (6/20/13). At their request, they also met in September for a "reunion" check-in meeting to discuss their career progress and challenges. The 2013-2014 NIAI is comprised of a core group of 17 new PIs. So far this group has met two times in 2013 to discuss: the MGH Research Landscape (10/8/13), Developing Yourself as a Mentor (11/12/13, and Introduction to ECOR and How to Get Involved to Get Promoted (12/4/13). Three additional meetings are planned for 2014.
- Conducted 41 individual advising meetings with members of the research community, including 20 faculty and 21 fellows/other research staff. We expect the current funding climate to bring in more faculty over time to reach out for career advice/career transitions.
- Sponsored the 7th annual **Research Fellows Poster Celebration**, an event to recognize the excellent research being done by our postdoctoral fellows with two lectures as part of the celebration: the Trends in Biomedical Science Lecture given by Emery Brown, MD, PhD,

Warren M. Zapol Professor of Anesthesia at HMS and the Research Career Development Lecture was given by Cynthia Fuhrman, PhD, Assistant Dean, University of Massachusetts Medical School. Eighty four research fellows submitted abstracts and presented posters, and a review committee chose the top twelve posters that received special recognition. A luncheon following the awards ceremony allowed the winning postdocs an opportunity to network with MGH leaders.

- Continued the **Career Advancement Series**, to help faculty and extend their academic career success. Programs included: Achieving Independence from Your Mentor (9/11/13), a 2-part series Modern Marketing for Scientists (10/30/13) and Papers, Proposals and Presentations (10/31/13) Approximately 114 researchers were in attendance.
- Increased the frequency of offerings in our **Responsible Conduct of Research Series** to assist NIH-funded trainees in the mandated RCR education requirements. In 2013 the ORCD offer seven credits of RCR training including: Responsible Authorship: Ethics and Guidelines (1/17/13), Peer Review: Guidelines and Practice (2/14/13), Mentoring: Responsibilities of Mentors and Mentees (4/3/13), The Lab: Avoiding Research Misconduct (6/13/13), Data Management and Data Integrity (7/15/13), Collaborative Science 9/24/13, and Peer Review of Journal Manuscripts (12/12/13) with approximately 325 researchers in attendance. The Peer Review session earned 2 hours of RCR credit due to pre-session work required of participants.
- Continued to offer seminars to enhance researchers' **Communications Skills**, including Applying for an NIH K Award (2/26/13), by Tracy Rankin, PhD (NIH), Iain Drummond, PhD, Ralph Weissleder, MD, PhD, and Dennis Brown, PhD, with approximately 35 researchers in attendance. Continued to sponsor and administer English as a Second Language classes for the research community, with a total of 174 students enrolled across the spring and fall sessions of 2013. Specifically geared towards scientists, the classes include training on written and oral presentations, as well as everyday conversations in the lab, for non-native speakers of English.
- Continued the popular **Grant Writing Workshop** (4/30/13) to help guide trainees and junior faculty to funding success. Approximately 80 researchers attended this session.
- Further expanded the **Industry Exploration Program (IEP)**: In collaboration with the Mass BioEd Foundation and our partner institutions (Brigham and Women's Hospital, Dana Farber Cancer Institute, and Boston University Medical School), we guided an expansion of the format of company visits, to accommodate additional postdocs per visit. The IEP is now in its fourth year of educating research fellows about career options in industry by facilitating group visits to local biotech companies.
- Advised the **Massachusetts General Postdoc Association (MGPA)**: The MGPA plays a key role in giving postdocs opportunities to make connections outside their laboratories, and provides excellent leadership opportunities to its most active members. The MGPA is led by an elected and/or appointed executive board and a planning committee that meets monthly to develop programs and priorities. In 2013, the MGPA helped to expand the Industry Exploration Program (IEP, see below), and ran programs on career advancement, (MGPA Annual Membership Meeting, 1/31/13; International MDs in the US: Building a Clinical and Research Career, 3/18/13, Self-Sponsored Green Card Information Session, 6/11/13, Panel Career Discussion and Vendor Fair, 7/18/13, and Academic Job Interviews Panel, 12/10/13), and networking (Networking and Recruitment BBQ for Postdocs, 5/28/13 and five Pub Nights, 3/29/13, 4/25/13, 6/14/13, 7/19/13, 8/30/13). Approximately 580 post docs attended these programs.
- Assisted the MGPA in the administration of the second year of the **MGPA Travel Award Program**. The awards are designed to defray travel cost to a scientific meeting and to encourage increased participation in the MGPA, by requiring each applicant to propose and lead a career development program. In 2013, five research fellows were selected for the $1000 awards, and three of these later achieved leadership positions in the MGPA In December 2013 the MGPA submitted an abstract to the National Postdoc Association annual

meeting (St. Louis, April 2014) describing the success of the awards program.

- Worked with hospital leadership and senior faculty on the Postdoc Salary Workgroup to institute a new policy on minimum salary requirements for MGH research fellows that became effective October 1, 2013.
- Celebrated **National Postdoc Appreciation Week** with an Ice Cream Social networking event for research fellows on 9/17/13 to acknowledge their contributions to the research community. Approximately 80 research fellows attended this event.
- Continued the **Orientation Program** for Research Fellows, now in its fifth year. This program assisted approximately 70 new postdocs during 2013 with small group lunch meetings aimed at communicating information on MGH resources and an introduction to ORCD staff and MGPA postdoc volunteers, on 2/13/13, 4/29/13, 7/9/13, 8/13/13, 9/27/13, 10/25/13, and 12/20/13.
- Modified the **Appointment Extension** process for research fellows who reach the 5-year term limit by requesting departments to provide additional information on the recent career plan. Fifty eight extensions were granted this year.
- Collaborated with several HMS, MGH and Partners offices to enhance initiatives for the research community, and assistance for individual cases. These offices include, MGH Human Resources and Partners Employee Relations, the Partners Employee Assistance Program, MGH Office of the General Counsel, and HMS Faculty Affairs.

Future Activities:

- Continue to 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.
- Re-engage the ORCD Committee by inviting a new group of junior research faculty members to advise the ORCD on the needs of junior faculty and provide guidance on future programming efforts.
- Create a comprehensive list of resources to help research faculty get involved with the MGH community beyond their laboratories (e.g. opportunities for committee involvement, teaching, and ECOR/Research Council participation).
- Co-lead the further growth of the Industry Exploration Program by working with member institutions to create a steering committee of postdoc volunteers. This will give leadership experience to postdocs and include them in the recruitment of biotech companies for future IEP visits.
- Contribute to efforts to assist researchers in transition due to loss of funding of the laboratory.
    - Support and advocate for the use of the non-faculty track Research Scientist position in order to retain highly trained individuals within our research community and increase awareness of/programs for alternative career opportunities (e.g., industry, scientific publishing, college teaching, lab management or administration)
- Continue programming for research trainees, in particular career exploration programs, and seminars to prepare them for future success in the changing research environment.
- Update the Guidelines for Research Fellows based on feedback from administrators, constituents, and the Postdoc Salary Workgroup.
- Continue to clarify and improve the process for granting extensions on the 5-year term limit on the research fellow position, for example by reviewing the CVs of postdocs requesting extensions beyond 6 years, and requiring a discussion between the ORCD director and PI in these cases.
- Continue collaborations with relevant offices and committees at MGH and Harvard, including Human Resources, Research Management, Executive Committee on Research (ECOR), HMS Faculty Affairs, and the Postdoctoral Office Consortium (PDOC) representing offices at HMS and hospital affiliates.

Graduate Student Division (GSD)

Center for Faculty Development

Thilo Deckersbach, PhD, Director

The Graduate Student Division (GSD), supported and funded by the Executive Committee on Research was created December 1, 2012. The GSD was designed and intended to serve the practical needs of graduate students from all academic institutions that are associated with clinical research faculty at MGH and foster a graduate student community at MGH. The goals of the Graduate Student Division are to 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 and establish relationships with area graduate schools.

Mission: The GSD addresses specific needs and career advancement of the graduate students at MGH. Graduate Student Division at MGH mission is to provide programs, services and resources, create a sense of community, help graduate students to grow professionally, and enhance the overall experience of the graduate students at MGH. The GSD hopes to extend its mission, by establishing relationships with the various graduate schools, attracting more graduate students at MGH, and by creating a welcoming community among the Principal investigators.

GSD Council: The GSD Advisory Council is comprised of senior faculty members and hospital leadership who meet twice a year to provide oversight and review GSD priorities and activities. GSD Council currently has thirteen GSD Council members. The GSD Council members provide advice and guidance to the GSD in relation to address the needs and participate in the planning phase for the programs for the graduate students. In 2013, GSD Council met once in July and discussed the student recruitment, potential involvement of undergraduate students and future GSD programs ideas.

GSD Committee: The GSD Committee is comprised of graduate students who meet four times a year to help identify graduate student needs as well as to design and implement activities. The GSD Committee was assembled in the summer 2013; it includes 11 members who met twice in 2013 and discussed Town Hall Feedback, assisted with BBQ planning, the GSD Graduate Student Celebration Day and provided input into educational session topics. The goal is for this group of graduate students to help other graduate students connect with their peers based on school, lab, location and more.

In the past year, the GSD has:

- Identified the current MGH graduate student constituency by reaching out to all known MGH Departments' Research Administrators and Principal Investigators to provide information on existing graduate students in the department/lab.
- Sent the registration survey to all identified graduate students and collected information including but not limited to student demographic information, school name, program type, program name, how many years in the program, name of the school advisor, what is the final degree, when is expected end date, purpose of joining MGH, etc.
- Collaborated with MGH Human Resources to create a monthly graduate student registration database update process.
- Identified current MGH Graduate Student demographics as of 11/01/2013 by school (Table 1) and location (Table 2).
- Conducted a series of **Town Hall Meetings**: Charlestown Navy Yard (04/12/2013), SIMCHES Research Center (05/23/2013) and MGH Main Campus (06/20/2013) to help identify areas of interest and needs of graduate students
- Provided seven one-on-one individual advising meetings with graduate students. We expect more graduate students to reach out for the advice as the GSD increases exposure among the graduate student community.
- Implemented and installed Taxi Voucher Program scanners at CNY and HMS locations, to enhance monitoring and documentation of Taxi Voucher usage during the year.

Table 1

SCHOOL/UNIVERSITY	NUMBER OF STUDENTS
Boston University	18
Harvard-MIT HST	4
HMS	42
Harvard University	63
International Schools	44
MIT	21
Other US Schools	21
Tufts University	4
UMASS	6
TOTAL STUDENTS	**225**

Table 2

LAB LOCATION	NUMBER OF STUDENTS
Broad Institute, 7 Cambridge Ctr	3
CNY Buildings	61
MGH Main campus	59
Not Specified	5
One Bowdoin Square	5
Other Location	3
Partners Research Building, 65 Landsdowne Street	6
Ragon Institute, 400 Technology Square	15
Richard B. Simches Research Building	62
Staniford Street	6
TOTAL STUDENTS	**225**

- Introduced the GSD Graduate Student 1st annual **BBQ** (08/01/2013), a networking event to help graduate students to get to know each other and establish relationships. Approximately 30 people attended the event.
- Established the **Career Advancement Series** for graduate students. First year programs included: Looking Your Best on Paper: Building a CV or Resume (10/16/13), Career Search Strategy: How to Identify Opportunities and Best Practices for Your Job Search (12/05/13). Approximately 60 graduate students attended these seminars.
- Sponsored the **MGH Graduate Student Community Celebration** (12/05/2013), an event to recognize the importance of graduate students to the MGH Research, and their achievements. Introductory remarks were given by Thilo Deckersbach, PhD followed by remarks from MGH Senior Vice President, Harry Orf, PhD. The event featured keynote speaker Lauren Celano, MBA, Founder and CEO, Propel Careers. Approximately thirty students attended the event. The program included luncheon, special celebration cake and prizes.
- Published the first edition of **"GSD Connect"**, a communication vehicle to highlight graduate student's research interests and a directory of students by location and school.
- Created MGH Graduate Student **Facebook group** and started the graduate student "Social Nights" for graduate students. The first **"Social Night"** was held 10/28/2013 with great response from the students.
- Created monthly GSD email to enhance communication of events and information to the graduate student community.

Future Activities:

- Continue to provide programs for MGH graduate students.
  - o Upcoming programs in the **Career Advancement Series** include: "How to get a pre-doc NRSA" seminar (2/14), "How to apply for a job" (3/13/14) and "Interviewing Skills" (5/7/14).
  - o Upcoming program in the **Communication Series** includes: "How to give a talk" (1/23/14.)
- Continue to work with the GSD committee to coordinate networking and exposure to industry.
- Establish communication and enhanced 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 and working with graduate programs.
- Develop collaborations with relevant offices and committees at MGH, Harvard and graduate schools.
- Develop content for GSD website and begin to create a list of resources to help graduate students.

Office for Clinical Careers (OCC)

Center for Faculty Development

Theodore A. Stern, MD, Director

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.

The **OCC Council** met twice this year and discussed: strategies to reach our target audience; data on academic promotion (by rank and by area of excellence); obstacles to promotion and ways to raise awareness; new programs on Clinician Teacher Skill Development; and Committee work accomplished.

The **OCC Committee** met twice this year and discussed: fostering a clinician educator community; creating an online repository of information for clinician educators; debunking myths around academic promotions, writing (e.g., scholarly works; facilitating Annual Career Conferences; highlighting clinical role models; and teaching resources.

In the past year, the OCC has:

- Developed a **"Clinician Teaching Skills Development Series"** in response to constituent feedback. This series covered areas important to teachers: "Enhancing Teaching Skills Surrounding Case Presentations and the Delivery of Feedback (2/6/13)", and "Improving Your Presentation Skills" (4/24/13). These sessions had approximately 30 faculty in attendance.
- Initiated a Longer Service Criteria awareness campaign to identify and communicate with eligible faculty and leadership to enhance the discussion around clinical faculty promotions.
- **Provided programs:**
    - **Career Advancement Series**: "Drafting Your Chief's Letter" (3/6/13 and 10/23/13), "MGH Promotions Process Demystified (5/7/13), Crafting Your CV Narrative (8/1/13) and Can I/ Should I Be Promoted?...Consider the Possibilities for Clinical Faculty (12/11/13) with approximately 100 faculty members in attendance.
    - **Professional Development**: Scholarly Writing Seminar (7/10/13), Academic Skills Training (7/24/13) and Improving Case Presentation through Effective Feedback (11/7/13) had approximately 30 attendees.
- Co sponsored several academic career advancement programs with the CFD programs throughout the year.
- Participated as a member of Executive Committee on Teaching and Education (ECOTE), to bridge the educational mission of the OCC and ECOTE, and contributed to the reorganization and change to overall purpose of the committee.
- Provided individual career ***advice and counseling***: This year, approximately ***85 faculty members*** visited the office. These visits covered the promotions process and readiness, career advancement, and CV critique.
- The OCC participated in an Allergy/Immunology department outreach meeting this year. In this meeting on 9/30/13, the HMS Promotion process was discussed with division faculty to enhance their knowledge. Approximately 15 faculty were in attendance.

Future Activities: the OCC looks forward to further implementation of ideas generated by its advisors and committee members:

- Continuing to educate senior leaders, promotions' committees, and faculty about academic career advancement
- Helping with job satisfaction in a broad-based fashion
- Building skills (including learning through observing and being observed, improving patient care and expertise as educators)
- Enhancing the community of clinician educators by assistance with building collaborations
- Providing recognition and rewards (e.g., clinician promotion luncheon.)
- Continuing to meet with individual faculty members and with departments to heighten awareness of OCC within the hospital community.

Office for Women's Careers (OWC)

Center for Faculty Development

Nancy Rigotti, MD, Director

The Office for Women's Careers (OWC) at MGH is a branch of the Center for Faculty Development (CFD) and was created to foster a gender equitable environment to assure that women and men faculty will be given the same opportunity to succeed in research and clinical careers at MGH. Through many programs and collaborations, the OWC provides career development resources for women and endeavors to build a sense of community among women faculty across the institution. The office focuses on reducing barriers to career advancement and meets with women faculty to advise them. 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.

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

The **OWC Council** is comprised of administrative and faculty leaders who review OWC programs and provide feedback on advocacy issues and other initiatives related to supporting MGH women faculty. They met twice this year to discuss promotion data for female faculty, advocacy issues for faculty who are new mothers; fundraising ideas, and to provide feedback on programmatic planning.

The **OWC Committee**, comprised of early- and mid-career women faculty, is enlisted to share the viewpoint of women faculty at the career stages most likely to benefit from our programs. They met two times in 2013, and shared feedback and ideas on the OWC's programs and initiatives, including suggesting topics and speakers for panel discussions, and offering ideas for improving programs such as the new Leadership Workshop for Women Faculty, the Claflin Consultation Initiative, and the creation of the new Women's Faculty Forum, and online resource.

In the past year, the OWC has:

- Created the OWC Women's **Faculty Forum**, MGH women faculty can share their experiences as women in academic medicine in essay format. The inaugural section of the Forum, MGH Dr. Mom, launched in July 2013, and essays published on the forum included: "Managing Child Related Sleep Deprivation", "Making it Better: A Faculty Mom's Ongoing Pursuit of Balance" and "Managing Call."
- Continued two popular program initiatives that began in 2011 to support faculty who are parents: The **Managing Parenthood and Your Career Series** continued to offer panel discussions with MGH faculty who shared their experiences on balancing a successful career with parenting (4/11/13, 11/21/13), and the Faculty Parents Group offered advice from child development experts in a small supportive group setting (2/15/13, 5/16/13, 10/3/13). There were 72 attendees at these sessions.
- Continued the successful annual workshop on **Leadership Strategies for Women Faculty** (5/9/13). The 2013 workshop, "Maximize Your Leadership Style: Know It, Grow It, and Use It!," featured Elizabeth Mort, MD as a special guest speaker. Twenty women faculty attended, and gained experiential lessons on how to influence without authority, and communicate within different power structures.

- Continued the **"Meet and Greet"** series of **networking breakfast events**, each featuring a prominent woman who is a leader in academic medicine, including Nancy J. Tarbell, MD (3/5/13), and Karen Carlson, MD (10/22/13) with approximately 34 faculty in attendance.
- Hosted a panel discussion to inform women faculty and trainees about the patent/IP process and encourage more women to consider this path for their research programs. The event, "Women Inventors Speak: How to Turn Your Ideas Into Patents" (3/29/13) was developed as a result of the OWC's discovery that only 10% of MGH patents disclosures come from women inventors.
- Hosted a full-day Business of Life seminar for women faculty with facilitator Allison Rimm on 7/31/13. Designed to help individuals create a strategic plan for their work and personal lives, this program has received extremely positive feedback from faculty in past sessions. Attendees at the 2013 session were also able to take advantage of one hour of personal coaching by Ms. Rimm. Sixteen faculty members participated in the individual consultation offering.
- Continued collaborations with ECOR on the **Claflin Distinguished Scholar Awards**, which continue to be awarded to six outstanding junior women faculty members per year. These awards are meant to provide bridge funding to help faculty sustain research productivity during their child-rearing years. Stipends of $50,000/year for the two years of the award are intended to be transitional funding for each recipient to help increase their ability to obtain significant additional government funding in the future. To celebrate the awards and current and former recipients, the annual Claflin Luncheon was held on 6/12/13 with 42 in attendance.
- Continued two successful programs to assist women faculty who are planning to apply for the Claflin Awards. The **Claflin Consultation Initiative**, which paired Claflin Award alumnae with new applicants, provided advice and mentoring during the application process. There were 15 initial applicants and 11 of these applicants were matched with alumnae in 2013, and two of the applicants won a Claflin award. In addition, we hosted a panel discussion (1/23/13) in which two recent Claflin awardees communicated advice and encouragement to potential applicants.
- Provided **individual advice and counseling** to women faculty. In 2013, approximately 16 women (15 faculty and 1 post doc) have visited the office to discuss career advice, the promotion process and/or specific conflicts.
- Celebrated **Women in Medicine month** with a special lecture by Luanne Thorndyke, MD, FACP, Vice Provost for Faculty Affairs and Professor of Medicine, University of Massachusetts Medical School, titled "The View from Above the Glass Ceiling". There were approximately 60 faculty members in attendance at this event.
- Published the twelfth annual **Tribute Book** to celebrate the accomplishments of MGH women faculty.
- Concluded a study of gender and HMS faculty promotions. Assisted by MGH administrative fellow Calvin Richardson, differences in time to promotion at different ranks for women versus men, as well as interactions between gender, professional degree, year of hire and department were reviewed. Follow-up data analyses were presented to the OWC Council and Committee in 2013 The main finding of this analysis was that the time to promotion from Instructor to Assistant Professor was significantly longer for female vs. male faculty, and that this significance was primarily carried by PhD's. The OWC is exploring ways to target our programming to women Instructors, including increasing mentoring opportunities for them and providing them with more professional involvement and leadership opportunities.
- Continued our advocacy efforts to create additional **lactation room space** to support women faculty and trainees to continue nursing their infants after maternity leave, in collaboration with HR and the Employee Assistance Program. In 2013, two new lactation spaces were created/upgraded (Bigelow 9 and 12) and support was garnered to identify future space in

the Yawkey and Lunder buildings. This effort was recognized with a Partners in Excellence Award this year.

- Continued participation on the Joint Commission on the Status of Women (JCSW)—an HMS committee formed to facilitate the development and contribution of women on Harvard campuses by expanding and improving the opportunities for the advancement of women. Donna Lawton, MS, Executive Director, Center for Faculty Development continued in her role as Dean's Representative to the JCSW Steering Committee which brings the voice of the hospital affiliates to the discussions.

Future Activities:

- Continue and expand professional development programs and workshops that meet the needs of women faculty, addressing in particular the challenges of career and parenting, and leadership issues for women. Based on feedback from the OWC Committee, we will increase programs and advocacy for women faculty who are not parents, including leadership training and networking events. Based on the promotion data analysis, we will target programs to women Instructors.
- Collaborate with Partners Research Ventures and Licensing to monitor ongoing gender differences in patent disclosures at MGH and develop programs, and develop additional programs to increase the participation of women faculty in patents and licensing related to their research.
- Continue to advocate for women faculty—especially women seeking flexibility in the work environment.
- Continue and expand the Claflin Consultation Initiative.
- Collaborate with the Mass General Postdoc Association to develop programs for women research fellows who represent a key pipeline of future investigators.
- Continue collaborations with MGH Multicultural Affairs Office, Department of Medicine Women in Medicine Committee and the Consortium of Harvard Affiliated Development and Diversity Offices (CHADD).
- Continue our successful Leadership Workshop for women faculty which will cover topics relevant to women faculty interested in leadership growth.
- Continue to 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.

CONTENTS

Director's Overview of the 2013 Progress Report of the Clinical Research Program (CRP)

William F. Crowley, Jr., MD
Director of Clinical Research, MGH

Founded in 1996, the CRP is now entering its 18th year and this is my final report as its Director. Thus, it is of interest to take a somewhat longer look backwards than just the past year at the institutional changes that have occurred because of this important institutional investment.

A. Background

MGH created the Clinical Research Program in response to formal reviews in 1992–94 by the hospital's Scientific Advisory Committee (SAC). During these three years, the SAC reviewed the status of PhDs, MD/PhDs, and finally Clinical Investigators. The PhD and MD/PhD presentations received positive reviews. However, the final presentation of this trio in 1994 reviewed the status of clinical investigation at the MGH and found it to be clearly problematic. The difficulties encountered reflected a relatively severe imbalance in the institutional investments for basic vs. clinical research that had been in place for some time. This negative review initiated a dialogue between SAC and MGH leadership relating to the ongoing under investment in clinical research infrastructure during the 1995 meeting. These circumstances changed abruptly when Sam Thier assumed MGH leadership in 1995. Formerly a member of SAC that had raised these issues in the first place, Sam moved decisively to establish an important investment in clinical research and the Clinical Research Program represented the embodiment of this commitment. He solicited the support of the MGH Trustees in the form of a commitment of $1.5M year for 5 years. In 2000, Sam's successor Jim Mongan expanded the CRP's funding to its present level of $2-2.8M annually.

The initial Institutional environment into which the CRP was launched was not a supportive one. The previous decades of heavy emphasis on and continued investments in basic research had been accompanied by considerable expansion for its infrastructure, it allocation of space, and its role in scientific leadership. Many viewed even a mild rebalancing of the MGH's research investments towards clinical research with skepticism. These skeptics feared that such investments would somehow detract from the centrality of the institutional commitment to basic research. Thus, initially the CRP's establishment faced moderate opposition by the leadership of the Executive Committee on Research (ECOR) and Research Administration.

B. Goals of the CRP

Since its inception, the CRP has had a simple and constant Mission Statement: ***To increase the quality, quantity, and efficiency of translating basic science advances into improved care for our patients.***

To accomplish this goal, it has pursued two broad strategies:

1) to assist Service Chiefs and Center Directors in recruiting and retaining our most talented physician-scientists and basic investigators to pursue careers in patient oriented research; and
2) to provide them with a nurturing institutional infrastructure to support their career growth, development, and retention.

C. Intramural vs. Extramural Activities of the CRP and its Director

Simultaneous with establishment of the CRP locally at the MGH, the Institute of Medicine (IOM) was also examining the national landscape of clinical research. In particular, they were focusing on the institutional obstacles and "translational blocks" that needed to be overcome to facilitate clinical research within Academic Medical Centers. Two important JAMA articles, contributed to significantly by the CRP Director, were published that helped redefine the conceptual framing, organizational

landscape, and vocabulary of clinical research at the national level. These considerations not only dovetailed with and fundamentally validated the MGH's Strategic Plan for Clinical Research; they also had a marked impact upon these problems nationally and legislatively. Coincident with these activities, the CRP Director established The Clinical Research Forum, an organization that evolved to become a national consortium of >60 Academic Health Centers focusing upon building their clinical research infrastructures. Thus, early on, the CRP established a strong synergy between its intramural programs and the changing extramural environment at the national level. This concurrence was not only useful in driving change institutionally but it was also quite helpful in both re-enforcing and validating the CRP's strategic efforts by these national perspectives. In retrospect, these synergies of the CRP's efforts proved to be quite critical to its ability to drive change intramurally in the face of considerable opposition.

D. The Intramural Program

The Clinical Research Program chose a divisional organizational structure with 7 specific Units: Information Technology, Education, Clinical Research Support, Clinical Effectiveness Research (formerly Disease Management), Biostatistics, Translational Medicine, and Genetics and Genomics (see attached reports). While the CRP initially established these first five units, new opportunities soon presented themselves and the complexity of our environment increased. It soon became clear that the addition of Translational Medicine and Genetics & Genomics Units was essential to our institution's future, especially if we hoped to refocus the original mission of the Disease Management Unit to a broader Clinical Effectiveness Research mandate. This new focus would be important to anticipate the upcoming Accountable Care Act's establishment of a Patient Centric Outcomes Research Institute (PCORI) that would represent a unique opportunity for the MGH to build its own clinical effectiveness infrastructure.

E. Subsequent Impacts upon the MGH

a. Education

As you can see from the attached annual progress reports, one of the greatest successes of the Clinical Research Program has been its broad/based institutional impact upon the education of clinical investigators. For example, in this past year, over 5,600 participants attended 244 individual lectures on clinical research given by our faculty. In addition, this number has continued to grow with each year of the CRP. Perhaps most impressive is that while the CRP has been putting these lectures online in the past 2 years, 5,000 additional participants viewed these lectures at their own convenience last year.

The result of these greater than 11,000 educational experiences in 2013 has been a marked enhancement of knowledge of clinical research across the entire institution. These rewards of the CRP's educational infrastructure should continue far into the future and represent an outstanding return on investment for the institution.

b. Finances

There has also been a striking growth in the quantity of clinical research at the MGH since the establishment of the CRP in contrast to relatively flat growth during 1994–6. Due to IT limitations of the MGH's databases overseeing research and its financial management, it is still not possible (now 18 years into this experience) to quantify accurately our institutional revenues directly attributable to clinical research. However, two pieces of data are relevant. The first occurred when the CRP attempted to quantify MGH human research revenues using new methods it established and validated (*Academic Medicine* (Taylor, et al.)). These studies revealed that 28% of the MGH's annual research revenues came from human research studies. This figure came as quite a surprise since the MGH's previous accounting had estimated this figure at only ~6%, largely based on its industrial trials. Secondly, using those industry-sponsored trials as the only surrogate we can readily access due to their lower indirect cost rate of 26% (vs. NIH of 77%), total direct costs from industry trials have increased from $5M in 1996 to >$33M recently and annual **indirect** costs have grown from

~$1.4M/yr to well over $7M annually. However, we should not view an increase in industrial trials as a primary goal of the CRP. Rather, it is merely a trailing (and only partial) indicator of success of clinical research that we can easily track as a surrogate marker of clinical research because of our continued inability to track NIH funding from human research studies where we believe the larger and more strategically important gains to our institution's future really lie. Most Importantly, when one looks at these ***new*** indirect cost revenues generated by industrial trials that have become available to the MGH since the 90's to the present, their net increase is more than the twice the actual budget of the Clinical Research Program. This marker thus shows that clinical research has now become a net revenue generator in the complex mix of money to research affairs.

c. Formation of a Community of Clinical Researchers

The establishment of a defined community of clinical researchers at the MGH has been one of the major cultural changes that the CRP has overseen. By the mid 90's, clinical investigators at the MGH mostly worked in virtual silos deep within their own Departments or Centers. Now, concerted efforts by the CRP have created there is a discernible and robust clinical research community at the MGH. Perhaps the most important was the institution of an **Annual MGH Clinical Research Day**, an intuitional celebration of clinical investigators and their work. The 2013 Clinical Research Day drew more than **263** abstracts! The second important element in forming a sense of community was the creation of a **Clinical Research Council** as a standing sub-committee of ECOR populated by clinical investigators from each Department or Center. This sub-Committee now provides ECOR with continued, broad-based input into the policies and structure of clinical research going forward. Finally, initiating **Annual Clinical Research Awards**, presented on Clinical Research Day and making sure that the Martin prizes included awards for clinical research have all introduced positive feedback for both clinical researcher and their teams and provided positive role models for young investigators. Collectively, these programs have synergized to a striking improvement in the awareness of the importance of clinical research to the MGH's future and a culture of pride in participating in its activities.

Another critical mandate of the CRP was the establishment of an **"Administrative Service Model"**. Rather than envisioning itself as a regulatory body like most other components of Research Administration, the CRP chose to view itself as an infrastructure to facilitate the work of clinical investigators and provide them with a service infrastructure to help accomplish their work. The current CRP website shows that all CRP's services and functions are now laid out according to the linear mapping of the clinical investigators' workflow. In addition, the understanding of all CRP Faculty is that they hold institutional service positions that only succeed when our clinical investigators work is easier.

With the support of Peter Slavin, our CEO, the Clinical Research Program established institutional **Clinical Innovation Awards** targeting practicing clinicians who wish to test and institute some reform that would improve the institutional processes regarding safety and quality. These awards enable the CRP to provide them with faculty mentoring, partial salary support, and key infrastructure such as study coordinators, biostatistics, and regulatory assistance to enable their efforts. These awards, annually selected from over two dozen applications, have resulted in marked improvements in clinical services in the areas of infrastructure, clinical effectiveness, population management, safety, and quality. In addition, Departments, the NIH, and ARRHQ all now fund several of these programs providing excellent amplification to these Clinical Innovation Awards agenda.

Finally, the CRP has turned our own infrastructure into a self-learning organization. This feature is evident by the organization of our **Annual Unit Reports** that follows in the manner in which they report their progress. Each Unit Report ends with discrete sections entitled **"Lessons Learned"** and **"Adaptations Planned"** in the coming year. This required feature of the CRP's Annual Progress Reports requires each Unit to be in touch with its end users and to modify their programs according to what works and what does not, having evaluated several options over time.

It is quite clear that when viewed collectively, the changes instituted by the CRP have led to important institutional changes in attitudes and operations regarding clinical research that has enhanced the MGH's ability to build Departmental infrastructures for clinical research. Most notable among these is the ability of Psychiatry to build a clinical trial network based upon an initial $35M grant successful application supported by the CRP that was awarded to Gary Sachs of the Psychiatry Department. The clinical effectiveness program in Radiology benefited in a similar fashion from the institutional investments made in the CRP. Finally, the MGH has assumed a National leadership position in Clinical Research by establishing The **Clinical Research Forum** and **"The Top 10 Clinical Research Accomplishments"** competition (now advertised nationally). Incidentally, in 2012 the MGH won three of these 10 awards nationally including the top award of this group, a feature that no other academic medical center has achieved.

F. Future Challenges

The MGH is now in a far better position to face the challenging future of clinical research in our newly constrained external environment. Like all Academic Medical Centers, the MGH faces increasingly challenging regulatory environments, restricted incomes from all of its traditional sources including NIH, DoD, AHRQ, PhRMA, Biotech, and philanthropy, and a dwindling pipeline of young physician scientists due to increasing loan indebtedness and decreasing likelihood of NIH funding. Nonetheless, it now faces these future challenges with a more solid foundation in clinical research than it had 2 decades ago and a stronger institutional commitment to translate the fruits of its investments in basic research into improved care of its patients. The future will contain new leadership for the CRP, the establishment of an exciting Translational Medicine Unit, and

opportunities for further integration of our administrative structures supporting research—all changes proposed in the 2012 CRP Directors Report. Each of these elements is now part of the new MGH Strategic Plan. It is my fondest hope that the mission of clinical research, i.e. the need to translate our basic science advances into improved care for our patients, would now become part of the MGH's Mission Statement going forward.

G. Concluding Remarks and Final Thoughts

One of the greatest pleasures of my professional career has been to serve as the MGH's Director of Clinical Research. This position has involved dealing with the talented Department Chairs and Center Directors, our gifted institutional leadership that has established, sustained, and grown its commitment to the CRP, and the enormous imagination and energy of our best and brightest trainees whose talent continues to excite and inspire me daily. The CRP's faculty and administration have been wonderfully committed to these missions and their service. It has been a pleasure to lead such a highly dedicated group. Most importantly, the ability to help our youngest, best, and brightest has been the daily joy of this position.

The MGH is a remarkable institution populated by extraordinary individuals operating at the highest levels who do heroic things every day. It is thus critical that our commitment to infrastructures for clinical research like the CRP match our other institutional assets. The ability to care for patients; to teach others how to do the same; and to perform research daily is a special privilege we as faculty here at the MGH share with our institutional leadership. The ability to channel our discoveries in basic science into improving the care and alleviating the human suffering of our patients is a remarkable and unique ability of an academic medical center that requires constant attention and continued investment. After all, it is our unique destiny and role in our nation's complex health care system. Nowhere do these complex missions synergize so well as here at the MGH, a special place indeed.

Figure 1: Clinical Trials Expenditures at MGH, FY 92-13

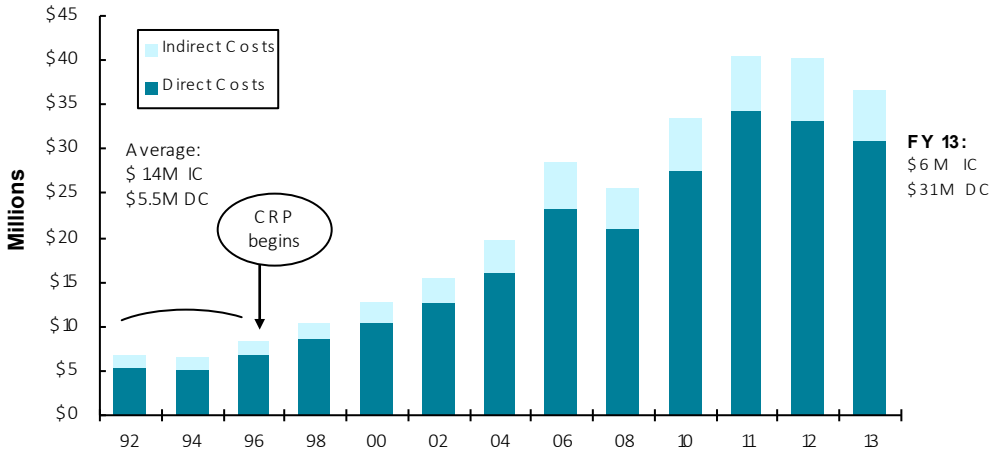
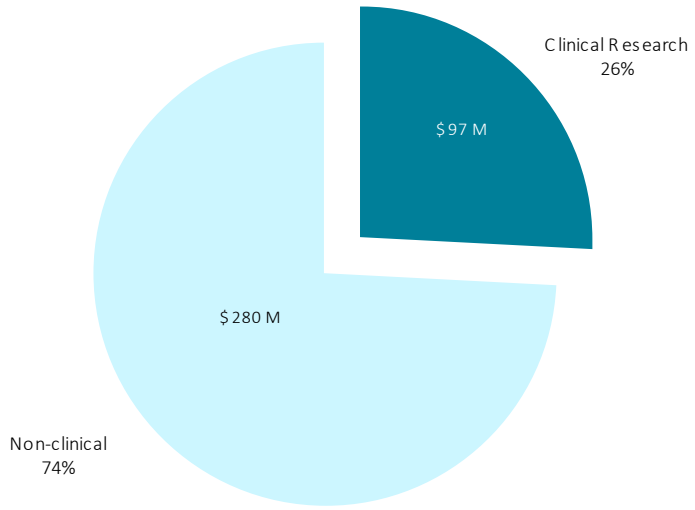


Figure 2: NIH and ARRA $ for Clinical Research in FY 13 - Estimated @ $97M



CRP Evaluation Tools and Updates on the Website

Liz Salomon, Ed.M., Project Manager

GOALS

Having launched the new CRP website in October of 2012, this year's goals were to further enhance this platform and develop additional online resources to support the work of the CRP. In particular, our focus this year was to develop, pilot and analyze online evaluation tools for the CRP's courses, consultations and services and to provide personalized online resources to recommend these services to members of the clinical research community.

ACCOMPLISHMENTS

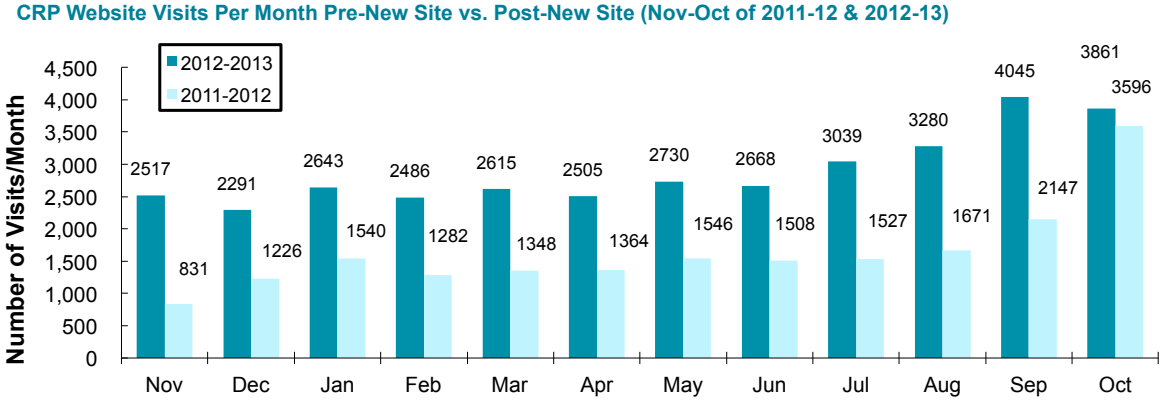
To be more responsive to the needs of those utilizing our resources, the CRP has developed online mechanisms for seeking evaluations of our consultations and services.

1) Since its launch on Clinical Research Day in October of 2012, the newly enhanced CRP website has continued to show marked increases in use from previous years. Figure A illustrates visits per month pre- and post- the launch of the new website which have continued to show steady improvements in use throughout the year. Particularly heavy website usage was noted leading up to and post Clinical Research Day in 2012 and 2013.

2) Additionally, this year the CRP began transferring all Clinical Research Education Unit (CREU) course evaluations into an online format. This process has greatly facilitated the evaluation process—both for respondents and those analyzing these results—and has allowed us to get real-time input about our Ed Unit's course offerings. Utilizing these tools as an opportunity for self-evaluation and self-reflection, these evaluations have provided the CRP with invaluable information as it continues to strive for excellence.

3) This year, the CRP has also developed evaluation tools for our consultation and support services. Based on Fred Reichheld and others at Bain and Company's idea of the Net Promoter Score (NPS), these evaluations tell us how likely CRP clients would recommend CRP consultations and services to a colleague and why. The CRP's ability to easily gather this information and integrate feedback received into our strategic plan has helped to inform our continued growth and capacity building.

The CRP website content continues to be updated on a regular basis as new information, resources



and courses are developed. Additional website enhancements, like a page dedicated to Patient-Centered Oriented Research (PCOR), continue to be added when time-sensitive needs like these are requested from the clinical research community. While the new CRP website continues to provide a growing roadmap for clinical research at MGH, this resource also supports the promotion of CRP courses and services.

Finally, this year the CRP launched its initial version of a Course Recommender for the Education Unit website. This online tool provides users with recommendations for courses based on their previous course attendance and offers users a personalized way to receive information about upcoming CRP courses.

LESSONS LEARNED

Throughout this past year the CRP has come to appreciate the growing importance of building online resources for the MGH clinical research community. As one respondent said on an Orientation Course evaluation survey, "[before even attending this course] I found a helpful introduction on the website." Having real-time resources like these is vital to members of a very busy and often changing clinical research environment and provides accessible support to those who need it whenever they desire. Additionally, creating the capability for service, consultation, and course recipients to evaluate our offerings in an online format provides a key source of data for our strategic planning and course creation efforts.

ADAPTATION PLANNED

In the coming year, the CRP will

a) continue to expand its online evaluation tools to assist in the consolidation of feedback about CRP consultations, services, and courses.

b) expand its ability to create more personalized mechanisms for suggesting courses and support services to members of the clinical research community.

c) continue to enhance its website's ability to reflect new resources and changes within the MGH clinical research community.

Recognizing that the coming year will be one of transition for the Clinical Research Program, Project Management staff will remain poised to be responsive to whatever might be required as we enter a new era of the CRP.

Clinical Research Support Office (CRSO)

Andrew A. Nierenberg, MD, Director

GOALS

The role of the MGH Clinical Research Support Office (CRSO) is to provide infrastructure and logistical support for clinical research faculty, particularly for early career investigators seeking training and transitional support as well as for established investigators.

Our goals are to:

- **Build** the pipeline of early career physician-scientists;
- **Support** clinical research infrastructures;
- **Facilitate** subject recruitment.

ACCOMPLISHMENTS

A. Clinical Research Faculty Mentoring with an Emphasis on NIH K Awards and the Patient Centered Outcomes Research Institute

CRSO and CRP faculty members mentor clinical researchers at MGH, with a focus on early and midcareer development. CRSO mentors augment departmental mentors to provide additional perspectives and a broader overview of clinical research career development. The goal is to help junior and mid-rank faculty advance their careers and their clinical research.

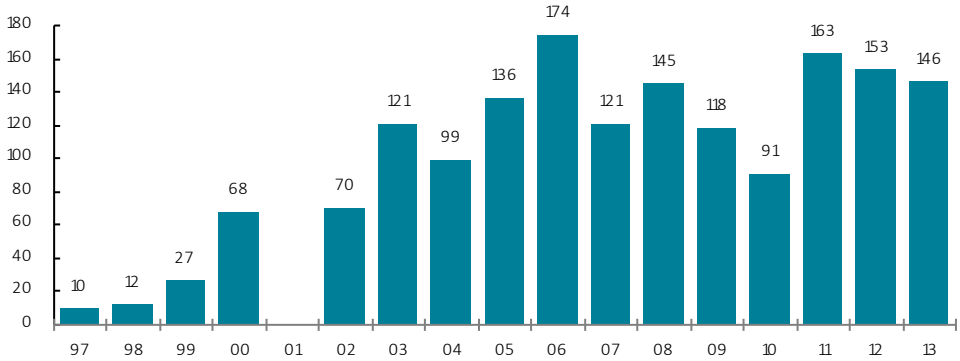
More than 146 faculty and research fellows reached out to the CRSO in 2013 (Fig. 1a). Dr. Nierenberg has staffed consultations ranging from junior faculty preparing new Career Development (K) grant applications to working with current K award recipients in applying for independent funding to consulting on resubmissions of federal grants and assisting with study design issues for new clinical studies and research networks.

In collaboration with the Clinical Research Education Unit (CREU), we designed and implemented the "Conquering the K" interactive workshop in Spring 2013. The workshop faculty included CRP faculty and senior K24 awardees. The full range of faculty provided a broad multifaceted overview from multiple clinical research areas. With the workshop, we expanded our services to 30 junior faculty and fellows and provided the K24 awardees with the opportunity to expand their mentoring portfolios. The seven session workshop included a mix of small group lectures and peer review of specific aims along with a mentor. Formal feedback from participants was quite positive and suggestions for improvement will allow us to modify and improve the workshop in 2014. Of note, the K workshop was part of the philosophy of the CRSO and CREU to shift from passive to active learning based on principles of adult learning.

Dr. Nierenberg also became the Co-Director of the CRP Clinical Research Education Unit (CREU). In this role, he helped plan the first MGH retreat for faculty interested in applying for grants from the Patient-Centered Outcomes Research Institute (PCORI) and participated in developing a Partners application for the PCORI Patient-Powered Research Network. The workshop, directed to MGH faculty who had applied to PCORI, was held on October 7, 2013. The workshop's speakers included Katrina Armstrong, MD, Physician-in-Chief, Department of Medicine; Susan Sheridan, MBA, PCORI's Director of Patient Engagement; MGH faculty recipients of PCORI funding, and members of the MGH Patient and Family Advisory Councils.

B. Utilization of CSRO Services

Figure 1a: CRSO: PIs Served per Year, 1997-2013

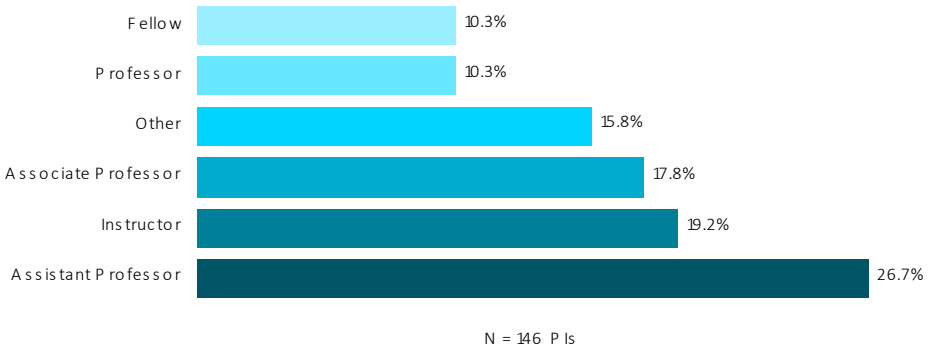


Fifty-eight of the 146 investigators (39%) utilized more than one CRSO service during 2013. These services including consulting with faculty on study implementation issues, accessing study coordinator support, utilizing Project Manager (PM) support to indentify potential funding opportunities and assistance with assembling the administrative sections of grant applications,

developing study budgets and training new staff to use the Budget Builder tool. PMs participate in the CRP's Study Coordinator Orientation Program for MGH's newly hired study staff; offer guidance and training on IRB submissions; and assist departments in training newly hired staff in tracking achievement of study milestones, invoicing sponsors and tracking payments, correcting errant patient care charges, and other practical interfaces with the Research Management and Financial Departments.

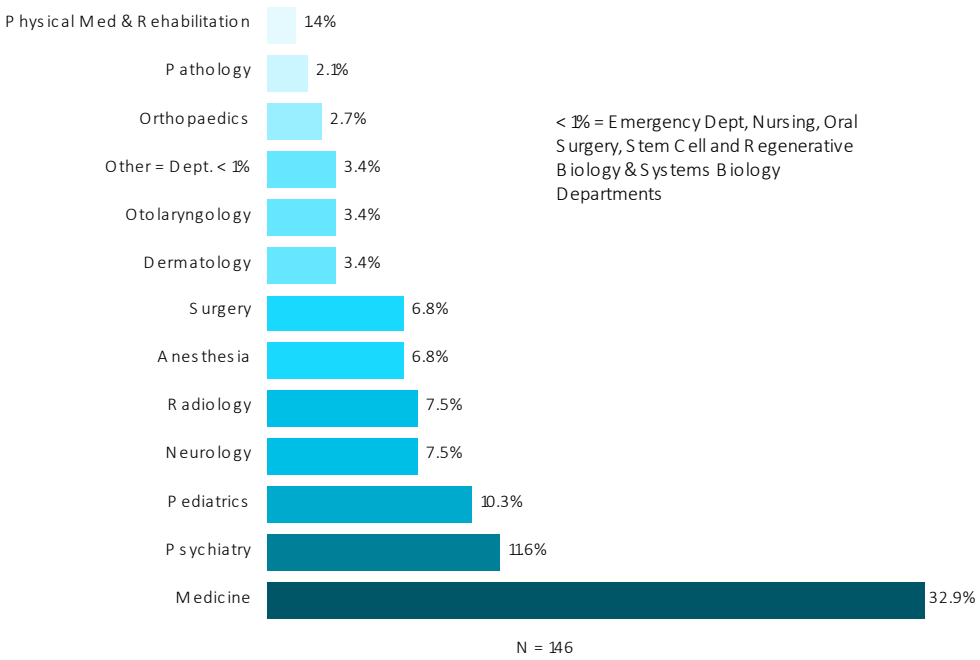
Of the 146 investigators assisted by CRSO faculty, PMs and coordinators, 47% were junior faculty members (instructors and assistant professors), 28.1% were senior faculty (associate professors and professors), 9.6 % were residents and fellows, and 15.8% were other non faculty professional staff such as doctorally prepared nurses, and department administrators (Fig. 1b).

Figure 1b: CRSO: PI's Served by Faculty Rank in 2013



These 146 investigators come from 17 departments. Collectively Medicine, Pediatrics, Pathology and Surgery accounted for the majority of all investigators served (Fig. 1c).

Figure 1c: CRSO: Served by Dept., 2013



B1. Study Coordinator Pool

Many clinical research investigators need staff to manage the day-to-day logistics of conducting clinical research. The CRSO fills this gap by providing temporary, as-needed, trained study coordinators.

1) In 2013, six fully funded CRP study coordinators supported a wide variety of clinical research projects directed by MGH clinical investigators. The CRSO study coordinator pool assists with all aspects of a clinical study for a flat hourly rate of $41 and *represents the only charged service of the CRP.* Study coordinators manage all day-to-day clinical study activities collection and entry, and study close out. In addition, study coordinators provide investigators and study staff with free advice and consultations on IRB submissions. CRP study coordinators supported 72 individual clinical investigators from 13 departments on 130 individual studies (Fig. 2a & 2b). It is not unusual for clinical investigators to contract with the CRP for experienced study coordinators on multiple studies. In addition, a growing number of investigators and study staff seeking advice and consultations on IRB submissions, either prior to their submission to the IRB or in drafting responses to the IRB's questions. Seventy of the 130 individual protocols, 53.8%, were PI-initiated studies funded under NIH subcontracts, foundations, and other support.

Figure 2a: Study Coordinators: Projects by Dept., 2013

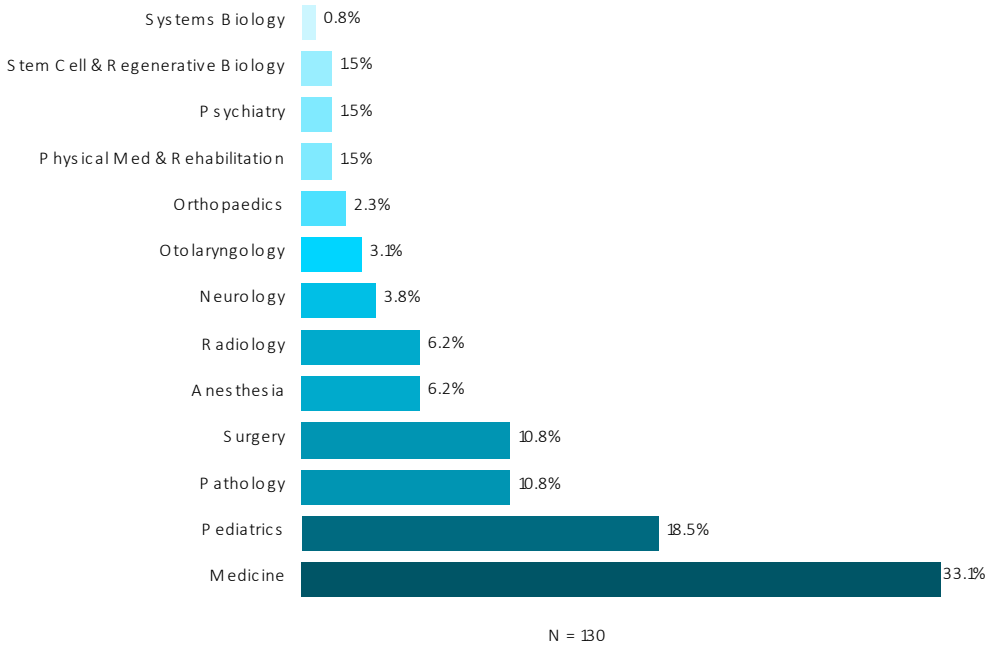
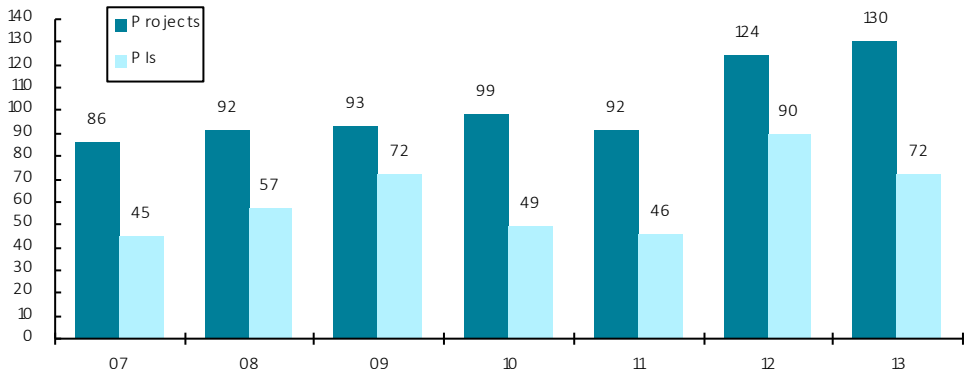


Figure 2b: Study Coordinators: Projects & PIs per Year, 2008 - 2013

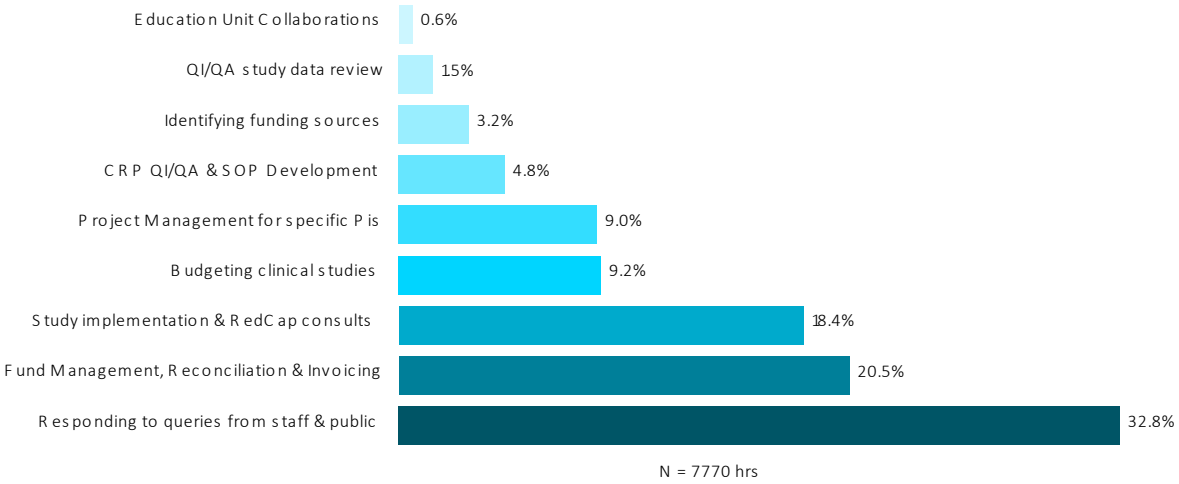


2) CRSO study coordinators play an important role in training other study staff throughout the MGH. These experienced study coordinators have been accredited by the Norman Knight Nursing Center for Clinical and Professional Development to train MGH non-nurse study coordinators in basic phlebotomy, measuring vital signs, and performing ECGs thus leveraging the CRP's programs into the clinical operations. Over 240 MGH study staff participated in these training programs in 2013. Since 2010, the CRSO in collaboration with the CRP's Education Unit has trained about 1000 MGH research coordinators. This service fills a critical training need for our clinical investigative community's staff.

B2. Project Management (PM) Support

To support the largely unmet needs of MGH clinical investigators for assistance in project and financial management, the CRSO developed a Project Manager (PM) service to address these issues free of charge. These PMs provided 51 MGH investigators conducting a total of 85 protocols with monthly reports detailing the precise status of their project's subject recruitment. They also verified fund expenditures, followed up to identify and remove errant grant charges, provided a realistic assessment of projected fund balances, and reviewed sponsor amendments which may affect study budgets. The PMs also invoiced sponsors based on achievement of study milestones, and managed final fund reconciliation and study fund close out allowing PIs to close study funds quickly and avoid deficits caused by untimely accounting practices. Perhaps more importantly, these PMs reduced the broader institutional problem of fund deficits resulting from poor tracking of crucial clinical research financial details. In addition to fund reconciliation, PMs also assist PIs by researching funding opportunities, budgeting clinical studies, participating in the CRP's Educational Unit programs, and advising on study implementation. (Fig. 2c Project Management consulting support for PIs 2013

Figure 2c: CRSO: Consulting Hours by Service Type in 2013



C. CRSO Support of the Partners Biorepository for Medical Discovery

Beginning in 2011, CRSO PM's and study coordinators initiated implementation support for the Partners Biorepository for Medical Discovery (PBMD) program in MGH clinics. CRSO study coordinators obtained patient consent, performed phlebotomy, collected and entered data into the PBMD tracking system. By 2013, the number of MGH clinics involved in the PBMD program expanded from a single clinic in 2011 to multiple investigators in multiple clinics throughout MGH. CRSO PMs facilitated start-up activity and rapid implementation of this PHS-wide resource and provided management support to tracked the overall productivity clinic-by-clinic and inform the leadership of essential infrastructure which allows clinics to successfully recruit subjects.

In 2013, 2650 MGH patients provided consent and specimens for the Biorepository and the CRSO began transition of the Partners Biorepository to dedicated management and coordinators who will assume responsibility for the project at MGH in 2014.

D. CRSO Career Development Tool Kit

In the past 15 years, the CRSO has developed a wide range of support services to meet clinical investigator needs for consultation on career development, as well as guidance on all phases of study implementation. We have also developed actively curated email lists of MGH junior clinical research faculty, applicants and recipients of K awards, research fellows, and graduates of the Harvard School of Public Health's Clinical Effectiveness course. These lists allow us to keep them up-to-date about CRP education, funding, and educational programs of particular interest to junior investigators. The CRSO and the CRP's Educational Unit also developed a new educational series specific for MGH applicants and junior faculty focusing on NIH Career Development Award applications (K08 and K23 awards). These new and highly practical services were well received because of their interactive features.

E. CRP Online Service Support

In 2009 and 2010, the CRP designed and launched an interactive intranet web resource (HUB) that allows MGH clinical investigators and their support staff to share their questions and study implementation problems with the wider clinical research community. HUB contains recordings and PowerPoint handouts of courses and training programs offered by the CRP's Education Unit which allows faculty to re-review material at time most convenient to them and on an as needed basis. Through HUB, investigators and staff can also access Key Clinical Research Resources provided by MGH, Harvard Medical School's Catalyst, and Partners for inclusion in their grant application's Resources and Environment sections.

As mentioned in section A, the CRSO also offers interactive workshops specifically for Clinical Investigators applying for an NIH K Awards. These workshops focus on practical approaches including timelines and grant structure, with an emphasis on the unique requirements of these grants. We offered the K workshops in March and October 2013 with 60 junior faculty and fellow attendees. The workshops also give senior investigators who already have a K24 an opportunity to mentor the larger MGH community beyond their departments. The attendee evaluations for both reported uniform Excellent and Good ratings on the content of the material provided. To further assist faculty applying for these K awards, the CRSO is continuing to assemble a library of K08 and K23 applications recently awarded to MGH junior faculty which will be made available to new applicants.

F. CRSO: RSVP for Health Database to Facilitate Subject Recruitment

The *Research Study Volunteer Program* (RSVP for Health) is a CRP-initiated study volunteer registry where pre-registered individuals receive information about clinical research studies that are active at the MGH. These include patients, families of patients, and normal volunteers. This program has been so successful that now both MGH and BWH research staff use this program as a resource to recruit study subjects. RSVP for Health saw its first full year of operation in 2005 and has had another year of steady growth in the number of registrants and in the number of MGH and BWH users. By the end of 2013, RSVP for Health contained over 23,305 registrants, up from 22,100 registered in 2012 (Fig. 3).

Of the 23,305 registrants we have accumulated in RSVP, almost 15,000 (64%) are women. Of the 23,305 total registrants 17,500 have indicated an interest in participating in studies as healthy volunteers or controls in addition to participating in therapeutic studies. RSVP serves as a critical resource for translational and physiologic/path physiologic studies.

The registrants' therapeutic interests reflect common disorders such as diabetes, obesity, mental health, cardiovascular disease, etc. In 2013, MGH investigators used the RSVP database to recruit subjects for 62 individual MGH protocols. The heaviest users are investigators in the departments of Medicine, Psychiatry, and Radiology. Of note, Dr. Nierenberg used the RSVP data in the only MGH PCORI application for a Patient Powered Research Network.

Figure 3: RSVP for Health: Registrants' Demographics

Category	Registrants	
	Count	%
Gender		
Female	14,939	64%
Male	7,284	31%
Not Recorded	1,082	5%
Total	**23,305**	**100%**
Race		
American Indian/Alaskan Native	97	0.4%
Asian	1,124	4.8%
Black or African American	2,864	12.3%
Native Hawaiian/Pacific Islander	75	0.3%
White	15,421	66.2%
Other	1,032	4.4%
Not Recorded	2,692	11.6%
Total	**23,305**	**100.0%**
Ethnicity		
Hispanic or Latino	1,566	6.7%
Not Hispanic or Latino	15,280	65.6%
Not Recorded	6,459	27.7%
Total	**23,305**	**100.0%**
Age		
<35	10,908	46.8%
36-45	3,426	14.7%
46-65	6,458	27.7%
66+	2,185	9.4%
Not recorded	328	1.4%
Total	**23,305**	**100.0%**
Contact Method		
Email	18,584	79.7%
Post	4,721	20.3%
Total:	**23,305**	**100.0%**

LESSONS LEARNED

The CRSO served a total of 168 individual investigators in 2012. During the year, we established several new services and also expanded our existing services. This support was distributed among different departments. Increasingly, we have focused CRPservices on junior faculty in recognition of importance in the clinical research "pipeline".

The creation of a Clinical Research "Help Desk" makes the process of referral to CRP, PHS and Catalyst resources straightforward, and use of this resource has grown considerably. The hands-on K award workshops continue to be popular. They were subscribed within an hour of posting and we had to turn away others who had wanted to participate. We had to limit registration because the intensive interactive format required small groups. While these workshops focused on the specific aims for the K awards and provided the participants to critique other's materials, it has become clear that many want to have instruction and guidance beyond the specific aims to successfully submit a K award.

Finally, it has become apparent that several departments have challenges with the IRB or with managing finances of clinical research. We need to identify these challenges earlier and explore preventative measures

ADAPTATIONS PLANNED

1. **Expand** specific email notices of CRSO services targeted to clinical researchers. Such 'push technology' should enhance serving the individual and varied needs of the MGH clinical research community.
2. **Integrate** CRSO assistance with departmental mentorship.
3. **Communicate** directly with mentors and department chiefs about how CRSO services can benefit their department.
4. **Encourage** department chiefs to consider having Associate Professors in their departments apply for K24 awards.
5. **Expand** the K Award workshop to include all aspects of grant submissions. To this end, we are piloting an expansive "Conquering the K" seminar in 2013.
6. **Facilitate** early career faculty to submit their first RO1.
7. **Create** a dashboard to obtain feedback from mentees and follow up on K award applications. Build a database of successful K awards to be used as models for applicants. Build the database of critiques to discover patterns of frequent errors. Analyze the efficacy of the program by obtaining data about the success rates of participants vs. non-participants as well as finding out the return on investment.
8. **Collaborate** with the SVP of Research to help implement the Life Registry and help clinical researchers leverage the Life Registry resource.

Clinical Research Education Unit (CREU)

Janet E. Hall, MD, and Andrew A. Nierenberg, MD, Co-Directors

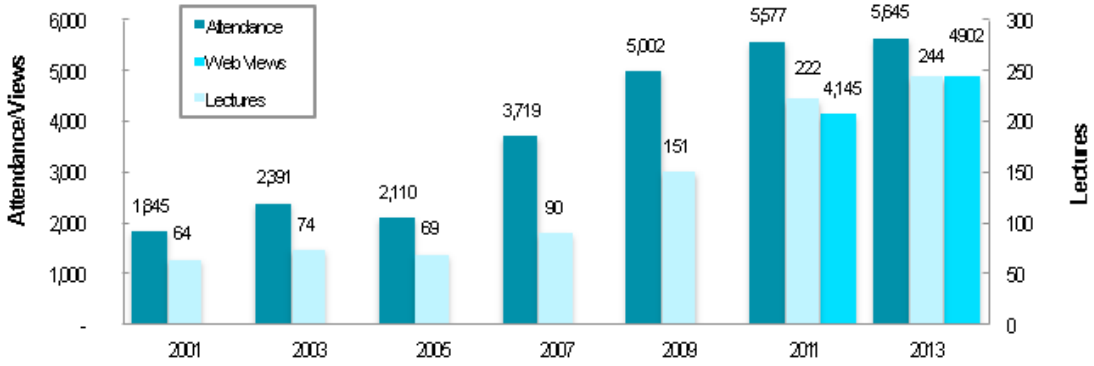
GOAL

The goal of the Clinical Research Education Unit (CREU) is to improve the quality and quantity of clinical research within the MGH by providing educational opportunities for clinical investigators and study staff. The CREU strives to fulfill the diverse and dynamic educational requirements of clinical investigators locally through development of innovative course content. In addition, the CREU provides educational programs for research nurses, project managers, coordinators and assistants, which are foundational and responsive to the ever-changing clinical research landscape. Well-trained, educated study staff is essential for the success of a clinical investigator.

ACCOMPLISHMENTS

CREU courses are extremely well attended and received (Fig. 1). This is a testament to the ongoing need for local educational programs for MGH clinical investigators and study staff. It is also indicative of the CREU's ability to adapt to changing needs, recruit appropriately talented course faculty, and identify current topics to be covered in course content.

Figure 1: Attendance, Online Views and Lectures, 2001 - 2013



(a) An attendee is counted once per course, regardless of whether the course is a single lecture or multiple sessions. (b) Views are the number of participants who reviewed a recording of a live course or handout from that course. Multiple online resources available; individuals may overlap.

The CREU saw a slight decrease in course attendance in 2013 compared with 2012, due in large part to fewer new hires attending our introductory courses, which provide a critical foundation for the conduct of clinical research. Fewer hires in 2013 are likely the result of a brief hiring freeze and less available funding for clinical investigators. The number of views for online courses remained steady.

In 2013, the CREU collaborated with multiple Units within the CRP as well as the Partners Human Research Committee (PHRC) and Quality Improvement Program (QI) to develop and launch several important new courses to meet the needs of the clinical research community:

1. Online: ***"What Makes a Good Article? How to Review Scientific Literature to Guide Your Research."*** The purpose of this course is to provide a list of questions for investigators to consider when reviewing an article. This online training will enable the reader to select the highest-quality studies to guide their research.
2. Workshop: ***"Conquering the K: Submitting an NIH Career Development Award"***: In collaboration with the CRSO, the CREU developed a seven session series providing step-by-step instruction by CRP faculty and K24 awardees on preparing an NIH Career Development award.
3. ***Multi-session, Live Course: "Introduction to Survey Research and Design"***: The Clinical Effectiveness Unit and the CREU worked jointly on developing a four session course on survey design, IRB implications, database development, use of social media and analysis.
4. Multi-session, Live Course: ***"Good Clinical Practice in Research at an Academic Research Institution"***: The Good Clinical Practice (GCP) series was developed in conjunction with the Partners Human Research Committee and the Quality Improvement Program. The purpose of this course is to provide clinical investigators and study staff with a strong working knowledge of GCP, which will foster regulatory compliance and quality study performance. The series is comprised of four half-day sessions.

In 2013, the CREU developed two online courses and is working with the CRP IT Unit to launch these courses in 2014. Investing time and effort in online education allowed for continued, innovated course development. It also supports clinical investigators and study staff by making courses readily accessible. New online courses developed in 2013 include:

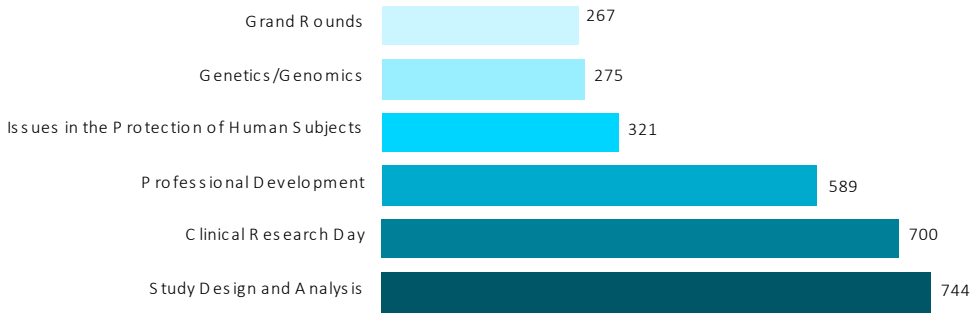
1. ***"Developing a Hypothesis."*** After reviewing course evaluations and participant responses from three distinct courses ***(Design and Conduct of Clinical Trials, Conquering the K: Apply for an NIH Career Development Award, Workshop on Study Design: Using MGH Clinical Care Date in Clinical Effectiveness Research)*** the need for instruction on developing a hypothesis became apparent. The CREU developed a 5 module online training on how to properly construct a hypothesis for statistical testing in a clinical research study.
2. ***"Study Staff Basic Skills Program."*** This is a 20-module online training for newly hired study staff or those with less than 2 years of experience in clinical research. The purpose of this online training is to provide new study staff with a solid foundation in clinical research as well as the same skill set when beginning their research career at MGH.

In 2013, the CREU continued to record and post courses on our website while tracking access. The CREU now has an extensive archive of past programs and a growing catalogue of recorded courses.

Investigator Program

The investigator track continues to be extremely popular with 2,896 attendees in 2013. Figure 2 illustrates investigator attendance for specific categories of courses.

Figure 2: Investigator Courses 2013. Attendance (%) per course category



The CREU has focused on developing a **core curriculum** to support junior investigators in their research careers that consists of the following four courses:

1. *"Fellows Orientation Part I and Part II"*
2. *"The Design and Conduct of Clinical Trials"*
3. *"Basic Biostatistics for Clinical Research"*
4. *"Good Clinical Practice in Academic Research Institution*

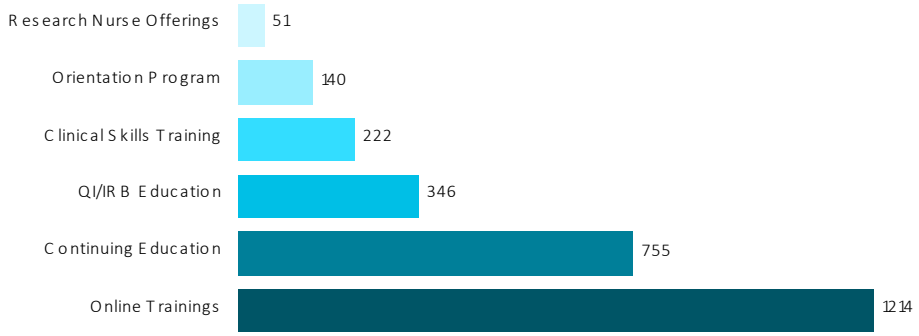
In addition to this core curriculum, the CREU offers more advanced courses to support clinical investigators in Genetics & Genomics (Genetic Code, Genetic Literacy, Responsible Conduct of 'Omics" Research), Clinical Effectiveness (Workshop on Study Design: Clinical Effectiveness Research, Introduction to Survey Design), Professional Development (Conquering the K: Applying for an NIH Career Development Award) and Biostatistics (Applied and Problem-Based Biostatistics).

In 2013 the "Design and Conduct of Clinical Trials" course was revised to include a session on designing device trials. Also in response to participant evaluations, the Clinical Effectiveness course "Workshop on Study Design: Clinical Effectiveness Research," was revised to include additional workshops for more hands-on experience using MGH clinical care data.

Study Staff Program

The study staff curriculum supports MGH clinical investigators by providing educational resources and training for study staff. This track is a widely used resource with 2,749 attendees in 2013. These educational and community-building opportunities provide study staff with updates on clinical research regulations and operations, all of which are critical for their role in supporting MGH clinical investigators. Figure 3 illustrates the distribution of study staff attendance for each of the course categories.

Figure 3: Study Staff Courses 2013. Attendance (%) per course category



The CREU also developed a core curriculum for study staff which consists of the following courses:

1. *"Introduction to Clinical Research" (online)*
2. *"Orientation Program: Clinical Research Resources at MGH"*
3. *"IRB/QI Roundtables"*
4. *"Good Clinical Practice in Academic Research Institution"*

A major initiative in 2013 was continuing with the Clinical Research Spotlight Series and IRB Hot Topics Series in collaboration with the PHRC. IRB Hot Topics for 2013 included: ***"Obtaining Surrogate Consent, Research Misconduct, and IRB Issues in Survey Research."***

The Spotlight Series, which is held monthly, focuses on study management issues. Topics for 2013 included:

1. *Clinical Trials. Gov: Implementation*
2. *Bio-specimen Processing Basics*
3. *Clinical Trials. Gov: Results*
4. *How to Communicate Effectively with Study Teams*
5. *Subject Remuneration and E-Check*
6. *Working with Study Subjects with Limited English Proficiency*
7. *Developing a Peer to Peer Auditing Program*
8. *Using Social Media in Clinical Research*
9. *Clinical Research Coordinator Support Group*

Two hundred twenty-two attendees (222) took advantage of the CREU's **Clinical Skills Trainings** (phlebotomy, ECG and vital signs) in 2013.

Continuing Education
The CREU offers several continuing education courses for physicians (CME) and nurses (CEU) and courses eligible for credit in the Responsible Conduct of Research (RCR) (Fig. 4).

Figure 4: CME, CEU, and RCR Accredited Course Hours 2013

Continuing Medical Education (CME), Continuing Education Units for Nurses (CEU), Responsible Conduct of Research (RCR)

Clinical Research Day
Clinical Research Day continues as an important venue to celebrate clinical research. Clinical Research Day showcases the CRP's efforts to build and support a viable community of clinical investigators and study staff across the institution. It is recognized as a platform for clinical investigators to present and receive attention and reward from the institution's leadership for their work, as well as a venue for interactions and collaborations amongst investigators Participation remained high with 263 abstracts submitted 21 team nominations and a vibrant and well-attended Poster Presentation session.

The tradition of Clinical Research Day is to highlight issues at the forefront of clinical research at the national level and to discuss these in terms of the MGH clinical research community. The 2013 theme was the role of translational research in academic medical centers. Elias Zerhouni, MD, President, Global R&D, Sanofi France, served as the keynote speaker. He captivated the audience with his presentation on the future of collaborations between academic health centers and industry. Following Dr. Zerhouni's keynote address, a panel discussion, led by Mason Freeman, MD, focused on the critical role of translational medicine capabilities in academic health centers and implications for research at MGH. Leaders in translational research provided their insight and suggestions on this topic to a diverse audience of clinical investigators.

LESSONS LEARNED

1. **Interest.** Interest in CREU educational programming at the local level remains high. There is a continuing demand for basic level courses as well as more advanced content for clinical investigators and study staff. (See Appendix A for full 2013 course listing).
2. **Curriculum.** In 2013, the CREU performed a systematic evaluation of the current curriculum and identified important gaps. The CREU identified courses that can be changed from a live format to an online format to improve availability.
3. **Access.** High attendance at CREU investigator courses in 2013 indicates that clinical investigators at MGH make frequent use of onsite continuing education. Local availability of courses that fit easily into busy work days combined with timely topics, CME and RCR credit, and outstanding faculty have been keys to the success of the CREU.

4. **Online Education.** Online education is a highly valuable resource to the MGH clinical research community. By making courses accessible at all times, the CREU is able to increase its impact and provide even better services and resources to the clinical research community. Placing more foundational and unchanging courses online will allow the CREU to better utilize the highly valuable time of its course faculty, focus its live courses on more current topic areas, and provide more interactive and in-depth in-person education.
5. **Building, Supporting and Celebrating the Clinical Research Community at MGH.** Clinical Research Day continues to meet this long-term goal. This event is remarkable for its dynamic nature, attendance, participation, and involvement of MGH leadership. Clinical investigators establish a cross-group platform of communication, technique sharing, and support that is essential to the future of clinical research at the MGH.

ADAPTATIONS PLANNED

1. The CREU will continue to invest in online education by enhancing and promoting its online education resources and creating additional online educational opportunities. New initiatives for 2014 include: ***"Basic Elements of Protocol Design and Development," and "Budgeting for a Clinical Research Study."***
2. The CREU is developing educational opportunities to help investigators prepare proposals for "Patient-Centered Outcomes Research". Interested in this type of clinical research is growing and will be made possible through new awards from the Patient Centered Research Institute (PCORI) and other funding bodies,
3. As the number of qualitative research projects increases at MGH, the CREU is developing a ***multi-session course on best practices*** for designing and implementing qualitative research studies.
4. The CREU will develop tools to evaluate the impact of participating in several of our more intense and personalized courses ***(Design and Conduct of Clinical Trials, Conquering the K: Apply for an NIH Career Development Award and Workshop on Study Design: Using MGH Clinical Care Date in Clinical Effectiveness Research)*** on the research careers of their attendees.
5. The CREU will adapt to ongoing changes in the research environment by continuing to develop, innovate, and create dynamic learning opportunities for study staff.

Appendix A: CRP Education Unit - Courses and Participation 2013 INVESTIGATOR PROGRAM	Attended*	Faculty	Lectures	Hours	Views**
Study Design and Analysis					
Introduction to Survey Research & Design	115	4	4	6	555
Basic Biostatistics for Clinical Research	243	1	4	6	979
Basic Biostatistics for Clinical Research: Working Sessions	117	1	4	6	382
Problem-Based Biostatistics	208	1	4	6	379
Design & Conduct of Clinical Trials	43	18	15	22	
Workshop on Study Design: Using MGH Clinical Care Data	18	8	5	7.5	
Genetics/Genomics					
Genetic Code	88	2	1	2.75	1,024
Genetic Literacy	66	5	1	2.25	
A Primer on Complex Trait Genetics: Principles for the Clinical Investigator	69	7	1	6.25	
Responsible Conduct of 'Omics' Research	52	11	2	8	
Issues in the Protection of Human Subjects					
Guidance for Obtaining Surrogate Consent	44	1	1	1.5	25
Maintaining Research Subject Privacy and Information Security	85	3	1	6	27
Ethics of Clinical Research Protocols	59	2	1	1.5	10
IRB Issues for the Bench and Desk Scientist	30	1	1	1	11
What Does the IRB Really Want? How to Write a Human Studies Protocol	54	1	1	1.5	
IRB Implications of Survey Research	23	1	1	1	
Whose Tells the IRB What to Do? The Effects of Case Law on Research Regulations	26	1	1	1.5	
Professional Development					
RedCAP Programming Training	200	1	7	10.5	
Conquering the K	28	19	7	14	
Clinical Research Fellows Orientation Part I: Starting Your Clinical Research Career at MGH	30	2	1	1.5	
Clinical Research Fellows Orientation Part II: Starting Your Clinical Research Career at MGH	32	11	1	4	72
How to Make a Poster	66	1	1	1	24
Good Clinical Practice	101	16	4	16	193
An Introduction to the Enhanced RPDR Tool	35	1	1	1	
How to Give a Presentation	97	1	1	1	
Grand Rounds					
Stem Cells and Chemical Biology: New Avenues to Study Schizophrenia and Bipolar Disorder	50	1	1	1	
Primary Ovarian Insufficiency and Menopause: Insights from Mendelian and Complex Genetics	92	1	1	1	
Hypothesis-Generating Research and Predictive Medicine	125	1	1	1	
Clinical Research Day					
Keynote Address and Panel Discussion	425	5	2	2	
Abstract Submission and Poster Session	275			2	
Total, Investigator Program	***2,896***	***128***	***76***	***142.8***	***3,681***

Appendix B: CRP Education Unit - Courses and Participation 2013 STUDY STAFF PROGRAM	Attended*	Faculty	Lectures	Hours	Views**
Orientation					
Orientation Program: Clinical Research Resources at MGH	140	11	5	23.75	40
Research Nurse Offerings					
RN Roundtable	51	6	6	6	
IRB/QI Roundtables					
Session I: Part I: New Submissions Initial Full Board Review	46	2	3	3	145
Session I: Part II: New Submissions	40	2	3	3	65
Session II: Part I: Continuing Review & Amendments	38	2	3	3	33
Session II: Part II: Source Documentation	44	2	3	3	23
Session III: Part I: Amendments & Reporting to the IRB	40	2	3	3	61
Session III: Part II: Protocol Adherents & Reporting Requirements	42	2	3	3	33
Session IV: Part I: Consent Form Writing	51	2	3	3	82
Session IV: Part II: Informed Consent Process	45	2	3	3	21
Clinical Skills Trainings					
ECG Training	48	1	9	22.5	
Phlebotomy	143	4	19	40	
Vital Signs Training	31	1	8	16	
Continuing Education					
ClinicalTrials.gov: An Introduction to Results Reporting	63	2	1	1	126
Hands-On MORA Training: Managing Monitor Online Record Access	20	1	7	7	
Audit Time: Is Your Site Prepared?	52	1	1	1.5	54
eIRB Training: Hands-on Introduction to eIRB	14	1	2	2	
Budgeting for Industry Sponsored Clinical Trials	20	2	1	1.5	20
Bio-specimen Processing Basics	51	1	1	1	59
Study Electronic Data Capture: StudyTRAX and REDCap	40	2	3	1	59
Workshop: Developing a Recruitment Campaign Using Social Media	11	4	1	2	57
ClinicalTrials.gov: Registration	18	1	1	1	27
StudyTRAX Training Session: General Overview	25	1	2	1	15
Clinical Trials Billing Series: Charge Capture & Billing Procedures	19	1	1	1	28
Operationalizing Clinical Research Protocol	30	1	1	2	41
Communicating within Study Teams	30	1	1	1	18
Clinical Trials Billing Series: Monitoring, Invoicing, and Corrections	12	1	1	1	36
Clinical Trials Billing Series: Clinical Trials with Investigational Devices or Approved Devices	6	1	1	1	34
Research Misconduct	42	2	1	1.5	36
The Principles of Clinical Research Data Management	57	1	1	1	26
Research Subject Remuneration and Reimbursement	45	2	1	1	23
Budgeting for Industry Sponsored Clinical Trials	18	3	1	1.5	30
Working with Study Subjects with Limited English Proficiency	12	2	1	1	25
Meet the Protocol Administrators & Mgrs of the PHS Human Research Office	33	18	1	1	1
Developing a Peer-to-Peer Auditing Program	31	4	1	1	3
Social Media in Clinical Research	58	1	1	1	
Clinical Research Coordinator Workshop	35	4	1	1	
StudyTRAX Training Session: Survey Research	13	1	1	1	
Online Trainings					
Research Patient Data Registry (RPDR)	31		9		
Good Clinical Practice and Study Management Basics	50		4		
Submitting your Medical Record Research Protocol to the IRB	10		5		
IATA Shipping Training for Transportation of Biological Materials and Dry Ice	908		5		
Infection Control Principles and Practice in Clinical Research	46		4		
Introduction to Clinical Research at MGH (online)	35		13		
Basics of Manuscript Writing for Clinical Researchers	104		4		
Subject Recruitment & Retention	25		8		
What Makes a Good Article? How to Review Scientific Literature to Guide Your Research	5		9		
Total, Study Staff Program	**2,749**	**99**	**168**	**168**	**1,221**
Grand Total	**5,645**	**227**	**244**	**311**	**4,902**

Information Technology Unit (ITU)

Henry C. Chueh, MD, MS, Director

GOALS

The broad goal of the Clinical Research Program's Information Technology Unit (ITU) is to support the increasing information technology needs of the MGH's clinical investigative community. Its specific approaches to meeting this goal are:

- To improve existing information management resources while creating a broad, new information management infrastructure to support the work of the clinical research community at MGH and PHS;
- To provide IT management support for MGH clinical investigators, including assisting in the recruitment of study subjects and supporting the Clinical Research Program's educational initiatives; and
- To establish ongoing partnerships with clinical researchers to pilot applications and studies with new clinical informatics-based interventions that will create reusable technology platforms.
- To envision and create transformative informatics and IT solutions for the clinical research community and beyond.

ACCOMPLISHMENTS

During the life of the program to date, the Information Technology Unit has added institutional value by supporting clinical investigators with a variety of informatics and IT solutions, both intramurally within the CRP, and extramurally across MGH and beyond. In addition, the CRP ITU has been responsible for some major innovations including the Partners RPDR and the informatics design of the i2b2 program, among others. Listed briefly below are some highlights:

- **Research Patient Data Registry (RPDR)**—The CRP ITU and envisioned and designed the initial version of the RPDR, a terabytes-scale clinical research database that has become a major research IT platform at Partners that has supported upwards of 100 Million dollars of grant funding.
- **i2b2**—As an extension of CRP ITU activities in clinical research data modeling, Dr. Henry Chueh was the Principal Investigator, architect, and author of the informatics core of the original i2b2 grant. Under the strong direction of Dr. Shawn Murphy and others, i2b2 has grown to be a national model for clinical research data management and analysis.
- **Data for Quality (D4Q)**—The CRP ITU, in collaboration with the CRP Outcomes Unit, envisioned models for data management that would support effective outcomes research analysis. Implemented and managed by the Center for Quality and Safety, the D4Q effort represents the integrative approach supported early on by the CRP.

  The D4Q data warehouse is used across MGH for clinical outcomes research and operations improvement.
- **Clinical trials visibility**—Before clinicaltrials.gov, the CRP ITU established a clinical trials listing website used across the MGH and BWH, providing visibility for study recruitment.
- **Monitor Online Record Access (MORA)**—MORA fills a clinical research community need to allow monitors to effectively audit clinical records for research purposes. The CRP ITU put MORA into production in 2012 and it has already saved an enormous amount of study staff time that is better utilized in direct research activities.

- **Population registries**—The CRP ITU established and supported activities (in collaboration with general medicine, primary care, rheumatology, infectious disease and others) that have led to population registries for clinical care that also serve as platforms to test clinical interventions. The Partners Population Health Management program currently relies on the TopCare IT platform that is derived from this groundbreaking CRP activity.
- **RSVP for Health (RSVP)**—Envisioned as a way to engage patients more directly in clinical research, RSVP was one of the first websites in the nation to allow patients to subscribe to clinical research areas of interest, and to also allow clinical investigators to connect to those patients anonymously for outreach.
- **Clinical Research Hub**—As an evolution of the CRP ITU's intramural support of the CRP Education Unit, the Hub is a knowledge management and learning platform that is designed for the future. When merged with investigator profiles, it can provide tracking, recommendation, and discovery of clinical research education.

More recently, our work in 2013 has focused on platform development and adaptation to enable meeting investigator needs in the changing information systems environment, while continuing to meet service needs of investigators. Platform development has focused on these areas:

- *Scalable knowledge management and online education tools for research*—making the Clinical Research Hub (hub.partners.org/crpedu) accessible to the broader research community.
- *Centralized Researcher profiles*—initiating development of a centralized researcher profiles tool that can be leveraged by the CRP and other groups interested in creating applications focused on supporting research.
- *eCare Engagement*—interface planning, development and testing to ensure clinical investigator access to clinical data in an era of Epic-based systems.
- *Dynamic Linkage Cohorts*—creation and maintenance prospectively of provider patient panels for research or analysis of operations.

Scalable knowledge management and online education tools for research

The CRP Hub Team builds and supports the knowledge management and learning management platform used by the Clinical Research Program *(hub.partners.org/crp)*. As the breadth and number of in-person courses offered through the CRP has grown, it has become difficult for research staff to find courses tailored to their specific needs. To help address this, the CRP Hub Team created a course recommendation tool that suggests new courses based on past courses that members of the research community have taken. This has been woven into the course catalog, making course discovery easier for the different research groups that the CRP serves. This course recommendation tool and a set of new authoring tools have helped to make the Hub platform more scalable and adaptable to researcher needs.

Progress toward Centralized Researcher profiles

Our support of researcher profiles in the context of an educational platform has revealed both the value of having meaningful, up-to-date profile data, and the difficulty of capturing detailed profile information as part of course registration. For 2013, we simplified course registration by automating as much of the profile data collection as possible. To accomplish this we catalogued the relevant data sources. This work resulted in conversations with the different data providers, the creation of requirements documents and the beginning of a collaboration aimed at creating centralized profile services. To support these automatically updated profiles in the future, we migrated and integrated into the Hub the profiles infrastructure developed by our partners at the UCLA Computing Technologies Research Lab.

eCare Engagement—interface planning, development and testing

The Information Technology Unit is based in the Laboratory of Computer Science (LCS), the Biomedical Informatics Division of the Department of Medicine, a unit with a track record of pioneering developments in health care informatics and a long history of "innovation in place" in clinical systems. The advent of eCare requires transitional adaptation of LCS+CRP collaborative innovations that are now in place. Some of these will necessarily be retired as a natural consequence of the implementation Epic as the single EHR for Partners. As noted in last year's report, "to support the graceful migration of existing clinical and research clients into the new systems environment, LCS will perforce become an internal center of expertise at using clinical and administrative data services available from the core Epic system to support external, value-added systems built for clinical and research purposes." During the past year, the unit has taken the first steps toward becoming such a center of expertise and service in the development of value-added applications at the edge of the core enterprise system. These steps have been necessary, if mundane: modernizing the LCS data feed infrastructure, participating in repeated cycles of eCare HL-7 message testing, participating in the eCare processes that are devising the replacements for our current diverse array of data sources used in research. This work lays the foundation for future innovations in service to researchers.

Dynamic Linkage Cohorts in Population Health and Research

In collaboration with Dr. Steven Atlas of the General Internal Medicine Unit, we have built a framework for a continuously updated representation of provider patient panels ("dynamic linkage cohorts") for use in both clinical research studies and population-based interventions. The dynamic linkage cohort methodology addresses the problem of "provider attribution" for primary care providers—determining by rule the most

appropriate primary care provider to attribute patient activity to. Provider attribution is a foundational issue in population health because it provides the denominators over which performance statistics are calculated. The methodology has been adopted as the provider attribution technique used in the Partners Population Health initiative. Since May 2011, MGH panels have been updated and saved in complete, ready-for-analysis datasets daily. These datasets constitute an important resource for investigators studying the impacts on care of population health initiatives. They are now being used to support numerous, ongoing IRB-approved studies. Extensions of the model have been developed in the past year as part of MGH's participation in the Primary Care Academic Innovations Collaborative.

MORA—Monitor Online Record Access

In collaboration with Partners Research Computing and the MGH Cancer Center Protocol office, the ITU implemented MORA, the Monitor Online Record Access tool, a tool for providing controlled, limited electronic access to study monitors and auditors. The tool saves research coordinators substantial time in supporting source data verification by monitors when compared with traditional paper-based approaches to this problem. In 2011, the CRP study coordinator pool beta-tested MORA. In 2012, MORA was gradually rolled out across MGH, DFCI and BWH, with regular training coordinated through the CRP Education Unit and the BWH Center for Clinical Investigation, and additional training sessions conducted by staff at the MGH Cancer Center Protocol Office and the Dana-Farber Clinical Trials Office. Since being released in 2012, MORA has been used at MGH on 117 protocols in more than 5000 sessions (Figure 2). In 2013, average monthly usage at MGH has been 189 sessions on 26 protocols. The most important pattern to note is that usage is concentrated among cancer protocols. At MGH, approximately 70% of the protocols on which MORA has been used have been cancer protocols. Usage on cancer protocols is more concentrated, as well: more than 90% of the MORA sessions have been for cancer protocols. The time and cost savings have been substantial.

Clinical Trials Recruitment Sites

We have supported clinical trial listing sites for MGH and Partners since 1998 and the RSVP for Health research volunteer registry since 2003. The clinical trial listing site clinicaltrials.partners.org continues to get strong usage as indicated in Fig. 1.

Figure 1: Activity (adjusted) on CRP website clinicaltrials.partners.org & crnet.mgh.harvard.edu

* From 1999-2010 four different technologies for measuring user activity have been used. Since 2010 the same tool has been used. Figures for earlier years have been adjusted to current equivalents using scale factors derived during periods when the methods of measurement overlapped.

Growth of the RSVP for Health research volunteer registry has persisted at approximately the level of the last several years, while usage has leveled off (Figure 2).

Figure 2: CRP Information Technology Unit – Metrics

• Clinical trials at Partners site sessions/month	
Sessions/month (9% increase from 2012 total)	6,927
• RSVP for Health	
New registrations in 2013 (12% decrease from 2012)	2,097
Cumulative registrants (7% increase from 2012)	23,623
Registrants sent one or more mailings (down 2% from 2012)	19,624
• MORA	
Cumulative MGH protocols with at least one monitor session with MORA (36% increase from 2012)	117
Cumulative number of times monitors reviewed MGH patient records for MGH protocols (up 1100% from 2012)	5,099

Research Patient Data Registry (RPDR)

The RPDR project, an innovation that was imagined and developed by the CRP's IT unit, is a successful and widely accessible research database that was expanded through a collaboration between the CRP, Laboratory of Computer Science (LCS), and Partners' Research Computing Group. It is now mature and has truly remarkable statistics. The RPDR has ~3,000 users throughout the Partners Healthcare System. It holds data on over 4.2 million patients and 1.8 billion coded records from patient encounters, labs and results, and other medical care. RPDR is one of the cornerstones for i2b2, another achievement that the CRP ITU was instrumental in starting, and that has become the de facto Partners standard to create open platforms for data analysis. i2b2 is one of the analytic pillars of the Harvard Catalyst's IT efforts, and has been adopted by over 60 other academic health centers. The scope and value of the RPDR continues to increase. The registry now contains patient demographic data, diagnoses and procedure data, pharmacy data, inpatient and outpatient encounter information, provider information, and laboratory data. Data from electronic health records, LMR and OnCall, are also included.

Ongoing Operations
In addition, the IT Unit has continued to support all of our previous applications and websites described above, including: clinicaltrials.partners.org, rsvpforhealth.org and MORA.

LESSONS LEARNED

Involve appropriate stakeholders in researcher profiles work
Reaching out to key stakeholders within Partners to identify sources for CRP community members' profile data resulted in us connecting to a recently started Partners initiative to create a unified identity management system. This initiative serves two important institutional purposes: information security auditing and coordination of user identities for the planned roll-out of the Epic EHR. We have taken the first steps to coordinating our efforts with this process, building on collaborative work we have done with UCLA and support from MGH Research leadership.

Focus on the future
The economist's dictum that sunk costs should be ignored when assessing future value must be rigorously adhered to during a time of significant organizational transformation. It would be easy, for instance, to look at the growth in MORA usage over the past year and a half and regret that current plans suggest that it be superseded by Epic's Release of Information module. While we continue to support MORA's user base, we recognize that the product's utility will wane once adoption of Epic's clinical system commences.

MORA constitutes only one example of this phenomenon. CRP-supported system innovations documented in solid research publications such as HIV FastTrack in MGH Infectious Disease and Rheumatology Oncall in MGH and BWH Rheumatology face difficult futures once eCare is adopted for clinical care in the units where they are used.

In these cases, it is important to focus on the new opportunities that may be created by the large scale transformation of the institutional infrastructure, and by the availability of new technologies, rather than on the difficulty of recreating in the Epic environment replicas of past innovations.

ADAPTATIONS PLANNED

Integrate MGH Research Profiles with the Partners Lighthouse (Identity Management) Project
One of our main focuses in 2014 will be on helping make sure that the planned centralized profile database of physicians, researchers, and staff will meet the needs of MGH research. To that end, we have helped form the MGH Research Profiles Team (currently consisting of personnel from Molecular Biology, the Center for Systems Biology, and the LCS).

Our explorations in 2013 have shown that the needed profile data is housed across diverse sources: PeopleSoft, Insight, InfoEd, Police & Security, MSO, MGH Research, and miscellaneous departmental databases. Each application built by MGH departments must request a feed from these sources, process the feed, and import into their own database. A centralized profile database with a granular "needs based" access, and a web services layer providing data access would streamline the current process significantly. We believe that 80% or more of the data that would sit in this centralized source could be applicable across all Partners entities. We will work with Partners IS to define how central identity management will be designed and implemented so that it can be leverage for the research community. Our early active participation will result in an installation that will benefit the needs of the entire research enterprise.

We will be working with the Partners IS Lighthouse team to: 1) identify key elements from various data providers to be included in the directory, 2) test two-way data exchange with the Hub, and 3) help define access control policies.

Continuing to acquire eCaredata interface expertise through supporting of transition to eCare of Population Health and Clinical Systems.
Historically, the Information Technology Unit, as part of the Laboratory of Computer Science, has been able to directly translate innovation in clinical information systems to

support clinical research. Expertise both in the way clinical information is represented at the institution, and in the technical details about the many different ways the information can be accessed, have been as valuable in researcher as in clinical care and population health.

The advent of Partners eCare is the most important event in the evolution of the Partners clinical and administrative infrastructure. The Laboratory's current involvement in supporting the transition of hospital systems to the Epic platform is enabling unit staff to acquire essential knowledge of how information in eCare is encoded, and how to process eCare data available directly from real-time data feeds (in HL-7) and data service calls, and indirectly from the Enterprise Data Warehouse, as well as from the RPDR .Users of LCS-support clinical systems and TopCare, the LCS-supported population health platform, will be the first to benefit from this developing LCS eCare expertise. LCS work on this transition will guarantee that as data from eCare becomes available to researchers, LCS will already have the skills and experience to enable researchers to use it.

Establishing a research registries service
To complement institutional support for investigator data management provided via REDCap and commercial EDC products, the Information Technology Unit is designing a research registry service to support the needs of mid-level research programs that need greater flexibility than can supported by a free product like REDCap, but that are not large enough to support a unit-based data management operation.

Key components of the service will be the design, implementation, testing and support of research registries using:

- Data dictionary development standards
- Model registry database designs
- Customizable institutional data feeds
- Sproutforms, a convenient tool for data capture configurable for different database designs
- Datasets presented in convenient form for import into statistical analysis packages

All will be based on a platform with full back-up and disaster recovery capability. We are currently negotiating with two units about potential projects to begin early in calendar year 2014.

Exploring development of a platform for engaging patients throughout the research life cycle
The conventional point of view on involvement of patients in research was to view them as potential research subjects. The ITU's past focus on patient recruitment tools reflected that point of view.

In the present environment in which there is a much higher expectation for patient participation in care, there is a growing expectation of involvement of patients in the research process. This point of view in particular is being promoted by the Patient Centered Outcomes Research Institute.

More broadly, the growth of technology-enabled democratization of project funding (Kickstarter) and product development (Quirky) lead us to conceive of a platform for patient engagement very different from a trials recruitment site.

We think this is the right moment to explore development of a platform for patient engagement through all phases of the research life cycle: idea development, funding, tissue acquisition, patient recruitment and dissemination of results.

Biostatistics Unit

Dianne Finkelstein, PhD, Director
Hang Lee, PhD, Lead Statistician

GOALS

The broad goal of the CRP's Biostatistics Unit is to support the biostatistical needs of the MGH's clinical research community by providing timely and onsite consultative biostatistical expertise. Specifically, the Biostatistics Unit's faculty:

- assist in the study design for clinical research grant applications prior to submission;
- support data analysis for IRB-approved clinical studies after funding is obtained;
- guide MGH's clinical investigators in the selection of the appropriate biostatistical methodology and interpretation of data for papers intended for submission to journals; and
- serve the CRP's educational mission via a biostatistics Lecture Series and individual tutorials in collaboration with the Education Unit.

ACCOMPLISHMENTS

1. Overview of Principal Activities:

In addition to the Unit Chief, six additional biostatistical faculty members from the MGH Biostatistics Center participate in the Unit supported by the CRP: David Schoenfeld, PhD, Hang Lee, PhD, Douglas Hayden, PhD, Eric Macklin, PhD, Hui Zheng, PhD, and Brian Healy, PhD Our pool of these MGH faculty PhD statisticians provides a full spectrum of local biostatistical expertise to match the early broad spectrum of needs of the MGH clinical research community.

CRP's policy is to offer free initial consultations of 4-6 hours to all MGH clinical investigators planning an IRB approved human study. Dr. Lee, Assistant Professor of Medicine and Director of the CRP's Biostatistical Consulting Laboratory, personally triages each of these initial inquiries to statistical consultants from MGH physician scientists, taking into consideration the nature of the investigator's need, inhouse biostatistical expertise, and time required.

The Unit also offers both formal lecture series in biostatistics and selective biostatistics work shop sessions of other clinical investigation training courses series, coordinated with the CRP's Education Unit. Together, we offered the annual CRP lectures, "Basic Biostatistics for Clinical Research", as well as individual tutoring on selected biostatistical topics (such as the contribution about Biostatistics support offered to MGH researchers in the "Tools and Technologies" segment of Research Council meeting. We also continued to provide Fellows and junior faculty members (mostly Instructors) MGH clinical investigators open access to the Unit's computing laboratory for their individualized statistical education and support for hands-on data analysis. The average usage was 1-3 hour long one visit per week. This locally available open resource is a powerful tool that allows our Unit to provide the type of individual support that is required to service the community.

The Unit also maintains and supports the MGH's institutional platform of common statistical IT packages, advanced statistical software, and other high capacity computing tools (workstations and a protected network system). These programs are fully supported by the MGH Biostatistics Center's computing facility and managed by the Biostatistics Center's Systems Manager, located at the Biostatistics Center, and the space provides a desktop computer loaded with statistical software. Computer programmers and staff research assistants aided the faculty consultations. These programs include SAS, STATA, Power and Sample Size, Graphad/Prizm, and SPSS connected to Partners Network, of these the last two (Graphad/Prizm and SPSS) were newly added to meet the increased volume of support request, specifically for basic science laboratory experiment and pharmacokinetics analysis using Prizm and factor- and item analyses, ROC analysis, and general

linear mixed effects model using SPSS, The lab also provided updated educational material including on-line tutorial books, and lecture notes developed by Dr. Healy, *http://hedwig.mgh.harvard.edu/biostatistics/software* and *http://hedwig.mgh.harvard.edu/biostatistics/stathelp.*

2. Education:
Drs. Finkelstein and Hayden are participants in delivering two single session CRP lectures the "Study Design: Statistical Perspective session of the Conquering the K: Submitting an NIH Career Development Award Proposal", and "Survey Design". Dr. Healy offers the annual CRP lecture, "Basic Biostatistics for Clinical Research", "Harvard Catalyst Certificate in Applied Biostatistics" which was offered to the local MGH investigators", and individual tutoring on selected biostatistical topics. The aforementioned computing lab supports also the formal course and was used by 30 researchers who received consultation for sessions averaging one hour in length. This volume was decreased compared to that of the previous two years (112 researchers in 2011, 50 in 2012). This is due to the effort that the expanded course curriculum over the past two years included more computational software applications and worked examples of data analysis. Until three years ago, Dr. Healy would do 50-70% of the lab based consultations for the whole investigators in Dr. Healy's course so they continue to meet with him within his extended office hour in the lab. As Catalyst consulting is offering typical tutoring on basic analysis methods, the volume of CRP tutoring had decreased and the topics and levels have become more specific and intermediate/advanced such as correlated longitudinal data, genetic analysis, and multiple imputations technique to deal with missing data arising from randomized clinical trials.

3. Individual Consultations:
The CRP supported 33 (26 new and 7 continued from the previous year) consultations (compared to 36, and 50 in 2011 and 2012 respectively) which were directed to the Unit exclusively from the CRP. The majority (88%) consultations were with junior investigators (Instructors, Assistant Professors, or Fellows, generally functioning in collaboration with senior faculty). Remaining 12% were the consultations with the investigators at Associate Professor and Professor levels, and others such as residents, medical students, research associates, and research nurses and pharmacists. Major areas of the investigator were Medicine (25%), Surgery (21%), Psychiatry (6%), and Pediatrics (9%), and others (ranged 2-7%) included Anesthesia, Dermatology, Graduate Medical Education, Rehabilitaion, Opthamology, and Nursing. A notable change in trend was the increase in the requested consultations from Ophtamology, Nursing, and Pharmacy. The typical consultations involved study design or analysis advice for manuscript preparation, handling IRB submissions, and education on special statistical method topics. The usage statistics (total of 33 consultations with 216 hours) by faculty ranks, departments/specialty, and service types are presented in Figs. 1–6.

Figure 1: Percent of Projects by Faculty Ranks

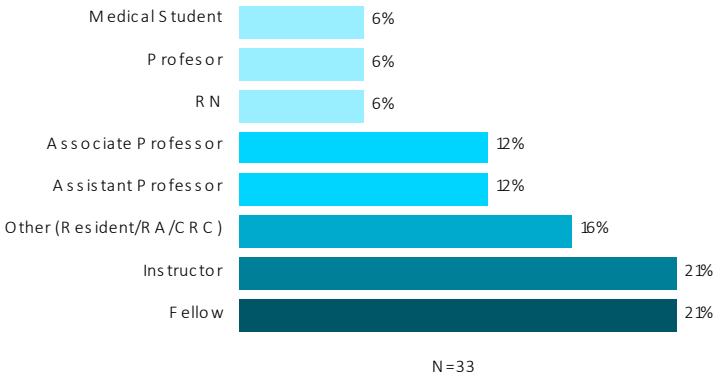


Figure 2: Percent of Projects by Department Specialty

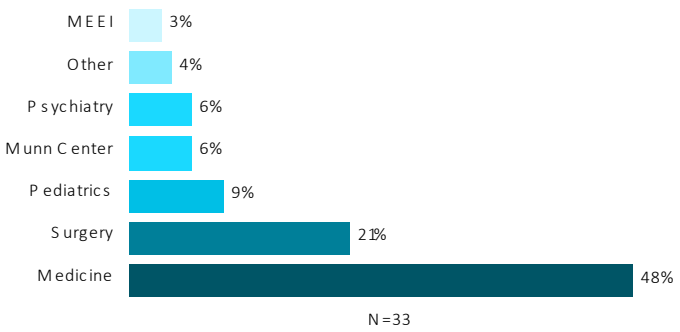


Figure 3: Percent of Projects by Project Types

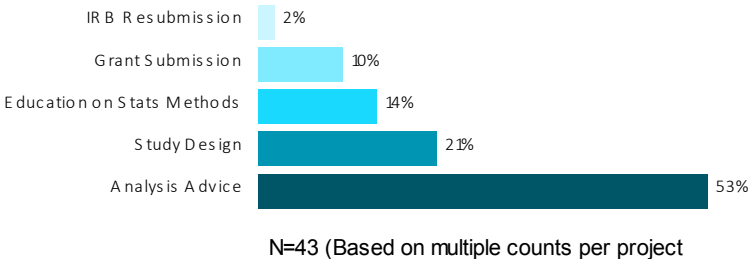


Figure 4: Project Hours by Faculty Ranks

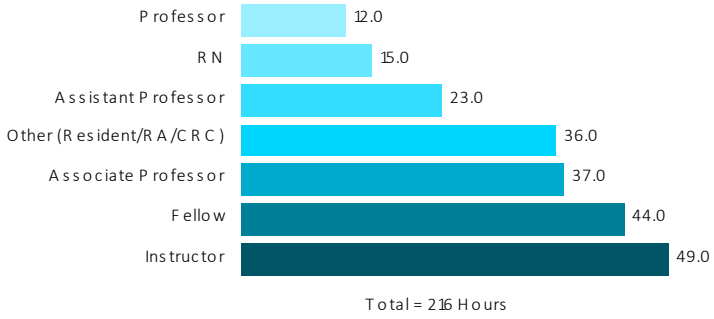


Figure 5: Project Hours by Department Specialty

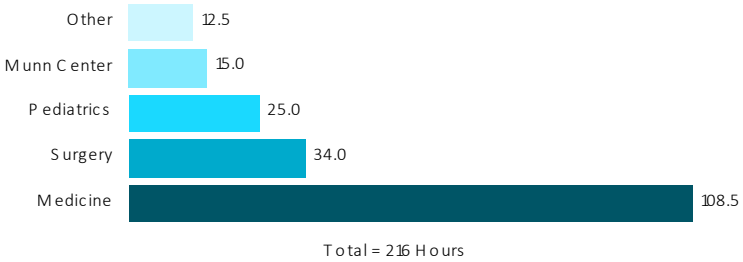
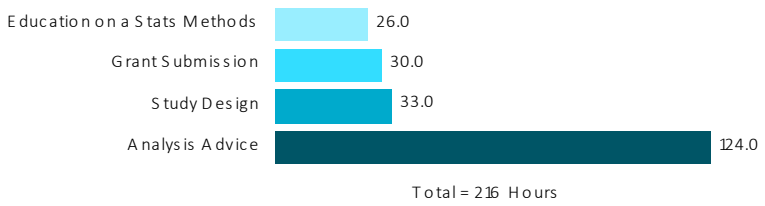


Figure 6: Project Hours by Project Types



In addition to these consultations, the Unit conducted consultations with 82 PIs who contacted the Unit for collaboration on grant submissions/resubmissions by means of a joint effort of the CRP and Catalyst because of the largely increased volume compared to the last year (49 PIs). This includes discussions on study design, contributing the statistical considerations to the application, and committing a portion of their time to the grant research if it is funded. If the grant is funded, the MGH statistician will then shift a portion of their activities to new personnel to make their time available to the new project. This requires support in hiring and mentoring new personnel to smoothly transition project work.

Harvard Catalyst also provides a consulting service for Harvard investigators and some of our statisticians provide consultations for both Catalyst and CRP. However the CRP efforts summarized above are distinct from those offered by Catalyst in several ways. First, the CRP short consultations are guided to the statistical group by CRP faculty and staff who are assisting with other aspects of supporting their individual projects (such as IRB submission, budget preparation etc): Thus these efforts are tightly coordinated by the type of 'one stop shopping' that is unique to the CRP. Second, both the educational milieu and technological support for the biostatistics support services offered by the CRP is local. Thus, courses and computer lab offered by CRP statisticians are available onsite at MGH and at times that are convenient for physician scientists with complex patient care and clinical responsibilities (in contrast to Catalyst courses which reside solely at the Longwood campus and during the daytimes only). Finally, statisticians working with investigators on preparations of their individual grant applications are then available to commit their time to the eventual execution of the grant and research effort as a member of the research team in contrast to Catalyst collaborations where only single consultations for design or analysis plans are supported and there is no commitment to future collaboration. Thus, the spectrum of support provided by CRP's Biostatistical Unit is complete, local (onsite), and comes with a commitment to be part of the research team—unique features that cover the full spectrum of services made available to MGH investigators that distinguish these efforts from the Catalyst supported functions.

LESSONS LEARNED

From Consulting Activities: Locality Matters A crucial function of the program is to provide MGH's clinical investigative community with local statisticians as interactive collaborators and/or co-investigators on their grant proposals through the consulting activities and laboratory serially over time. As evidenced by the markedly increased number of submitted grants in collaboration with Biostatistics Unit increased (from 49 in 2012 to 82 in 2013), it is essential that these collaborations lead to the statistician becoming an active member in the research team if the projects are to be maximally successful as opposed to merely initial preparatory consultations. Such close and evolving interactions are enormously facilitated by the singular and onsite commitment of the CRP Biostatistics Unit to the investigators of the MGH. During the year, Biostatistics Unit offered PhD or MA statistician support (from 5-50% FTE) to several investigators in the MGH, including Drs. James Perrin (Pediatrics), Andrew Nierenberg (Psychiatry), Donna Felsenstein (Infectious Disease), Kenneth Freedberg (Infectious Disease/MPEC), Steven Safren (Psychiatry). In response to a rising

demand for short-term fee-for service consults for data analysis we have opened a Biostatistics Core. This service partners with the CRP service as we are able to offer free CRP consults for "Statistical Analysis Plans", which are then carried out by the Core statisticians. This has been especially useful to departments like psychiatry or nursing who do not have sufficient funding to support a stable portion of a statistician's (FTE) time, but who have a growing need for statistical analysis of their research studies.

From the educational mission: The Need is Expanding The annual CRP Basic Biostatistics Course has enrolled over 300 clinical investigators. Many of the MGH's evolving clinical investigative community are now alumni and have developed a collegial relationship with the Biostatistics Unit through our consultative support activities or tutorials. In many cases, these alumni have become part of ongoing research teams that fully integrates the MGH's biostatistics faculty and results in vastly improved applications as well as quality of ultimate outcomes. There are also educational components within the individual biostatistical consulting projects, several of which have become crucial and now required components of NIH career development awards (K series) that often require statistician co-mentors, a role particularly facilitated by our onsite presence. In response to this expanding demand for biostatistics education, we will expand the biostatics offerings in the coming year in collaboration with the CRP's Ed Unit This collaborative support was launched with a very successful short course in Biostatistics given by Dr. Brian Healy. The course has expanded to offer online homework and blogs for communication between faculty and students. A particularly popular unique aspect of his program is the open office hours where investigators are invited to drop in and discuss their research proposals and analyses. This service also includes standing statistical computing and consult lab in dedicated space contiguous to the Biostatistics Unit. There is an interest in providing additional online lectures and tools to allow investigators to learn statistics at their own timing and pace.

ADAPTATION PLANNED

Unfortunately, many MGH investigators still submit grant proposals with insufficient statistical input and support; these are typically much less successful than those utilizing our services. Hence, it would be useful if the MGH could establish some new mechanism whereby the CRP's biostatistical review could be inserted into the grant submission process, allowing at least 2-4 weeks prior to submission. This additional support would be especially useful for grants that are availing themselves of the MGH's bridge funding to improve the yield on this institutional investment. Similarly, a mandatory statistical review prior to any IRB approval of all clinical studies coincident with that of IRB review or even required prior to it would ensure that study designs are compatible with research goals and might streamline use of valuable committee time. It would be useful if CRP offered a researchers website, with announcements of investigators who recently won grant awards. A useful start would be to create this page which would only be available to CRP staff and faculty describing the projects and potentials for collaboration. Finally, the institution must continue to advertise the availability of statistical support to our clinical investigators more widely and effectively. Dr. Finkelstein regularly attends ECOR meetings as a non-voting member of ECOR; and the members of MGH IRB Panel A (Drs. Finkelstein, Lee, and Hayden attending in the bi-weekly review board meetings), and such attendance would continue increasing visibility of Biostatistics Unit at the MGH.

Genetics & Genomics Unit (GGU)

Susan Slaugenhaupt, PhD & Jordan Smoller, MD, ScD, Co-Directors

GOALS

The missions of the Clinical Research Program's Genetics and Genomics Unit (GGU) are threefold:

- provide consultative support to clinical investigators initiating genetic and genomic studies at MGH;
- educate and support clinical investigators already performing such studies through educational programs and process improvements; and
- serve as a link between the MGH clinical research community and the educational and technological platforms in genetics and genomics of the Partners HealthCare System and the greater Harvard Medical community.

As genomic medicine becomes a reality, the GGU continues to make significant progress in arming MGH clinical research teams with the knowledge and tools needed to incorporate or expand genetics in their clinical research studies.

ACCOMPLISHMENTS

Genetic and genomic research has arrived at a singular moment in which the technology, expertise, and resources for transformative discovery and clinical translation are now feasible. The GGU is fortunate to be situated within a network of world-class scientific and medical research communities that are driving innovation and translational investigation. To enhance the scientific opportunities and resources available to MGH investigators, the GGU has developed collaborative relationships with other key genetics and genomics centers and investigators. Through this network, the GGU has been able to connect MGH investigators with core facilities, consultation and educational opportunities across the larger Partners, Harvard, and MIT communities.

In 2012, the GGU formed a strategic alliance with the *Partners Biorepository for Medical Discovery (PBMD)*. Drs. Slaugenhaupt and Smoller, co-directors of the GGU, were selected to be co-PIs of the PBMD effort at MGH. Biorepositories, particularly those containing samples from consented subjects with links to electronic medical records, are increasingly a crucial resource for scientific discovery and the development of personalized medicine. Through our alliance with the PBMD we hope to facilitate a substantial expansion of the phenotypic and biological sample resource and increase investigator participation at MGH. During this past year, we have continued to broaden this relationship and work to operationalize the biobank at MGH. The study coordinator staff of the Clinical Research Program (CRP) has played a critical role in supporting investigator initiated sample collection and banking through the PBMD at MGH, and the GGU will continue to coordinate these efforts.

The ***MGH Life Registry*** is a new program that grew out of the MGH Strategic Planning Initiative. The GGU co-Directors played a crucial role in the development of the business plan for the Life Registry and in designing its integration into the clinical mission at MGH. This effort will engage our patients and allow them to contribute to our collective efforts to improve healthcare delivery at MGH. The creation of the Life Registry will enable MGH investigators to better characterize disease, identify targets for therapy, and enable personalized medicine in the future. The GGU co-directors will continue to develop this initiative and will work to engage our clinical staff in this effort during the coming year.

The ***MGH Center for Human Genetic Research (CHGR)*** is a trans-disciplinary research center devoted to human genetics and encompassing scientists and laboratories fromnumerous departments at MGH (including neurology, psychiatry, medicine, surgery, and pediatrics). As senior faculty members at CHGR, Dr. Smoller (Director of CHGR's Psychiatric and Neurodevelopmental Genetics Unit) and Dr. Slaugenhaupt have been able to enlist other CHGR faculty to participate in the GGU's research consultation and educational programs. The core facilities of CHGR are also available to MGH investigators seeking genotyping services. Dr. Slaugenhaupt also manages the CHGR's clinical and phenotyping research space on Simches 2, which provides clinical resources (exam rooms, interview/observation rooms, phlebotomy stations, and a specimen preparation lab) for phenotypic characterization of research participants.

The ***Partners Center for Personalized Genetic Medicine (PCPGM)*** is devoted to promoting genetics and genomics in research and clinical medicine and to realizing the promise of personalized medicine by accelerating the integration of genetic knowledge into clinical care. PCPGM offers CLIA-certified genetic testing for a variety of medical applications, core facilities for genotyping, sequencing and gene expression analysis, and IT solutions for the integration of genetics and clinical care. The PBMD is also housed within the PCPGM, and Drs. Smoller and Slaugenhaupt regularly attend the PCPGM management meetings and play a critical role in linking MGH to this resource.

The ***Broad Institute of MIT and Harvard*** is a leading research institute in the areas of genomics, molecular medicine, and the development of novel therapeutic approaches. As an Associate Member of the Broad, Dr. Smoller is able to facilitate access to Broad resources and core facilities for MGH researchers involved in genetic and genomic research. Members of the Broad community have also played an active role in the educational offerings of the GGU and the Broad's highly regarded series "Primer on Complex Trait Genetics" has been offered as a one-day course by the GGU for the past several years.

The ***Harvard Catalyst*** is a pan-Harvard enterprise devoted to facilitating clinical and translational research. Drs. Smoller and Slaugenhaupt are leading the Catalyst Translational Genetics and Bioinformatics education program, with the goal of expanding the genetics curriculum and the associated faculty involved in peer teaching efforts. As more investigators are incorporating genetics into their research, there has been a correspondingly greater need for statistical genetics services at MGH that are not the domain of traditional biostatisticians. After a needs assessment, the GGU has addressed this demand by forging close links to the biostatistical and bioinformatics communities at MGH and other Harvard institutions. As a result, consultations in these areas are now available free of charge to all MGH clinical investigators.

The Genetics and Genomics Unit has thus effectively bridged the gap between these Harvard-wide resources and has significantly enhanced the interactions and research programs of MGH investigators. The GGU has grown in scope and expertise while broadening the level of service provided to MGH and it plays a critical role in forging cross-disciplinary and cross-institutional connections while maintaining a focus on MGH.

Departmental Grand Rounds Program in Genetics and Genomics

The highly successful MGH Seminars in Genetics and Genomics Clinical Grand Rounds Program is developed annually in collaboration with the CRP's Education Unit. The goal of these seminars is to make maximal utilization of the individual clinical departmental Grand Rounds program settings to highlight opportunities and advances in geneticresearch to the clinical community. In this way, both clinicians and clinical investigators can hear of the opportunities made available to them by the latest genetic advances in the context of the individual clinical care issues of their specialty. Such 'context setting' in clinical arenas will ultimately be crucial to the broader adaption of genetics to personalize

medicine in several specialties. Each lecture is thus dedicated to a Genetics & Genomics topic based in clinical medicine and centered on a disease state and clinical case presentation. Through this series, genetic education is embedded within each department and reaches a unique population of clinicians and clinical investigators. The 2013 GGU Grand Rounds Series is illustrated in Fig. 1.

Figure 1: 2013 Grand Rounds

Medical Grand Rounds

March 14

Stem Cells and Chemical Biology: New Avenues to Study Schizophrenia and Bipolar Disorder
Rakesh Karmacharya, M.D., Ph.D., Assistant Professor of Psychiatry, HMS

March 28

Primary Ovarian Insufficiency and Menopause: Insights from Mendelian and Complex Genetics
Corrine Welt, M.D., Associate Professor of Medicine, HMS

May 30

Hypothesis-Generating Research and Predictive Medicine
Leslie G. Biesecker, MD, Genetic Diseases Research Branch, National Human Genome Research Institute

Educational Curriculum

In collaboration with the CRP's Education Unit, the GGU updated its 2012 curriculum primarily in response to feedback from past course participants. This curriculum is primarily aimed at clinical investigators with some specific courses for clinical research coordinators, nurses, and study staff. Course evaluations were extremely positive for each course, rating consistently "very good" to "excellent".

In 2012, the GGU developed a core genetics curriculum to meet the needs of a variety of learning levels in which the GGU draws heavily on faculty in the MGH Center for Human Genetic Research as instructors. This core curriculum is the cornerstone of our program and was taught in 2013. We will continue to focus on the needs of MGH clinical investigators as we create the 2014 curriculum in conjunction with the Harvard Catalyst education group, led by Drs. Smoller and Slaugenhaupt, to expand the MGH's broad educational courses in genetics and genomics. In 2013, the GGU expanded its curriculum by adding a new course, Responsible Conduct of "Omics" Research. This course, which was co-sponsored by Harvard Catalyst, provided a practical introduction to human subjects issues in genetic research and biobanking, data sharing and data use agreements, identifiability, conflict of interest, and other issues relevant to "omics" research. The course was extremely well-received. Fig. 2 lists the 2013 GGU courses and faculty.

Figure 2: 2013 Genetics and Genomics Courses

- **"Welcome to the Genetic Code: An Overview of Basic Genetics"**
  This introductory course reviewed fundamental language and concepts including DNA anatomy and genome organization; genotype-phenotype correlations; basic population genetics; and genotyping.
  Attendees – 88
  Faculty included: *Susan Slaugenhaupt, Ph.D., Jordan Smoller, M.D., M.Sc.*

- **"Genetic Literacy: An Intermediate Guide to Understanding the Language and Concepts of Modern Genetic Research"**
  A course designed to briefly describe the terminology, technologies, and methodologies of modern genetics. Intended for clinicians, investigators, nurses and other clinical research staff with an interest in genetics and genomics.
  Attendees – 66
  Faculty included: *Benjamin Neale, Ph.D., Charles Lee, Ph.D., Joshua Levin, Ph.D.*

- **"A Primer on Complex Trait Genetics: Principles for the Beginning Investigator"**
  This course provided clinical investigators who want to keep up with the changing face of genetic research an excellent opportunity to learn the essential elements of complex trait genetics and gain the latest insights from expert faculty from the Center for Human Genetic Research and the Broad Institute of Harvard and MIT.
  Attendees – 69
  Faculty included: *David Altshuler, M.D., Ph.D., James Gusella, Ph.D., Benjamin Neale, Ph.D., Mark Daly, Ph.D., Christopher Newton-Cheh, M.D., M.P.H., David Beier, M.D., Ph.D., David Milan, M.D., Sean Wu, M.D., Ph.D.*

- **"Responsible Conduct of 'Omics' Research"**
  This exciting new course looking at complex challenges that have become widespread due to rapid advances in genomic technologies, large scale data sharing, and the emerging integration of genetic and biomarker findings into clinical setting. Investigators throughout the Harvard community have increasingly expressed a need to adapt Responsible Conduct of Research training to this new and changing environment.
  Attendees – 90
  Faculty included: *Jordan Smoller, M.D., Sc.D., Elizabeth Hohmann, M.D., Ross McKinney Jr., M.D., Alexandra Shields, Ph.D., Lisa Lehmann, M.D., PhD., W. Nicholson Price II, J.D., Ph.D., Lisa Lehmann, M.D.,PhD., Pearl O'Rourke, M.D., Gretchen Brodnicki J.D., Wendy Wolf, Ph.D., Paula Sciabarrasi, Brent Richter, Patrick Taylor, J.D*

As shown in Fig. 3, the GGU's educational curriculum served a broad range of junior and senior faculty as well as trainees.

Figure 3: Course Attendee's Academic Rank

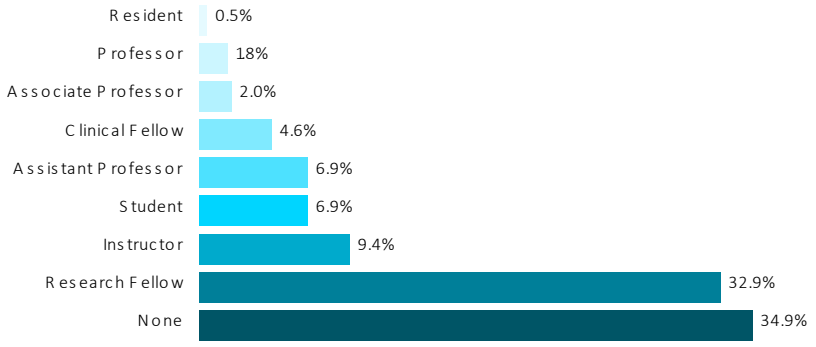
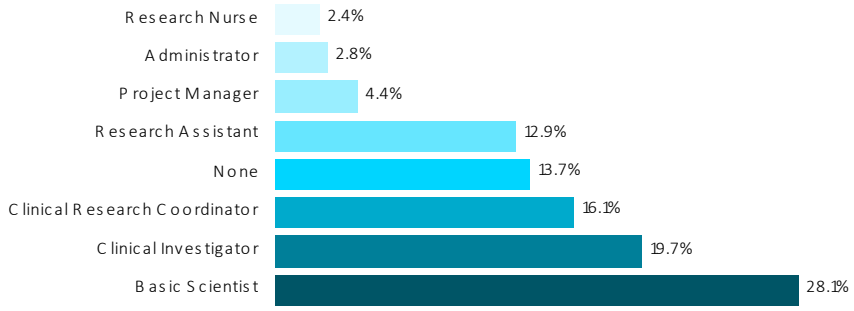


Figure 4: Course Attendee's Research Role



Consultations to Investigators

One of the GGU's goals is to provide consultation and triage for the MGH clinical research community. A consult request is completed online by individual investigators at all academic levels requesting help in genetic study design and execution, human subject protection, career advice, and/or identification of particular resources. Requests are triaged by the GGU and assigned to specific consultants depending on expertise and availability. By collaborating with the Harvard Catalyst's Translational Genetics and Bioinformatics Program (TGBP), the GGU has widened the pool of expertise available to clinical investigators at MGH. In 2013, ten MGH investigators received consultations through joint efforts of the Genetics and Genomics Unit. Investigators came from the following departments, centers, or units: Cardiology, Psychiatry, Neuroendocrinology, Neurology, Urology, and Renal.

Access to the GGU Resources

The Genetics and Genomics webpage within the CRP website has been updated with available resources. The website offers the research community a wealth of educational information and links to resources both within the MGH and beyond.

LESSONS LEARNED

1. Collaboration with Harvard Catalyst

Since the establishment of the CRP's Genetics and Genomics Unit antedated the Catalyst by several years, it served as an important model for the Harvard Catalyst's development of the Translational Genetics and Bioinformatics Program (TGBP). Dr. Smoller was chosen by Catalyst Leadership to direct the TGBP, and Dr. Slaugenhaupt played a critical role as director of education. The TGPB, in partnership with the GGU, provided consultation services to Harvard investigators, and co-sponsored many educational offerings developed in the GGU. In May 2012, Catalyst suspended the successful genetics consultation service. Despite recent refunding of the Harvard Catalyst, this service will continue to be available only through the GGU at MGH. The ever-changing goals and services offered by the Catalyst highlight the importance of the ongoing support offered to MGH investigators by the GGU.

2. Need for expanded availability of services for bioinformatics, computational biology, and statistical genetics.

As a growing number of investigators engage in clinical research involving genetics and genomics, there is an increasing need for sophisticated bioinformatic and computational support. Although the MGH community includes leading experts in these areas, their ability to collaborate and consult is, of course, not infinite. Many clinical and translational investigators are accumulating datasets that may harbor discoveries, and there is a risk that computational and bioinformatic resources will become a rate-limiting step in mining these data and may slow progress in translational research. Expansion of resources in this area (including bioinformatic or analytic core services) may be needed to address these needs.

3. Need for basic genetics education and expansion of online resources
Every year our introductory course offerings, Genetic Code and Genetic Literacy, draw large crowds and the course evaluations highly praise the basic level of the material taught. It has become increasingly clear that the MGH's need for basic genetics instruction is growing as research in all disciplines is increasingly incorporating genomics. We also provide the opportunity for students enrolled in Genetic Code to pre-submit specific questions that they would like answered. In 2013, we had over 400 questions, and we tried to touch on most of the topics during our lectures and/or during the question and answer period. This service has proved extremely popular as it provides an accessible and widely used forum for individuals to ask any question in an 'anonymous' fashion which is important since many clinical investigators are embarrassed at their ignorance in these new technologies. Lastly, we recognize the increasing need for additional online courses and resources. In 2013, our basic course 'Welcome to the Genetic Code' was recorded and made available online and it had over 1000 hits, highlighting the importance of our continued efforts to expand online offerings.

4. Need for diverse and specialized course offerings
The field of genetics and genomics is evolving rapidly, and every year brings new technology and innovations that soon become essential components of clinical research in this area. Thus, we note the continued need for the development of new courses and resource fairs focusing on the latest technology, for example exome and genome sequencing, epigenetics, and proteomics which is a relatively unique problem for our Unit but one that is characteristic of rapidly moving new technologies.

5. Need for expansion of our successful Grand Rounds series
As described above, our collaboration with specific clinical departments to invite speakers focused on using the tools of genetics and genomics to attack a specific clinical problem of interest to the department has been very successful. These talks are very well-received and they have brought in speakers who would not be 'typical' invitees for grand rounds lectures. That said, increasing the number and breadth of clinical departments involved will be a key future goal.

ADAPTATION PLANNED

1. The Genetics and Genomics Unit will continue to work closely with its network of collaborating investigators and centers (CHGR, PCPGM, Broad, and Harvard Catalyst's TGBP) to address the ever-growing needs of the clinical research community at MGH and beyond. These collaborations have led to increased access to resources for MGH investigators, an increased pool of expertise, and expanded opportunities for collaborations. We will continue to serve all academic levels, from clinical fellows to senior investigators, and focus on making connections that will benefit MGH scientists.
2. We will continue to improve our basic genetics curriculum in response to course evaluations and feedback from follow-up surveys. The ability of registrants to ask specific questions at the time of registration has been very well received and enables us to target specific course topics. We will investigate incorporation of this format into other courses.
3. We will continue to expand our curriculum in collaboration with the Harvard Catalyst to meet the demand for specialized courses. Upcoming offerings include:
    - Nanocourses. We will continue to offer half-day nanocourses that provide more advanced education on special topics in the genomics field (including proteomics, pharmacogenomics, use of bioinformatics tools, sequencing, and epigenetics). Topics for these courses are solicited from the community and are often based on evaluations from the core modules. The nanocourse curriculum is updated annually to incorporate emerging methods, tools and technologies. Sample courses include: "Epigenetics", "Pharmacogenetics", "Proteomics", "Metabolomics", "RNA-Seq", and "Next-Generation Sequencing".

- Introduction to "Omics" Research (in development). This 5-day course will draw on expert faculty across the disciplines relevant to omics research and will provide an intensive introduction to the methods, tools, and technologies. Each day will comprise a morning session of lectures followed by an afternoon session of hands-on training in the use of analytic/bioinfomatic methods and tools covered during the morning session.
- "Bedside to Bench to Bedside" (in development) This new course, offered annually, will target clinicians and clinical investigators who seek to expand their involvement in research by identifying opportunities for translating clinical observations to scientific discovery. Topics covered will include: identifying clinical opportunities for discovery (e.g. unusual patients/pedigrees) ; accessing cores, tools, and technologies for data analysis, clinical interpretation of DNA sequence data; design of biomarkers and novel therapeutics.

4. The GGU will continue to act as the docking point for the Life Registry and the Partners Biobank and will work to fully integrate the operations of the biobanking efforts into the clinical mission at MGH in 2014.
5. In 2013, we will pilot recording all of our courses for online posting to increase availability and access to the MGH clinical research community.
6. Educational opportunities will be expanded in 2013 in an effort to keep pace with the rapidly evolving technologies in this area. We are already planning a new Flagship Course "Introduction to "Omics" Research". This annual 5 day course will provide an intensive introduction to the landscape of methods, tools, and technologies involved in omics and systems biology research.
7. "Responsible Conduct of '-Omics' Research" which will provide a practical introduction to human subjects issues in genetic research and biobanking, data sharing and data use agreements, conflict of interest, and other issues relevant to "omics" research.
8. "Bedside to Bench to Bedside" will target clinicians and clinical investigators who seek to expand their involvement in research by identifying opportunities for translating clinical observations to scientific discovery. Topics covered will include: identifying clinical opportunities for discovery (e.g. unusual patients/pedigrees); accessing cores, tools, and technologies for data analysis; clinical interpretation of DNA sequence data; and design of biomarkers and novel therapeutics.
9. To expand the clinical department Grand Rounds series, we will reach out to additional departments with strong research programs, including Anesthesia and Critical Care and Surgery.
10. The GGU will work with the PBMD to facilitate a substantial expansion of the phenotypic and biological sample repository and increase investigator participation at MGH.

Translational Medicine Unit (TMU)

Mason W. Freeman, MD, Director

GOALS

The TMU's overall goal is to facilitate that form of clinical research that moves basic scientific discoveries and new technologies toward the clinic to improve diagnostic capabilities and therapeutic interventions.

Specifically, the TMU works with investigators to:

Advance projects from pre-clinical findings that suggest clinical benefit through the required stages of development necessary to test the concepts in human trials. This work involves:

a) Clarifying the development pathway necessary for a given idea to be taken forward;

b) Providing an assessment of the feasibility and cost of pre-clinical studies, including pharmacology, manufacturing, and toxicology;

c) Obtaining an Investigation of a New Drug (IND) license from the FDA;

d) Preparing the IND for electronic submission;

d) Conducting meetings with relevant regulators at the FDA; and

e) Assisting in the writing of clinical protocols for submission to the Partners IRB

These activities are typically time-intensive projects and require significant commitments on the part of the TMU staff to become familiar with the details of individual investigator's projects in order to facilitate meaningful interactions with the FDA, external contract research organizations, or third part vendors whose expertise is needed to enable a translational project to advance.

ACCOMPLISHMENTS

- The TMU continued to play a key role in encouraging transformation in the internal administrative processes that make it difficult for outside entities to partner with the MGH in conducting translational trials. The workgroup for reviewing IRB reviews of multi-center trials was convened in 2013 and the TMG director was a member of the committee. The committee concluded that the outsourcing of selected multi-center trials to an external, reputable IRB was both feasible and desirable and the Partners Office of Human Studies (OHS), led by Dr. Pearl O'Rourke, is now formulating a set of guidelines that can be implemented to enable investigators to identify studies that would qualify for this process and then proceed down the out-sourced review pathway. A new workforce committee has now been impanelled and the TMG Director will again serve as a member on that committee. It is tasked with designing benchmarks and processes by which the Partners IRB performance in reviewing human studies can be measured. The goal in making the IRB accountable for its review process and procedures is to identify areas where improvements might be made. The TMU continues to play a catalytic role in moving the issue of timely IRB reviews to the forefront of discussions on the clinical research agenda at Partners and the MGH.
- The MGH Strategic Planning Process, initiated in April of 2012, has nearly been completed. In the research sector, three proposals have emerged, one of which is the creation of a Translational Research Center. Dr. Freeman co-chaired the committee in charge of the Translational Research Center concept, along with Dr. Merit Cudkowicz of Neurology, and the committee has submitted a detailed business plan that has outlined the expansion of translational activities at MGH. Much of the content of this proposal has been based on the work of the Translational Medicine Unit of the CRP. The proposal includes plans for a new in-patient clinical trial facility that will work synergistically with the CRC as well as an administrative structure that can promote internal project development as well as partner more effectively with external biopharma companies and non-profit foundations. The Strategic Plan focusing on the Translational Research Center has received endorsement by the oversight committee of the overall Strategic Plan and a final decision on beginning implementation is expected in January 2014.
- The Harvard NHLBI innovation grant that was submitted last year, to which the TMU made a major contribution, was officially awarded in September 2013. This award was one of three made nationally, with the other two going to a five campus consortium of the University

of California and to a consortium of academic hospitals in Ohio. Harvard received the most funding of the three awards, with $12m over 7 years, out of a total of $32m the NHLBI earmarked for the program. Dr. Freeman is one of the 5 members of the Harvard Steering committee for the grant and his domain of expertise will be focused on therapeutic drug development. Joe Loscalzo at the Brigham is the PI of the grant.

- Dr. Yuan-Di Halvorsen played a critical role in enabling Dr. Curtis Cetrulo of Surgery to receive a $4m Dept of Defense award for hand transplantation. The work is centered on providing military victims of traumatic hand amputations the opportunity to regain function. Working closely with the surgeons, Dr. Halvorsen was able to prepare documents that enabled the FDA to accept the proposed hand transplantation program, which was a prerequisite for the DOD to provide funding for the work. As the surgical team had no significant experience in dealing with FDA processes and procedures, they have indicated that without the assistance of the TMU they would not have been able to secure this funding.
- The TMU provided consultative services to a variety of MGH investigators in 2013, a partial list of which is highlighted below to indicate the kind of services TMU provides.
    a. Dr. Xiaying Wang continued to work closely with the TMU in progressing his annexin stroke therapy. The TMU worked with the RVL office to help strategize opportunities for the additional funding needed to advance the program and to interview a potential CEO for a spin-out company that might be the vehicle for that funding input. The NHLBI funded program at the MGH has yearly milestones that must be met and the TMU is playing a critical role in the production and formulation of the drug that were critical to the milestone accomplishments. The MGH is slated to receive ~ $6m via this program if all the milestones are met.
    b. The long-term collaboration with Ed Ryan on the development of a cholera vaccine was successful in enabling this project to receive NIAID funding for further development of the vaccine. This funding enables vaccine formulation to occur via an approved vendor of the NIH and should advance the program to the stage of clinic readiness.
    c. Other investigators from GI, Cardiology, and Neurology were provided extensive consultations on grant proposals or career development plans that had a significant translational component.
    d. Dr, Freeman organized and chaired a session of the Clinical Research Forum held in Washington DC in April 2013. Leaders from Duke and UCSF provided summaries of their ongoing translational research efforts, including a frank discussion of what has and hasn't worked at their institutions.
- The TMU's novel oral, small molecule SGLT2 inhibitor for the treatment of type 2 diabetes successfully completed the major hemoglobin A1c outcome portion of its phase has successfully completed its phase 2b trial of ~300 patients. In addition, a first in patient trial of the same drug has been initiated in Japan, with the TMU providing oversight of that development work. This now marks the fourth non-US country that the TMU has entered in its clinical trial program (Canada, Mexico, Columbia, and Japan). These trials are giving the TMU an enormous experience with both clinical and regulatory authorities outside the US that should be extremely important for the MGH Translational Center, once the latter opens
- Dr. Freeman co-directed the Harvard-wide translational medicine course that was held again on the Longwood campus in June 2013. This course, the first of its kind in the country, ran daily for two weeks and involved ~ 55 post-doctoral students with MD, MD/PhD, and PhD degrees from across the entire Harvard community, including a sizable MGH contingent. The course provides a training foundation in the processes and regulatory hurdles involved

in taking novel drugs, devices, and diagnostics from the laboratory bench into clinical trials. Faculty from the FDA, biotech, pharma, NIH, and the academic world all participated in this course.

- Dr. Freeman met individually with fellows or junior faculty members from Infectious Diseases, GI, Cardiology, and Neurology to provide career counseling sessions in the field of translational research.
- On November 22, 2013, Drs Freeman and Dr. Halvorsen met at the RVL offices with Chris Coburn and Reza Halse of RVL, along with medical leaders from Pfizer, Novartis, Vertex, Biogen-Idec, J&J, and Dyax, to discuss the translational needs of the companies and how the MGH could better serve them. This meeting provided very strong support for the Translational Research Center concept that has been proposed by the MGH Strategic Planning Committee. All of the companies indicated that they would be eager to perform trials in collaboration with the new center once it was operational.

LESSONS LEARNED

- The unique ability of AHCs to identify translational opportunities uncovered in their own patient populations has emerged as a critical differentiator of their value. Leveraging these opportunities is vital to the future success of AHC's in the biomedical research enterprise and several of the most sophisticated AHC's have begun to implement programs that capture this opportunity. In this regard, the MGH is currently not at the leading edge and clearly trails places such as UCSF, Duke, and Vanderbilt in its investment in the key infrastructures required for a leadership position.
- Despite the first lesson learned, translational research efforts that are emerging at academic health centers around the country are still grappling with defining their precise role and service offerings. It is clear that the biopharma industry is seeking more productive interactions and is willing to invest in their local academic institutions, provided those institutions organize their activities in order to satisfy the time and cost constraints that are now a reality in the industry. Feedback from Boston's local biopharma community makes clear that the MGH's proximity to these organizations is a major competitive advantage for us. This means that timely near-term investments can quickly catapult us into a leadership position
- The Translational Research Center proposal that has been submitted to the Strategic Planning Committee of the MGH incorporates all of the key lessons the TMU has learned about productive interactions with biopharma-these include the need for timely IRB review, master service agreements to speed contracting, and the value of identifying well phenotyped patients for clinical trials who can be speedily enrolled.
- Fellowships in Translational Research will require hands-on, intensive supervision, which underscores the need for a dedicated facility in which this training can take place.

ADAPTATION PLANNED

- As outlined in prior years reports, we have embedded our effort in several federal grant proposals that were submitted with investigators who are not members of the TMU serving as PI's. The success of the NHLBI innovation center grant and the NHLBI stroke proposal demonstrate that this strategy can work to provide financial support for the effort of members of the TMU. We plan to extend this model to sponsored research grants that will be funded by private companies.
- The magnitude of the MGH commitment to a new and expanded translational research center should be clear by early 2014 and this should significantly expand the demand for TMU services.

Clinical Effectiveness Research Unit (CERU)

James B. Meigs MD, MPH, Clemens Hong, MD, MPH, and Eric G. Campbell PhD, Co-Directors

GOALS

The Clinical Research Program's Clinical Effectiveness Research Unit (CERU) has three main objectives:

1. To support clinical research aimed to improve the clinical practice of medicine
2. To provide mentorship and practical advice for academic research careers in clinical epidemiology and effectiveness, especially in the MGH-Partners system
3. To support clinical investigators who employ these disciplines to study and improve operations improvement efforts in the MGH-Partners healthcare system

The CERU focuses specifically on the "Second Translational Block" that exists between clinical trial results and the implementation of their advances into clinical practice. Together with the Clinical Research Program's Informatics and Educations Units, the CERU seeks to establish and support the MGH's clinical research infrastructure necessary for clinical effectiveness research, rigorous patient-oriented biomedical investigation that uses comparative effectiveness, clinical outcomes, and allied research approaches to improve our current healthcare delivery. We support trainees at all levels but are primarily focused on MGH's junior faculty investigators. The Clinical Research Program (CRP) believes that from an institutional perspective, patient oriented comparative effectiveness research is one of the most important growth areas in clinical research given the challenges that we face in improving the effectiveness, efficiency, and equity of health care delivery, and progress into learning and improving healthcare delivery systems. Increasingly, organizations will need to be more accountable and transparent necessitating a great need for high quality information to guide thoughtful, data-driven and value-based improvement in patient care in the near future. Careers in this area are increasingly fundable offering the possibility for stable research as well as data-oriented administration especially now that the Affordable Care Act and its Patient Centered Research arm, PCORI, will be funded. Coincident with these externally and internally driven mandates will be a growing need for attracting our best and brightest clinical investigators into this field and providing them with a support matrix like the CRP's CERU to assure their retention and career development.

ACCOMPLISHMENTS

Support for Clinical Effectiveness Research (CER)

In response to increasing health care costs, the need for payment reform, and the continuing gap between evidence and practice, the Federal Government has substantially increased available funding to support comparative effectiveness research (CER). Defined as the conduct of research comparing the benefits and harms of different health care interventions and strategies, CER seeks to assess a wide range of health outcomes for diverse patient populations and subgroups. This research requires the development, expansion, and use of data sources and methods to determine comparative effectiveness and disseminate the results.

The CERU provides MGH's clinical investigative community the only MGH program for individual mentorship in the domains of epidemiology, study design, questionnaire and survey methods, and use of large clinical databases. The CERU also provides data management and analytic support for investigators, operational planning for the use of clinical care data for clinical research, assistance with grant and Internal Review Board (IRB) preparation, and serves as a resource for locating potential funding.

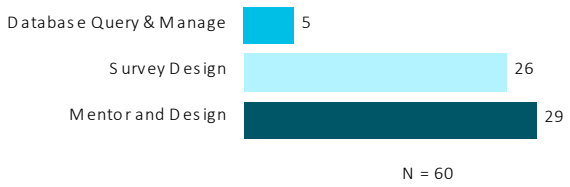
Mentorship and Consultation

The research that the CERU support seeks to address second translational block issues, i.e. translating evidence from clinical studies into clinical practice. During 2012–2013, the CERU provided mentoring services, consultation on career mentoring, hypothesis generation, study design and survey development, and data analysis/data management to the MGH community. The counts and distribution of 55 consults provided in 2012–2103, and the wide breadth of the additional CERU administrative services, available hospital-wide, included advice on IRB submissions, data assembly and management, IT implementation and application, data acquisition and analysis methods, are shown below. In 2012–2013, the CERU served 13 Departments and 7 Academic Ranks as shown in the Figures below. The 55 consultations were provided to 51 faculty members, 83% of whom were junior investigators.

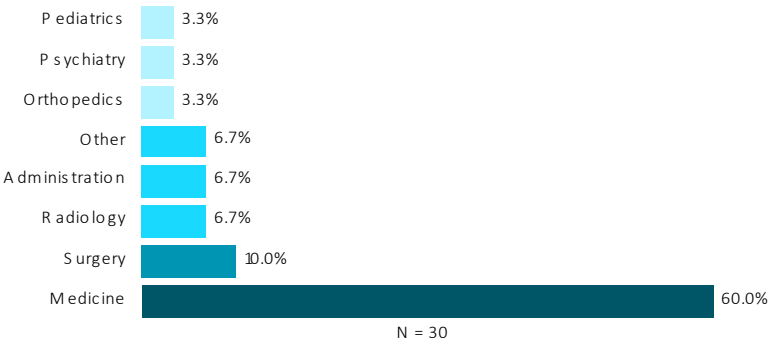
Database Consulting and RPDR support: Wei He, M.P.H. and Sue Regan, PhD provide database consulting and RPDR support services, including: obtaining and providing cleaned RPDR, TSI, IDX and other electronic data searches in Access file format, review of protocol and data collection forms and review of existing or planned data entry systems. In addition the service offers training in skills for day-to-day management of ongoing projects in Access databases such as report and query design, integrating external sources of data (e.g. from laboratories, other sites), and data export for analysis.

Survey Consultation Service: Eric Campbell, PhD, Professor of Medicine and member of MGH's Institute for Health Policy and HMS, provides survey consultations and advice for all aspects of study design, execution and interpretation of survey data.

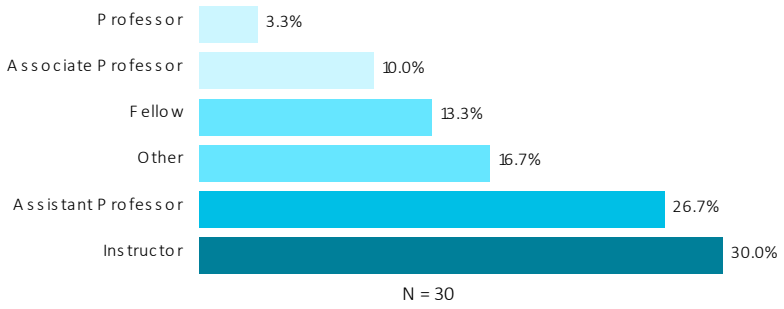
Numbers of CRP CERU Consults, 2013



Clinical Effectivness Unit (CERU): Consultations by Dept. 2013



Clinical Effectivness Unit (CERU): Consultations by Rank 2013



Clinical Innovation Award (CIA): Translating Clinical Insights into Improved Care

The Clinical Innovation Award (CIA) program was initiated in 2005 in collaboration with the CEO, Peter Slavin, MD Solicitation and evaluation of research proposals to integrate clinical insights into improved patient care are conducted using and NIH type review and award model. In 2011, CIA operations were transferred to MGH's Department of Quality and Safety and where it continues to be supported by Michael Jaff, D.O., MGH Leader, Care Redesign. MGH physicians, nurses, and allied health professionals participating in active Care Redesign or Patient Affordability are eligible to apply for these awards. The award supports a portion of the PI's salary to allow protected time to devote to the project (up to 20%); research infrastructure support necessary to carry out the project (e.g. biostatistics, project management, informatics development, study coordinators for data collection, and research assistant/ study coordinator support); and faculty co-mentorship (with the Quality and Safety Office) from the MGH Clinical Research Program to help design, execute and evaluate the projects.

The five awards made in the 2012–2013 cycle are shown in the Table.

2013 Clinical Innovation Award Recipients

PROJECT	LEADERS	ALIGNMENT
IMPACT (Improving Care After Chemotherapy): Through the project, advanced care nurses will call patients with non-small lung cancer or colorectal cancer who are receiving chemotherapy to discuss side effects and how to manage their symptoms. The goal of IMPACT is to improve patient outcomes and reduce utilization, which will improve the quality of care provided and reduce costs.	Theresa McDonnell, ACNP & Jennifer Temel, MD	Lung and Colon Cancer Care Redesign Teams
Enhancing Shared Decision Making for Patients with Acute Low Back Pain: The project will test whether or not using a patient education tool and clinical decision support at the time of diagnosis for acute low back pain improves patients' experience, outcomes, and efficiency.	Leigh Simmons, MD & Karen Sepucha, Ph.D.	Back Pain Care Redesign Team
Remote Glucose Monitoring for More Efficient Insulin Titration in the Patient Centered Medical Home (PCMH): This project will assess the benefits of integrating remote glucose monitoring, through the Diabetes Connect platform, into the MGH Diabetes Care Redesign insulin initiation/titration process. The goal is to increase the volume of patient encounters with the Diabetes Champion without increasing the overall time spent on insulin management.	Nancy Wei, MD	Diabetes Care Redesign Team
Improving the Health of Patients with COPD in the integrated Care Management Program (iCMP): This project will focus interventions on COPD patients in the Integrated Care Management Program (iCMP), including patient education, care plans, and exercise through a remote tablet monitoring system.	COPD Care Redesign Team: Paul Currier, MD; Fiona Gibbons, MD; Michael Sullivan, DPT; Christine Kaliris; Joan Strauss; Sanjay Chaudhary; Ryan Thompson, MD; Joanne Kaufman; Mary Neagle	COPD Care Redesign Team
Applying Systems Engineering and Improvement Science to the MGH Emergency Department (ED): This project will use current systems engineering science to improve frequently utilized processes to reduce ED length of stay and patient care cost, and thus improve the value of care provided, focusing on the processes for urinalysis and plain film radiography.	Benjamin White, MD	Patient Affordability

The status of 5 awards is as follows:

Title: Enhanced shared decision making for patients with acute low back pain

PIs: Leigh Simmons, MD and Karen Sepucha, PhD
Project aims: improve patient's decision making and confidence in their ability to self-mange their back pain; reduce inappropriate imaging studies and specialty referrals without negatively impacting on health outcomes.

Progress to date: The protocol, including patient surveys and letters has been approved by the IRB. A core study team has been identified to implement the study in the Medical Walk-In Unit and in Internal Medicine Associated Urgent Care clinic. Patients previously seen for back pain in the clinics were identified and several have completed a telephone needs assessment which is allowing the study team to finalize the survey instruments.

Title: Applying systems engineering and improvement science in the MGH Emergency Department

PI: Benjamin White, MD
Project aims: to use current systems engineering science to improve frequently utilized processes in order to reduce ED LOS and patient care costs; improve the value of care provided.

Progress to date: the protocol has been approved by the IRB. The PI has finalized plans for the initial interventions and confirmed and completed pre-intervention needs analysis and data collection. The PI has piloted interventions within both processes including a more rapid urinalysis collections and analysis processed and a technologist-based radiology transport pilot process. Preliminary results are being analyzed.

Title: IMPACT: Improving Care after Chemotherapy

PI: Theresa McDonnell, RN, NP and Jennifer Temel, MD
Project Aims: to examine changes in patient-reported symptoms during the first two cycles of neoadjuvant or adjuvant chemotherapy for NSCLC and CRC among patients who receive standard care plus a practice nursing intervention relative to patients who receive standard care alone.

Progress to date: The protocol has been approved by the IRB. The PI held two focus groups with the MGH Cancer Center NP staff to obtain their perceptions of our current model of post-chemotherapy care and the proposed intervention. The feedback from the focus groups has been analyzed and incorporated into the project intervention design. The study team established a research plan and developed a REDCap research database and developing the staff orientation plan for NPs who will be participating in the protocol. Accrual of study subjects has begun.

Title: Randomized Controlled Trial of a Multifaceted Tablet Based Intervention for Preventing Readmissions for Patients with COPD

PI: Paul Currier, MD, Fiona Gibbons, MD, Michael Sullivan, PHS Information Systems
Project Aims: reduce COPD related readmissions in the iCMP cohort compared to a control group at 90 days; improve level of activity in the group receiving intensive physical therapy as measured on the 6 minute walk test at 90 days.

Progress to date: the research project consists of a RCT of the MGH integrated Care Management Program (iCMP) management of COPD patients admitted to hospital. Groups randomized to intervention would receive the tablet; the control group will receive an evaluation of their physical capacity at the beginning and end of the study. The Tablet will facilitate tracking patient metrics such as symptoms, oximetry, medicine compliance, and physical activity. Pertubations in these metrics will be reported to the patient's Nurse Care Manager and/or PCP who will reach out to the patient. The study team has defined the details of the study process flow for obtaining informed consent; evaluating educational triggers to be loaded onto the tablet; electronic alerts to the study coordinator when a patient in the iCMP/COPD cohort utilizes the ED and/or is admitted to the hospital; defining the home-based exercise program, and Identifying post study survey tools.

Title: Remote glucose monitoring to improve insulin titration in the patient-centered medical home

PI: Nancy Wei, MD

Project Aims: Assess the benefit of integrating remote glucose monitoring into the Diabetes Care Redesign insulin initiation/titration process on improving clinical efficiency (frequency and quality of diabetes-related encounters), provider and patient satisfaction, and glycemic control (HbA1c change).

Progress to date: PI has established the participating practices (Beacon Hill Primary Care, MGH Back Bay, Revere Health Center, Charlestown Health Center, and Bulfinch Medical Group).In collaboration with the Center for Connected Health, the PI has determined the appropriate remote monitoring tools and the protocol was approved by the IRB in November 2013. The monitoring devices will be available for clinical use from the Center for Connected Health at the beginning of December. IRB approval and immediate generation of potential participant lists for the practice DCC teams to review. The MGH Clinical Research Program will support recruitment efforts beginning in December 2013. The PI is meeting with the participating practices to finalize the recruitment process and integration of the remote monitoring system into their clinical work flow including how to provide the patients with the devices and educating them to their use.

CERU Clinical Effectiveness Research Course: Workshop on Study Design: Using MGH Clinical Care Data for Clinical Effectiveness Research

Since 2010, the CERU has offered a Clinical Effectiveness Research course in collaboration with the CRP Education Unit. This 5-session workshop takes about 20 investigators step-by-step through the process of defining a CER hypothesis, obtaining expedited IRB approval for a data query, designing an RPDR data query, and converting the "raw" clinical data received in a research-caliber analytic database. The 2012–2013 curriculum is shown in the Table below.

Date	Session	Content	Format	Required Coursework
Session 1 Nov. 5 3:30-5pm Garrod-Mendel	***Framing a Testable Hypothesis*** James Meigs, MD, MPH Clemens Hong, MD IRB –Megan Morash	**Introduction to Epidemiology:** • Instruction on developing a testable hypothesis from a clinical question. • Instruction on choosing the appropriate study design. • Defining exposure and outcome. • Identifying potential biases and confounders related to your clinical question and to using clinical care data. • Instruction on how to prepare a medical records IRB submission.	Lecture & Discussion	**Assignments to be completed prior to Session I:** ☐ Review required readings (3 articles)
Session 2 Nov. 12 3:30-5pm Garrod-Mendel	***Using MGH Clinical Care Data*** Steve Atlas, MD 3:30-4:00pm **Overview of Research Using the *Research Patient Data Registry (RPDR)*** Clemens Hong, MD Stacey Duey 4:00-4:30pm Questions 4:30-5:00pm	**Using Large Databases:** • Highlight large databases available for use at MGH for research purposes. • Validation studies of large databases. • Use of large databases for quality improvement research. **Introduction to Research Using the RPDR** • What is the RPDR? • Validate outcomes - what data can and cannot be obtained using RPDR • Present examples of research projects that used the RPDR for data collection	Lecture & Discussion	**Assignments due for Session 3:** ☐ Prepare a written hypothesis and outline a study design - to be discussed during the workshop (bring 5 copies). ☐ Review online training module for medical records IRB submissions.

Date	Session	Content	Format	Required Coursework
Session 3 Nov. 19 3:30-5pm Garrod-Mendel	***Workshop: Developing a Testable Hypothesis and Choosing a Study Design*** James Meigs, MD, MPH Clemens Hong, MD	• Developing a testable hypothesis from a clinical question. • Choosing the appropriate study design to answer a clinical question.	Workshop	**Assignments due for Session 4:** ☐ Prepare and submit your medical records review application to the IRB for review and approval. *It must be approved before Session 4.* ☐ Obtain access to RPDR, complete RPDR online training, and follow instructions on Assignment Sheet for RPDR workshop preparation.
Session 4 Dec. 10 3:30-5pm Garrod-Mendel	***Research Patient Data Registry (RPDR) and Demonstration Workshop*** Stacey Duey	**Working with RPDR:** • Create an RPDR query using class project • Request data using the RPDR data wizard. • Understand the data returned in a query	Workshop	**Assignments due for Session 5:** ☐ Prepare a 1 page project outline to be discussed in small groups during the Workshop in session 5 ☐ Include: - Hypothesis - Study design - RPDR search strategy - Results (if you have any) - Future direction for project
Session 5 Dec. 17 3:30-5pm Garrod-Mendel	***Project Discussion*** James Meigs, MD, MPH Clemens Hong, MD	Divide into small groups and discuss your project and obtain feedback from the participants and preceptors.	Workshop	Goal is to have a project draft to move onto the next step of a consultation with an expert on using the RPDR.

No class on 11//13. If you need assistance preparing your IRB submission or using RPDR see assignment sheet for details on office hours.

CRP Facilitation for Obtaining PCORI Funding: Building Infrastructure for Patient and Stakeholder Engagement in Research

The Patient Centered Outcomes Research Institute (PCORI), authorized by Congress through the Affordable Care Act will provide 3.5 billion dollars in funding for clinic research through 2019. This represents the single largest increase in clinical research and comparative effectiveness research funding of our era. However, the mandate for patient and stakeholder engagement in the formulation,

implementation and dissemination of research represents a paradigm shift for which clinical researchers are currently inadequately equipped to respond without additional support. To address this low success rate and increase patient and stakeholder engagement in research, the CRP CERU took the lead in organizing a response to increasing funding opportunities both from PCORI, other NIH institutes and foundations for increased patient/stakeholder engagement in research.

In October 2013 the CERU convened an interactive multi-stakeholder meeting, where patients, investigators from multiple disciplines and PCORI representative began to identify gaps and challenges faced by MGH investigators as we seek to meaningfully engage patients and stakeholders in this new paradigm of research. This wide ranging discussion included presentation on patient engagement, detailed discussion and question and answer on PCORI's approach to funding, patient and researcher panel discussions, and group activities and facilitated discussion on what the CRP and MGH practically do to build out the infrastructure to meaningfully engage patients in research. The conference generated potential next steps including practical workshops on patient engagement, patient and researcher education activities through the CRP's Education Unit, and review of summary statements and creation of a tip sheet and boilerplate templates to support researchers preparing PCORI grants. Further, the group favored exploring other institutional activities including a patient family advisory council focused on research, interim funding for PCORI investigators, review of IRB provisions surrounding PCORI grants, and development of informatics tools to support patient identification and engagement in research.

Overlap with Harvard Catalyst: None
The CRP's CERU is a unique local resource for MGH clinical investigators engaged in clinical effectiveness research. Consulting, mentoring and resource linking for clinical effectiveness research are not offered through Harvard Catalyst, especially for training in uses of clinical research resources at MGH.

LESSONS LEARNED
The CERU has become a successful and well-established part of the MGH research and operations mission. The CERU helps create an institutional environment of research curiosity and collaboration across different departments and between administrators and researchers in areas that are crucial for our evolution towards creating a data driven, learning environment for our healthcare system, as we transition to an accountable care organization. The CERU represents a very strong MGH institutional commitment to research infrastructure, consulting, and career development in Comparative Effectiveness, Clinical Outcomes, Clinical Epidemiology, Care Redesign, Patient Affordability and Accelerating Improvements in Efficiency research. In this sense MGH remains visionary in clinical research support, as nothing comparable is available elsewhere in Partners or the Harvard Catalyst systems.

ADAPTATIONS PLANNED
CERU adaptations to its support services considered for 2013–2014 will provide the consultative and mentoring expertise for MGH investigators interested in using the MGH and wider Partners clinical data resources to:

- Define patient cohorts for further study
- Develop patient and provider recruitment strategies for clinical trials or for survey-based research
- Create patient clinical research databases for epidemiological studies, quality improvement and operations research
- Formulate testable hypotheses and rigorous study designs
- Prepare grant proposals
- Increase support for rigorous operations research, especially that focused on Care Redesign and Patient Affordability

We provide a critical and unique platform of institutional resources to connect clinicians, MGH leadership and clinical investigators with study design and IT expertise. These collaborations are the fount of new solutions to disease management and healthcare delivery problems at MGH. Collaborations also nurture new careers in patient oriented clinical investigation and increasingly support MGH operational leaders seeking data-oriented administrative careers.

Adapting to changing environments going forward, including the ongoing implementation of an Accountable Core Organization (ACO) model, we will continue to develop clinical research personnel capability and clinical research infrastructure. A major adaptive initiative of the CERU is to further establish highly detailed retrospective, longitudinal data resources for high quality clinical epidemiology research. Such research will inform ongoing and future real time population research infrastructure development. These efforts are in natural collaboration with Dr. Meigs and Hong's MGH General Medicine Division colleagues Dr. Steve Atlas, Director and PI of the MGH Primary Care Operation Improvement's Linked Loyalty Cohort and Dr. Jeanne Triant, Co-Director, and the infrastructure of the General Medicine Unit's Practice-Based Research Network (PBRN)'s Linkage Cohort. The Linkage Cohort-PBRN are mirror-image clinical operations-clinical research resources that increasingly serve clinical research goals and hospital quality improvement, evaluation, and patient care efforts.

The MGH CRP CERU is actively building a research data infrastructure that helps MGH become a learning health care delivery system. The approach leverages high quality data to both improve front line healthcare delivery and conduct clinical effectiveness, clinical outcomes, health services, and operations research. Strongly linked to these efforts is our ongoing focus on career mentorship for clinical epidemiology/effectiveness investigators. We continue to develop a strong cohort of MGH researchers pursuing academic careers in clinical effectiveness, clinical outcomes, and health services research. Ultimately, these combined efforts will help the MGH position itself well to transition to an ACO and to compete successfully for the increasing federal resources to support CER and patient centered outcomes research

Adaptions under development

Pipelines and Consults: The CERU is always seeking to find new ways to identify talented future MGH research faculty by increasing interactions with trainees (residents and fellows) through consulting with faculty in positions to mentor these individuals. As an example, the Harvard Center for Primary Care at Harvard provided ~$5 million in funds to Harvard affiliated teaching hospitals, including Internal Medicine Associates and the Chelsea Healthcare Center at MGH to transform the delivery of primary care in the practices in which internal medicine and primary care residents train. An explicit goal of the funding is to involve residents and medical students that work in these practices in operations improvement and the generation of academic products for this work. Dr. Hong currently provides active consultation to multiple primary care junior faculty leaders that are working with residents on practice improvement projects and clinical effectiveness research. This will continue to provide the opportunity to both engage existing MGH faculty in research activities and identify and support trainees with high potential for research careers who work with MGH faculty on operational research projects.

Expand model for Operational Research Engagement: Dr. Hong remains a member of the Massachusetts General Physicians Organization (MGPO) Performance Analysis and Improvement (PAI) publications group. Through this role and other opportunities, the CERU provides consultative support to the MGPO in analysis, evaluation, and publication efforts surrounding the MGPOs quality improvement activities. Dr. Hong continues to lead efforts to expand the CERU's role in supporting MGH faculty and operational leaders in developing research questions and methods that lead to publications in peer-reviewed literature. The goal is to create a self-supporting model for the MGH in operational research activities, and expand access to CERU resources to operational leaders interested in developing hypotheses and designing rigorous evaluations of their operational projects.

Patient Engagement and Research

Given the immense opportunity that PCORI represents for MGH's clinical research enterprise, the CRP plans to lead institution-wide efforts in building infrastructure to compete for PCORI and other patient engagement funding proposals. Building on the CERU's robust support infrastructure and recommendations from the multi-stakeholder meeting, the CRP intends to pursue 5 major areas for work moving forward:

1) Lead creation of a PCORI working group consisting of MGH investigators. The working group will identify needs and advocate for changes to support MGH PCOR investigators, including overseeing development of a research patient-family advisory council, IT tools to support identification of patients interested in engaging in research, reviewing IRB provisions to align with PCOR approaches, and pursuing interim funding for PCOR investigators and seeking additional qualitative support for PCOR research activities. The PCORI working group will also explore pre-submission grant review or consultation services for PCOR researcher responding to PCORI funding opportunities. The working group will help build a community of PCOR investigators at MGH.
2) Create workshops and courses through the CRP education unit to support PCOR researchers. This will entail workshops and courses training patients and other stakeholders and PCOR investigators for meaningful stakeholder engagement in research. The content will contain practical content focused on implementation challenges (engaging and selecting the right patients for PCOR, education for patients on research approaches) and methods (e.g. qualitative/facilitation approaches)
3) Support linkages between researchers and patients. We will work with patient-family advisory councils and work towards development of a patient-family advisory council to support greater engagement of patients in research. We will also work with the CRP IT unit to considering adapting the RSVP platform, designed for engagement of patients in clinical trials, to identify and engage patients as collaborators on research teams.
4) Create ongoing process for reviewing PCORI developments, past grants and summary statements and prepare tip sheets (do's and don'ts, guidelines and recommendations) and boilerplate templates for use in future MGH PCORI proposals.
5) Create a dedicated CRP webpage to support researchers interested in patient and stakeholder engagement in research. The website will house education materials, a tip sheet, boilerplate templates, and other materials from ongoing review of PCORI materials, and past grants submissions and summary statements.

Additional considerations include adding or changing personnel available through the CERU to assist CER investigators, including supporting development of qualitative expertise to support PCOR by adding a qualitative researcher as a CERU consultant, and bringing or supporting development of a patient research engagement expert by adding a patient research engagement expert. Through these activities, CRP hopes to create a robust infrastructure to support development of PCOR researchers at MGH and improve MGH's success rate in competing for PCORI funding while making research more relevant to patients and families at the same time.

Research Space Management Group

Program Review 2013

Michael L. Fisher, LP.D, Director

Department Overview

The Research Space Management Group (RSMG) fosters an equitable and cost-effective use of research space and resources through data collection, unbiased analysis, resource administration and efficient project management while maintaining MGH and government policies. Partnering with the MGH research community and hospital leadership, RSMG provides operational and client services to facilitate research efforts.

RSMG is responsible to the Executive Committee on Research (ECOR) for all aspects of research space allocation and management. The Group works with ECOR, the Research Space Advisory Group (RSAC), MGH Research Management, and MGH leadership to develop and implement research space allocation strategies that support overall institutional research objectives while, at the same time, optimizing the use of current and projected research space.

The Department is responsible for planning reassignments and relocations, renovations of existing space, and the construction of new research space. It strives to improve and coordinate processes for the introduction and utilization of space utilization criteria, density metrics, benchmark construction standards, and equipment standards for use during programming, planning, and design to ensure adherence to the principle of exchangeable functionality.

RSMG compiles annual surveys of departmental research space utilization and reviews the results with Department/Center Chiefs or Program Directors to review past performance, anticipate changing space needs, and to develop plans for anticipating future research space requirements. Research Summary Reports which list annualized MTDC expenditures and IC recoveries, as well as nasf and densities, are provided to the Senior Vice President for Research, Center Directors, and Department and Unit Chiefs throughout the year upon request.

The Research Space Management Group is responsible for developing and ensuring adherence to safeguards designed to prevent loss, damage, or theft of all equipment purchased with research funding valued at $5,000 and above. Responsibilities include maintaining an equipment inventory database, tracking equipment locations, completing regularly scheduled audits, overseeing equipment disposition, and providing advice concerning the use of research-related equipment.

Another important task which contributes to standardization and significant-cost savings involves the creation of furnishing plans for all research renovation and construction plans; this entails working closely with the eventual user, the architects, and the vendor to ensure that present and future needs are met, ordering the furniture, and coordinating its delivery and installation.

RSMG manages the research facilities on both the main campus and in the Charlestown Navy Yard providing on-site day-to-day interface with the research community and numerous support departments. RSMG operations staff is on call 24/7 to respond to critical building issues affecting research areas. The RSMG facilities team also manages the Research Support Services Core which provides essential services (autoclaving, glass washing, coordination of a limited number of central copiers, darkrooms, and media preparation), to research groups in a cost-effective and efficient manner.

Staff Transitions

The Department experienced a number of transitions in critical positions over the past year but was able to continue to provide data, services, analyses, and project expertise and management to the research community. Lauren Barsanti who was a member of the RSMG group for ten years providing an expertise in a number of areas, including data analysis, resigned to accept a position in the Psychiatry Department. Maureen Lynch, a former laboratory manager with extensive bench experience, joined us as a Space Analyst in the fall and has integrated well with the RSMG family and proved to be a quick learner. Erin Venezia became a part-time member of the Service Core last spring and is doing an excellent job of providing key services to the Core's clients. We are presently actively recruiting to fill our existing vacancy.

FY '13 Achievements

During FY '13 the Research Space Advisory Committee (RSAC) reviewed, discussed, and provided recommendations on several issues relating to optimal use of existing and potential MGH research space. The committee is co-chaired by the Senior Vice President for Research and the Chief of Psychiatry; membership includes senior leadership from MGH Research Departments, and senior members of the RSMG Staff. The Committee is charged with maximizing opportunities to accommodate research growth and improve recovery of indirect costs (IC) without increasing the MGH research footprint.

In FY '13, renovations were completed on the build-out of new laboratory space at 400 Technology Square in Cambridge for the Phillip T. and Susan M. Ragon Institute for AIDS Research. The 50,300 nasf square foot facility includes a BL3 lab that will provide scientists in the community with access to a dedicated cell-sorter, the only such facility within 45 miles of Boston. It also includes a mouse vivarium, 12 tissue culture rooms, and a 160 seat conference center with state of the art audio-visual and audio-conference capabilities.

As part of the backfill process for the former Ragon space in Building 149, a number of laboratories were allocated space after a comprehensive application and review process. Overall, six Departments and one Center will receive additional space totaling approximately 20,000 nasf. Allocation amounts approved by RSAC range from 600 nasf to 6,000 nasf. The additional space allocations helped to fulfill several outstanding space requests which were necessary in many cases to meet program requirements, house state of the art equipment, and provide core services for multiple groups.

During the year, numerous design/development and furniture meetings were held with these groups to ensure that the redesigned laboratory space would meet a majority of their requirements while, at the same time, provide much needed upgrades to aging building infrastructure. After many meetings and detailed reviews of programs and equipment, construction documentation was completed this past summer. As a result of this work in FY '13, Phase I which involved renovations to the dry office areas on the 4th and 5th floors of 149 was completed in January of this year. The lab renovations on the 6th floor (Phase II), currently stalled due to an unexpected delay involving the receipt of final permits, will resume shortly and should be completed this summer. The 5th floor (Phase III) laboratory renovation is expected to be complete by late fall if everything goes according to plan.

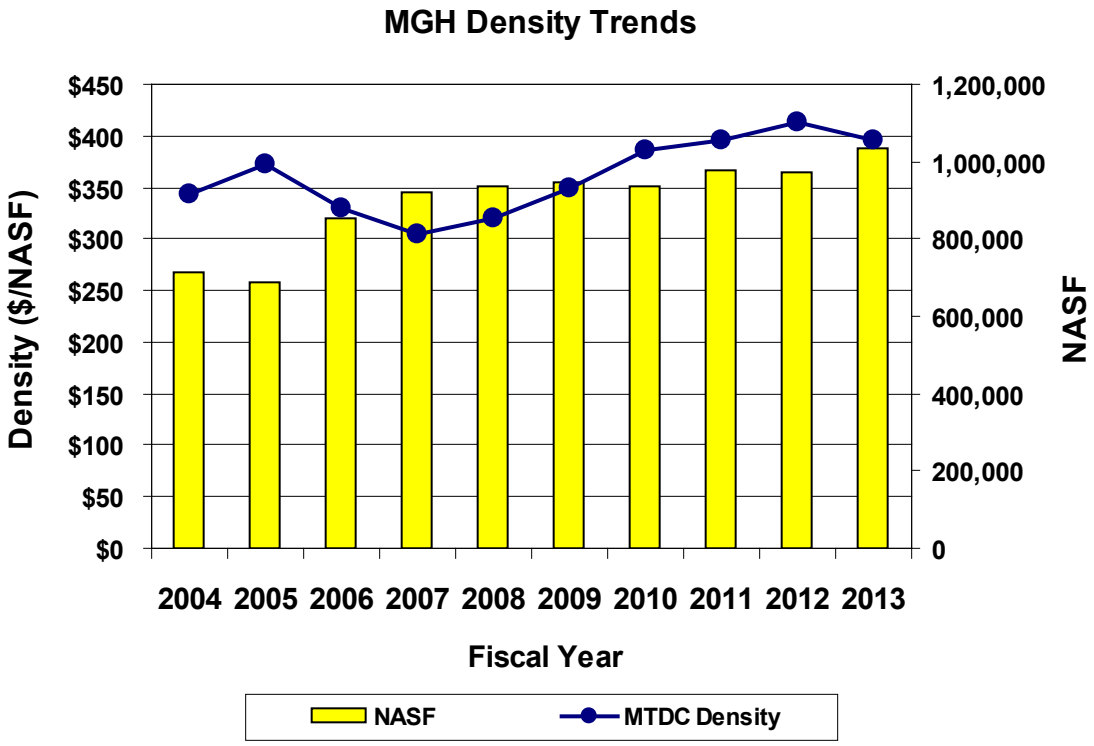
Working with RSAC, in FY'13 RSMG was also able to negotiate and implement the allocation of additional space to several groups with space needs. On the main campus, the Surgery and Neurology Departments, as well as the Wellman Center, added sufficient wet lab space to positively impact their research. In Building 149 an investigator in the Wellman Center was allocated a small amount of additional laboratory space for his program and he gained the opportunity to work closely with collaborative scientists in the CBRC.

In addition to the Ragon Backfill Project, RSMG initiated and coordinated numerous projects during the year that helped to further densify MGH research space. In total, RSMG completed 41 construction and renovation projects totaling over $31 million and involving more than 90,000 nasf. RSMG currently has 33 projects in process totaling over $11M and covering over 100,000 nasf.

Density Activity

As shown in the graph below, in FY '13, overall MGH onsite research IC density decreased by 10% from the FY '12 density to $167/nasf. During the same period, MGH's onsite research footprint grew by approximately 6.5%.

One factor in the decrease of IC density in FY '13 was the addition of 50,300 nasf of onsite research space at 400 Tech Square for the new Philip T. and Susan M. Ragon Institute. Additionally the hospital added 16,900 nasf of leased research space at the Shriners Burn Institute in FY '13.



Survey Activity

In 2013 RSMG analysts surveyed all of the Research Departments and Thematic Centers to confirm research space allocations and provide the information required for database and floor plan modifications. As part of the survey process this past year there was particular focus on the designated locations for all research activities, to ensure that "non-research" space (i.e., space not supported by research dollars) was identified.

With the assistance of many Principal Investigators, research administrators, and grant managers, RSMG was successful in identifying locations for the activity supported by over 1,750 funds, previously unassigned to research-supported sites. Of these, approximately 1,100 are identified as clinical trials, with the balance a mix of clinical research, training, foundation, and sundry funds.

As a consequence of this effort, RSMG and Institutional leadership are closer to understanding and documenting where all research activity occurs, at both onsite and offsite locations. Going forward and with the guidance of leadership, we will visit and evaluate these locations to better define the space, the activity within the space, and the appropriate IC rate for funding associated with the space.

Space Management System Database Development

Throughout Fiscal Year 2013, MGH's RSMG continued its collaboration with Partners Real Estate and Facilities and Brigham and Women's Hospital's RSMG on a redesign of the Space Management System (SMS) database. The project is managed by the Partners IS Research Applications Group. User testing which began in the spring of 2013 led to further discussions regarding both MGH and BWH specifications, system usability and efficiency, reporting capabilities, data migration, and final implementation.

With both Institutions and the Applications Group working together, one more round of testing is expected in mid February with the expectation of "going live" in mid March. This new enterprise system is web based and will provide a secure repository of information regarding research space, people, agreements, and assets at MGH and BWH. Future plans include making this system available to other Partners institutions where research is conducted.

MGH Research Safety Committee

The Senior VP for Research initiated an intensive effort to improve the effectiveness and visibility of Safety awareness within the MGH research community during this year. RSMG provided floor plans of all research departments for the inaugural Safety Committee meeting and updated the floorplans to indicate responsibilities of the Departmental Safety Coordinators. The Department also created and manages the master spreadsheet of all departmental safety coordinators and their many delegates. The Director of RSMG is a member of the small Research Safety Executive Committee as well as the larger Committee, while RSMG staff members are active members of the five task forces established as part of this initiative.

Research Capital Equipment

During 2013, RSMG received information on 518 newly purchased pieces of capital equipment and reviewed each item to determine if it met eligibility criteria for inclusion in the Research Equipment Inventory Database; 100% were deemed eligible items. These items, which can be placed in any MGH building where research occurs, were located and tagged following which detailed data about the equipment was entered into the database.

RSMG conducts annual statistical "mini-audits" (as approved by MGH's external auditors) to validate the accuracy of the equipment records maintained in the Research Equipment Inventory Database (an integral component of SMS). These audits provide RSMG, Research Management, Research Finance, Capital Accounting, and the external auditors with frequent feedback concerning the adequacy of various components of the capital management process allowing for mid-course process improvements when indicated.

Six audits were performed during 2013; a total of 610 pieces of equipment were randomly selected. Total population size of equipment eligible for audit was 3,616; this is a statistically acceptable sample of the total population of research equipment at MGH. According to applicable audit guidelines, a successful audit is defined by audit success of 99% or greater.

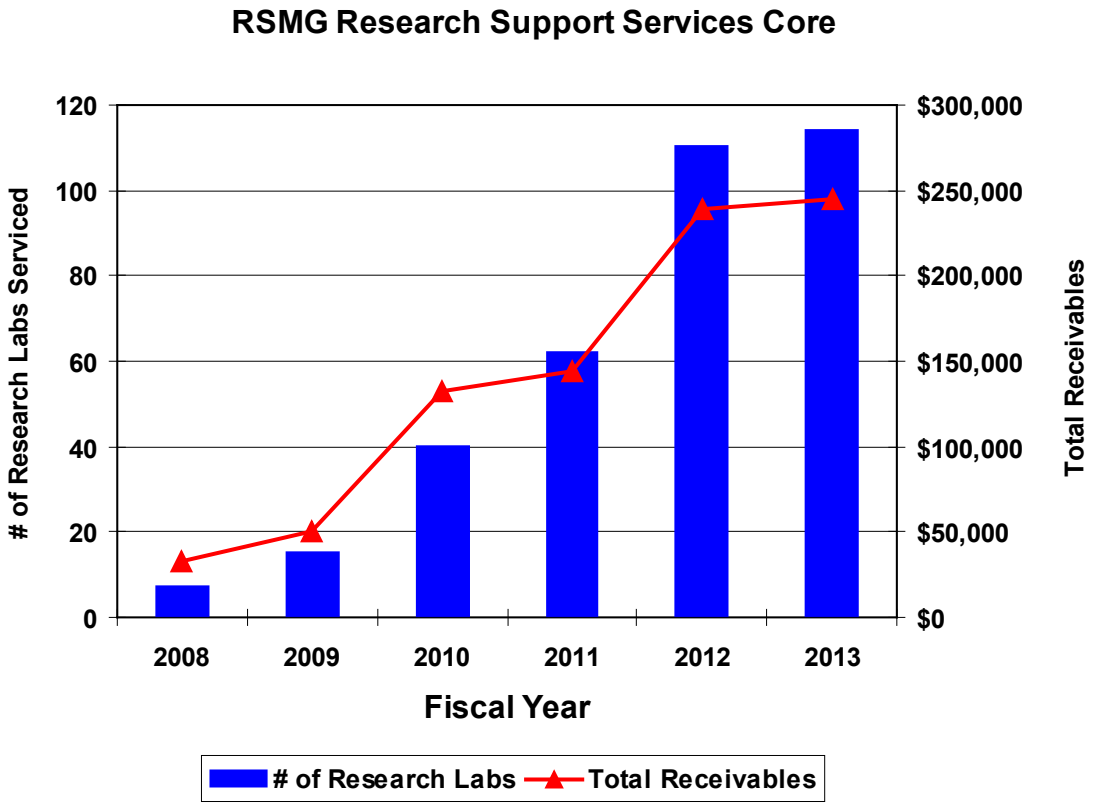
Audit Type	Audit Success
Equipment purchased with Federal and Non-Federal sources valued at $1500 - $4999	99%
Equipment purchased through Federal Contracts valued at $5000 or greater	100%
Equipment purchased with Federal sources valued at $5000 and greater	99%
Equipment purchased with Federal and Non-Federal sources valued at $5000 or greater	100%
Equipment categorized as Category N (Due-Diligence)	100%
Equipment purchased with Non-Federal sources valued at $5000 or greater	100%

RSMG Glass Washing Core

During Fiscal Year 2013, the RSMG Glass Washing Core provided services to labs in the Simches Research Center, the MGH Main Campus, and Building 149. Services included centralized CO2, the use of centralized copiers, cable TV, glass washing, autoclaving, and sterilized water for laboratory use.

Free services offered to the laboratories at all locations include access to film developers, emergency back-up freezers, conference room booking, and audiovisual support. Lab rounds to assist Lab Managers with emergency contact lists, administrative and safety issues, and to troubleshoot other pressing lab issues/needs, are conducted on a bimonthly basis. Core staff members are on call 24/7/365 to assist with laboratory needs.

There was a modest increase in the number of labs that requested the services offered by the Core during Fiscal Year 2013. At the researchers' request, we added an option for sterilized water in the Simches Research Center, and plan to offer more services designed with convenience in mind during FY' 14. The Core is a break-even operation to provide essential services to researchers at a reasonable cost. Total receivables from the glass washing/autoclaving, centralized CO2, and cable TV rose by 2.3% from $238,764 (FY '12) to $244,362 (FY '13).



Looking Ahead in 2014

In 2014, RSMG and the Research Community can look forward to the completion of several major projects. Phase I and II of the Ragon Backfill project will be finished and Phase III should be done early in FY '15. Neurology's new Clinical Trial Unit at Charles River Plaza will also be ready for occupancy in FY '14. Ongoing funding and new projects involving a number of departments such as the Cancer Center, Medicine, Psychiatry, Imaging, Surgery, and the Center for Wellman Labs will also be completed, allowing these groups to better utilize their research space and meet their scientific objectives.

RSMG will also actively participate in the planning for the relocation of a number of research functions from leased space to the former Spaulding Rehabilitation building on Nashua Street.

Another major planning process for which RSMG is responsible is developing options for occupancy by Research of the tenth floor of Building 149 following the relocation of Partners Information Services to a new building.

RSMG faces the challenge of numerous space requests, totaling approximately 85,000 nasf. Working with RSAC, we will develop viable space options to provide as many solutions as possible for critical research initiatives dependent on specific space requirements. Members of the RSMG staff are in constant touch with their contacts to ensure that we know about Departmental research space requirements, many times even before the a formal request for space is submitted.

Overview of Laboratory Animal Care and Use at MGH

Donna Matthews Jarrell, DVM
Director, Center for Comparative Medicine

Over one-third of the entire annual research budget at MGH involves animal models of one kind or another. On any given day, approximately 100,000 mice and assorted numbers of rats, guinea pigs, rabbits, sheep, pigs, non-human primates, and amphibians plus 35,000 zebrafish are housed and used within 95,000 square feet dedicated for such purposes on both hospital campuses. In addition, the hospital operations 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 the addition of BL-2/BL-3 rodent housing capabilities in 2013 that supports the Ragon Institute in Cambridge, MA.

The MGH Institutional Animal Care and Use Committee (IACUC) govern the use of animals in biomedical research at MGH, as required by federal and state laws and regulations and accreditation standards. Vertebrate species are maintained in accordance with the "Guide for the Care and Use of Laboratory Animals" (National Research Council, 2010), and animal protocols must be approved by the IACUC before the requisite animals can be ordered and experiments begun. Currently, there are more than 1000 active protocols being performed by over 360 principal investigators.

MGH is registered with the U.S. Department of Agriculture Animal and Plant Health Inspection Service (Certificate No. 4-R-014) and the Massachusetts Department of Public Health (License No. MA-0022) as a licensed animal research facility. MGH has an approved Letter of Assurance (File No. A3596-01) with the NIH Office of Laboratory Animal Welfare confirming compliance with Public Health Service policies pertaining to laboratory animal care and use. The hospital has been accredited by the Association for the Assessment and Accreditation of Laboratory Animal Care International (AAALAC) since 1993.

Center for Comparative Medicine

The Center for Comparative Medicine (CCM) is the central laboratory animal care service to MGH investigators. 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 rederivation, and consultation in animal modeling and protocol design. These services are provided by 140 employees, including seven staff veterinarians (six of whom are board-certified in laboratory animal medicine or veterinary clinical pathology).

New or improved CCM services implemented in the past year include:

1. Rodent Breeding/Colony Management software program, sponsored by ECOR, now available to the MGH research community which provides a comprehensive solution for managing rodent breeding colonies with more secure data storage, graphics and report writing capabilities and easy interface with other data management software resources.
2. Webinar-based animal users' orientation sessions which decrease the amount of actual staff time required when seeking access to the animal facilities.
3. New diagnostic testing paradigm for health assessment of imported rodents resulting in a more than 50% decrease in quarantine time without compromising the quality of the rodent health assurance program allowing researchers to incorporate new models into their research programs quicker.
4. A variety of new clinical pathology assays, especially in the area of hematology, that utilize micro-volumes (<20 uL) associated with mouse experimentation allowing for more accurate results and requiring less animals per experiment.

Publications from the Center for Comparative Medicine over the past year include:

1. Staropoli JF, Haliw L, Biswas S, Garrett L, Hölter SM, Becker L, Skosyrski S, Da Silva-Buttkus P, Calzada-Wack J, Neff F, Rathkolb B, Rozman J, Schrewe A, Adler T, Puk O, Sun M, Favor J, Racz I, Bekeredjian R, Busch DH, Graw J, Klingenspor M, Klopstock T, Wolf E, Wurst W, Zimmer A, Lopez E, Harati H, Hill E, Krause DS, Guide J, Dragileva E, Gale E, Wheeler VC, Boustany RM, Brown DE, Breton S, Ruether K, Gailus-Durner V, Fuchs H, de Angelis MH, Cotman SL. **Large-scale phenotyping of an accurate genetic mouse model of JNCL identifies novel early pathology outside the central nervous system.** PLoS One. 2012; 7(6):e38310.
2. Brown DE, Libby SJ, Moreland SM, McCoy MW, Brabb T, Stepanek A, Fang FC, Detweiler CS. **Salmonella enterica Causes More Severe Inflammatory Disease in C57/BL6 Nramp1G169 Mice Than Sv129S6 Mice.** Vet Pathol. 2013 Feb 27.
3. Yildirim E, Kirby JE, Brown DE, Mercier FE, Sadreyev RI, **Scadden DT**, Lee JT. **Xist RNA is a potent suppressor of hematologic cancer in mice.** Cell. 2013 Feb 14; 152(4):727-42.
4. Sun CC, Vaja V, Chen S, Theurl I, Stepanek A, Brown DE, Cappellini MD, Weiss G, Hong CC, Lin HY, Babitt JL. **A hepcidin lowering agent mobilizes iron for incorporation into red blood cells in an adenine-induced kidney disease model of anemia in rats.** Nephrol Dial Transplant. 2013 Jan 22.
5. Ramsey H, Zhang Q, Brown DE, Steensma DP, and Wu MX (2013) **Stress-induced hematopoietic failure in the absence of immediate early response gene X-1.** Haematologica (in press) 98:xxxdoi:10.3324/haematol.2013.092452.

The Multicultural Affairs Office

Program Review 2013

Elena B. Olson, JD, Executive Director

Background:

The Multicultural Affairs Office (MAO) has evolved into a Hospital-and community-wide resource that works with virtually all departments at MGH. MAO's staff includes an Executive Director, as well as 2 additional full-time administrative staff. MAO's part-time physician staff includes a manager of trainee affairs (works with trainees), a program director for multicultural education, as well as 3 Associate Directors who are intricately involved in MAO's initiatives. A multi-disciplinary advisory board co-chaired by Drs. Winfred Williams (founding director of MAO) and Peter Slavin (MGH President), and comprised of chiefs of service, hospital and MGPO leadership, trustees, an HMS Dean, as well as senior faculty underrepresented in medicine (URM), provides advice and assistance with the strategic direction of the office.

Mission:

MAO'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. We believe this mission is crucial to enhancing the quality of patient care, and advancing the research, education and community mission of MGH. MAO has three broad-based objectives:

1. Professional leadership and workforce diversity
2. Multicultural Education
3. Community Outreach

Accomplishments:

1. OVERALL: ENGAGEMENT OF LEADERSHIP/DEPARTMENTS

Five years ago, MAO's Advisory Board developed a framework to address accountability for diversity and inclusion in each department. As board co-chair, Peter Slavin, MD, MGH president, requested that clinical departments develop a departmental diversity action plan. Although several departments began developing plans, it was not until last year that all 19 clinical departments became fully engaged. Currently, 13 clinical departments have committees that address diversity issues, ranging from the research pipeline to multicultural education initiatives. Accountability is evident in several departments whose chiefs are chairing or serving on these committees and financially support designated faculty to lead this work.

MAO and the President's Office convened these department diversity leaders (including Patient Care Services and Human Resource representatives) to share ideas and strategies and identify common challenges and potential solutions, and established the Diversity Leaders group which meets quarterly. MAO also helped create a central resource with a SharePoint site and metrics, and collaborated on many departmental efforts, including expanding the number of visiting professors and grand round speakers invited to Mass General.

2. PROFESSIONAL LEADERSHIP AND WORKFORCE DIVERSITY

A. MAO sponsors national and local outreach programs that target students, physicians and researchers who are underrepresented in medicine at different levels of their education and expose them to the many resources for training in the sciences at MGH. Following is a list of its most recent accomplishments:

- The Summer Research Trainee Program (SRTP)—In its 21st year at MGH, SRTP selects 15 URM junior and senior college, as well as 1st and 2nd year medical students, through a vigorous national competition to partake in an 8-week research session at MGH. These students are paired with MGH preceptors in a basic science laboratory, clinical or health policy research sites. Over 98% of the undergraduates who have completed SRTP have gone

onto medical school or graduate school in the sciences. Many alumni have pursued careers in academic medicine, and several are currently in our residency and fellowship training programs and on staff at MGH.

- The URM Medical Students Mentorship Program is designed to pair medical students underrepresented in medicine from Harvard Medical School with physician/research mentors from MGH and other Harvard affiliated hospitals. The URM Mentorship Program currently has approximately 90 active student mentees paired with faculty mentors, 45 (mentee) alumni, and a total of over 80 mentors available to mentor these students.
- Harvard Medical Student Outreach. MAO provides active outreach, mentorship and guidance to minority HMS students. MAO staff meet HMS students with their Primary Clinical Experience and those doing rotations at MGH on site to provide counseling and advice. The Office also holds bi-annual welcoming and recognition receptions for minority students to network with MGH residents, faculty and MGH program directors and chiefs of service.
- Other Student Outreach. Over the past years, MAO hosted leadership conferences and national meetings for the two largest URM medical student groups in the country: the Student National Medical Association and the Latino Medical Student Association. MGH faculty and trainees at MGH served on panels and attended networking events to provide guidance in pursuing careers in academic medicine.
- Recruitment of URM residents. Since 2000, MAO has been collaborating with the 21 residency programs at MGH (including integrated programs) to help recruit URMs to training programs. As part of this effort, MAO staff meet individually with minority applicants to share not only information about what it is like to train and work at the MGH but about what it is like to do this as a physician of color. MAO staff met with numerous minority candidates during the 2012-13 recruitment season and hosted a total of 11 receptions, which gave URM residents and faculty an opportunity to provide further insight to the candidates. MAO also held revisit days, inviting back top ranked applicants to revisit MGH. This effort has proven to be a very effective recruitment strategy for several programs. In 2013, the number of URMs matched at MGH was 14%, with a record match of URMs in several programs.
- Recruitment of URM researchers. MAO began a collaboration this year with the Department of Anesthesia to create the SARUMM fellowship, which immerses residents who are interested in investigation to a distinct research project during their training.

B. MAO also plays a crucial role in the retention and development of URM residents and fellows at MGH. Following are a number of recent accomplishments under this initiative:

- During the MGH bicentennial year (2011), MAO organized the first ever URM alumni reunion inviting back numerous URM graduates to MGH. The event included a weekend of activities ranging from networking to career development and healthcare reform panel sessions. Over 170 current and past URMs participated in the activities. We hope to repeat this in the coming years.
- In 2001, MAO established the first Organization of Minority Residents and Fellows at MGH. The OMRF is run by a resident board elected by fellow trainees. The purpose of this organization is to provide an interdisciplinary forum for URM residents, which addresses issues of career guidance, mentorship, networking, and community outreach; and assists with recruitment of incoming residents.
- Hospital & MGPO leadership and MAO staff have been meeting with chiefs of service of programs with minority residents since 2003 in an attempt to track and retain promising URM trainees for fellowship training and/or junior faculty positions at MGH. In 2009, over 60% of URM clinical fellows graduating were retained on staff.
- The Career Development Liaison Program 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.

- Seminars and forums on career development, mentorship, fellowship opportunities, etc.
- Receptions welcoming URM incoming residents and acknowledging accomplishments of graduating residents.

C. Faculty Development Initiatives:

- In 2006, Hospital & MGPO leadership and MAO staff began meeting with department and division chiefs in an attempt to track, develop and promote URM faculty at MGH. These meetings are also used as a vehicle to enhance retention of residency and fellowship graduates into junior faculty positions.
- Faculty focus groups were created to identify needs and assess solutions for MGH URM faculty. As a result of these focus group recommendations, each department is designing and implementing a proposal to create a department specific Diversity Action Plan.
- MAO is a founding member of the Multicultural Women in Academic Medicine Group, which was created to provide a venue for women faculty and trainees throughout the Harvard teaching hospitals to network with each other.
- Minority Faculty Development Awards (MFDA)—to date, 27 awards have been granted and 90% of recipients continue to be retained and developed as faculty at MGH. In order to accommodate the demand, the awards are separated into 2 categories:

a. Physician-Scientist Development Award (PSDA)—designed for fellows and junior faculty in research. The PSDA awards a total of $120,000 over the course of 4 years, and includes up to $30,000 per year of grant funding and loan forgiveness.

b. Clinician-Teacher Development Award (CTDA)—this award is designed for all URM faculty pursuing a career as a clinician, educator or community leader. The CTDA awards a total of $120,000 over the course of 4 years, and includes both a grant and loan forgiveness component. The group of MFDA winners meets periodically during the year for career advice and workshops.

- Held fifth annual Award Recognition Ceremony honoring 2013 MFDA recipients and including a poster presentation of the prior MFDA winners (2003-2013).
- The Chester Pierce Research Society—a bi-monthly luncheon scientific session designed in honor of MGH's first African American full Professor, providing minority researchers a unique opportunity to present their research to colleagues and others in the MGH community.
- URM faculty mentoring program—In 2011–12, in collaboration with the Center for Faculty Development, MAO piloted a structured mentoring program for URM junior faculty. We have matched 28 URM faculty to senior faculty mentors in various departments, and many remain mentored by their original mentors.
- MAO has focused on increasing the visiting lectureships and grand round speakers who are URM. Our collaborations with several departments and Harvard Medical School have brought in over 6 national renowned URMs to MGH in 2012, and several more in 2013.
- Faculty development conferences, career seminars and roundtable discussions, many in collaboration with HMS Office for Diversity and Community Partnership.
- Founding member of the Consortium of HMS Hospital Affiliate Offices for Faculty Development and Diversity (CHADD) to collaborate on common issues relating to URM, Women and Research community, e.g., race and ethnicity data collection, chief search training.
- URM faculty directory created for purposes of networking, recruitment and referrals.
- MAO staff provides career counseling and advice to URM faculty at MGH, and work as advocates to help URM faculty rise through the HMS faculty appointment promotions process.

- Updated publication of the URM history project entitled: The Untold Story: URM Pioneers at MGH, highlighting the contributions of many URMs who were "firsts" at MGH. This project is currently featured in MGH Museum for History and Innovation.

D. Faculty/Chief Recruitment Initiatives:

- MAO supports Chief Search Committees and assists them with training and identifying national URM senior faculty for Chief openings.
- MAO and the HMS Office for Diversity and Community Partnerships developed a database of non-HMS URM faculty to identify potential speakers, visiting professors as well as faculty recruits. The database is populated by referrals of HMS and teaching hospital faculty.

E. Grants/Fundraising:

- MAO assists and collaborates with numerous MGH departments in applying for and obtaining training and research grants for these departments.
- In late 2011, MAO began an active fundraising campaign focused on two of its banner research programs: SRTP (for students) and MFDA (awards for faculty). The fruits of our labor were rewarded with generous donations in 2012 and 2013. The MAO friends committee helped identify four generous donors to MAO, including a generous gift of $125,000 dedicated to SRTP and smaller gifts from current MGH employees that are the seeds of an endowment fund.

3. MULTICULTURAL EDUCATION AND TRAINING

- MAO, through Dr. Joseph Betancourt, Program Director for Multicultural Education, has developed a cross-cultural education curriculum involving e-learning programs, didactic seminars and a film series, at MGH. This curriculum has been implemented for residents in the Department of Internal Medicine, MGPO physicians, non-clinical healthcare staff, and Harvard medical students. An e-learning program (Quality Interactions) was offered for first time as part of the MGPO incentive program, with 90% faculty participation.
- Health Disparities Committee/Outreach/Research—Recent research shows that minorities suffer poorer health outcomes when compared to the majority of Americans and Boston residents. Dr. Betancourt directs the Disparities Solutions Center and co-chairs the MGH Health Disparities Committee with Joan Quinlan, the Director of MGH Community Benefit Program, that evaluates issues of quality, education and awareness, and patients' experience in care and access to care at MGH. MAO also sponsors forums on health disparities issues throughout the year.
- Teamwork and Communication training in the DOM—MAO has worked closely with the Departments of Medicine and Pediatrics over the past three years to develop a pilot for physicians and nurses to improve communication and teamwork through the lens of diversity. Currently, this effort is still in its pilot phase in Pediatrics, having completed the "train the trainer", and the eight hour training curriculum for a group of physician and nursing leaders, as well as for medicine residents. Pediatrics residents and nurses have completed four hours of training, half of the curriculum.

4. COMMUNITY HEALTH

- The MAO Executive Director Served as co-chair of the Community-Education Subcommittee for the MGH Strategic Plan in 2013. This sub-committee developed a proposal to education the entire MGH community on community health and cultural competency in 2014 and beyond.
- As the programs at MAO continue to evolve, we find ourselves more involved in programs affecting the community affiliated with MGH, especially through the Center for Community Health Improvement and mentoring the younger generation of elementary and middle school students to become interested in Science, Technology and Math.

In The Future:

- This is a critical moment to address the challenges that MGH is facing with regard to the dearth of URM NIH funded investigators who are underrepresented in medicine. 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. Although national URM demographics are grim, MGH's numbers fall below the national NIH data. While the NIH is looking at ways in which to address this issue broadly, MGH is in a unique position to address this issue locally, especially given its recent strategic planning efforts.

MAO's proposal is to tackle this issue from two fronts—investing in the academic research careers of the URM pipeline (students, trainees, faculty); and developing current URM faculty who are (could be) in the pipeline for independent NIH sponsored research grants. Given our wide expertise in research, career development and pipeline programs at MGH, the best approach is to collaborate with MAO, ECOR, Research Management and the CFD on this effort. We have set up committees to address this issue and plan to tackle implementation in 2014.

- Continue to work with MAO Advisory Board and each department chief to develop diversity actions plan in each department, which will include specific strategies for recruitment, retention and development of URMs in each department.
- Expand recruitment of senior URM faculty throughout MGH departments, especially through use of new database and Visiting lectureships.
- Expand connections with URM alumni, many of whom attended MAO's first alumni reunion.
- Publish several ongoing studies, including MAO as best practice model in the nation, as well as outcomes and qualitative studies showing the positive impact of MAO programs, ie, the MFDA, the URM Mentoring Program, and VISIONS training.
- Design studies regarding the status and advancement of URM MGH graduates in academic medicine.
- Continue Visiting lecturers, faculty development conferences, seminars and round tables in conjunction with the MGH Center for Faculty Development, the HMS Office for Diversity and Community Partnerships, and partnerships with other MGH departments.
- Continue multicultural education of URM trainees and faculty.
- Continue efforts with recruitment and development of URM residents, fellows, and faculty, including networking opportunities for senior faculty.
- Implement Cross-Cultural Curriculum throughout MGH departments and senior leadership.

The MAO Staff:

Administrative Full-Time Staff:

Elena Olson, JD, *Executive Director*
Paola Miralles, *Program Manager*
Klara Bustamante, *Office coordinator*

Part-Time Faculty Staff:

Winfred Williams, MD, *Co-Chair, Advisory Board*
Alexy Arauz Boudreau, MD, MPH, *Associate Director*
Joseph Betancourt, MD, MPH, *Program Director for Multicultural Education*
Jocelyn Carter, MD, *Manager of Trainee Affairs*
Sherri Ann Burnett-Bowie, MD, *Associate Director*
Michael Watkins, MD, *Associate Director*

The MGH Thematic Research Centers

Overview

The MGH Thematic Centers have continued to thrive in 2013 as described in the individual reports that follow. As the Centers developed, each defined its own structure and style reflecting the differences in their science, their funding needs and challenges, and their histories. In recognition of this development, in 2010 the Thematic Centers' reporting relationship to ECOR changed from a group report to individual reports regarding their programs and science. This has continued to work well, as it has allowed ECOR to review the science performed in each center while taking into account their diverse character.

Governance of the Thematic Centers has gradually evolved since they were created. For the first several years, the Thematic Centers Executive Committee provided a forum for identifying opportunities to build collaborations and to address common concerns among the Centers. The Thematic Centers Executive Committee gradually became less active over recent years, reflecting the need to address differing concerns of the Centers.

Today, the Center Directors continue to report to Dr. Peter Slavin, the President of MGH, through a reporting line to the Chair of ECOR, Dr. Robert Kingston, Chief, Molecular Biology. (Dr. Kingston has provided the oversight of the Thematic Centers since 2006, first as Chair of the Thematic Centers Executive Committee, then as ECOR Vice Chair beginning in 2009 and now as ECOR Chair.)

The Centers have also continued to have an administrative reporting line to the MGH Senior Vice President for Research Management, Dr. Harry Orf. Many issues of concern have been addressed via meetings of administrators of the Centers with Mr. Gary Smith, who then reports on these discussions to Drs. Orf and Kingston.

The Centers have distinct fiscal and administrative needs. We have continued to progress in the development of appropriate fiscal goals to allow planning for long term sustainability of the Centers. Beginning in 2009, the Hospital assumed additional responsibility for administrative support for the Centers, with the arrangement tailored to the specific needs of each Center; that support continues. ECOR has continued to provide financial support towards administrative costs of the Centers as well. Progress continues to be made in the area of financial management of the Centers, of growing importance as the support for the Centers' research continues to grow. Drs. Orf and Kingston meet with each Center director each fall to discuss fiscal and scientific advances and issues.

The Centers also continue to have the challenge of reaching those in both the MGH community and the research community beyond MGH who would be interested in the research in the Centers and who could contribute to and benefit from that research. Technologies that are present in the Centers are regularly presented to the entire MGH community at Research Council meetings as well as at ECOR meetings. Members of the Centers are also involved in teaching courses to graduate students at MGH to help increase the number of students who join the MGH community.

In 2010, Dr. Kingston and Dr. Bringhurst (former Vice President for Research Management)began planning a five year review of the four original Centers, with input from the Center Directors on the format of these reviews and this planning continued into 2011. The Center for Regenerative Medicine (CRM) was reviewed in December 2011 and the Center for Human Genetic Research was reviewed in January of 2012. Drs. Orf and Kingston have continued this review program, and the Center for Computational and Integrative biology was reviewed in January, 2013. These reviews were conducted by two senior faculty from outside the MGH and two Chiefs of Service from inside the MGH.

The science in all three Centers was viewed as outstanding by the review panels. Structural issues were noted in all Centers. The Center for Regenerative Medicine is intertwined with the new Harvard Department of Stem Cell and Regenerative Biology, with several members holding joint appointments and Dr. David Scadden in a leadership role for both the Center and the Department.

This creates complications due to the physically separate location of the Department (mainly Cambridge) and the Center (MGH Simches), and the need for scientists to have a physical presence in both locations. The Center for Human Genetic Research has a complicated fiscal structure that results in very limited amounts of discretionary money. This will require attention in order to facilitate the day-to-day running of this Center and this reality also impacts how recruitment of new faculty might be accomplished. The Center for Computational and Integrative Biology has a diverse and tremendously talented faculty. This group of people is more spread out, physically, than those in the other Centers. While the principal investigators all have strong interactions, this issue limits interactions between members of the laboratory. Mechanisms are being considered that might help to increase interaction.

History of the Centers

In 2003, the MGH Executive Committee On Research (ECOR) established and seeded four new thematic research centers to advance biomedicine by focusing on biological processes as whole systems. The Centers were to be multidisciplinary, collaborative, and multi-departmental.

Three Centers were established at the outset: The Center for Computational and Integrative Biology (CCIB), with Dr. Brian Seed as Director; the Center for Regenerative Medicine and Technology (now Center for Regenerative Medicine or CRM), with Dr. David Scadden as Director; and the Center for Human Genetic Research (CHGR), with Dr. James Gusella as Director.

Another Center was designated during this period as well: the Wellman Laboratories, based in the MGH Dermatology Department, requested and received recognition by ECOR as an MGH Center and was renamed the Wellman Center for Photomedicine (WCP), with Dr. Rox Anderson named as the Director.

The fourth center envisioned by ECOR was not launched pending further development of its focus and direction. In 2004, the intellectual vectors converged on systems biology as the focus for this Center, and a national search for a Director for the MGH Center for Systems Biology was launched as a joint search of the MGH and Harvard Medical School, co-chaired by Dr. Daniel K. Podolsky and Dr. Lewis Cantley. After a search of nearly two years, Dr. Ralph Weissleder, Director of the MGH Center for Molecular Imaging Research, was appointed the Director of the new Center for Systems Biology. That Center was launched in 2007 and has established their programs , all of which is described in the Center's report which follows.

Through the Thematic Center Executive Committee, the Directors have together addressed the many strategic and administrative challenges of building these interdisciplinary Centers. Among these areas have been developing appropriate IP policies; defining membership levels in Centers and associated benefits and responsibilities; establishing common standards and policies for animal facilities; and establishing effective plans for grants management; IRB and animal protocols management; core facilities management; facilities management.

The Directors have identified opportunities for scientific partnerships and collaborations across Centers. Unexpected but exciting new conversations about specific scientific problems appear to have been enabled by the creation of the Centers. The very naming of these Centers has meant that Center Directors, whose work and research focus would otherwise have remained unknown to researchers in some other fields, are being invited to speak and new and fruitful collaborations are emerging.

The specific activities of all five Centers are highlighted in the sections that follow.

Center for Computational and Integrative Biology

Center Overview

CCIB

Brian Seed, PhD, Director

Awards and Achievements

Fred Ausubel was elected recipient of the Thomas Hunt Morgan Medal of the Genetics Society of America

Gary Ruvkun delivered the University College of London 2013 Prize Lecture in Clinical Science.

Jen Sheen was awarded the Martin Gibbs Medal of the American Society of Plant Biologists.

Jack Szostak was elected a Fellow of the American Academy of Cancer Researchers, received the IUBMB Medal of the International Union of Biochemistry and Molecular Biology, the Butcher Award of the University of Colorado, Boulder, and delivered the Spitzer Lecture at the University of Southern California as well as the First Rita Levi-Montalcini Memorial Lecture, BergamoScienza.

Ramnik Xavier was named the Kurt J. Isselbacher Professor of Medicine and delivered the Tsuchiya Memorial Lecture as well as the University of Michigan Yamada Lectureship.

Research Programs

AUSUBEL LABORATORY

Pathogenic microbes employ a variety of methods to overcome host defenses, including the production and dispersal of molecules that are toxic to their hosts. *Pseudomonas aeruginosa*, a Gram-negative bacterium, is a pathogen of a diverse variety of hosts including mammals and the nematode *Caenorhabditis elegans*. We recently identified three small molecules in the phenazine class that are produced by P. aeruginosa strain PA14 that are toxic to *C. elegans*. We demonstrate that 1-hydroxyphenazine, phenazine-1-carboxylic acid, and pyocyanin are capable of killing nematodes in a matter of hours. 1-hydroxyphenazine is toxic over a wide pH range, whereas the toxicities of phenazine-1-carboxylic acid and pyocyanin are pH-dependent at non-overlapping pH ranges. We found that acidification of the growth medium by PA14 activates the toxicity of phenazine-1-carboxylic acid, which is the primary toxic agent towards *C. elegans* in our assay. Pyocyanin is not toxic under acidic conditions and 1-hydroxyphenazine is produced at concentrations too low to kill *C. elegans*. These results suggest a role for phenazine-1-carboxylic acid in mammalian pathogenesis because PA14 mutants deficient in phenazine production have been shown to be defective in pathogenesis in mice. More generally, these data demonstrate how diversity within a class of metabolites could affect bacterial toxicity in different environmental niches.

To develop additional insight into how *P. aeruginosa* disrupts host biology, we studied how P. aeruginosa kills *C. elegans* in a liquid-based pathogenesis model. We found that P. aeruginosa-mediated killing does not require quorum-sensing pathways or host colonization. A chemical genetic screen revealed that iron chelators alleviate *P. aeruginosa*-mediated killing. Consistent with a role for iron in *P. aeruginosa* pathogenesis, the bacterial siderophore pyoverdin was required for virulence and was sufficient to induce a hypoxic response and death in the absence of bacteria. Loss of the *C. elegans* hypoxia-inducing factor HIF-1, which regulates iron homeostasis, exacerbated *P. aeruginosa* pathogenesis, further linking hypoxia and killing. As pyoverdin is indispensable for virulence in mice, pyoverdin-mediated hypoxia is likely to be relevant in human pathogenesis.

Selected Publications

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Kirienko N.V., Kirienko D.R., Larkins-Ford J., Wahlby C., Ruvkun G., Ausubel F.M. Pseudomonas aeruginosa disrupts Caenorhabditis elegans iron homeostasis, causing a hypoxic response and death. Cell Host Microbe. 13:406-16. (2013)

CCIB

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FREEMAN LABORATORY/TRANSLATIONAL MEDICINE GROUP (TMG)

ABCA12 mutations disrupt the skin barrier and cause harlequin ichthyosis. We previously showed *ABCA12*-/- skin has increased glucosylceramide (GlcCer) and correspondingly lower amounts of ceramide (Cer). To examine why loss of *ABCA12* leads to accumulation of GlcCer, de-novo sphingolipid synthesis was assayed using [14C]-serine labeling in ex-vivo skin cultures. A defect was found in β-glucocerebrosidase (GCase) processing of newly synthesized GlcCer species. This was not due to a decline in GCase function. *ABCA12*-/- epidermis had 5-fold more GCase protein (n=4, $p<0.01$), and a 5-fold increase in GCase activity (n=3, $p<0.05$). As with *ABCA12*+/+ epidermis, immunostaining in null skin showed a typical interstitial distribution of the GCase protein in the *ABCA12*-/- stratum corneum. Hence, we tested whether the block in GlcCer conversion could be circumvented by topically providing GlcCer. This approach restored up to 15% of the lost Cer products of GCase activity in the *ABCA12*-/- epidermis. However, this level of barrier ceramide replacement did not significantly reduce trans-epidermal water loss function. Our results indicate loss of *ABCA12* function results in a failure of precursor GlcCer substrate to productively interact with an intact GCase enzyme and supports a model of *ABCA12* function that is critical for transporting GlcCer into lamellar bodies.

Selected Publications

Haller J.F., Cavallaro P., Hernandez N.J., Dolat L., Soscia S.J., Welti R., Grabowski G.A., Fitzgerald M.L., Freeman M.W. Endogenous beta-glucocerebrosidase activity in *ABCA12*-/-epidermis elevates ceramide levels after topical lipid application but does not restore barrier function. J Lipid Res. (2013)

HUNG LABORATORY

Work in my laboratory focuses on mechanisms of antibiotic-mediated death and the identification of new targets for therapeutic intervention for important global diseases. We have also begun to study mechanisms by which pathogens exert toxic influences on their hosts. One such mechanism, pyroptotic cell death induced by anthrax lethal toxin, is a model for inflammasome-mediated caspase-1 activation. We discovered 7-desacetoxy-6,7-dehydrogedunin (7DG) in a phenotypic screen as a small molecule that protects macrophages from LT-induced death. Using chemical proteomics, we identified protein kinase R (PKR) as the target of 7DG and show that RNAi knockdown of PKR phenocopies treatment with 7DG. Further, we show that PKR's role in ASC assembly and caspase-1 activation induced by several different inflammasome stimuli is independent of PKR's kinase activity, demonstrating that PKR has a previously uncharacterized role in caspase-1 activation and pyroptosis that is distinct from its reported kinase-dependent roles in apoptosis and inflammasome formation in lipopolysaccharide-primed cells. Remarkably, PKR has different roles in two distinct cell death pathways and has a broad role in inflammasome function relevant in other diseases.

Although new antibiotics are urgently needed to combat the global tuberculosis pandemic the development of new small molecules has been hindered by a lack of validated drug targets. We identified a 4,6-diaryl-5,7-dimethyl coumarin series that kills *M. tuberculosis* by inhibiting fatty acid degradation protein D32 (FadD32), an enzyme that is required for biosynthesis of cell-wall mycolic acids. They effectively block bacterial replication both in *vitro* and in animal models of tuberculosis, validating FadD32 as a target for antibiotic development that works in the same pathway as the established antibiotic isoniazid. Targeting new steps in well-validated biosynthetic pathways in antitubercular therapy is a powerful strategy that removes much of the usual uncertainty surrounding new targets and *in vivo* clinical efficacy, while circumventing existing resistance to established targets.

Selected Publications

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JOUNG LABORATORY

Rapid advances in the use of transcription activator-like effector nucleases (TALENs) and transcript-directed genome editing approaches based on Clustered Regularly Interspaced Short Palindromic Repeat (CRISPR) guided nucleases (RNA guided nucleases, RGN) have transformed our ability to make targeted gene knockouts in zebrafish and a variety of other important model organisms. In addition to developing the underlying technology for gene editing and gene therapy applications, we have begun to exploit the precise genome targeting capabilities latent in the nucleic acid recognition properties of TALENS and CRISPT/Cas9 complexes.

Genome-wide studies have defined cell type-specific patterns of DNA methylation that are important for regulating gene expression in both normal development and disease. However, determining the functional significance of specific methylation events remains challenging, owing to the lack of methods for removing such modifications in a targeted manner. We developed an approach for efficient targeted demethylation of specific CpGs in human cells using fusions of engineered transcription activator-like effector (TALE) repeat arrays and the TET1 hydroxylase catalytic domain. Using these TALE-TET1 fusions, we demonstrated that modification of critical methylated promoter CpG positions can lead to substantial increases in the expression of endogenous human genes. The approach provides a strategy for understanding the functional significance of specific CpG methylation marks in the context of endogenous gene loci and validates programmable DNA

CCIB

demethylation reagents with potential utility for research and therapeutic applications.

We have also used a human cell-based reporter assay to characterize off-target cleavage of CRISPR-associated (Cas)9-based RGNs. We found that single and double mismatches were tolerated to varying degrees depending on their position along the guide RNA (gRNA)-DNA interface. We also readily detected off-target alterations induced by four out of six RGNs targeted to endogenous loci in human cells by examination of partially mismatched sites. The off-target sites we identified harbored up to five mismatches and many were mutagenized with frequencies comparable to (or higher than) those observed at the intended on-target site. Our work demonstrates that RGNs can be highly active even with imperfectly matched RNA-DNA interfaces in human cells, indicating that care will be necessary in applying these powerful tools to potential therapeutic applications.

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RUVKUN LABORATORY

Genetic and biochemical analyses of RNA interference (RNAi) and microRNA (miRNA) pathways have revealed proteins such as Argonaute and Dicer as essential cofactors that process and present small RNAs to their targets. Well-validated small RNA pathway cofactors such as these show distinctive patterns of conservation or divergence in particular animal, plant, fungal and protist species. We compared 86 divergent eukaryotic genome sequences to discern sets of proteins that show similar phylogenetic profiles with known small RNA cofactors. A large set of additional candidate small RNA cofactors have emerged from functional genomic screens for defects in miRNA- or short interfering RNA (siRNA)-mediated repression in *Caenorhabditis elegans* and *Drosophila melanogaster*, and from proteomic analyses of proteins co-purifying with validated small RNA pathway proteins. The phylogenetic profiles of many of these candidate small RNA pathway proteins are similar to those of known small RNA cofactor proteins. We used a Bayesian approach to integrate the phylogenetic profile analysis with predictions from diverse transcriptional coregulation and proteome interaction data sets to assign a probability for each protein for a role in a small RNA pathway. Testing high-confidence candidates from this analysis for defects in RNAi silencing, we found that about one-half of the predicted small RNA cofactors are required for RNAi silencing. Many of the newly identified small RNA pathway proteins are orthologues of proteins implicated in RNA splicing. In support of a deep connection between the mechanism of RNA splicing and small-RNA-mediated gene silencing, the presence of the Argonaute proteins and other small RNA components in the many species analysed strongly correlates with the number of introns in those species.

Adaptation to nutrient scarcity depends on the activation of metabolic programs to efficiently use internal reserves of energy. Activation of these programs in abundant food regimens can extend life span. However, the common molecular and metabolic changes that promote adaptation to nutritional stress and extend life span are mostly unknown. We identified a response to fasting, enrichment of ω-6 polyunsaturated fatty acids (PUFAs), which promotes starvation resistance and extends *Caenorhabditis elegans* life span. Upon fasting, *C. elegans* induces the expression of a lipase, which in turn leads to an enrichment of ω-6 PUFAs. Supplementing *C. elegans* culture media with these ω-6 PUFAs increases their resistance to starvation and extends their life span in conditions of food abundance. Supplementation of *C. elegans* or human epithelial cells with these ω-6 PUFAs activates autophagy, a cell recycling mechanism that promotes starvation survival and slows aging. Inactivation of *C. elegans* autophagy components reverses the increase in life span conferred by supplementing the *C. elegans* diet with these fasting-enriched ω-6 PUFAs.

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SEED LABORATORY

Epoxyeicosatrienoic acids (EETs) confer vasoactive and cardioprotective functions. Genetic analysis of the contributions of these short-lived mediators to pathophysiology has been confounded to date by the allelic expansion in rodents of the portion of the genome syntenic to human CYP2J2, a gene encoding one of the principle cytochrome P450 epoxygenases responsible for the formation of EETs in humans. Mice have eight potentially functional genes that could direct the synthesis of epoxygenases with properties similar to those of CYP2J2. As an initial step towards understanding the role of the murine Cyp2j locus, we have created mice bearing a 626-kb deletion spanning the entire region syntenic to CYP2J2, using a combination of homologous and site-directed recombination strategies. A mouse strain in which the locus deletion was complemented by transgenic delivery of BAC sequences encoding human CYP2J2 was also created. Systemic and

CCIB

pulmonary hemodynamic measurements did not differ in wild-type, null, and complemented mice at baseline. However, hypoxic pulmonary vasoconstriction (HPV) during left mainstem bronchus occlusion was impaired and associated with reduced systemic oxygenation in null mice, but not in null mice bearing the human transgene. Administration of an epoxygenase inhibitor to wild-type mice also impaired HPV. These findings demonstrate that Cyp2j gene products regulate the pulmonary vascular response to hypoxia.

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SHEEN LABORATORY

Meristems encompass stem/progenitor cells that sustain postembryonic growth of all plant organs. How meristems are activated and sustained by nutrient signalling remains enigmatic in photosynthetic plants. Combining chemical manipulations and chemical genetics at the photoautotrophic transition checkpoint, we found that shoot photosynthesis-derived glucose drives target-of-rapamycin (TOR) signalling relays through glycolysis and mitochondrial bioenergetics to control root meristem activation, which is decoupled from direct glucose sensing, growth-hormone signalling and stem-cell maintenance. Surprisingly, glucose-TOR signalling dictates transcriptional reprogramming of remarkable gene sets involved in central and secondary metabolism, cell cycle, transcription, signalling, transport and protein folding. Systems, cellular and genetic analyses uncovered TOR phosphorylation of E2Fa transcription factor for an unconventional activation of S-phase genes, and glucose-signalling defects in e2fa root meristems. Our findings establish pivotal roles of glucose-TOR signalling in unprecedented transcriptional networks wiring central metabolism and biosynthesis for energy and biomass production, and integrating localized stem/progenitor-cell proliferation through inter-organ nutrient coordination to control developmental transition and growth.

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STUART LABORATORY

Phagocytosis is a fundamental cellular process that is pivotal for immunity as it coordinates microbial killing, innate immune activation and antigen presentation. An essential step in this process is phagosome acidification, which regulates many functions of these organelles that allow phagosomes to participate in processes that are essential to both innate and adaptive immunity. Here we report that acidification of phagosomes containing Gram-positive bacteria is regulated by the NLRP3 inflammasome and caspase-1. Active caspase-1 accumulates on phagosomes and acts locally to control the pH by modulating buffering by the NADPH oxidase NOX2. These data provide insight into a mechanism by which innate immune signals can modify cellular defenses and establish a new function for the NLRP3 inflammasome and caspase-1 in host defense.

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SZOSTAK LABORATORY

Efforts to recreate a prebiotically plausible protocell, in which RNA replication occurs within a fatty acid vesicle, have been stalled by the destabilizing effect of Mg2+ on fatty acid membranes. We have found that the presence of citrate protects fatty acid membranes from the disruptive effects of

CCIB

high Mg2+ ion concentrations while allowing RNA copying to proceed, while also protecting single-stranded RNA from Mg2+-catalyzed degradation. This combination of properties has allowed us to demonstrate the chemical copying of RNA templates inside fatty acid vesicles, which in turn allows for an increase in copying efficiency by bathing the vesicles in a continuously refreshed solution of activated nucleotides. Until this paper, the conditions for RNA template copying chemistry were incompatible with protocell membrane integrity. The combination of effects developed in this study allowed us, for the first time, to copy an RNA template inside a fatty acid model protocell vesicle.

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TOMPKINS LABORATORY

A cornerstone of modern biomedical research has been the use of mouse models to explore basic pathophysiological mechanisms, evaluate new therapeutic approaches, and make go or no-go decisions to carry new drug candidates forward into clinical trials. Systematic studies evaluating how well murine models mimic human inflammatory diseases have been nonexistent, however. We have shown that although acute inflammatory stresses from different etiologies result in highly similar genomic responses in humans, the responses in corresponding mouse models correlate poorly with the human conditions and also with one another. Among genes changed significantly in humans, the murine orthologs are close to random in matching their human counterparts (with correlation coefficients, R2, of between 0.0 and 0.1). In addition to proposing needed improvements in the current animal model systems, our results support a higher priority for translational medical research to focus on the more complex human conditions rather than relying on mouse models to study human inflammatory diseases.

Within the realm of burn-mediated trauma, data on which to basis efficacy of different care and treatment modalities remain relatively underdeveloped. Although data exist on burn survival, there is little information on long-term burn recovery. Patient-centered health outcomes are useful in monitoring and predicting recovery and evaluating treatments. An outcome questionnaire for young adult burn survivors was developed and tested. A 5-year (2003-2008) prospective, controlled, multicenter study included burned and nonburned adults ages 19 to 30 years. The Young Adult

CCIB

Burn Outcome Questionnaires were completed at initial contact, 10 days, and 6 and 12 months. Factor analysis established construct validity. Reliability assessments used Cronbach α and test-retest. Recovery patterns were investigated using generalized linear models, with generalized estimating equations using mixed models and random effects. Burned (n = 153) and nonburned subjects (n = 112) completed 620 questionnaires (47 items). Time from injury to first questionnaire administration was 157 ± 36 days (mean ± SEM). Factor analysis included 15 factors: Physical Function, Fine Motor Function, Pain, Itch, Social Function Limited by Physical Function, Perceived Appearance, Social Function Limited by Appearance, Sexual Function, Emotion, Family Function, Family Concern, Satisfaction With Symptom Relief, Satisfaction With Role, Work Reintegration, and Religion. Cronbach α ranged from 0.72 to 0.92, with 11 scales >0.8. Test-retest reliability ranged from 0.29 to 0.94, suggesting changes in underlying health status after burns. Recovery curves in five domains, Itch, Perceived Appearance, Social Function Limited by Appearance, Family Concern, and Satisfaction with Symptom Relief, remained below the reference group at 24 months. We conclude that the Young Adult Burn Outcome Questionnaire is a reliable and valid instrument for multidimensional functional outcomes assessment. Recovery in some domains was incomplete

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XAVIER LABORATORY

Autophagy is an evolutionarily conserved catabolic process that directs cytoplasmic proteins, organelles and microbes to lysosomes for degradation. Autophagy acts at the intersection of pathways involved in cellular stress, host defense, and modulation of inflammatory and immune responses; however, the details of how the autophagy network intersects with these processes remain largely undefined. Given the role of autophagy in several human diseases, it is important to determine the extent to which modulators of autophagy also modify inflammatory or immune pathways and whether it is possible to modulate a subset of these pathways selectively.

We have identified small-molecule inducers of basal autophagy (including several FDA-approved drugs) and characterized their effects on IL-1β production, autophagic engulfment and killing of intracellular bacteria, and development of Treg, TH17, and TH1 subsets from naïve T cells. Autophagy inducers with distinct, selective activity profiles were identified that reveal the functional architecture of connections between autophagy, and innate and adaptive immunity. In macrophages from mice bearing a conditional deletion of the essential autophagy gene Atg16L1, the small molecules inhibited IL-1β production to varying degrees suggesting that individual compounds may possess both autophagy-dependent and autophagy-independent activity on immune pathways. The small molecule autophagy inducers constitute useful probes to test the contributions of autophagy-related pathways in diseases marked by impaired autophagy or elevated IL-1β and to test novel therapeutic hypotheses.

CCIB

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Center for Human Genetic Research

Center Overview

CHGR

James Gusella, PhD, Director

MISSION

Human genetics continued to be an extremely active area of groundbreaking biomedical research in 2013, building upon the genome-wide definition of common normal human genetic variation, both sequence and dosage differences, and moving increasingly to a focus on rare or unique variations enabled by advanced DNA sequencing technologies. The mission of the MGH Center for Human Genetic Research (CHGR) is to employ 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, and is completed when the knowledge gained delivers benefit back to the patient population in the forms of improved diagnosis, disease management and treatments. We aim to pursue this mission both by the individual investigations of our faculty members and by making the genetic research cycle paradigm accessible to other basic and clinical researchers at the MGH. As an interdepartmental, interdisciplinary Center with resident faculty who are expert at different stages of the genetic research cycle, including both laboratory-based and clinical researchers, we pursue our investigations both within the CHGR and through overlapping disease-related collaborations, virtual centers and programs with investigators located elsewhere at the MGH and beyond. The CHGR houses a number of shared facilities to support genetic investigations (cell line banking, DNA extraction, genotyping, DNA sequencing, bioinformatics, confocal microscopy), a DNA Diagnostics Laboratory to offer clinical testing for rare disorders, a Clinical Genetic Research Facility to provide clinic-like space for phenotyping and blood-draws and the Clinical Genetics Program, which offers clinical services in genetics, primarily in association with the MGH Hospital for Children. The past year has been an extremely successful one for the CHGR, with continued scientific progress on all fronts.

2013 PROGRESS

The CHGR had another successful year in the wake of the very positive 5 year review completed in 2012. In the past year, we began a center-wide strategic planning process involving all faculty which we expect to complete early in 2014. This planning has focused on the strength of our partnership-based approach to driving forward all phases of the genetic research cycle, across a range of clinical disciplines. The ongoing efforts of CHGR faculty have produced more than 300 papers in the past year, many reflecting the increasing resolution and power of genomewide genotyping in complex disease, exome sequencing in both rare and complex disease, and DNA sequencing to characterize structural variations in the human germline. Similarly, we have continued to have a major focus on the development of induced pluripotent stem cell models of disease for characterization of pathogenic mechanisms and development of interventions. In keeping with our mission, many of our research studies were carried out through interdisciplinary teams with members at the MGH, across the city and around the world. At the MGH, the CHGR continues to interact with a large and collaborative group of non-resident affiliated faculty, comprising 57 individuals representing a wide range of departments and disciplines. Overall, the CHGR remains very strong and well funded, with ~$36.4 million in grant funding ($28.8M direct/ $7.6M indirect), supporting the research of over 300 investigators and staff.

The past year, we recruited Aarno Palotie, formerly a Senior Group Leader at the Sanger Center, as a new senior faculty member of the CHGR. Dr. Palotie is also Research Director of the Human Genomics Program at the Institute for Molecular Medicine, FIMM in Helsinki, Finland and investigates the genetic predisposition of traits affecting the central nervous system, particularly migraine, epilepsy, schizophrenia and autism. At the junior level, we added Jong-Min Lee, a computational molecular biologist, and Inh-Sik Seong, a talented biochemist, to our independent faculty as

CHGR

Assistant Professors in Neurology. Importantly, in partnership with the Department of Neurology and with the participation of the Departments of Psychiatry and Molecular Biology, we were able to successfully retain Michael Talkowski in an independent Assistant Professor position, although he had been heavily recruited by a number of other first-rank institutions.

In the past year, the excellence of our faculty was recognized by the naming of three of our members as 2013 MGH Research Scholars (Susan Slaugenhaupt, Sekar Kathiresan, Jose Florez). Dr. Slaugenhaupt was also named Chair of the Scientific Advisory Board for the NIGMS Human Genetic Cell Repository (Coriell Institute) and as a member of the Board of Trustees of Eckerd College. In addition, Vamsi Mootha, a faculty member in both CHGR and Molecular Biology, was honored by being chosen to become an Investigator of the Howard Hughes Medical Institute and was also named to give the Keilin Memorial Lecture by the Biochemical Society. Notably, Jordan Smoller, head of the Psychiatric and Neurodevelopmental Genetics Unit of CHGR was promoted to Professor of Psychiatry and also served as the Chair of the XXIst World Congress of Psychiatric Genetics held here in Boston. Our cooperative, collaborative, interdisciplinary approach garnered the Team Award at MGH Clinical Research Day again this year (this time by a group led by Chris Newton-Cheh) and also the Translational Award (to Mike Talkowski's group). Indeed, early in 2013, Dr. Talkowski's work was also honored by the Martin Prize for Clinical Research and was named one of the "Top 10" clinical research achievements of 2012 by the National Clinical Research Forum.

SELECTED NOTABLE PUBLICATIONS

1. Agarwala V, Flannick J, Sunyaev S; GoT2D Consortium, Altshuler D. Evaluating empirical bounds on complex disease genetic architecture. Nat Genet. 2013; 45:1418-27. PubMed PMID: 24141362.

This paper combines large-scale empirical data and computer simulations to address a question of high interest to human genetics and the future of "personalized" or "precision" medicine: what is the architecture underlying the genetic basis of common human diseases. That is, to what extent is the genetic basis of disease due to rare variants of large effect (that might prove highly predictive in the clinic), and to what extent due to many common variants of weak effect. This paper argues that available data are not yet sufficient to address this question, but pending results from large scale sequencing studies will soon narrow the bounds.

2. Arora P, Wu C, Khan AM, Bloch DB, Davis-Dusenbery BN, Ghorbani A, Spagnolli E, Martinez A, Ryan A, Tainsh LT, Kim S, Rong J, Huan T, Freedman JE, Levy D, Miller KK, Hata A, Del Monte F, Vandenwijngaert S, Swinnen M, Janssens S, Holmes TM, Buys ES, Bloch KD, Newton-Cheh C, Wang TJ. Atrial natriuretic peptide is negatively regulated by microRNA-425. J Clin Invest. 2013; 123:3378-82. PubMed PMID: 23867623; PubMed Central PMCID: PMC3726159.

This work further characterized a genetic variant that influences atrial natriuretic peptide and blood pressure and demonstrated the impact of the genetic variant in individuals selected on the basis of genotype who underwent dietary and intravenous sodium challenge. In addition, the work identified a novel ANP regulatory mechanism: the genetic variant interrupts a microRNA-binding site, thereby releasing individuals with the minor allele from the negative regulatory effect of miR-425.

3. Cross-Disorder Group of the Psychiatric Genomics Consortium; Genetic Risk Outcome of Psychosis (GROUP) Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. Lancet. 2013; 381:1371-9.

The largest genome-wide analysis of psychiatric disorders to date identified 4 loci that confer risk across five child- and adult-onset disorders that are treated as distinct in clinical practice: autism spectrum disorder, ADHD, bipolar disorder, major depressive disorder and schizophrenia. In addition, aggregate polygene risk score analysis demonstrated cross-disorder sharing of common genetic risk factors. Pathway analyses identified a specific biological pathway – voltage-gated calcium channel signaling – as contributing to the pathogenesis of multiple psychiatric disorders, supporting the value of pursuing this pathway as a therapeutic target for psychiatric disease. The study provides a strong

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impetus pushing psychiatry beyond descriptive syndromes toward the goal of an etiologically-informed nosology.

4. Devan WJ, Falcone GJ, Anderson CD, Jagiella JM, Schmidt H, Hansen BM, Jimenez-Conde J, Giralt-Steinhauer E, Cuadrado-Godia E, Soriano C, Ayres AM, Schwab K, Kassis SB, Valant V, Pera J, Urbanik A, Viswanathan A, Rost NS, Goldstein JN, Freudenberger P, Stögerer EM, Norrving B, Tirschwell DL, Selim M, Brown DL, Silliman SL, Worrall BB, Meschia JF, Kidwell CS, Montaner J, Fernandez-Cadenas I, Delgado P, Greenberg SM, Roquer J, Lindgren A, Slowik A, Schmidt R, Woo D, Rosand J, Biffi A; International Stroke Genetics Consortium. Heritability estimates identify a substantial genetic contribution to risk and outcome of intracerebral hemorrhage. Stroke. 2013; 44:1578-83. PubMed PMID: 23559261; PubMed Central PMCID: PMC3684199.

This study definitively demonstrated that risk of intracerebral hemorrhage has a strong genetic component and that there are variants in multiple gene regions that influence risk of disease. Finding these variants and identifying the mechanisms whereby they influence risk of disease is the most promising path available to developing new treatments.

5. Do R, Willer CJ, Schmidt EM, Sengupta S, Gao C, Peloso GM, Gustafsson S, Kanoni S, Ganna A, Chen J, Buchkovich ML, Mora S, Beckmann JS, Bragg-Gresham JL, Chang HY, Demirkan A, Den Hertog HM, Donnelly LA, Ehret GB, Esko T, Feitosa MF, Ferreira T, Fischer K, Fontanillas P, Fraser RM, Freitag DF, Gurdasani D, Heikkilä K, Hyppönen E, Isaacs A, Jackson AU, Johansson A, Johnson T, Kaakinen M, Kettunen J, Kleber ME, Li X, Luan J, Lyytikäinen LP, Magnusson PK, Mangino M, Mihailov E, Montasser ME, Müller-Nurasyid M, Nolte IM, O'Connell JR, Palmer CD, Perola M, Petersen AK, Sanna S, Saxena R, Service SK, Shah S, Shungin D, Sidore C, Song C, Strawbridge RJ, Surakka I, Tanaka T, Teslovich TM, Thorleifsson G, Van den Herik EG, Voight BF, Volcik KA, Waite LL, Wong A, Wu Y, Zhang W, Absher D, Asiki G, Barroso I, Been LF, Bolton JL, Bonnycastle LL, Brambilla P, Burnett MS, Cesana G, Dimitriou M, Doney AS, Döring A, Elliott P, Epstein SE, Eyjolfsson GI, Gigante B, Goodarzi MO, Grallert H, Gravito ML, Groves CJ, Hallmans G, Hartikainen AL, Hayward C, Hernandez D, Hicks AA, Holm H, Hung YJ, Illig T, Jones MR, Kaleebu P, Kastelein JJ, Khaw KT, Kim E, Klopp N, Komulainen P, Kumari M, Langenberg C, Lehtimäki T, Lin SY, Lindström J, Loos RJ, Mach F, McArdle WL, Meisinger C, Mitchell BD, Müller G, Nagaraja R, Narisu N, Nieminen TV, Nsubuga RN, Olafsson I, Ong KK, Palotie A, Papamarkou T, Pomilla C, Pouta A, Rader DJ, Reilly MP, Ridker PM, Rivadeneira F, Rudan I, Ruokonen A, Samani N, Scharnagl H, Seeley J, Silander K, Stančáková A, Stirrups K, Swift AJ, Tiret L, Uitterlinden AG, van Pelt LJ, Vedantam S, Wainwright N, Wijmenga C, Wild SH, Willemsen G, Wilsgaard T, Wilson JF, Young EH, Zhao JH, Adair LS, Arveiler D, Assimes TL, Bandinelli S, Bennett F, Bochud M, Boehm BO, Boomsma DI, Borecki IB, Bornstein SR, Bovet P, Burnier M, Campbell H, Chakravarti A, Chambers JC, Chen YD, Collins FS, Cooper RS, Danesh J, Dedoussis G, de Faire U, Feranil AB, Ferrières J, Ferrucci L, Freimer NB, Gieger C, Groop LC, Gudnason V, Gyllensten U, Hamsten A, Harris TB, Hingorani A, Hirschhorn JN, Hofman A, Hovingh GK, Hsiung CA, Humphries SE, Hunt SC, Hveem K, Iribarren C, Järvelin MR, Jula A, Kähönen M, Kaprio J, Kesäniemi A, Kivimaki M, Kooner JS, Koudstaal PJ, Krauss RM, Kuh D, Kuusisto J, Kyvik KO, Laakso M, Lakka TA, Lind L, Lindgren CM, Martin NG, März W, McCarthy MI, McKenzie CA, Meneton P, Metspalu A, Moilanen L, Morris AD, Munroe PB, Njølstad I, Pedersen NL, Power C, Pramstaller PP, Price JF, Psaty BM, Quertermous T, Rauramaa R, Saleheen D, Salomaa V, Sanghera DK, Saramies J, Schwarz PE, Sheu WH, Shuldiner AR, Siegbahn A, Spector TD, Stefansson K, Strachan DP, Tayo BO, Tremoli E, Tuomilehto J, Uusitupa M, van Duijn CM, Vollenweider P, Wallentin L, Wareham NJ, Whitfield JB, Wolffenbuttel BH, Altshuler D, Ordovas JM, Boerwinkle E, Palmer CN, Thorsteinsdottir U, Chasman DI, Rotter JI, Franks PW, Ripatti S, Cupples LA, Sandhu MS, Rich SS, Boehnke M, Deloukas P, Mohlke KL, Ingelsson E, Abecasis GR, Daly MJ, Neale BM, Kathiresan S. Common variants associated with plasma triglycerides and risk for coronary artery disease. Nat Genet. 2013; 45:1345-52. PubMed PMID: 24097064.

CHGR

Triglycerides are transported in plasma by specific triglyceride-rich lipoproteins; in epidemiological studies, increased triglyceride levels correlate with higher risk for coronary artery disease (CAD). However, it has been unclear whether this association reflects causal processes. This paper reported mapping of 185 common variants for plasma lipids (P < 5 x 10–8 for each) across which the strength of a variant's effect on plasma triglycerides is highly correlated with the magnitude of its effect on CAD, even after accounting for potential effects of each variant on LDL cholesterol and/or HDL cholesterol. These results suggest that triglyceride-rich lipoproteins causally influence risk for CAD.

6. Lee JM, Galkina EI, Levantovsky RM, Fossale E, Anne Anderson M, Gillis T, Srinidhi Mysore J, Coser KR, Shioda T, Zhang B, Furia MD, Derry J, Kohane IS, Seong IS, Wheeler VC, Gusella JF, MacDonald ME. Dominant effects of the Huntington's disease HTT CAG repeat length are captured in gene-expression data sets by a continuous analysis mathematical modeling strategy. Hum Mol Genet. 2013; 22:3227-38. PubMed PMID: 23595883; PubMed Central PMCID: PMC3723309.

Huntington's disease is caused by expansion of a polymorphic CAG trinucleotide repeat that acts as a functional polymorphism, modulating activities of the multifunctional huntingtin protein. In patients. there is a strong genotype-phenotype relationship between CAG length and rate of pathogenesis prior to clinical diagnosis of this disease, which typically occurs only in mid-life. This paper provides the proof-of-principle that even in peripheral tissues, this quantitative relationship provides an effective route to separating subtle molecular consequences of the repeat length from the many sources of noise inherent in biological systems. It thereby points a path to identifying pathogenesis-relevant molecular mechanisms as potential therapeutic targets decades before clinical appearance of disease.

7. Leussis MP, Berry-Scott EM, Saito M, Jhuang H, de Haan G, Alkan O, Luce CJ, Madison JM, Sklar P, Serre T, Root DE, Petryshen TL. The *ANK3* bipolar disorder gene regulates psychiatric-related behaviors that are modulated by lithium and stress. Biol Psychiatry. 2013; 73:683-90. PubMed PMID: 23237312.

Logue MW, Solovieff N, Leussis MP, Wolf EJ, Melista E, Baldwin C, Koenen KC, Petryshen TL, Miller MW. The ankyrin-3 gene is associated with posttraumatic stress disorder and externalizing comorbidity. Psychoneuroendocrinology. 2013; 38:2249-57. PubMed PMID: 23796624; PubMed Central PMCID: PMC3775967.

This pair of papers demonstrates that the ankyrin 3 gene, one of the strongest risk genes for bipolar disorder, regulates sensitivity to stress and may be associated with another stress-related disorder in humans, posttraumatic stress disorder (PTSD), findings that could be applied to the development of new treatments for psychiatric disorders.

8. Lojewski X, Staropoli JF, Biswas-Legrand S, Simas AM, Haliw L, Selig MK, Coppel SH, Goss KA, Petcherski A, Chandrachud U, Sheridan SD, Lucente D, Sims KB, Gusella JF, Sondhi D, Crystal RG, Reinhardt P, Sterneckert J, Schöler H, Haggarty SJ, Storch A, Hermann A, Cotman SL. Human iPSC models of neuronal ceroid lipofuscinosis capture distinct effects of *TPP1* and *CLN3* mutations on the endocytic pathway. Hum Mol Genet. 2013 Dec 6. [Epub ahead of print] PubMed PMID: 24271013.

The neuronal ceroid lipofuscinoses (NCLs) are collectively the most frequent neurodegenerative disorders of childhood and, after onset in a previously healthy child, lead progressively to complete debilitation and death. This paper reports the first iPSC models for two major genetic forms of NCL, and the development of assays that measure early NCL-related phenotypes for therapeutic drug screening studies.

9. Pinto RM, Dragileva E, Kirby A, Lloret A, Lopez E, St Claire J, Panigrahi GB, Hou C, Holloway K, Gillis T, Guide JR, Cohen PE, Li GM, Pearson CE, Daly MJ, Wheeler VC. Mismatch repair genes *Mlh1* and *Mlh3* modify CAG instability in Huntington's disease mice: genome-wide and candidate approaches. PLoS Genet. 2013; 9:e1003930. PubMed PMID: 24204323; PubMed Central PMCID: PMC3814320.

CHGR

In the first description of an unbiased genetic mapping approach to uncover a disease modifier in a precise genetic mouse model of Huntington's disease, a quantitative trait locus (QTL) was found to be associated with somatic expansion of the HTT CAG repeat. Genetic knockout experiments and cross-strain comparisons of likely candidate genes then pinpointed Mlh1 and Mlh3 as two novel modifiers of repeat instability encoding subunits of the MutLgamma complex, whose role in somatic cells has to-date been unclear. This suggests that a "non-canonical" mismatch repair process distinct from that traditionally described for global genome maintenance is involved in somatic CAG expansion and may lead to novel means of specifically intervening, with the potential to slow the rate of disease onset and/or progression.

10. SIGMA (Slim Initiative in Genomic Medicine for the Americas) Type 2 Diabetes Consortium. An ancient haplotype carrying four missense SNPs in SLC16A11 is a common risk factor for type 2 diabetes in Mexico. *Nature* 2013; Dec 25 2013 Dec 6. [Epub ahead of print].

The members of the SIGMA Type 2 Diabetes Consortium conducted a genome-wide association study in 9,000 Latino cases of type 2 diabetes and normoglycemic controls, and detected a strong association of a haplotype carrying four missense variants in SLC16A11 with type 2 diabetes. The haplotype was introgressed into modern humans from Neandertals, and is present at much higher frequencies in Native American populations than in Europeans or Africans. Expression of SLC16A11 in cells causes an increase in triacylglycerols, in a pattern similar to that seen in a lipidomic signature predictive of type 2 diabetes in a European population cohort.

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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. Our faculty is comprised of individuals who hold appointments in the Departments of Medicine, Surgery, Orthopedics and Psychiatry and affiliations to the MGH Cancer Center and Pulmonary Unit, the Harvard University Department of Stem Cell and Regenerative Biology, the Broad Institute and the Harvard Stem Cell Institute.

The CRM is directed by Dr. David Scadden and co-directed by Dr. Konrad Hochedlinger.

Investigators within the Center include:

Andrew Brack, PhD, Associate Professor of Medicine
The Brack lab's interests lie at the interface between adult stem cell biology and tissue regeneration of skeletal muscle. Their focus is on the molecular pathways that control cell fate decisions of the adult muscle stem cell (the satellite cell) to effectively regenerate adult skeletal muscle. The lab is supported by the NIH, the Plastic Surgery Foundation and the Muscular Dystrophy Association.

Chad Cowan, PhD, Associate Professor of Medicine/Stem Cell and Regenerative Biology
The Cowan lab focuses on understanding the contribution of environmental and genetic factors in the development of metabolic disease. The Cowan lab is a split venture. The majority of Dr. Cowan's personnel are housed at the Harvard University Department of Stem Cell and Regenerative Biology. Dr. Cowan and his research connection to the clinic will continue to hold a footprint at the CRM. His research is funded by Roche Pharmaceuticals and the NIH.

Nabeel El-Bardeesy, Associate Professor of Medicine (Cancer Center)
The Bardeesy Laboratory focuses on understanding the genetic program for pancreatic cancer initiation and progression. The lab has generated a series of genetically engineered mouse models and primary pancreatic cell culture systems for these studies. Pancreatic ductal adenocarcinoma (PDAC) is among the most lethal of human cancers. Although a recurrent set of gene mutations has been identified in this cancer type, this information has not translated into significant improvements in patient outcome. The laboratory focuses on understanding the genetic program for PDAC initiation and progression. The Bardeesy lab is funded by the NIH, Merck, Agios, Samuel Maxman Cancer Research Foundation.

Jenna Galloway, PhD, PhD, Assistant Professor of Surgery (Orthopedics)
Dr. Galloway is the most recent faculty recruit to the MGH CRM beginning 11/1/2012. Dr Galloway's primary interest is understanding how tendons and ligaments form, organize, and regenerate with the ultimate goal of applying this knowledge towards the development of improved therapies for tendon and ligament injuries. Her research is funded by the NIH and the Harvard Stem Cell Institute.

Konrad Hochedlinger, PhD, Professor of Medicine/Stem Cell and Regenerative Biology (Cancer Center)
The Hochedlinger lab is using in *vitro* and *in vivo* model systems to further characterize the role of pluripotency genes in stem cell self-renewal, reprogramming and cancer. Stem cells have the dual potential to self-renew and give rise to differentiated cells. The Hochedlinger lab is supported by the NIH, a Jr Investigator Award from the Howard Hughes Medical Institute, the Harvard Stem Cell Institute and internal funding.

Jayaraj Rajagopal, MD, Assistant Professor of Medicine
The Rajagopal lab seeks to isolate and culture lung stem cells and to understand their role in normal lung epithelial homeostasis and in regeneration after tissue injury. The Rajagopal lab is funded by internal funds, the Cystic Fibrosis Foundation, the Harvard Stem Cell Institute, NIH, The New York Stem Cell Foundation, Massachusetts Eye and Ear Infirmary and DOD.

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Eric Liao, MD, PhD, Assistant Professor of Surgery (Plastic Surgery)
Dr. Liao's program looks to improve understanding of the developmental genetic basis of facial morphogenesis. The goal of the lab is to investigate fundamental genetic regulation of facial development, with a focus on translating basic science discoveries to clinical advances. The Liao lab is funded by the Plastic Surgery Education Foundation, Shriner's Hospital and internal funding.

Hanno Hock, MD, PhD, Assistant Professor of Medicine (Cancer Center)
The Hock lab is interested in the molecular control of normal and malignant stem cells with an emphasis on the hematopoietic system. Dr. Hock also serves as the Director of the HSCI-MGH Flow Cytometry Core. The Hock lab is currently funded by internal funds as well as NIH and HSCI.

Raul Mostoslavsky, MD, PhD, Assistant Professor of Medicine (Cancer Center)
Research in the Mostoslavsky laboratory focuses on a family of proteins first discovered in yeast that plays a critical role in many human diseases, including cancer. Most of the work in the Mostoslavsky lab focuses on the Sir2 mammalian homolog known as SIRT6. Research suggests that SIRT6 modulates glucose metabolism and DNA repair and may function as a tumor suppressor gene. Using transgenic mouse models and other experimental systems, they are exploring the role of SIRT6 in tumorigenesis and other disease processes. The lab is funded by the Massachusetts Life Sciences Center, NIH and the MGH Scholars program.

Harald Ott, MD, Instructor of Surgery (Thoracic Surgery)
In the laboratory for organ regeneration, the Ott lab is currently further developing perfusion decellularized scaffolds as a platform for organ engineering by developing conditions suitable for human organs, deriving adult cell populations from patients, designing human size bioreactor systems, and developing human organ culture conditions. The laboratory is linked to the Harvard Stem Cell Institute, MIT, Harvard Medical School, the New England Organ Bank, and the clinical departments of MGH. The lab is funded by the NIH and United Therapeutics.

Sridhar Ramaswamy, MD, Associate Professor of Medicine (Cancer Center)
The Ramaswamy lab looks to identify important cancer gene networks that are essential in human cancer metastasis and drug resistance, to guide the development and clinical use of new cancer drugs and diagnostics. The Ramaswamy lab is funded by the NIH, Stand up 2 Cancer, The American Association of Cancer Research, Howard Hughes Medical Institute and internal funding.

Amar Sahay, PhD, Assistant Professor of Psychiatry
The Sahay lab is focuses on mouse models to assess how adult **neurogenesis** affects mood and cognition. He is particularly interested in evaluating drug based methods of modifying neural stem cell function to alter complex behaviors in adults as a means of improving human therapies for psychiatric disease. The Sahay lab is currently funded by the NIH, the Whitehall Foundation, the Ellison Medical Foundation and internal funding.

Shobha Vasudevan, PhD, Assistant Professor of Medicine (Cancer Center)
Dr. Vasudevan's lab is investigating the mechanisms of gene expression regulation by microRNAs and other noncoding RNAs, their regulation and interconnections with AU-rich 3'UTR elements in response to quiescent and hypoxic conditions in tumors and germ stem cells. These studies should provide greater understanding of the versatile roles of regulatory noncoding RNAs in the pathogenesis of cancers and developmental disorders and lead to novel approaches in small RNA-based therapeutic applications. Her laboratory is funded by the Smith Family Foundation, the Leukemia Research Foundation, The Leukemia and Lymphoma Society, The V Foundation, The Cancer Research Institute and internal funding.

Joseph Vacanti, MD, John Homans Professor of Surgery (Pediatric Surgery/Tissue Engineering)
The Vacanti lab is focused on tissue engineering and their research lies at the interface between basic and translation work where they focus on regenerating or replacing diseased organs and tissues. Combining the disciplines of medicine, molecular and developmental biology, material science, and

CRM

biotechnology, they have applied tissue engineering principles to design and engineer replacement tissues. The Vacanti lab is funded by internal funds and the Department of Defense.

David Scadden, MD, Gerald and Darlene Jordan Professor of Medicine, Professor and co-chair Harvard University Department of Stem Cell and Regenerative Biology
The Scadden laboratory focuses on the hematopoietic stem cell and its microenvironment or niche. The lab is affiliated with the HSCI, Broad Institute and the Cancer Center. It is funded by the NIH, The Harvard Stem Cell Institute, Glaxo-Smith Kline, Mass Life Sciences Center, and the Leukemia and Lymphoma Society.

INTERACTIONS

CRM has extensive interactions with other investigators at MGH and in the broader Harvard and MIT communities. CRM helped galvanize the establishment of the Harvard Stem Cell Institute (HSCI), which is co-directed by Dr. Scadden and Dr. Douglas Melton. As an important confederated partner of HSCI, CRM brings specific features that augment other elements of HSCI, including unique stem cell clinical investigation expertise and ongoing collaborative clinical trials using stem cell transplantation as well as emphasis in technologies that will ultimately be critical for the success of stem cell based medicine (bioengineering, biomaterials expertise, close links to *in vivo* imaging capability and a GMP facility for sophisticated cell manipulation).

Dr. Scadden is the Co-chair of the Department of Stem Cell and Regenerative Biology (SCRB) of Harvard University, the first department between faculties in Harvard's history. Several CRM faculty participate as faculty of SCRB actively teaching at the undergraduate and graduate level.

Ongoing collaborations continue with a team of investigators, led by Dr. Scadden and Drs. Eric Olson and Jay Schneider, of the University of Texas Southwest Medical Center, received one of 18 grants awarded by the National Heart Lung and Blood Institute to study progenitor cell biology. They seek to examine how the microenvironment within heart, lung, and bone marrow controls progenitor cell fate, and study progenitor cell types in the cardiac and pulmonary contexts.

Dr. Scadden continues his NIH collaboration with Dr. Raghu Kalluri, at the MD Anderson in Texas. This team will evaluate the contributions of bone to bone metastasis relating to prostate cancer. Dr. Scadden also has a new collaboration with Dr. David Mooney, at the Harvard University School of Engineering and Applied Sciences. This project looks at specific cellular and molecular components of the hematopoietic stem cell microenvironment *in vivo* to create an ex vivo environment permitting the self-renewal and multilineage differentiation of stem cells. The Scadden lab will contribute cells from normal and genetically engineered mouse strains and humans for the development of the 3D tissues constructs.

Jay Rajagopal is currently collaborating with the Massachusetts Eye and Ear infirmary to help train a laryngologist in the laboratory. In the past year he has continued to collaborate with investigators from the Draper laboratories and the University of Massachusetts.

Investigators within the Center, including David Scadden, Andrew Brack and Jenna Galloway, have teamed with investigators from the MGH Department of Orthopedics and Division of Sports Medicine and the MGH Endocrine Unit to form the Muskuloskeletal Regeneration Consortium (MRC). This group meets monthly to discuss their current research and significant issues within the musculoskeletal field, drawing upon the groups expertise and multidisciplinary nature. 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.

The Center is also undertaking a unique collaboration with the Harvard Stem Cell Institute and their Bioinformatics program. The collaboration brings the necessary bioinformatics expertise to the Center in a much needed way.

EDUCATION

CRM faculty participates actively in undergraduate level courses at Harvard and graduate level courses at Harvard, MIT and HST. Andrew Brack continues to teach BBS courses at MGH. CRM holds

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bi-monthly lab seminars which shares the research being down within the CRM community. Jay Rajagopal leads the Research Mentor Program for the Department of Medicine's Residency Program.

The Center has continued its relationship with the MGH Center for Community Improvement (CCI). This past summer researchers mentored undergraduate college students who were involved in this program. This upcoming summer the CRM plans to host 2 additional students through this program.

PHILANTHROPIC SUPPORT

CRM, the MGH Development Office and CRM's Advisory Board have initiated a venture philanthropy fund (the Innovation Fund) and are actively pursuing fund raising goals in conjunction with the hospital capital campaign.

PUBLICATION HIGHLIGHTS

Andrew Brack, PhD

Brack AS. Ageing of the heart reversed by youthful systemic factors! *EMBO J.* 2013 Aug 14;32(16):2189-90. doi: 10.1038/emboj.2013.162. Epub 2013 Jul 16.

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Nabeel El-Bardeesy, PhD

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Center for Systems Biology

Center Overview

CSB

Ralph Weissleder, MD, PhD, Director

(report prepared 12/03/13)

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.

Investigator Labs at the Center for Systems Biology

Bernstein, Bradley, MD, PhD. Professor of Pathology

The Bernstein laboratory studies chromatin and epigenetic regulation at a genome-wide scale. Notable findings include the discovery of epigenetic mechanisms in pluripotent stem cells, the systematic identification of enhancer 'switches' in the human genome that coincide with DNA sequence variants associated with common diseases, and the characterization of regulatory circuits that underlie certain forms of cancer.

Breton, Sylvie, PhD. Professor of Medicine

The Breton laboratory specializes in the cell biology of membrane transport. Using a multidisciplinary approach including high-resolution laser scanning confocal microscopy, three-dimensional reconstructions of single cells, and electrophysiological techniques, their focus is primarily on luminal acidification, and water/solute transport in the male reproductive tract and the kidney.

Brown, Dennis, PhD. Professor of Medicine

The goal of the Brown laboratory is to understand how membrane transport vesicles interact with accessory proteins and with components of the cytoskeleton to modulate cell function via various membrane transport proteins in physiological and pathophysiological conditions. The aim of the research is to understand how physiologically-relevant processes of fluid and electrolyte transport across epithelia are regulated at the cell and molecular levels in kidney, the male reproductive tract and other organ systems.

Higgins, John, MD. Assistant Professor of Systems Biology

The Higgins laboratory is investigating the dynamics of human pathophysiologic processes by developing mathematical descriptions of complex human disease phenotypes and how they change over time. The research combines medical insight, dynamic systems theory, and experiments utilizing microfluidics, video processing, flow cytometry, simulation, and large-scale analysis of medical databases. The ultimate goals of this research are to advance understanding of the dynamics of human pathophysiology, and to improve patient diagnosis, monitoring, and treatment.

Lin, Charles, PhD. Associate Professor of Dermatology

The Charles Lin group is interested in developing cutting-edge optical imaging techniques for *in vivo* cell tracking and molecular imaging studies. The laboratory's primary research focus is the development of minimally invasive optical techniques for *in vivo* imaging of stem cells and hematologic

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malignancies. They are currently actively engaged in several multidisciplinary collaborative studies with experts across the fields of stem cell biology, immunology, and cancer biology.

Herbert Lin, MD, PhD. Associate Professor of Medicine
The overall theme of the laboratory is to understand the role of the TGF-β/BMP signaling pathway in health and disease. By studying this complex signaling system, their aim is to generate new knowledge that will lead to novel therapeutic options for conditions such as chronic kidney disease, hemochromatosis and anemia in chronic disease.

Nahrendorf, Matthias, MD, PhD. Associate Professor of Radiology
The Nahrendorf laboratory studies the complex cellular and molecular changes after myocardial infarction at the systems level. Main targets of interest are innate immune cells, particularly monocytes and macrophages, both key players in cardiovascular disease. In addition, precursors of these cells are studied, including hematopoietic stem cells in the bone marrow. Multimodal imaging, as well as hybrid approaches, are used to fuse molecular data with anatomical information in order to obtain not only a systematic understanding of inflammation at a basic level but also to maintain a rigorous translational perspective.

Pittet, Mikael, PhD. Associate Professor of Radiology
The Pittet laboratory performs research on the host immune response *in vivo*, dysregulation of which has been implicated in several inflammatory disorders including cancer, atherosclerosis, myocardial infarction and asthma.Their aim is to gain a better understanding of immune cell production, trafficking activity, and mediation of regulatory or effector functions. To achieve this goal, the team uses multiple experimental tools including classic molecular and cellular techniques, microsurgical procedures together with *in vivo* imaging modalities. The group also collaborates extensively with other investigators locally, nationally as well as internationally.

Shaw, Stanley, MD, PhD. Assistant Professor of Medicine
The Shaw laboratory studies human phenotypes at varying scales, including baseline or chemically perturbed phenotypes of cells derived from the peripheral circulation, nanoparticle-based imaging techniques and data mining of Electronic Medical Records (EMRs) to phenotype patients at population scale, together with genetic and epigenetic analysis of associated blood specimens. The overall goal is to use these phenotypes to understand the functional consequences of disease mutations and generate new therapeutic hypotheses.

Stone, James, MD, PhD. Associate Professor of Pathology
The Stone Laboratory studies mechanisms underlying human vascular diseases, such as atherosclerosis and vasculitis.

Swirski, Fil, PhD. Assistant Professor of Radiology
The Swirski laboratory utilizes a range of cell, molecular and imaging techniques to elucidate how innate immune cells contribute to cardiovascular disease. The primary goal is to identify and elucidate how leukocyte communication shapes the course of disease. Experiments combine state-of-the-art animal models, classical cell biology tools, molecular profiling, as well as *in vivo* molecular imaging technologies.

Weissleder, Ralph, MD, PhD. Professor of Systems Biology and Radiology
The Weissleder group is focused on imaging and quantitatively assessing the effects of cancer treatments using a variety of techniques including whole body and intravital microscopic imaging, novel chemical approaches for perturbing systems, and innovative sensing/chip strategies including nanotechnology approaches. The goals are to obtain quantitative and systems-wide global measurements, to perform dynamic serial measurements, and to integrate multiple and various data sets into models. Increasingly, work in the laboratory has been focused on reconciling the gap that exists between imaging and traditional cell biology research, but in an *in vivo* setting.

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Publications and scientific accomplishments in 2013

CSB faculty have published approximately 120 articles over the last year and over 350 articles over the last 3 years. Of those published in 2013, several have appeared in high profile journals. Selected publications from each laboratory are highlighted below (for full listings of all 38 faculty please see: http://csb.mgh.harvard.edu/publications):

Bernstein Laboratory

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Breton Laboratory

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- Roy, J.W., et al., Circulating aldosterone induces the apical accumulation of the proton pumping V-ATPase and increases proton secretion in clear cells in the caput epididymis. **Am J Physiol Cell Physiol**, 2013. 305(4): p. C436-46.
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Brown Laboratory

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Charles Lin Laboratory

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Herbert Lin Laboratory

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Nahrendorf Laboratory

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Shaw Laboratory

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Stone Laboratory

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Swirski Laboratory

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Weissleder Laboratory

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Platform leaders

Bioimaging Platform (Vinegoni, Nahrendorf):

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- S. Lee, C. Vinegoni, P. Fumene Feruglio, R. Weissleder. Improved intravital microscopy via

CSB

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Core activities

Mouse Imaging Platform *(Nahrendorf; http://csb.mgh.harvard.edu/mouse_imaging).* There are currently 66 ongoing mouse imaging projects, generating ~25,000 images per week from investigators across MGH and Harvard. To date, 565 individual scientific projects, involving over 8 million images, have been completed.

Cell Microscopy Core *(Brown; http://csb.mgh.harvard.edu/microscopy).* The Core currently serves over 70 active users across the entire MGH community.

Research Informatics Core *(Pivovarov; http://ric.csb.mgh.harvard.edu/).* The Core provides software development and web hosting services to all departments and laboratories across the Partners

community and beyond. There are currently 18 active projects.

CSB

Grants

The CSB currently has 54 active grants and approximately 30 pending grants. New and noteworthy grants include:

- RO1AI104695-01: Innate Response Activator B cells in Bacterial Lung Infection (PI: Fililp Swirski, PhD). September 1, 2013 thru August 31, 2014. $435,000 total costs.
- 1R33CA174560-01A1: Validation and Advanced Development of Emerging Analysis Technologies for Cancer Research (Sunney Xie, PhD; Ralph Weissleder, MD, PhD). December 1 2013–November 30, 2018, ($349,140)
- 1R01HL117829-01A1: Cell-Cell Interaction in Heart Failure (PI: Matthias Nahrendorf). December 1 2013–November 30, 2018.
- 1R01HL121020-01: The Role of the Bone Marrow in Atherosclerosis (PI: Matthias Nahrendorf). September 1, 2013–August 31, 2018.
- 1P01AG043353-01: Aging of the Heart (MGH subcontract: PI Matthias Nahrendorf). December 1, 2012–November 30, 2017; $486,865 (5 years) total costs.
- 4R37DK042956-21: Regulation of proton pump trafficking in kidney-Merit extension (PI: Dennis Brown). April 22, 2013–March 31, 2018. $407,065 total costs per year.
- Zeiss sponsored research agreement (Brown): Developing Helium Ion Microscopy for Biological Specimens; July 1, 2013–June 30, 2014; $30,000 total costs
- Siemens Subcontract: Predictive Analytics and Dashboard for Population Management (sub with MIT - PI: Stanley Shaw, MD) February 15, 2013–September 30, 2013. $345,499 total costs
- Gates Foundation Award (OPP1086203): Inhibitors of tRNA-Synthetases as Novel Antimalarials (PI: Ralph Mazitschek PhD), May 1 2013 to April 20, 2014. $100,000 total costs.
- GlycoMimetics Award: Targeting E-selecting in Cardiovascular Disease (PI: Matthias Nahrendorf). May 7 2013–May 6, 2014. $120,000 total costs.
- 1R01HL114477: Pathogen Specific Imaging of Endocarditis (PI: Matthias Nahrendorf), June 15 2013 to May 31 2017. $419,661 per year.
- AHA Foundation Award: RNA interference-mediated gene silencing of IRF5 in Myocardial Infarction (PI: Gabriel Courties). July 1 2013–June 30, 2015, $89,000 total costs.
- R21DK092619-01: Role of Novel Gene Fam49b in Phophatidylserine Synthesis in Podocyte and Maintenance of Glomerular Filter Function (Hua (Jenny) Lu). September 2012 thru August 2014. $150,000 total costs.
- CCNE Alliance Challenge Project: High Resolution PK/PD Imaging of Novel PT Nanoparticles (PIs: Ralph Weissleder, Omid Farokhzad and Stephen Lippard). September 1 2013 thru August 31, 2015; $250,658 total costs.
- 1K99HL121076-01: Effect of Diabetes on Myelopoiesis and Atherosclerosis (PI: Partha Dutta, PhD) December 1, 2013–August 31, 2018.
- Partnership for Clean Competition: Detecting Blood Doping by Measuring RBC Population Dynamics (PI: John Higgins, MD). Effective date: September 2013.
- R01DK096015-1: Role of AQP2 in epithelial cell migration and tubular repair after injury (PI: Hua (Jenny) Lu). Sept. 1, 2013 – Aug. 31, 2018 $326,093 total costs per year
- 1U01HL114476-01: Multiscale Modeling of Sickle Cell Anemia: Methods and Validation. (Co-PI John Higgins). September 1, 2013 – May 31, 2018.

CSB

- Mathematical Model-based Algorithms for Anemia Prediction. (PI: John Higgins). Abbott Diagnostics ($80,000 total costs).
- Lustgarten Award: Exosomes as a diagnostic and prognostic biomarker in pancreatic ductal adenocarcinoma (PDAC). (PI: Ralph Weissleder, MD, PhD), December 1 2013 thru November 30 2016, ($1,260,000 total costs)
- 2RO1EB010011: Novel Clickdyes for Biomedical Sensing. (PI: Ralph Weissleder, MD, PhD), April 1, 2014 thru March 31, 2019; ($2,173,998 total costs)
- 1RO1HL122208-01: Single Cell Imaging of the Heart (PI: Ralph Weissleder, MD, PhD), April 1, 2014 thru March 31, 2019 ($2,172,491 total costs)
- 2RO1HL095612-06: Monocyte and macrophage behavior in atherosclerosis (PI: Fil Swirski, PhD), April 1, 2014 thru March 31, 2019 ($2,151,578 total costs)

Awards, Nominations and Promotions

- Promotion to Professor: Sylvie Breton, PhD; Brad Bernstein, MD; Charles Lin, PhD (pending)
- Promotions to Associate Professor: Matthias Nahrendorf, MD, PhD, Mikael Pittet, PhD.
- Promotion to Assistant Professor: Nicolas Da Silva, MD, Hua Lu, MD, PhD
- Ralph Weissleder was appointed the Thrall Family Professor of Radiology as of Aug 1, 2013
- Dennis Brown, PhD, was awarded an Honorary Doctorate of Science by his alma mater, the University of East Anglia, Norwich, UK at a congregation held on Thursday July 18th, 2013. The honor was bestowed in recognition of his contributions to cell biology and physiology. The following week on July 25th, he gave the prestigious Robert Pitts Lecture in Renal Physiology at the International Union of Physiological Sciences meeting in Birmingham, UK.
- Herbert Y. Lin was appointed the position of Director of Translational Research in the Division of Nephrology.
- Filip Swirski, PhD has received the Goodman Award

Patents and Inventions for FY13

- 9 new inventions were filed by CSB members in FY2013
- 15 new patents were issued in FY13 bringing the total of patents from CSB investigators to over 100 patents.
- Licensees of technologies developed in CSB include Perkin Elmer, T2 Biosystems, iTi Health, Millipore, Ferrumax Pharmaceuticals, Exosome Diagnostics and CSL Behring.
- There are a number of on-goings license/collaboration discussions with potential partners, including Nanostring, BioLegend, Huzhou Shuwen Biotechnologies and Quantum Diamond Technologies

R. Rox Anderson, MD, Director

WCP

Overview

The field of Photomedicine encompasses all of light's beneficial, harmful, diagnostic, therapeutic, surgical, medical and technological aspects in biology and medicine. Wellman is the largest research center in this field, with 250 research personnel among 13 diverse, interactive laboratories. We pursue basic questions and technology solutions for problems in many different organ systems. Trauma, infection, cancer, atherosclerosis, immunity and skin disease are prevalent themes. We are technology leaders for *in vivo* microscopy; tissue imaging and spectroscopy; light-activated drug treatments; optical diagnostics; biocompatible optics; laser surgery; and integration of these with other technologies. The Wellman Center is a nucleus of the MIT-Harvard H.S.T. program, and works openly with many other universities.

Center Highlights for 2013

Growth & Support

- WCP grew by ~9%, to 252 people, including 32 full-time faculty and 17 affiliated faculty.
- WCP fosters and actively supports photomedicine research throughout MGH. There are ~70 substantial collaborations in progress between WCP and other researchers at MGH / HMS.
- Adequate nearby space for growth remains our #1 challenge.
- This year, working with the MGH Research Space Management Group, WCP acquired opened a 1588 square foot laboratory for Conor Evans in CNY, and added a 489 square foot wet lab space on Thier-3.
- About $850k was spent in 2013 on renovations of laboratory space.
- FY13 research expenditures were $26.3 million.
- Research revenues were $28.2 million (includes IP revenues).
- WCP has almost 100 currently active research grants from NIH, DOD, industry, and NSF.
    - A healthy trend has been the growth in NIH grants, which represent about 55% of total research support for the Center, including a program project grant and a biomedical research program grant.
    - 25% of WCP research is supported by Dept. of Defense grants and contracts.
    - 20% of WCP research is industry sponsored, usually in concert with IP licenses.
- WCP inventions yielded about $5.6 million total to MGH from patent royalties in 2013.
- WCP uses most of its royalty and IP license share, to maintain a discretionary central fund.
- These funds are mainly used for (1) start-up support of new faculty recruited by competitive search, (2) renovations of antiquated buildings to make space suitable for modern research, (3) core research equipment, (4) graduate student program support, and (5) special projects in WCP labs.

Faculty Promotions and New Faculty

- WCP now includes 5 Professors, 7 Associate Professors, and 5 Assistant Professors.
- In 2013, there were 5 promotions to Instructor.

Innovation & Technology Transfer

Moving discoveries and innovations all the way into medical practice is central to our mission of actually helping people, brings scientists and clinicians together, and creates new opportunities. Wellman accounts for several of MGH's top 10 patents based on 2013 royalties. About 30 discoveries and inventions now in the WCP "pipeline" are well beyond the proof-of-concept stage, moving

Wellman Center for Photomedicine

Center Overview

WCP toward clinical applications. An internal core at WCP facilitates Translational Research by identifying, tracking and fostering progress of these pipeline projects.

Education

- WCP offers competitive support for graduate students, research and clinical fellowships
- 29 graduate and 6 undergraduate students conducted research in Wellman.
- WCP faculty taught five graduate courses, at Harvard and MIT.
- WCP hosted the Photomedicine Lecture Series, two CME courses, the annual MGH Laser Safety course, special topics lectures and conferences.
- 2013 marked the 11th year of Wellman's **Summer Institute in Biomedical Optics**, led by Andy Yun PhD. Twelve undergraduate students enrolled.
- WCP hosted three international educational programs
    - MGH is one of 4 collaborating institutes for graduate student training in biomedical optics.
    - 3 graduate students enrolled in the Tokyo University summer exchange program (9th year), supported by a grant to the University of Tokyo.
    - 7 undergraduate students enrolled from KAIST University majoring in electrical, chemical, mechanical engineering and the biological sciences.
    - 1 undergraduate student enrolled from Tongji Univeristy (Shanghai)

Bullock Research Fellowships

This endowed fellowship for collaborative research at WCP is possible by a gift from the Bullock family. Announced throughout HMS, competitive proposals are reviewed every autumn. In 2013, three Bullock Fellowships were awarded for research to begin in 2014. The fellows will study (a) a novel image-guided and light-activated therapeutic strategy for glioblastoma (G. Obaid, PhD in the Hasan and Vakoc laboratories); (b) the role of AML quiescent cells and their microenvironment in determining drug resistance (T Oki, MD PhD in the Lin laboratory, collaborating with D. Scadden); (c) dual modality imaging of coronary artery disease (G Ughi, PhD in the Tearney laboratory collaborating with F Jaffer).

Some Research Highlights of 2013 (a small fraction of WCP publications)

WCP faculty published ~ 130 peer-reviewed research papers in 2013.

Rox Anderson laboratory

Tam J, Wang Y, Farinelli WA, et al. Fractional Skin Harvesting: autologous skin grafting without donor-site morbidity. Plast Reconstr Surg Glob Open 2013;1:e47; published online 25 September 2013.

There is high morbidity from standard split-thickness skin grafting (STSG), which leaves scarring and disfigurement in both the donor and treatment sites. This paper describes the first practical alternative to STSG that does not cause scarring. A large number of very small full-thickness skin columns were harvested and applied to deep wounds using a novel device. Full-thickness functional new skin forms in the wound, and the donor site heals rapidly, without scarring.

Brett Bouma laboratory

Villiger M, Zhang EZ, Nadkarni S, Oh WY, Vakoc BJ, Bouma BE. Spectral binning for mitigation of polarization mode dispersion artifacts in catheter-based optical frequency domain imaging. Optics Express. 2013;21(4):16353-69.

Microscopic imaging of collagen and smooth muscle cells *in vivo* would have many important applications, from the characterization of the structural integrity of atherosclerotic plaques to the guidance of biopsy for early cancer detection. We have developed a method for accurate quantitative

WCP

birefringence mapping through minimally invasive catheters and endoscopes and thereby imaging of collagen and smooth muscle cells. This paper describes the enabling technology and its validation.

Conor Evans laboratory

Klein, O J, Y K Jung, and C L Evans. 2013. "Longitudinal, Quantitative Monitoring of Therapeutic Response in 3D in Vitro Tumor Models with OCT for High-Content Therapeutic Screening." *Methods.* (September 3). doi:10.1016/j.ymeth.2013.08.028. PMCID: 24013042.

In vitro three-dimensional models of cancer have many features of tumors found *in vivo*, but can be large, complex, heterogeneous, and difficult to track and quantify using standard imaging tools. By optimizing both optical coherence tomography and 3D culture systems, quantitative therapeutic screens were created using in vitro 3D cultures, gaining insights into therapeutic mechanisms.

Michael Hamblin laboratory

Photodynamic therapy of murine mastocytoma induces specific immune responses against the cancer/testis antigen P1A. Mroz P, Vatansever F, Muchowicz A, Hamblin MR. Cancer Res. 2013 Nov 1;73(21):6462-70. doi: 10.1158/0008-5472.CAN-11-2572.

This paper showed that photodynamic therapy with the vascular photosensitizer verteporfin was able to induce an anti-tumor immune response in a mouse tumor with a naturally occurring tumor antigen. Antigen-specific cytotoxic T-lymphocytes were induced that were able to track down and destroy metastatic tumor deposits thus providing permanent cures and adoptive protection against cancer in naïve mice. The fact that the tumor model expressed the same type of antigen as many patient tumors suggests that the immune stimulating effect of PDT could have clinical application.

Tayyaba Hasan laboratory

(1) Rizvi I, Gurkan UA, Tasoglu S, Alagic N, Celli JP, Mensah LB, Mai Z, Demirci U, Hasan T. Flow induces epithelial-mesenchymal transition, cellular heterogeneity and biomarker modulation in 3D ovarian cancer nodules. Proc Natl Acad Sci U S A. 2013 May 28; 110(22):E1974-83. doi: 10.1073/pnas.1216989110.

The role of flow as a physical modulator of metastatic ovarian cancer biology is explored in a bioengineered microfluidic device for 3D tumor growth. The system integrates hydrodynamic and matrix-based cues to elucidate the roles of fluidic forces and stromal communication as determinants of tumor heterogeneity. A flow-induced increase in epithelial-mesenchymal transition is observed, with a concomitant post-translational upregulation of EGF receptor expression and activation. These changes indicate a motile and aggressive tumor phenotype.

Irene Kochevar laboratory

Cherfan D, Verter EE, Melki S, Gisel TE, Doyle FJ, Scarcelli G, Yun SH, Redmond RW, Kochevar IE. Collagen cross-linking using Rose Bengal and green light to increase corneal stiffness. Invest Ophthalmol Vis Sci, 2013;54(5):3426-33.

We demonstrated that a light-activated, collagen crosslinking process stiffens the cornea, thus potentially inhibiting progressive protrusion of the corneal surface in keratoconus, a disease characterized by thinning of the corneal stroma. Advantages of our approach include the ability to treat thin corneas, short treatment time and preservation of stromal keratocytes.

Charles Lin laboratory

Carlson AL, Fujisaki J, Wu J, Runnels JM, Turcotte R, Lo Celso C, Scadden DT, Strom TB, Lin CP. Tracking single cells in live animals using a photoconvertible near-infrared cell membrane label. PloS ONE 2013;8(8):e69257. PubMed PMID: 23990881; PubMed Central PMCID: PMC3753322

Longitudinal tracking of single cells in live animals is demonstrated, using a laser beam to selective highlight individual cells by changing its color (photoconversion). The highlighted cells can be tracked from one imaging session to the next, allowing the animal to wake up in between. This technique is useful for imaging where stem cells proliferate and differentiate after transplantation.

Wellman Center for Photomedicine

Center Overview

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Seemantini Nadkarni laboratory

Tripathi, M., Hajjarian, Z., van Cott E.M., Nadkarni, S.K. Assessing blood coagulation status with laser speckle rheology, J Biomedical Express 2013 (in press).

A novel optical approach, Laser Speckle Rheology (LSR), was devised to evaluate a patient's coagulation status by measuring the viscoelastic properties of blood during coagulation. Our results report a close correlation between coagulation metrics measured using LSR and conventional coagulation results of activated partial thromboplastin time, prothrombin time and functional fibrinogen levels, creating the unique opportunity to evaluate a patient's coagulation status in real-time at the point of care.

Robert Redmond laboratory

Redmond RW, Rajadurai A, Udayakumar D, Sviderskaya EV, Tsao H. Melanocytes are selectively vulnerable to UVA-mediated bystander oxidative signaling. J Invest Dermatol 2013; Nov 11 doi:10.1038/jid.2013.479 (Epub ahead of print)

UV-A (320-400 nm) radiation, which is copiously present in sunlight, was discovered to induce a "bystander" response in melanocytes. The bystander response results from intercellular signaling due to release of oxidative intermediates from nearby UV-A exposed cells, in melanocytes that have not themselves been exposed. This may explain some of the potent effects of UV-A on skin pigmentation.

Gary Tearney laboratory

Gora M.J., Sauk J.S., Carruth R.W., Gallagher K.A., Suter M.J., Nishioka N.S., Kava L.E., Rosenberg M., Bouma B.E., Tearney G.J. (2013). Tethered capsule endomicroscopy enables less invasive imaging of gastrointestinal tract microstructure. Nature Medicine 19(2), 238-40. PMCID: PMC3567218

This manuscript describes the invention and human demonstration of an optomechanically engineered pill that is swallowed and obtains microscopic images of the entire esophagus as it descends the organ via peristalsis. This device may be used screening large populations for early GI tract neoplasia in an inexpensive and pain-free manner.

Hensin Tsao laboratory

Ji Z, Kumar R, Taylor M, Rajadurai A, Marzuka-Alcalá A, Chen YE, Njauw CN, Flaherty K, Jönsson G, Tsao H. Vemurafenib synergizes with nutlin-3 to deplete survivin and suppresses melanoma viability and tumor growth. Clin Cancer Res. 2013 Aug 15;19(16):4383-91.

Almost all BRAF-targeted treatment trials for melanoma demonstrate strong early responses, followed by eventual relapse. Maximizing upfront lethality might be the best strategy to mitigate this downstream resistance. We noted earlier that BRAF(V600E) mutations were most often associated with a normal p53 protein; this apoptosis-inducing tumor suppressor gene is merely held in check with heightened activity of MDM2-family proteins. We developed a line of preclinical in vitro and *in vivo* studies to show the feasibility of dual BRAF(V600E) inhibition with vemurafenib and p53 rescue through HDM2 antagonism. The combination synergistically induced apoptosis in cell lines, and suppressed tumor growth in animals. Furthermore, we identified survivin as a critical target co-repressed by both vemurafenib and nutlin-3 suggesting that therapeutic synergy could be mediated by a convergence of regulation. This work has triggered the development of clinical trial at MGH using combination BRAF inhibition and HDM antagonism spearheaded by Dr. Keith Flaherty.

Benjamin Vakoc laboratory

(1) Zhang Z, Oh WY, Villiger M, Chen L, Bouma B, and Vakoc BJ. Numerical compensation of system polarization mode dispersion in polarization-sensitive optical coherence tomography. Optics Express 21:1163-1180 (2013)

This work demonstrates a new method for dramatically improving polarization-sensitive optical coherence tomography, an optical imaging technology with numerous potential clinical applications.

WCP

We are now working to demonstrate this approach in pilot clinic studies in ophthalmology and interventional cardiology.

(2) Snuderl M, Batista A, Kirkpatrick ND, et al. Targeting placental growth factor/neuropilin 1 pathway inhibits growth and spread of medulloblastoma. Cell. 2013 Feb 28;152(5):1065-76

This work demonstrates the potential and mechanistic foundation for targeting placental growth factor in medulloblastoma. It is part of a continuing effort to place cutting-edge optical imaging technologies in the Steele Laboratory at MGH, for cancer studies.

Mei Wu laboratory
Ramsey H, Zhang Q, Brown DE, Steensma DP, Lin CP, Wu MX. Stress-induced hematopoietic failure in the absence of immediate early response gene X-1. Haematologica 2013; Sep 20. [Epub ahead of print].

This paper describes a new animal model of early myelodysplastic syndromes (MDS). The clinical significance is that this represents the first animal model to study progress of the disorder, and may delineate etiology of the disease.

Andy Yun laboratory
Choi M, Choi JW, Kim S, Nizamoglu S, Hahn SK, Yun SH. Light-guiding hydrogels for cell based sensing and optogenetic synthesis *in vivo*. Nature Photonics 2013;7:987-994.

Matchstick-sized, transparent polymer implants containing synthetic cells that are genetically modified to activate in response to light can provide specific and local in-body therapies. As a first demonstration of the medical utility of such implants, light-controlled regulation of blood glucose levels in diabetic mice is demonstrated, in which blue light was supplied through an optical fiber to the implant, inducing cells in the implant to synthesize a protein that stimulates insulin production. Such implants could be important for a wide range of diagnostic and therapeutic applications.

Key Achievements/Publication Highlights for 2013

CONTENTS

Anesthesia, Critical Care and Pain Medicine

Jeanine Wiener-Kronish, MD, Chief

1. Purdon PL, Pierce ET, Mukamel EA, Prerau MJ, Walsh JL, Wong KFK, Salazar-Gomez AF, Harrell PG, Sampson A, Cimenser A, Ching S, Kopell N, Tavares-Stoeckel CL, Habeeb K, Merhar R, Brown EN. Electroencephalogram signatures of loss and recovery of consciousness from propofol. Proceedings of the National Academy of Sciences, 2013 Mar 19;110(12):E1142-51. doi: 10.1073/pnas.1221180110. Epub 2013 Mar 4. PMID: 23487781.

This research provides a detailed characterization of how the electroencephalogram (EEG) changes as a patient loses consciousness and recovers consciousness under general anesthesia induced by propofol. This work demonstrates that that there are specific EEG signatures associated with unconsciousness. Tracking these signatures provides a clinically useful way of knowing how unconscious a patient is under general anesthesia.

2. Solt K, Van Dort CJ, Chemali JJ, Taylor N, Brown EN. Electrical stimulation of the ventral tegmental area induces reanimation from general anesthesia. Anesthesiology, In Press, 2013.

In clinical practice, emergence from general anesthesia is treated as a passive process dictated by the pharmacokinetics of anesthetic drug clearance. Our group previously reported that methylphenidate (Ritalin) induces reanimation, or active emergence, from general anesthesia. Methylphenidate acts by blocking dopamine reuptake in the brain, so we hypothesized that intracranial electrical stimulation of dopamine neurons would induce reanimation from general anesthesia. The ventral tegmental area (VTA) and the substantia nigra (SN) are the two main dopamine nuclei in the brain. We discovered that VTA stimulation, but not SN stimulation, induces reanimation from general anesthesia. The role of dopamine neurons in behavioral arousal has not been well characterized previously, and our data suggest that VTA neurons (but not SN neurons) play a critical role in promoting wakefulness.

3. Stewart DS, Hotta M, Li GD, Desai R, Chiara DC, Olsen RW, Forman SA.Cysteine substitutions define etomidate binding and gating linkages in the α-M1 domain of γ-aminobutyric acid type A (GABAA) receptors. J Biol Chem. 2013 Oct 18;288(42):30373-86. doi: 10.1074/jbc.M113.494583. Epub 2013 Sep 5.

Etomidate is a potent general anesthetic that acts through GABA-A receptors, binding at sites formed in part by alpha subunit transmembrane M1 domains. This study aimed to define amino acid residues on alpha-M1 that contact etomidate or otherwise mediate its effects at the molecular level.

A series of 13 single amino acids bracketing the etomidate-photolabeled residue alpha-M236 were mutated to cysteines. The cysteine substituted receptors were expressed in Xenopus oocytes and their function was studied using two-micro electrode voltage-clamp electrophysiology. Each mutant was characterized for GABA sensitivity, etomidate sensitivity, and functional effects of covalently modifying the engineered cysteine with para-chloromercuribenzene sulfonate (pCMBS). Modifiable mutants were further tested to see how etomidate affected cysteine modification. In silico docking of etomidate to a structural homology model of wild-type GABA-A receptors was also performed.

We found that most mutants reduced GABA sensitivity while maintaining etomidate sensitivity. Cysteines engineered into the outer third of alpha-M1 (Q229 to M237) were modified by pCMBS faster in the presence vs. absence of GABA. Etomidate further accelerated modification of most cysteines, consistent with its stabilization of open-channel states. Modification of three cysteine-substituted amino acids, L232C, M236C, and T237C, was inhibited by etomidate.

Our results indicate likely steric proximity between etomidate and three residues on a short segment of alpha-M1 that is strongly linked to channel gating. They are consistent with in silico docking calculations showing etomidate bound in its inter-subunit transmembrane sites with its long axis approximately orthogonal to the transmembrane axis.

4. Zhang X, Xin X, Dong Y, Zhang Y, Yu B, Mao J, Xie Z. Surgical incision-induced nociception causes cognitive impairment and reduction in synaptic NMDA receptor 2B in mice. J Neurosci 2013, 33:17737-17748.

Up to 80 percent of surgical patients in the U.S. have some level of postoperative pain, and several studies have suggested that pain could contribute to the development of postoperative cognitive dysfunction. This is the study to demonstrate that surgical incision-induced pain in mice selectively reduces the expression of synaptic NMDA receptor 2B in the medial prefrontal cortex. This leads to hippocampus-independent cognitive impairment, as measured by the Fear Conditioning Test. These effects may be due to an elevation of TNF-a and CDK-5 caused by pain from the surgical incision. These data suggest that pain may play a role in inducing postoperative cognitive dysfunction.

Cancer Center

Daniel A. Haber, MD, PhD, Director

David P. Ryan MD, Chief, Division of Hematology Oncology

1. Shaw et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med.*2013 Jun 20;368(25):2385-94.

Extending from initial discoveries relating to the exquisite responsiveness of treatment-refractory EML4-ALK mutant non-small cell lung cancer (NSCLC) to the ALK inhibitor crizotinib (Kwak et al, *N Engl J Med*, 2011), a multi-institutional clinical trial led by Dr. Alice Shaw demonstrated the superiority of this targeted therapy compared with chemotherapy for the initial treatment of this genetically-driven non-smokers form of lung cancer, culminating in FDA approval. Ongoing research into mechanisms of acquired resistance to crizotinib led by Dr. Jeff Engelman(Awad et al., *N Engl J Med*. 2013) are leading to new and even more effective targeted therapies for this disease.

2. Ryan et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med*. 2013 Jan 10;368(2):138-48.

While virtually all patients with advanced prostate cancer respond initially to androgen withdrawal therapy (ADT), the disease recurs in a form that is resistant and requires second line treatments. In this international trial of the androgen synthesis inhibitor Abiraterone acetate, with major participation by MGH investigator Dr. Matthew Smith, clinical effectiveness was demonstrated following the development of resistance to first line luprolide. Abiraterone treatment is now considered standard of care for castration-resistant prostate cancer.

3. Black et al. KDM4A lysine demethylase induces site-specific copy gain and rereplication of regions amplified in tumors. *Cell.* 2013 Aug 1;154(3):541-55.

Epigenetic alterations are increasingly appreciated as major contributors to cancer. Here, the laboratory of Dr. Johnathan Whetstine collaborating with Drs. Gaddy Getz and Nick Dyson, demonstrated that expression changes in a specific chromatin regulator, KDM4A, induces DNA amplification at specific chromosomal regions. This newly discovered mechanism is likely to contribute to oncogene amplification and other chromosomal abnormalities in multiple different cancers.

4. Yu et al. Circulating breast tumor cells exhibit dynamic changes in epithelial and mesenchymal composition. *Science.* 2013 Feb 1;339(6119):580-4.

Epithelial-Mesenchymal Transition (EMT) has been proposed as a mechanism whereby stationary epithelial cells acquire migratory properties and invade into the bloodstream. Here, a multidisciplinary team of molecular biologists, bioengineers, computational biologists and clinicians led by Drs. Maheswaran, Haber, Toner, Ramaswamy and Bardia demonstrated that EMT is indeed triggered in breast cancer circulating tumor cells (CTCs) and that this phenomenon is

reversibly modulated as a function of therapeutic interventions. Clusters of mesenchymal CTCs were discovered in the circulation, and their RNA sequencing identified physiological regulators of EMT. Ongoing research into CTCs at the single cell level has recently been enabled by a new MGH microfluidic device (Ozkumur et al., *SciTransl Med 2013*).

CIMIT

John A. Parrish, MD, Chief Executive Officer

1. CIMIT successfully augments and facilitates multi-institutional grant applications

Principal Investigators John Parrish (CIMIT), David Golan (HMS), and Joseph Loscalzo (BWH), received a 7-year, $12 million grant from NHLBI for "Boston Biomedical Innovation Center" to: 1) develop an integrated infrastructure that would expand the universe of commercializable technologies for heart, lung, blood, and sleep disorders; 2) place these opportunities in the proper evaluative context through an engagement ("seed it"), solicitation ("find it"), and selection ("pick it") strategy; 3) efficiently and effectively bring those selected to an appropriate exit point from the development process; and 4) provide the educational and mentoring infrastructure necessary for the development of the proper entrepreneurial skills among academic innovators.

2. The CIMIT commitment to Military Medicine

Since its start in 1998, CIMIT has been dedicated to improving the care of our wounded warriors. In 2013, CIMIT was invited by the Department of Defense to compete for funding under the Joint Warfighter initiative and was awarded $4.25 million for projects to improve the diagnosis and care of wounded warriors. This award will further the research of six MGH investigators: Jerome Ackerman, Tianhong Dai, Marc De Moya, Rajiv Gupta, Mark Ottensmeyer, and Yongquing Li.

CIMIT plans to significantly grow its capabilities to serve as a coordinating center for innovations to advance military medicine.

3. CIMIT's healthcare innovation model accepted for publication in *IEEE Pulse*

IEEE Pulse, the flagship publication of the Engineering in Medicine & Biology Society, invited CIMIT to publish its healthcare innovation model. "CIMIT: A Model for Accelerating the Healthcare Innovation Cycle", authored by John Parrish, Steven Schachter, Penny Carleton, Mike Dempsey, Diane Spiliotis, and John Collins, is in press. The article is in the January/February issue, which is set to mail January 22nd. The article will be available online at IEEE Xplore on or about January 20th (http://ieeexplore.ieee.org/xpl/RecentIssue.jsp?punumber=5454060)

4. CIMIT-in-the-Cloud: CoLab

Health systems across the globe are increasingly recognizing the need to build innovation capacity as a way to address the triple challenge of an aging population, need to improve access to care, and shrinking budgets. Many are turning to CIMIT to leverage its expertise and experience in stimulating, managing and measuring innovation. In response, CIMIT has codified its methodology in a secure, scalable, cloud-based collaboration platform (CIMIT CoLab®). With an initial focus on improving CIMIT's own operations, CoLab has rapidly become a critical resource for organizations within the CIMIT community as well as the world-over in improving their innovation capacity. By way of example, the National Health Service in England has adopted CoLab as its nation-wide innovation platform. Several very successful applications were launched in 2013, including the Specializes Services Commissioning Innovation Fund and Innovation Portfolio, the Regional Innovation Fund and the SBRI Programme. So far, CoLab has facilitated submission of more than 1500 ideas and proposals from collaborative teams representing more than 4,000 clinicians, researchers and companies for these initiatives. Further expansion is planned in 2014.

Key Achievements/Publication Highlights for 2013

Dermatology

David E. Fisher MD, PhD

1. Yana G. Kamberov, Sijia Wang , Jingze Tan, Pascale Gerbault, Abigail Wark, Longzhi Tan, Yajun Yang, Shilin Li, Kun Tang, Hua Chen, Adam Powell Yuval Itan, Dorian Q. Fuller, Jason Lohmueller, Junhao Mao, Mark G. Thomas, Li Jin, Daniel E. Lieberman, Clifford J. Tabin, Bruce A. Morgan, Pardis C. Sabeti. Modeling recent human evolution in mice by expression of a selected EDAR variant. (2013) Cell 152(4):691-702. PMID: 23415220

This study examined the genetic basis for lower hair follicle density in humans as compared to hairy mammals. The evolutionary transition appears to have involved replacement of dense hair follicles with alternative formation of dense eccrine sweat glands. The presence of a robust eccrine sweat appendage mechanism likely afforded major evolutionary robustness to humans, through enhanced heat dissipation and consequently improved long distance running capacity (relative to predators).

2. Praetorius C, Grill C, Stacey SN, Metcalf AM, Gorkin DU, Robinson KC, Van Otterloo E, Kim RS, Bergsteinsdottir K, Ogmundsdottir MH, Magnusdottir E, Mishra PJ, Davis SR, Guo T, Zaidi MR, Helgason AS, Sigurdsson MI, Meltzer PS, Merlino G, Petit V, Larue L, Loftus SK, Adams DR, Sobhiafshar U, Emre NC, Pavan WJ, Cornell R, Smith AG, McCallion AS, Fisher DE, Stefansson K, Sturm RA, Steingrimsson E. A Polymorphism in IRF4 Affects Human Pigmentation through a Tyrosinase-Dependent MITF/TFAP2A Pathway. *Cell*. 2013 Nov 21;155(5):1022-33.

A significant genetic linkage exists between the IRF4 gene and skin pigmentation as well as skin cancer risk. To understand the underlying role of IRF4 in this risk, the current study examined its participation within the major melanin synthetic pathway which is controlled within melanocytes by the transcription factor MITF and the albinism gene tyrosinase.

3. Gurkar AU, Chu K, Raj L, Kim YB, Dunn SE, Mandinova A, Lee SW. Identification of ROCK1 kinase as a critical regulator of Beclin1 mediated autophagy during metabolic stress. Nature Communication 4: 2189 (July), 2013.

This study examined the intracellular signals which accompany a cell's response to metabolic stress. It demonstrated a key regulatory pathway which controls the process of digesting the cell's internal organelles in order to maintain sufficient energy stores under such conditions, which are likely to be important in cancer and other contexts.

4. Ping Yuan, Koichi Ito, Rolando Perez-Lorenzo, Christina Del Guzzo, Jung Hyun Lee, Che-Hung Shen, Marcus W. Bosenberg, Martin McMahon, Lewis C. Cantley, Bin Zheng. 2013. Phenformin enhances the therapeutic benefit of BRAFV600E inhibition in melanoma. Proc. Natl. Acad. Sci. USA. 110:18226-31.

This study identified AMPK as the long-sought kinase for BRAF Ser729, a critical regulatory site. We also proposed that AMPK activators could be used to prevent the development of cutaneous squamous cell carcinomas associated with BRAF-targeted therapy. This paper was previewed in **Molecular Cell** and highlighted by **Cancer Discovery, Science Signaling** and **Faculty of 1000**.

Emergency Medicine

David Brown, MD

1. Hasegawa K, Hiraide A, Chang Y, Brown DF. Association of prehospital advanced airway management with neurologic outcome and survival in patients with out-of-hospital cardiac arrest. JAMA 2013;309:257-266.

In this nationwide population-based cohort study of adults with out-of-hospital cardiac arrest between 2005 and 2010, we found that cardiopulmonary resuscitation with prehospital advanced

airway management, whether endotracheal intubation or supraglottic airways, was associated with a decreased likelihood of 1-month survival and neurologically favorable survival compared to conventional bag-valve-mask ventilation. Our observations contradict the assumption that aggressive airway intervention is associated with improved outcomes and provide an opportunity to reconsider the approach to prehospital airway management in this population.

2. Sarode R, Milling TJ Jr, Refaai MA, Mangione A, Schneider A, Durn BL, Goldstein JN. Efficacy and safety of a 4-factor prothrombin complex concentrate in patients on vitamin K antagonists presenting with major bleeding: a randomized, plasma-controlled, phase IIIb study. Circulation. 2013 Sep 10; 128(11):1234-43.

We performed a randomized controlled clinical trial to compare a 4-factor prothrombin complex concentrate (4F-PCC) with plasma for urgent vitamin K antagonist reversal in patients with major bleeding. We found that 4F-PCC is an effective alternative to plasma for urgent reversal of vitamin K antagonist therapy.

3. Nelson BD, Stoklosa H, Ahn R, Eckardt M, Walton E, Burke TF. Use of uterine balloon tamponade for control of post-partum hemorrhage by community-based health providers in South Sudan. Int J Gynaecol Obstet 2013;122(1):27-32.

This empirical study was significant in that it demonstrated the effectiveness of an ultra low-cost uterine balloon tamponade (UBT) package for community health workers in managing post-partum hemorrhage in South Sudan. This study has informed the design of subsequent roll outs of our UBT intervention in Kenya, Ghana, Senegal, Sierra Leone, and Nepal.

4. Reisner AT, Heldt T. A computational model of hemorrhage and dehydration suggests a pathophysiological mechanism: Starling-mediated protein trapping. Am J Physiol Heart Circ Physiol. 2013 Feb 15;304(4):H620-31.

The model was validated for a range of blood loss patterns and prehydration states, replicating group-averaged behavior (i.e., within 1 or 2 SEs) of the rate and quantity of vascular refill and the associated cardiac output during slow, moderate, and rapid ongoing blood losses, the restitution after the cessation of blood loss, and the absence of restitution in dehydrated subjects. The model suggested that the earlier phase of restitution, i.e., transcapillary fluid shifts, was antagonistic to the later phase of restitution, i.e., protein return via lymphatics. The phenomenon was termed Starling-mediated protein trapping.

Imaging

James A. Brink, MD, Chairman

Advanced X-Ray Imaging Science (AXIS) Center

Rajiv Gupta, MD, PhD, Director

1. Ando M, Sunaguchi N, Wu Y, Do S, Sung Y, Louissaint A, Yuasa T, Ichihara S, Gupta R. Crystal analyser-based X-ray phase contrast imaging in the dark field: implementation and evaluation using excised tissue specimens. Eur Radiol. 2013 Sep 19. [Epub ahead of print] PubMed PMID: 24048725.

Traditional X-ray imaging uses attenuation differences between various tissue types as the primary source of tissue contrast. This paper describes a new X-ray imaging technique called X-ray dark-field imaging (XDFI) that exploits phase rather than attenuation to distinguish different tissues. We demonstrate, using a variety of human tissue specimens, that the soft tissue discrimination capability of XDFI are at least one order of magnitude better than conventional X-ray imaging.

2. Van der Eerden AW, Khalilzadeh O, Perlbarg V, Dinkel J, Sanchez P, Vos PE, Luyt C, Stevens RD, Champfleur NM, Delmaire C, Tollard E, Gupta R, Dormont D, Laureys S, Benali H, Vanhaudenhuyse A, Galanaud D, Puybasset L, for the NICER (Neuro Imaging for Coma Emergence and Recovery)

Consortium. White matter changes in comatose survivors of anoxic ischemic encephalopathy and traumatic brain injury: a comparative diffusion tensor imaging study. Radiology 2013, (ahead of print), DOI: http://dx.doi.org/10.1148/radiol.13122720.

Severe traumatic brain injury (TBI) leads to demyelination of the affected white matter, and encephalomalacia of the involved gray matter. Heretofore, the temporal course of these changes was unknown. Via a longitudinal study of comatose patients, this paper establishes that there is a progressive decline in morphological parameters of the TBI affected white matter for up to two years. After that time point, the changes stabilize.

3. González RG, Copen WA, Schaefer PA, Lev MH, Pomerantz SR, Rapalino O, Chen JW, Hunter GJ, Romero JM, Buchbinder BR, Larvie M, Hirsch JA, Gupta R. The Massachusetts General Hospital acute stroke imaging algorithm: an experience and evidence based approach. J NeuroIntervent Surg 2013;0:1–6. doi:10.1136/neurintsurg-2013-010715

Using an evidence-based approach, this paper describes the role of various imaging modalities in the work of acute stroke. The MGH algorithm for patient triage in the emergency room is described.

Athinoula A. Martinos Center for Biomedical Imaging

Bruce Rosen, MD, PhD, Director

1.Setsompop K, Kimmlingen R, Eberlein E, Witzel T, Cohen-Adad J, McNab JA, Keil B, Tisdall MD, Hoecht P, Dietz P, Cauley SF, Tountcheva V, Matschl V, Lenz VH, Heberlein K, Potthast A, Thein H, Van Horn J, Toga A, Schmitt F, Lehne D, Rosen BR, Wedeen V, Wald LL. Pushing the limits of in vivo diffusion MRI for the Human Connectome Project. NeuroImage 2013, 80 p 220-33.

In this work we describe our 2-year effort to construct “the ultimate diffusion scanner”. In this joint project with Siemens Heathcare, we re-engineered a 3T scanner from the ground up to optimize diffusion MRI. This included a novel parallel gradient drive for a massive gradient coil capable of 300mT/m gradient strength and full slew rate of 200T/m/s. We demonstrate the nearly 10x increase in sensitivity for high-b value diffusion tractography.

2. Hadjikhani N, Zurcher N, Rogier O, Ruest T, Hippolyte L, Ben-Ari Y, Lemonnier E. Improving emotional face perception in autism with diuretic bumetanide: a proof-of-concept behavioral and functional brain imaging pilot study. Autism 2013, in press.

This paper shows the behavioral and brain activation changes induced by a 10 months treatment of individuals with autism with a bumetanide, indicating enhanced emotion recognition, and opening the potential of a very promising new treatment for autism.

3. Napadow V, Sheehan J, Kim J, LaCount L, Park K, Kaptchuk T, Rosen BR, Kuo B. The Brain Circuitry Underlying the Temporal Evolution of Nausea in Humans. Cerebral Cortex, 2013 23(4):806-13. PMCID: PMC3593575

Nausea is a universal human experience. It evolves slowly over time, and brain mechanisms underlying this evolution are not well understood. Our functional magnetic resonance imaging (fMRI) approach evaluated, for the first time, brain activity contributing to and arising from nausea produced by motion sickness. This breakthrough was possible via several novel aspects of experimental design, including a custom-built head coil constructed at the Martinos Center that allowed for a much wider visual field of view with our visual nauseogenic stimulation.

Cardiac MR PET CT Program

Udo Hoffmann, MD, MPH, Director

1. Neilan TG, Mongeon FP, Shah RV, Coelho-Filho O, Abbasi SA, Dodson JA, McMullan C, Heydari B, Michaud GF, Roy JM, Blankstein R, Jerosch-Herold M, Kwong RY. Myocardial Extracellular Volume Expansion and the Risk of Recurrent Atrial Fibrillation after Pulmonary Vein Isolation in Patients with Hypertension. Journal of the American College of Cardiology: Cardiovascular Imaging, JACC Cardiovasc Imaging. 2013 Nov 20.

The ability to characterize myocardial fibrosis is seen as a key to understand occurrence of conduction abnormalities in the heart. Here, we validated a novel T1 based CMR measure, the myocardial extracellular volume (ECV) for quantification of diffuse myocardial fibrosis and then demonstrated that ECV predicted the recurrence of atrial fibrillation after pulmonary vein isolation in patients with hypertension.

2. Ahmed W, Schlett CL, Uthamalingam S, Truong QA, Koenig W, Rogers IS, Blankstein R, Nagurney JT, Tawakol A, Januzzi JL, Hoffmann U. Single resting hsTnT level predicts abnormal myocardial stress test in acute chest pain patients with normal initial standard troponin. JACC Cardiovasc Imaging. 2013 Jan;6(1):72-82.

In this study, we demonstrate that that resting hsTnT levels predict myocardial perfusion abnormalities and coronary artery disease in patients presenting with acute chest pain suggesting that resting hsTnT could serve as a powerful triage tool in chest pain patients in the ED before diagnostic testing and improve the effectiveness of patient management.

3.Truong QA, Hayden D, Woodard PK, Kirby R, Chou ET, Nagurney JT, Wiviott SD, Fleg JL, Schoenfeld DA, Udelson JE, Hoffmann U. Sex differences in the effectiveness of early coronary computed tomographic angiography compared with standard emergency department evaluation for acute chest pain: the rule-out myocardial infarction with Computer-Assisted Tomography (ROMICAT)-II Trial. Circulation. 2013 Jun 25;127(25):2494-502.

This study demonstrates that among patients presenting with acute chest pain to the ED, women have more normal CCTA examinations than men but similar normalcy rates for functional testing supporting an early CCTA strategy as an attractive option in women presenting to the ED with symptoms suggestive of acute coronary syndrome.

Center for Advanced Medical Imaging Sciences

Georges El Fakhri, PhD, Director

1. Motion compensation for brain PET imaging using wireless MR active markers in simultaneous PET-MR: phantom and non-human primate studies. *Huang C., Ackerman J.L., Petibon Y., Normandin M., Brady T.J., El Fakhri G., Ouyang J. NeuroImage 2014; in press.*

Motion artifacts from head motion are one of the major hurdles in brain PET. In this work, we use wireless MR active markers to track head motion in real time during a simultaneous PET-MR brain scan and incorporate the motion measured by the markers in the listmode PET reconstruction. The proposed wireless technique successfully removed motion artifacts from the reconstructed images and yielded accurate quantitation of brain metabolism with motion present.

2. Dual Tracer PET Using Generalized Factor Analysis of Dynamic Sequences. El Fakhri G, Trott C., Sitek A., Bonab A., Alpert N. Mol. Imag. Biol. 2013; 15(6): 666-674.

With SPECT, simultaneous imaging of two physiological processes relies on discrimination of the energy of the emitted gamma rays, whereas the application of dual-tracer imaging to PET imaging has been limited by the characteristic 511-keV emissions. To address this limitation, we developed a novel

approach based on generalized factor analysis of dynamic sequences (GFADS) that exploits spatio-temporal differences between radiotracers and applied it to simultaneous imaging of F18-FDG (brain metabolism) and C11-raclopride (D2). We show theoretically and verify by simulation and measurement that GFADS can separate FDG and raclopride measurements that are made nearly simultaneously.

3. Martinez-Quintanilla, J., Bhere, D., Heidari, P., He, D., Mahmood, U., Shah, K. Therapeautic efficacy and fate of bimodal engineered stem cells in malignant brain tumors. *Stem Cells.* 2013 Aug;31(8):1706-14. doi: 10.1002/stem.1355.

Therapeutically engineered stem cells (SC) are emerging as a very effective tumor specific therapeutic approach for different cancer types. However, the assessment of the long-term fate of therapeutic SC post-tumor treatment is critical if such promising therapies are to be increasingly translated into clinical practice. In this study, we developed an efficient stem cell-based therapeutic strategy that simultaneously allows killing of tumor cells and assessment and eradication of stem cells after treatment of highly malignant brain tumors. These finding s demonstrate the development and validation of a novel therapeutic strategy that has implications in translating stem cell based therapies in cancer patients.

4. A Concise Radiosynthesis of the Tau Radiopharmaceutical, [18F]T807. Shoup, T., Yokell, D., Rice, P., Jackson, R., Livni, E., Johnson, K., Brady, T., Vasdev, N. Labelled Compd. Radiopharm. 2013; 56: 736-740.

Fluorine-18 labelled 7-(6-fluoropyridin-3-yl)-5H-pyrido[4,3-b]indole ([18F]T807) is a potent and selective agent for imaging paired helical filaments of tau (PHF-tau) and is among the most promising PET radiopharmaceuticals for this target in early clinical trials. Our goal was to develop a robust and facile method for production of this promising radiopharmaceutical to investigate a range of tauopathies1 and traumatic brain injuries. The present study reports a simplified one-step method for the synthesis of [18F] T807 that is broadly applicable for routine clinical production The methodology described herein can facilitate multi-center trials and widespread use of this radiopharmaceutical for tauopathy imaging.

Center for Molecular Imaging Research

Ralph Weissleder, MD, Director

1. Pulli B, Ali M, Forghani R, Schob S, Hsieh K L-C, Wojtkiewicz GR, Linnoila JJ, Chen JW. Measuring myeloperoxidase activity in biological samples, PLoS One, 2013, 8(7), e67976.

Enzymatic activity measurements of the highly oxidative enzyme myeloperoxidase (MPO), which is implicated in many diseases, are widely used in the literature, but often suffer from non-specificity and lack of uniformity. We validated a highly specific and sensitive assay protocol that should be used as the standard method for all MPO activity assays in biological samples. Extracellular MPO activity gives an estimate of the oxidative stress in inflammatory diseases, while intracellular MPO activity correlates well with tissue neutrophil content.

2. Saxena; A., Kessinger; C.W., Thompson; B. Jaffer, F. "High-resolution optical mapping of inflammatory macrophages following endovascular arterial injury." Mol Imaging Biol 2013, 15, 282-289.

Inflammation following arterial injury mediates vascular restenosis, a leading cause of cardiovascular morbidity. Here we utilize intravital microscopy (IVM) and a dextran-coated nanosensor to spatially map inflammatory macrophages in vivo following endovascular injury of murine carotid arteries. We demonstrate that the macrophage response to arterial injury can be imaged in vivo using IVM-based molecular imaging, and shows a higher macrophage influx at day 14 compared to day 28 post-injury.

3. Rho J, Chung J, Im H, Liong M, Shao H, Castro CM, Weissleder R, Lee H (2013) Magnetic Nanosensor for Detection and Profiling of Erythrocyte-Derived Microvesicles. ACS Nano PMID:24295203 During the course of their lifespan, erythrocytes actively shed phospholipid-bound microvesicles (MV).

In stored blood, the number of these erythrocyte-derived MVs has been observed to increase over time, suggesting their potential value as a quality metric for blood products. We report on a new nanotechnology platform capable of rapid and sensitive MV detection in packed red blood cell units. Our results show that MV counts increase over time and, thus, could serve as an effective metric of blood aging. Furthermore, our studies found that MVs have the capacity to generate oxidative stress and consume nitric oxide.

Institute for Technology Assessment

Scott Gazelle, MD, PhD, Director

1. Contribution of the Lung Cancer Policy Model to the USPSTF guidelines on lung cancer screening for individuals at high risk.

Pamela McMahon, Chung Yin (Joey) Kong, and other research staff at the ITA worked with the Agency for Healthcare Research and Quality (AHRQ) to translate the results of the National Lung Screening Trial (NLST) into population-level outcomes through the Cancer Intervention and surveillance Modeling Network (CISNET). The results informed the development of new lung cancer screening guidelines for the U.S. that were released in draft form in 2013. Estimates show that approximately 7 million people in the U.S. fall into this high risk group. This research has had substantial impact on cancer screening policy at the national level.

2. Patient and Societal Value Functions for the Testing Morbidities Index, Medical Decision Making, August 2013.

Dr. J. Shannon Swan developed a preference-based and summated scale for scoring the Testing Morbidities Index (TMI) classification—which measures short-term effects of diagnostic testing on quality of life. The index is a brief 7-item instrument and has the ability to use both a patient-based and societal perspective. This index can be used to measure the impact of a range to diagnostic tests to understand the burden of these procedures—including a range of cancer screening tests including mammography and colonoscopy.

3. Trends in Esophageal Cancer - Hur C, Miller M, Kong CY, Dowling EC, Nattinger KJ, Dunn M, Feuer EJ. Trends in esophageal adenocarcinoma incidence and mortality. Cancer. 2013 Mar 15;119(6):1149-58.

This manuscript examines temporal trends in esophageal adenocarcinoma (EAC) incidence and mortality within the U.S. population and additionally explores these trends within subgroups of the population, given the increased incidence of EAC in the past several decades. Dr. Hur and his group concluded that EAC incidence and incidence-based mortality rates continue to rise in the US, although at a slower rate in more recent years. In early stage cancers, incidence-based mortality and incidence rates have diverged primarily because incidence–based–mortality rates have plateaued beginning in the late 1990s. Although EAC continues to be less common in women, the rate of increase in EAC incidence is similar in both genders.

4. Patients with testicular cancer undergoing CT surveillance demonstrate a pitfall of radiation-induced cancer risk estimates: the timing paradox. Pandharipande PV, Eisenberg JD, Lee RJ, Gilmore ME, Turan EA, Singh S, Kalra MK, Liu B, Kong CY, Gazelle GS. Radiology. 2013 Mar;266(3):896-904.

Dr. Pandharipande and colleagues used simulation modeling to project outcomes of young patients with testicular cancer who undergo frequent surveillance CT after orchiectomy. Her team compared life expectancy losses and lifetime mortality risks attributable to testicular cancer, to life expectancy losses and lifetime mortality risks attributable to radiation-induced cancers from CT. Their findings illustrated a pitfall of lifetime risk metrics, namely, that these metrics do not account for the delayed timing of radiation-induced cancers over the course of a patient's lifetime. As a result, radiation-induced cancer risks may be overemphasized relative to more immediate health risks in many clinical settings.

Key Achievements/Publication Highlights for 2013

Neuroprotection Research Laboratory

Eng Lo, PhD, Director

1. Cerebrovascular degradation of TRKB by MMP9 in the diabetic brain. Navaratna D, Fan X, Leung W, Lok J, Guo S, Xing C, Wang X, Lo EH J Clin Invest. 2013; 123:3373-3377.

This study demonstrates that microvessels in diabetic brain upregulate metalloproteases that degrade neuronal trophic factor receptors. Disruption of neurovascular trophic coupling in diabtetes and metabolic disease makes the brain more vulnerable to stroke and neurodegeneration.

2. Oligodendrocyte precursors induce early blood-brain barrier opening after white matter injury. Seo JH, Miyamoto N, Hayakawa K, Pham LD, Maki T, Ayata C, Kim KW, Lo EH, Arai K. J Clin Invest. 2013; 123:782-786.

This study shows that over-production of metalloproteases by oligodendrocyte precursor cells may damage the blood-brain barrier in white matter. Targeting these endogeneous responses may help alleviate white matter disease in CNS disorders.

3. Inhibition of 12/15-lipoxygenase as therapeutic strategy to treat stroke. Yigitkanli K, Pekcec A, Karatas H, Pallast S, Mandeville E, Joshi N, Smirnova N, Gazaryan I, Ratan RR, Witztum JL, Montaner J, Holman TR, Lo EH, van Leyen K. Ann Neurol. 2013; 73:129-135.

This study shows that 12/15-lipoxygenase may mediate both acute injury as well as delayed inhibition of neuronal rewiring after cerebral ischemia. Targeting these enzymes may promote stroke recovery.

4. Dysfunction of annexin A2 contributes to hyperglycaemia-induced loss of human endothelial cell surface fibrinolytic activity. Dai H, Yu Z, Fan X, Liu N, Yan M, Chen Z, Lo EH, Hajjar KA, Wang X. Thromb Haemost. 2013; 109:1070-1078.

This study shows that endogenous annexin-2 is glycated by hyperglycemia, thus explaining the resistance of diabetic patients to thrombolysis. Targeting these mechanisms may enhance thrombolytic therapies for a large segment of stroke patients.

Neurovascular Research Laboratory

Cenk Ayata, MD, Director

1. Selective ROCK2 inhibition in focal cerebral ischemia. Lee JH, Zheng Y, von Bornstadt D, Wei Y, Balcioglu A, Daneshmand A, Yalcin N, Yu E, Herisson F, Atalay YB, Kim MH, Ahn YJ, Balkaya M, Sweetnam P, Schueller O, Poyurovsky MV, Kim HH, Lo EH, Furie KL, Ayata C. Ann Clin Transl Neurol 2013 doi: 10.1002/acn3.19

Translational principles in drug development are vigorously applied in this comprehensive preclinical safety and efficacy testing of a selective rho-associated kinase (ROCK) type 2 inhibitor in ischemic stroke. In collaboration with industry, we show for the first time that ROCK2 is the relevant ROCK isoform as a therapeutic target in stroke. The data also show that ROCK2 has equivalent efficacy with non-isoform-selective inhibitors, but still provides an excellent safety profile for rapid clinical translation. The comprehensive dataset forms the foundation for the phase II clinical trial in acute ischemic stroke currently seeking IND status.

2. Rho-kinase inhibition improves ischemic perfusion deficit in hyperlipidemic mice. Shin HK, Huang PL, Ayata C. J Cereb Blood Flow Metab. 2013 Nov 6. doi: 10.1038/jcbfm.2013.195. [Epub ahead of print]

We build upon our translational track record in stroke therapeutics by elegantly demonstrating the efficacy of rho-associated kinase (ROCK) in a comorbid animal model of experimental stroke. We show that ROCK inhibition is highly efficacious in the presence of severe hyperlipidemia, increasing the clinical relevance of the therapeutic target. We also show that inhibition of peri-

infarct depolarizations is one mechanism to improve stroke outcome that synergizes with the cerebral hemodynamic benefit afforded by ROCK inhibitors in acute focal cerebral arterial occlusion. Altogether, data underscores the need to further develop and test ROCK inhibitors in acute stroke.

3. Hyperlipidemia disrupts cerebrovascular reflexes and worsens ischemic perfusion defect. Ayata C, Shin HK, Dileköz E, Atochin DN, Kashiwagi S, Eikermann-Haerter K, Huang PL. J Cereb Blood Flow Metab. 2013 Jun;33(6):954-62. doi: 10.1038/jcbfm.2013.38. Epub 2013 Mar 13.

Here we provide a comprehensive analysis of the impact of hyperlipidemia on resting cerebral blood flow and fundamental cerebrovascular reflexes that help maintain tissue homeostasis in the brain. The data show that moderate to severe hyperlipidemia chronically reduces cerebral perfusion by increasing the vascular resistance, and disrupts functional coupling, autoregulation and hypercapnic hyperemia. In the presence of a focal cerebral arterial occlusion, hyperlipidemic animals develop significantly larger perfusion defects suggesting diminished collateral flow. These data are the first to demonstrate that worse stroke outcomes in hyperlipidemia are in part caused by vasomotor paralysis.

4. Multiparametric, longitudinal optical coherence tomography imaging reveals acute injury and chronic recovery in experimental ischemic stroke. Srinivasan VJ, Mandeville ET, Can A, Blasi F, Climov M, Daneshmand A, Lee JH, Yu E, Radhakrishnan H, Lo EH, Sakadžić S, Eikermann-Haerter K, Ayata C. PLoS One. 2013 Aug 7;8 (8):e71478. doi: 10.1371/journal.pone.0071478. Print 2013.

In this technology implementation study we apply optical coherence tomography as a non-invasive tool to longitudinally quantify the hemodynamic and cerebrovascular morphological changes during acute stroke and weeks into the recovery period. The data reveal dynamic changes in cerebral blood flow and collateral development in stroke recovery, and provide a valuable tool to study the impact of therapeutic interventions targeting cerebrovascular plasticity.

Medicine

Katrina Armstrong, MD

Biostatistics Center

Dianne Finkelstein. PhD

1. Liedke PE, Finkelstein DM, Szymonifka J, Barrios CH, Chavarri-Guerra Y, Bines J, Vasconcelos C, Simon SD, Goss PE. Outcomes of Breast Cancer in Brazil Related to Health Care Coverage: A Retrospective Cohort Study. Cancer Epidemiol Biomarkers Prev. 2013 Dec 13.

A national, retrospective cohort of 3,142 patients drawn from a representative sample of Brazilian medical centers was selected. Clinical and demographic data and type of healthcare coverage were retrieved by chart review. Patients with public health coverage presented with more advanced disease at diagnosis ($P < 0.001$). DFS and OS for patients presenting with stage 0-II disease did not differ according to the type of healthcare coverage, whereas a significant difference in outcomes was seen for stage III-IV patients ($P = 0.002$ and $P = 0.008$, respectively). No association was found for the type of health coverage with either DFS or OS, but there was an association for postrelapse survival ($P < 0.001$). Earlier diagnosis and treatment of breast cancer could improve outcomes of women with public health coverage in Brazil.

2. Goss PE, Smith IE, O'Shaughnessy J, Ejlertsen B, Kaufmann M, Boyle F, Buzdar AU, Fumoleau P, Gradishar W, Martin M, Moy B, Piccart-Gebhart M, Pritchard KI, Lindquist D, Chavarri-Guerra Y, Aktan G, Rappold E, Williams LS, Finkelstein DM; TEACH investigators. Adjuvant lapatinib for women with early-stage HER2-positive breast cancer: a randomised, controlled, phase 3 trial. Lancet Oncol. 2013 Jan;14(1):88-96. doi: 10.1016/S1470-2045(12)70508-9. Epub 2012 Dec 10. Erratum in: Lancet Oncol. 2013 Feb;14(2):e47.

We investigated the efficacy and safety of adjuvant lapatinib for patients with trastuzumab-naive HER2-positive early-stage breast cancer, started at any time after diagnosis. This study was a

placebo-controlled, multicentre, randomized blinded phase 3 trial. Women outpatients from 405 [corrected] centres in 33 countries [corrected] with HER2-positive early-breast cancer who had previously received adjuvant chemotherapy but not trastuzumab were randomly assigned (1:1) to receive daily lapatinib (1500 mg) or daily placebo for 12 months. Between 2006 and 2008, 3147 were assigned to lapatinib or placebo. After a median follow-up of 47·4 months, 210 (13%) disease-free survival events had occurred in the lapatinib group versus 264 (17%) in the placebo group (hazard ratio [HR] 0·83, 95% CI 0·70-1·00; p=0·053). Among centrally confirmed HER2-positive women, patients on lapatinib had a significantly longer disease-free survival (HR 0·82, 95% 0·67-1·00; p=0·04). Thus lapatinib might be an option for women with HER2-positive breast cancer who do not or cannot receive adjuvant trastuzumab.

3. Lu KH, Skates S, Hernandez MA, Bedi D, Bevers T, Leeds L, Moore R, Granai C, Harris S, Newland W, Adeyinka O, Geffen J, Deavers MT, Sun CC, Horick N, Fritsche H, Bast RC Jr. A 2-stage ovarian cancer screening strategy using the Risk of Ovarian Cancer Algorithm (ROCA) identifies early-stage incident cancers and demonstrates high positive predictive value. Cancer. 2013 Oct 1;119(19):3454-61. doi: 10.1002/cncr.28183. Epub 2013 Aug 26.

A 2-stage ovarian cancer screening strategy was evaluated that incorporates change of carbohydrate antigen 125 (CA125) levels over time and age to estimate risk of ovarian cancer. Women with high-risk scores were referred for transvaginal ultrasound (TVS). A single-arm, prospective study of postmenopausal women was conducted. Participants underwent an annual CA125 blood test. Based on the Risk of Ovarian Cancer Algorithm (ROCA) result, women were triaged to next annual CA125 test (low risk), repeat CA125 test in 3 months (intermediate risk), or TVS and referral to a gynecologic oncologist (high risk). A total of 4051 women participated over 11 years. The average annual rate of referral to a CA125 test in 3 months was 5.8%, and the average annual referral rate to TVS and review by a gynecologic oncologist was 0.9%. Ten women underwent surgery on the basis of TVS, with 4 invasive ovarian cancers (1 with stage IA disease, 2 with stage IC disease, and 1 with stage IIB disease), 2 ovarian tumors of low malignant potential (both stage IA), 1 endometrial cancer (stage I), and 3 benign ovarian tumors, providing a positive predictive value of 40% (95% confidence interval = 12.2%, 73.8%) for detecting invasive ovarian cancer. The specificity was 99.9% (95% confidence interval = 99.7%, 100%). All 4 women with invasive ovarian cancer were enrolled in the study for at least 3 years with low-risk annual CA125 test values prior to rising CA125 levels. ROCA followed by TVS demonstrated excellent specificity and positive predictive value in a population of US women at average risk for ovarian cancer.

4. Rosenthal AN, Fraser L, Manchanda R, Badman P, Philpott S, Mozersky J, Hadwin R, Cafferty FH, Benjamin E, Singh N, Evans DG, Eccles DM, Skates SJ, Mackay J, Menon U, Jacobs IJ. Results of annual screening in phase I of the United Kingdom familial ovarian cancer screening study highlight the need for strict adherence to screening schedule. J Clin Oncol. 2013 Jan 1;31(1):49-57. doi: 10.1200/JCO.2011.39.7638. Epub 2012 Dec 3.

Between May 6, 2002, and January 5, 2008, 3,563 women at an estimated ≥ 10% lifetime risk of OC/FTC were recruited and screened by 37 centers in the United Kingdom to establish the performance characteristics of annual transvaginal ultrasound and serum CA125 screening for women at high risk of ovarian/fallopian tube cancer (OC/FTC) and to investigate the impact of delayed screening interval and surgical intervention. Sensitivity for detection of incident OC/FTC at 1 year after last annual screen was 81.3% (95% CI, 54.3% to 96.0%) if occult cancers were classified as false negatives and 87.5% (95% CI, 61.7% to 98.5%) if they were classified as true positives. Positive and negative predictive values of incident screening were 25.5% (95% CI, 14.3 to 40.0) and 99.9% (95% CI, 99.8 to 100) respectively. Four (30.8%) of 13 incident screen-detected OC/FTCs were stage I or II. Compared with women screened in the year before diagnosis, those not screened in the year before diagnosis were more likely to have ≥ stage IIIc disease (85.7% v 26.1%; P = .009).

Cardiology

G. William Dec, MD

1. Do R, Willer CJ, Global Lipids Genetics Consortium, Daly MJ, Neale BM, Kathiresan S. Common variants associated with plasma triglycerides and risk for coronary artery disease. *Nat Genet.* 2013 Nov; 45(11):1345-52. doi: 10.1038/ng.2795. Epub 2013 Oct 6.

Triglycerides are transported in plasma by specific triglyceride-rich lipoproteins; in epidemiological studies, increased triglyceride levels correlate with higher risk for coronary artery disease (CAD). However, it is unclear whether this association reflects causal processes. We mapped 185 common variants for plasma lipids ($P < 5 \times 10-8$ for each) and across these variants, we observed that the strength of a variant's effect on plasma triglycerides is highly correlated with the magnitude of its effect on CAD, even after accounting for potential effects of each variant on LDL cholesterol and/or HDL cholesterol. These results suggest that triglyceride-rich lipoproteins causally influence risk for CAD.

2. Arora P, Wu C, Khan AM, Bloch DB, Davis-Dusenbery BN, Ghorbani A, Spagnolli E, Martinez A, Ryan A, Tainsh LT, Kim S, Rong J, Huan T, Freedman JE, Levy D, Miller KK, Hata A, Del Monte F, Vandenwijngaert S, Swinnen M, Janssens S, Holmes TM, Buys ES, Bloch KD, Newton-Cheh C, Wang TJ. Atrial natriuretic peptide is negatively regulated by microRNA-425. *J Clin Invest.* 2013;123:3378-82.

This work further characterizes a genetic variant that influences atrial natriuretic peptide and blood pressure. We demonstrated the impact of the genetic variant in individuals selected on the basis of genotype who underwent dietary and intravenous sodium challenge. In addition, we identified a novel ANP regulatory mechanism: the genetic variant interrupts a microRNA-binding site, thereby releasing individuals with the minor allele from the negative regulatory effect of miR-425.

3. Wang TJ, Ngo D, Psychogios N, Dejam A, Larson M, Ramachandran V, Ghorbani A, O'Sullivan J, Cheng S, Rhee EP, Sinha S, McCabe E, Fox C, O'Donnell C, Ho J, Florez J, Magnusson M, Pierce K, Souza A, Yu Y, Carter C, Light P, Melander O, Clish C, Gerszten RE. 2-Aminoadipic acid is a biomarker for diabetes risk. *Journal of Clinical Investigation* 2013 Oct 1;123(10):4309-17. PMID:24091325

Type 2 diabetes mellitus affects an estimated 366 million people worldwide, making the identification of those at risk for the disease a public health priority. The Gerszten group developed a platform to measure intermediary metabolites in individuals who developed diabetes and propensity-matched controls from participants who were followed for 12 years as part of the Framingham Heart study. They found that levels of a novel metabolite, 2-aminoadipic acid (2-AAA), had the strongest association with future diabetes. They went to show that this was not an epiphenomenon, as administration of 2-AAA to mice lowered fasting plasma glucose levels, regardless of diet. Moreover, 2-AAA enhanced insulin secretion in both human and mouse pancreatic beta cells. These findings suggest that plasma measurements of 2-AAA could help identify candidates for interventions to help prevent type 2 diabetes and highlights a new pathway for further investigation in the context of cardiometabolic disease.

4. Hwang WY, Fu Y, Reyon D, Maeder ML, Tsai SQ, Sander JD, Peterson RT, Yeh JR, Joung JK. Efficient genome editing in zebrafish using a CRISPR-Cas system. *Nat Biotechnol.* 2013;31(3):227-9.

This is the first report demonstrating that a bacterial RNA-guided nuclease can be reprogrammed into a highly efficient gene-editing tool in zebrafish. We and others have previously shown that zebrafish is a powerful model organism for discovering candidate therapeutics of human diseases. The CRISPR/Cas system is now becoming a mainstay of zebrafish genome engineering, enabling large-scale in vivo functional genomics studies.

Key Achievements/Publication Highlights for 2013

Endocrine

Henry Kronenberg , MD

1. Finkelstein JS, Lee H, Burnett-Bowie SA, Pallais JC, Yu EW, Borges LF, Jones BF, Barry CV, Wulczyn KE, Thomas BJ, Leder BZ. Gonadal steroids and body composition, strength, and sexual function in men. *N Engl J Med*. 2013 Sep 12;369(11):1011-22. doi: 10.1056/NEJMoa1206168.

Finkelstein et al try to cut through the fog of misunderstanding about the appropriate levels of testosterone in normal men by addressing the dose-response relationships regarding several biologically meaningful endpoints, such as body composition, muscle strength and sexual function. The elegant experimental design allowed to investigators to determine how much each action of testosterone was direct or, instead, required conversion of the administered testosterone to estrogen (estradiol). They found that fat accumulation, the parameter most sensitive to testosterone deficiency, depended on conversion of testosterone to estrogen, while muscle strength depended only on testosterone levels. Sexual interest and function depended both on testosterone and estrogen. These studies should allow a more useful and focused series of definitions of hypogonadism in men, and suggest possible therapeutic roles for estrogen in men.

2. Mannstadt M, Harris M, Bravenboer B, Chitturi S, Dreijerink KM, Lambright DG, Lim ET, Daly MJ, Gabriel S, Jüppner H. Germline mutations affecting Gα11 in hypoparathyroidism. *N Engl J Med*. 2013 Jun 27;368(26):2532-4. doi: 10.1056/NEJMc1300278.

Mannstadt et al investigated patients in two families with autosomal dominant hypoparathyroidism and identified distinct mutations in the α subunit of G11, one of the heterotrimeric G proteins known to mediate the actions of the calcium-sensing receptor in the parathyroid gland. Presumably, because of inadequate intracellular signaling, the patients secreted inappropriately how levels of parathyroid hormone and presented with hypocalcemia. This paper shows that G11 is essential for mediating the actions of the calcium-sensing receptor in humans. The finding of overactive G11αprotein, present in essentially all cells of the body, leading to an organ-limited illness like hypoparathyroidism, also suggests a unique sensitivity of the parathyroid system to abnormalities of G11 signaling. These findings may lead to new therapeutic approaches to treating the hyperparathyroidism of renal failure and in other settings.

3. Tsai JN, Uihlein AV, Lee H, Kumbhani R, Siwila-Sackman E, McKay EA, Burnett-Bowie SA, Neer RM, Leder BZ. Teriparatide and denosumab, alone or combined, in women with postmenopausal osteoporosis: the DATA study randomised trial. Lancet. 2013 Jul 6;382(9886):50-6. doi: 10.1016/S0140-6736(13)60856-9. Epub 2013 May 15.

Previous work had shown that combination of teriparatide (PTH 1-34) with a bisphosphonate (alendronate) increased bone density LESS than with terapartide alone. Here Tsai et al show that, in contrast, combination of teriparatide with denosemab, a monoclonal antibody that powerfully blocks the action of RANKL and therefore blocks bone resorption, increases bone mass in the spine and hip more than either agent alone. In fact, these increases in one year were greater than with any currently reported therapy for osteoporosis. These findings suggest a novel therapy for those with severe osteoporosis and point toward a new research agenda for optimizing such combinations.

4. Papaioannou G, Inloes JB, Nakamura Y, Paltrinieri E, Kobayashi T. let-7 and miR-140 microRNAs coordinately regulate skeletal development. Proc Natl Acad Sci U S A. 2013 Aug 27;110(35):E3291-300. doi: 10.1073/pnas.1302797110.

Papaioannou et al examine the roles of let-7 microRNAs in the growth plates of mouse bones. They suppressed let-7 microRNA through overexpression of lin28, a known suppressor of let-7 expression. In stem cells, let-7 has been shown to limit cell proliferation but the authors found, instead, that in growth chondrocytes, let-7 stimulates cell proliferation. By lowering both let-7 and another microRNA, mir140, the authors show that the resultant mice have a dramatic growth defect.

The importance of this work involves showing that the actions of let-7 are more tissue-specific than previously realized and showing the vital importance of microRNAs in regulating bone growth.

Endocrine/Diabetes Unit

Joseph Avruch, MD

1. Scientific Achievement/Publication

Deborah Wexler MD (Diabetes) and Stephanie Eisenstat MD (General Medicine) were honored with the 2013 Nathaniel Bowditch Prize which recognized their significant contributions to enhance the delivery of quality patient care while also reducing the cost of that care. Specifically, their leadership of the MGH Diabetes Care Redesign team led to significant improvements in insulin management and generated enormous momentum for diabetes care improvement across the institution. The processes they created was implemented in all primary care practices by the Primary Care Transformation Council in the first half of 2013.

Wexler DJ, Beauharnais CC, Regan S, Nathan DM, Cagliero E, Larkin ME.

Impact of inpatient diabetes management, education, and improved discharge transition on glycemic control 12 months after discharge.

Diabetes Res Clin Pract, 2012; 98(2):249-56. PMCID 23036785.

2. Look AHEAD Research Group, Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, Evans M, Foreyt JP, Ghazarian S, Gregg EW, Harrison B, Hazuda HP, Hill JO, Horton ES, Hubbard VS, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Kitabchi AE, Knowler WC, Lewis CE, Maschak-Carey BJ, Montez MG, Murillo A, Nathan DM, et al. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145-54.

David Nathan MD-among his major contributions in 2013 were the publication of the main results of the 12-year LookAHEAD study that demonstrated the role of an intensive lifestyle intervention on cardiovascular disease.

Nathan DM, Buse JB, Kahn SE, Krause-Steinrau H, Larkin ME, Staten M, Wexler D, Lachin JM; GRADE Study Research Group. Rationale and Design of the Glycemia Reduction Approaches in Diabetes: a Comparative Effectiveness Study. Diabetes Care 2013;36:2254-61.

In addition, the Glycemia Reduction Approaches in Diabetes: a Comparative Effectiveness (GRADE) Study, designed and led by Dr. Nathan as national PI (D. Wexler as MGH site PI) was launched after more than 3-years of planning. It is the largest multicenter clinical trial that has been launched by NIDDK, NIH in the past 5 years.

3. Sequence variants in SLC16A11 are a common risk factor for type 2 diabetes in Mexico.The SIGMA Type 2 Diabetes Consortium Nature (2013) doi:10.1038/nature12828

David Althshuler MD, PhD, Jose Florez, MD, PhD, and colleagues in the SIGMA Type 2 Diabetes Consortium published in Nature on Dec. 25 2013 the discovery of a gene whose variants that bears mutations in its coding sequence represent an important risk factor for T2DM in Mexican and Latin American individuals, probably acquired via genetic admixture with Neaderthals.

4. Homogeneous expansion of human T-regulatory cells via tumor necrosis factor receptor 2. Okubo Y, Mera T, Wang L, Faustman DL. Sci Rep. 2013 Nov 6;3:3153. doi: 10.1038/srep03153.PMID:24193319

Denise Faustman MD PhD is pursuing the use of BCG for immunomodulation of the autoimmunity of Type 1 Diabetes and the understanding of its mechanism. In this paper she describes a technique that enables the expansion in vitro of human T regulatory cells to potent suppressor cells of the immune response. This is achieved through the use of selected agonistic monoclonal antibodies to the

human TNFR2 receptor. The discovery that a specific agonist to human TNF receptor-2 is sufficient to initiate and support Treg expansion leads the way to possible therapeutic application of these cells, expanded in vitro or in vivo.

Endocrine/Neuroendocrine Unit

Anne Klibanski, MD

1. Makimura H, Murphy CA, Feldpausch MN, Grinspoon SK. The effects of Tesamorelin on phophocreatine recovery in obese subjects with reduced GH. J Clin Endocrinol Metab. 2013 (In Press).

Obese subjects demonstrate reduced growth hormone concentrations. In this study we investigated the novel hypothesis that augmenting endogenous GH secretion would result in improved mitochondrial function. We used P31 spectroscopy to assess the effects of tesamorelin, a 1-44 amino acid GHRH analogue, demonstrating highly significant relationships between increased IGF-I levels and pCR recovery, an index of mitochondrial function. These data using a directed hormonal approach to improve metabolic dysfunction have significant implications for the treatment of obesity and other syndromes with reduced GH function.

2. Lawson EA, Holsen LM, Desanti R, Santin M, Meenaghan E, Herzog DB, Goldstein JM, Klibanski A. Increased hypothalamic-pituitary-adrenal drive is associated with decreased appetite and hypoactivation of food-motivation neurocircuitry in anorexia nervosa. Eur J Endocrinol. 2013; 169(5):639-47.

Anorexia nervosa (AN), a psychiatric disorder characterized by self-induced starvation, is associated with increased hypothalamic-pituitary-adrenal (HPA) drive and hypercortisolemia. We studied the relationship between HPA hormone secretion, appetite and fMRI activation of food motivation neural circuitry in women with active AN, weight-recovered AN and healthy controls. Fasting and postprandial cortisol levels were high in AN and associated with decreased perception of homeostatic and hedonic appetite and fMRI hypoactivation of food motivation neural circuitry. These findings suggest that HPA activation may contribute to the maintenance of AN by the suppression of appetitive drive.

3. Bredella MA, Gerweck AV, Lin E, Landa MG, Torriani M, Schoenfeld DA, Hemphill LC, Miller KK. Effects of GH on body composition and cardiovascular risk markers in young men with abdominal obesity. J Clin Endocrinol Metab. 2013; 98(9):3864-72. PMCID: PMC3763970.

Visceral adiposity is associated with increased cardiometabolic risk and decreased growth hormone (GH) secretion. This randomized, placebo-controlled study demonstrated that GH replacement in abdominally obese men improves body composition including liver fat, mitochondrial function, and markers of cardiovascular risk and suggests that relative GH deficiency may be a contributing factor to the increased cardiovascular risk observed in individuals with abdominal adiposity.

4. Ackerman KE, Pierce L, Guereca G, Slattery M, Lee H, Goldstein M, Misra M. Hip structural analysis in adolescent and young adult oligo-amenorrheic and eumenorrheic athletes and non-athletes. J Clin Endocrinol Metab. 2013; 98(4):1742-9

Bone structure is a better determinant of fracture risk than DXA measures of bone density. However, bone structure is difficult to assess at the hip, where CT scanning would result in significant radiation exposure. This study used a novel strategy called hip structural analysis (using DXA) to determine structural measures at the hip, and reported that athletic activity confers benefits for hip structural parameters independent of areal BMD, although this advantage is lost in amenorrheic athletes.

Endocrine/Reproductive Endocrine Unit

William F. Crowley, Jr., MD

1. Margolin DH, Kousi M, Chan YM, Lim ET, Schmahmann JD, Hadjivassiliou M, Hall JE, Adam I, Dwyer A, Plummer L, Aldrin SV, O'Rourke J, Kirby A, Lage K, Milunsky A, Milunsky JM, Chan J, Hedley-Whyte ET, Daly MJ, Katsanis N, Seminara SB. Ataxia, dementia, and hypogonadotropism caused by disordered ubiquitination. *N Engl J Med*. 2013 May 23;368(21):1992-2003. doi: 10.1056/N. Eng.J.Med. oa1215993. Epub 2013 May 8.

Gordon Holmes Syndrome is a devastating neurodegenerative disease characterized by the simultaneous occurrence of reproductive failure and cerebellar ataxia, leading to death in the 4-5th decade of life. This study demonstrates that abnormal ubiquitination--the process of tagging proteins for degradation that is critical for the health of the cerebellum and the reproductive cell populations in the hypothalamus/pituitary is defective in these cases (NEJM, 2013). Novel homozygous mutations in RNF216 and OTUD4 which encode an E3 ubiquitin ligase and a deubiquitinase respectively, were identified in affected siblings. Zebrafish studies revealed epistatic interactions between RNF216 and OTUD4. Hippocampal neurons from a deceased patient contained ubiquitin-immunoreactive intranuclear inclusions indicating possible similarities between RNF216-associated neurodegeneration and other protein aggregates disorders. This is the first link between disordered ubiquitination in neurodegenerative disease and reproductive endocrine dysfunction and highlights the power of whole-exome sequencing in combination with functional studies to unveil complex genetic interactions that inform disease causality.

2. Kasippillai T, MacArthur DG, Kirby A, Thomas B, Lambalk CB, Daly ML, Welt CK. Mutations in eIF4ENIF1 Are Associated with Primary Ovarian Insufficiency, J. Clin. Endocrinol. Metab. 2013;98:E1534-1539.

Using whole exome sequencing in a family with multiple affected women premature ovarian failure, we identified a novel, dominantly-inherited nonsense mutation in eIF4ENIF1 that segregates within the pedigree. The gene encodes a protein specifically expressed in developing oocytes that may cause ovarian dysfunction by protein sequestration. This study demonstrates a novel importance for eIF4ENIF1 in oocyte development and ovarian function and opens the investigation of an important new systems biology pathway in oocyte development, i.e. proteins that regulate translation initiation.

3. Chew S, Balasubramanian R, Chan WM, Kang PB, Andrews C, Webb BD, MacKinnon SE, Oystreck DT, Rankin J, Crawford TO, Geraghty M, Pomeroy SL, Crowley WF Jr, Jabs EW, Hunter DG, Grant PE, Engle EC. A novel syndrome caused by the E410K amino acid substitution in the neuronal ɕtubulin isotype 3. Brain. 2013 Feb;136(Pt 2):522-35

Kallmann Syndrome (KS) (hypogonadotropic hypogonadism and anosmia) is often a clinical feature in many human developmental disorders. This work describes detailed phenotypes of 8 unrelated KS patients who harbor a de novo missense mutation (E410K) in TUBB3, a neuronal-specific protein, αtubulin isotype 3. Patients with the TUBB3 E410K mutation display marked pleotropy with multi-system syndromic phenoytpe that includs KS, stereotypic midface hypoplasia, intellectual disabilties and, in some cases, vocal cord paralysis, tracheomalacia and cyclic vomiting. The definition of this TUBB3 E410K syndrome now allows clinicians to identify affected individuals and predict the mutation based on clinical features alone. Since no other mutations in TUBB3 were associated with this phenotype, it also reveals valuable structure-function information about TUBB3's interaction with other tubulin interacting proteins.

Key Achievements/Publication Highlights for 2013

Gastrointestinal

Ramnik Xavier, MD

1. Nishihara R, Wu K, Lochhead P, Morikawa T, Liao X, Qian ZR, Inamura K, Kim SA, Kuchiba A, Yamauchi M, Imamura Y, Willett WC, Rosner BR, Fuchs CS, Giovannucci E, Ogino S, Chan AT. Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013 Sept 19; 369(12):1095-105. PMID: 24047059

This study provides the most compelling evidence to date that colonoscopy reduces the risk of developing or dying from colorectal cancer more powerfully than does sigmoidoscopy, a similar procedure that examines only a portion of the colon. The investigation also identifies molecular features that may help explain tumors that are diagnosed despite an individual's having recently undergone colonoscopy. This study provides a rationale for an individual to consider colonoscopy as a preferred test depending on their personal medical situation.

2. Liou AP, Paziuk M, Luevano JM Jr, Machineni S, Turnbaugh PJ, Kaplan LM. Conserved shifts in the gut microbiota due to gastric bypass reduce host weight and adiposity. Sci Transl Med. 2013 Mar 27; 5(178):178ra41. PMID: 23536013

This study demonstrates that Roux-en-Y gastric bypass (RYGB) in mice alters the gut microbial population and that transfer of this altered microbiota to non-operated, germ-free mice induces weight loss and decreased fat mass in the recipient animals despite increased food intake. These findings provide the first empirical evidence that changes in the gut microbiota contribute to reduced host weight and adiposity after bariatric surgery.

3. Chiang HS, Zhao Y, Song JH, Liu S, Wang N, Terhorst C, Sharpe AH, Basavappa M, Jeffrey KL, Reinecker HC. GEF-H1 controls microtubule-dependent sensing of nucleic acids for antiviral host defenses. *Nat Immunol.* 2014 Jan;15(1):63-71. PMID: 24270516

Viral targeting of dynein-based transport mechanisms play an important role for intracellular movements and replication of viral pathogens. We show that the activation of the microtubule and dynein motor complex-associated guanine nucleotide exchange factor GEF-H1, encoded by Arhgef2, is essential for sensing of foreign RNA by RIG-I-like receptors. GEF-H1-deficient macrophages have a profound defect in the induction of IFN-β following detection of synthetic dsRNAs including HMW and LMW poly(I:C) and 5 ppp-dsRNA. The recognition of viral RNA and synthetic dsRNA in the MAVS pathway required the nucleotide exchange activity of GEF-H1. Furthermore, microtubule networks were required for the activation and interaction of GEF-H1 with TBK1 for IRF3 phosphorylation and subsequent induction of Ifnb1 gene expression. Generation of Arhgef2 deficient mice revealed a pronounced signaling defect that prevented antiviral host responses to encephalomyocarditis virus and influenza A virus. In conclusion, our findings identify GEF-H1 as an antiviral signaling component that directs utilization of TBK1 in the MAVS-dependent nucleic acid detection pathways for the sensing of ssRNA virus infection and induction of IFN-β expression and secretion.

4. Gala MK, Mizukami Y, Le LP, Moriichi K, Austin T, Yamamoto M, Lauwers GY, Bardeesy N, Chung DC. Germline mutations in oncogene-induced senescence pathways are associated with multiple sessile serrated adenomas. *Gastroenterology.* In press.

We have identified new genetic variants associated with the development of sessile serrated adenomas. This is a newly recognized type of premalignant colonic polyp that accounts for many of the interval colon cancers that occur soon after colonoscopy. Linked to oncogene-induced senescence pathways, these variants offer new insights into SSA pathogenesis as well as a tool for risk assessment.

5. Fusco DN, Brisac C, John SP, Huang YW, Chin CR, Xie T, Zhao H, Jilg N, Zhang L, Chevaliez S, Wambua D, Lin W, Peng L, Chung RT (co-corresponding), Brass AL. A genetic screen identifies interferon-α effector genes required to suppress hepatitis C virus replication. *Gastroenterology.* 2013 Jun;144(7):1438-49, 1449.e1-9. PMID: 23462180

Using functional genomics and high content microscopy, we performed a whole-genome screen for host factors required for IFNα-mediated suppression of fully infectious hepatitis C virus. We identified 120 mostly novel IFN effector genes, followed by validation and HCV lifecycle analyses of 9 select IFN effectors. These findings implicate previously uncharacterized host factors in host-mediated control of viral infection. These factors can now be targeted for novel, host-directed antiviral design against a wide range of viral infections.

General Medicine

Geriatrics, Hospital Medicine, Primary Care/Stoeckle Center

Joshua Metlay, MD, PhD

1. Clair C, Rigotti NA, Porneala B, Fox CS, D'Agostino RB, Pencina MJ, Meigs JB. Association of smoking cessation and weight change with cardiovascular disease among adults with and without diabetes. JAMA. 2013;309:1014-21.

The investigative team tested the hypothesis that weight gain following smoking cessation does not attenuate the benefits of smoking cessation among people with and without diabetes using prospective data from the Framingham Offspring Study. After a mean follow-up of 25 years, among people without diabetes, compared with smokers, recent quitters had a hazard ratio (HR) for CVD of 0.47 (95% CI, 0.23-0.94) and long-term quitters had an HR of 0.46 (95% CI, 0.34-0.63 even after adjustment for traditional CVD risk factors and weight change. Results were similar among people with diabetes. The data show that smoking cessation was associated with a lower risk of CVD events and weight gain that occurred following smoking cessation did not modify this association, supporting a net cardiovascular benefit of smoking cessation despite subsequent weight gain.

2. Percac-Lima S, Ashburner JM, Bond B, Oo SA, Atlas SJ. Decreasing Disparities in Breast Cancer Screening in Refugee Women Using Culturally Tailored Patient Navigation. J Gen Intern Med. 2013;28:1463-8.

This paper reported the results of a retrospective program evaluation of a patient navigator program for refugee women designed to decrease disparities in breast cancer screening. Over a three year period, linguistically and culturally-tailored patient navigators decreased disparities over time in breast cancer screening among female refugees from Somalia, the Middle East and Bosnia.

3. Baggett TP, Hwang SW, O'Connell JJ, Porneala BC, Stringfellow EJ, Orav EJ, Singer DE, Rigotti NA. Mortality Among Homeless Adults in Boston: Shifts in Causes of Death Over a 15-year Period. JAMA Internal Medicine 2013;173(3):189-195.

Dr. Baggett and colleagues assessed all-cause and cause-specific mortality rates in a cohort of 28 033 adults 18 years or older who were seen at Boston Health Care for the Homeless Program from January 1, 2003, through December 31, 2008. The investigators determined that the all-cause mortality rate among homeless adults in Boston remains high and unchanged since 1988 to 1993 despite a major interim expansion in clinical services. Drug overdose has replaced HIV as the emerging epidemic. Interventions to reduce mortality in this population should include behavioral health integration into primary medical care, public health initiatives to prevent and reverse drug overdose, and social policy measures to end homelessness.

4. Singer DE, Chang Y, Borowsky LH, Fang MC, Pomernacki NK, Udaltsova N, Reynolds K, Go AS. A new risk score to predict ischemic stroke and other thromboembolism in atrial fibrillation: The ATRIA Study Stroke Risk Score. J Am Heart Assoc. 2013;2:e000250.

Accurate prediction of stroke risk is central to individualized use of anticoagulants to prevent stroke in atrial fibrillation (AF). Current risk scores (e.g., CHADS2) are mediocre risk prediction tools. We developed a novel stroke risk prediction score using the community-based ATRIA AF cohort (n=13,559) and validated the score in the ATRIA-CVRN cohort (n = 25,306), both assembled from patients in Kaiser Permanente, California health plans. The resulting ATRIA stroke risk score was

more rigorously developed and performed substantially better than currently used stroke risk schemes. It should aid in deciding for which AF patients the considerable stroke preventive benefit of anticoagulants outweighs their risk of hemorrhage.

Infectious Diseases

Stephen Calderwood, MD

1. Hickman SE, Kingery ND, Ohsumi TK, Borowsky M, Wang LC, Means TK, El Khoury J. The microglial sensome revealed by Direct RNA Sequencing. *Nature Neuroscience*, 2013 Dec; 16(12): 1896-905.

This paper includes two major findings. First, microglia constantly survey their environment and sense any changes in this environment and respond to these changes, but the set of genes they use to perform this major task had not been identified. In this study, a novel technology was used called Direct RNA Sequencing to establish (for the first time) the quantitative microglia transcriptome and define this set of genes, which was newly defined as "The Sensome". Second, the effect of normal healthy aging on the microglia transcriptome and sensome were evaluated and found, contrary to existing belief, that with normal healthy aging microglia become more neuroprotective. This is a paradigm-changing finding that indicates that in the brain, microglia are trying to "fend off" the effects of aging. The datasets generated by these studies are applicable not only to study normal microglial functions, but are important for a wide variety of CNS disorders including Alzheimer's disease, Parkinson's disease, Multiple Sclerosis, Traumatic Brain injury and CNS infections. This recent paper is receiving a high level of online attention and is considered in the top 5% of all papers published and tracked by Altmetric since they started tracking papers.

2. Karlsson EK, Harris JB, Tabrizi S, Rahman A, Shlyakhter I, Patterson N, O'Dushlaine C, Schaffner SF, Gupta S, Chowdhury F, Sheikh A, Shin OS, Ellis C, Becker CE, Stuart LM, Calderwood SB, Ryan ET, Qadri F, Sabeti PC, LaRocque RC. Natural selection in a Bangladeshi population from the cholera-endemic Ganges River Delta. Sci Transl Med. 2013 Jul 3;5(192):192ra86. doi: 10.1126/scitranslmed.3006338.

Cholera kills hundreds of thousands of people a year, and the disease's heartland is the Ganges River Delta of India and Bangladesh. Researchers from the Massachusetts General Hospital Division of Infectious Diseases, in collaboration with investigators at the Broad Institute of Harvard/MIT and the International Center for Diarrheal Disease Research in Dhaka, Bangladesh, found evidence that the genomes of people in Bangladesh have developed ways to combat the disease. Using a statistical technique that pinpoints sections of the genome that are under the influence of natural selection, the researchers found that natural selection has left its mark on 305 regions in the genome of the subjects from Bangladesh. They further identified that cholera was the driving force behind many of these genomic changes, particularly in genes encoding potassium channels and genes related to inflammatory responses. This research provides a powerful example of the impact infectious diseases have had on human evolution. Understanding how humans have evolved in response to cholera might also help researchers devise more potent vaccines against the disease.

3. Mansour MK, Tam JM, Khan NS, Seward M, Davids PJ, Puranam S, Sokolovska A, Sykes DB, Dagher Z, Becker C, Tanne A, Reedy JL, Stuart LM, and Vyas JM. Dectin-1 activation controls maturation of β-1,3-glucan-containing phagosomes. 2013. *Journal of Biological Chemistry*. Apr 22. 288(22):16043-54.

Using synthetic fungal-like particles that contain a monodispersed array of fungal carbohydrate (created in the laboratory), these results support a model where Dectin-1 not only controls internalization of β-1,3-glucan containing cargo and triggers proinflammatory cytokines, but also

acts as a master regulator for subsequent phagolysosomal maturation through Syk activation in professional antigen presenting cells.

4. Walensky RP, Ross EL, Kumarasamy N, Wood R, Noubary F, Nakamura YM, Godbole SV, Panchia R, Sanne I, Weinstein MC, Losina E, Mayer KH, Chen YQ, Want L, McCauley M, Gamble T, Seage GR, Cohen MS, Freedberg KA. The cost-effectiveness of HIV treatment as prevention: analysis of HPTN 052. *N Eng J Med* 2013;369:1715-25.

In collaboration between MGH researchers and the HPTN 052 Trial team, Walensky et al used a mathematical model simulating HIV treatment, transmission and costs to project five-year and lifetime outcomes of the infected participants in India and South Africa. Five-year survival was 93% and 83% for those of patients receiving early vs. delayed ART. At five years, early compared to delayed ART also saved money in South Africa and was cost-effective in India. Across patient lifetimes, early ART was very cost-effective in both countries. The initial HPTN 052 Trial demonstrated patients receiving early ART lead healthier lives and protect their partners from infection. This current collaborative analysis also demonstrated, regardless of the country, that the investment is a superb one, over both the short- and long-term.

Medical Practice Evaluation Center

Kenneth Freedberg, MD, and Rochelle Walensky, MD, MPH

1. Walensky RP, Ross EL, Kumarasamy N, Wood R, Noubary F, Nakamura YM, Godbole SV, Panchia R, Sanne I, Weinstein MC, Losina E, Mayer KH, Chen YQ, Want L, McCauley M, Gamble T, Seage GR, Cohen MS, Freedberg KA. The cost-effectiveness of HIV treatment as prevention: analysis of HPTN 052. *N Engl J Med* 2013; 369: 1715-25.

In a collaboration between MGH researchers and the national HIV Prevention Trials Network (HPTN) 052 team, Walensky et al. used a mathematical model of HIV treatment, transmission, and costs to project five-year and lifetime outcomes of the infected participants in India and South Africa. Five-year survival was 93% compared to 83% for those patients receiving early compared to delayed antiretroviral therapy (ART). At five years, early compared to delayed ART saved money in South Africa and was cost-effective in India. Across patient lifetimes, early ART was very cost-effective in both countries. The initial HPTN 052 Trial demonstrated that patients receiving early ART led healthier lives and protected their partners from HIV infection. This analysis expanded the clinical findings and demonstrated that, regardless of the country, investment in early HIV treatment is a superb one, over both the short- and long-term.

2. Walensky RP, Sax PE, Nakamura YM, Weinstein MC, Pei PP, Freedberg KA, Paltiel AD, Schackman BR. Economic savings versus health losses: the cost-effectiveness of generic antiretroviral therapy in the United States. *Ann Intern Med* 2013; 158: 84-92.

This study focused on the availability of generic forms of antiretroviral therapy (ART) for HIV disease in the United States. For the nearly 150,000 people on initial ART regimens in the US and the 2,500 new cases initiating ART in the coming year, Walensky et al. found that a move to generic-based regimens would save about $920 million in the US, with minimal if any change in clinical outcomes. Given the many important and proven therapies now available for HIV as well as other chronic diseases, this study quantified a way in which substantial savings could be realized and directed to other diseases, including new therapies for hepatitis C. It was named one of the top 10 HIV research findings of 2013 at the Infectious Diseases Society of America (IDSA) national meeting.

3. Ciaranello AL, Perez F, Engelsmann B, Walensky RP, Mushavi A, Rusibamayila A, Keatinge J, Park JE, Maruva M, Cerda R, Wood R, Dabis F, Freedberg, KA. The cost-effectiveness of World Health Organization 2010 guidelines for prevention of mother-to-child HIV transmission in Zimbabwe. *Clin Infect Dis* 2013; 56: 430-46.

Ciaranello et al. developed a simulation model to project the impact of alternative strategies to prevent mother-to-child HIV transmission (PMTCT) for a cohort of HIV-infected, pregnant women in Zimbabwe. Working with the Zimbabwe Ministry of Health, the Elizabeth Glaser Pediatric AIDS Foundation, and local organizations providing care for pregnant women and children, the MGH team examined the costs and clinical benefits of four previous and current World Health Organization (WHO)-recommended PMTCT regimens. Compared to a simpler regimen recommended in 2010, providing women with 3-drug antiretroviral therapy (ART) during pregnancy and breastfeeding was projected to improve combined (maternal plus pediatric) life expectancy from 37.9 to 38.3 years. Despite the higher upfront medication costs, this strategy was also projected to save money by averting costly pediatric HIV infections. Dr. Ciaranello presented this work to the WHO in late 2012, contributing to 2013 international guidelines for HIV therapy.

4. Venkatesh KK, Becker JE, Kumarasamy N, Nakamura YM, Mayer KH, Losina E, Swaminathan S, Flanigan TP, Walensky RP, Freedberg KA. Clinical impact and cost-effectiveness of expanded voluntary HIV testing in India. *PLoS ONE* 2013; 8: e64604.

With over 2.4 million people living with HIV, India has the second largest number of HIV-infected in the world. Dr. Freedberg directed an analysis in collaboration with investigators in Chennai, India which found that population-wide voluntary HIV screening every five years in India offers substantial clinical benefits and is highly cost-effective, with an incremental cost-effectiveness ratio of $1,900/YLS. This paper was highlighted in the June 15, 2013 issue of The Economist as it described the major impact and value of such testing in India, and has been presented to the National AIDS Control Organization of India.

Mongan Institute for Health Policy

Lisa Iezzoni, MD

1. Fung V, Price M, Busch AB, Landrum MB, Fireman B, Nierenberg A, Dow WH, Hui R, Frank R, Newhouse JP, Hsu J. Adverse clinical events among medicare beneficiaries using antipsychotic drugs: linking health insurance benefits and clinical needs. Med Care. 2013 Jul;51(7):614-21

The Medicare Part D prescription drug program provides special formulary protections for antipsychotics, but does not exempt these drugs from cost-sharing requirements. We found that standard Part D cost-sharing was associated with reductions in antipsychotic drug use, with the largest declines among beneficiaries with the clearest indications for use, i.e., those with diagnoses of schizophrenia and bipolar disorder. Indicators of clinical harm, including hospitalizations and emergency department visits, were greatest in these populations as well. Failure to align out-of-pocket costs with clinical goals resulted in poor access to antipsychotics for beneficiaries with serious mental illness.

2. Donelan K, DesRoches CM, Dittus RS, Buerhaus PI. Physician and nurse practitioner perspectives on primary care practice, *N Engl J Med*. 2013 May 16;368(20):1898-906

This national survey of physicians and nurse practitioners providing primary care services is the first to explore comparative perceptions of scope of practice restrictions and nurse practitioner-led practices. The study received widespread public and policy attention and highlighted the critical barriers that will have to be addressed to achieve policy solutions about health workforce supply. The authors focus on the need for clarity in roles, interprofessional teamwork and education so that patients can understand and work with their health care teams.

3. Pachucki MA, Jacques PF, Christakis NA. Social network concordance in food choice among spouses, friends, and siblings.Am J Public Health. 2011 Nov;101(11):2170-7. Epub 2011 Sep 22.

Investigators examined longitudinal associations in diet patterns in a cohort of 3418 socially-connected adults over a ten-year period to ascertain possible peer influence on one's eating habits. While spouses tended to be more similar than friends or siblings in their food choices, certain

diet patterns appeared to be socially transmissible regardless of relationship type. Specifically, individuals who follow a diet distinguished by high amounts of alcohol and snacks appear to share this diet with their connected peers.

4. Park ER, Gareen I, Jain A, Ostroff JS, duan F, Sicks JD, Rakowski W, Diefenbach M, Rigotti N. Examining Whether Lung Screening Changes Risk Perceptions: NLST Participants at 1-year Follow-up. Cancer. 2013;119 :1306-1313.

The National Lung Screening Trial (NLST) compared lung cancer mortality rates among high risk current and former smokers with a minimum 30-pack/year smoking history and found that low dose computed tomography (CT) screening reduced lung cancer mortality by 20% relative to screening with chest x-ray. The aim of this study was to assess the effects of lung screening and test result, on risk perceptions that might underlie smoking behavior changes one-year following an initial lung screen. We found that lung screening does not significantly change risk perceptions for lung cancer or smoking related disease. We recommend that tobacco risk communication and cessation become an integral part of the lung screening process.

Nephrology Division

Ravi Thadhani, MD, MPH

1. Powe CE, Evans MK, Wenger J, Zonderman AB, Tamez H, Berg A, Bhan I, Karumanchi SA, Powe NR, Thadhani R. Vitamin D Binding Protein and Vitamin D Status in White and Black Americans. N Eng J Med 2013 Nov 21;369(21):1991-2000. PMID: 24256378

In the Healthy Aging in Neighborhoods of Diversity across the Life Span cohort we found community-dwelling black Americans, as compared with whites, had low levels of total 25-hydroxyvitamin D and vitamin D–binding protein, resulting in similar concentrations of estimated bioavailable 25-hydroxyvitamin D. Racial differences in the prevalence of common genetic polymorphisms provide a likely explanation for this observation.

2. Yu C, Fornoni A, Weins A, Hakroush S, Maiguel D, Sageshima J, Chen L, Ciancio G, Faridi MH, Behr D, Campbell KN, Chang JM, Chen HC, Oh J, Faul C, Arnaout MA, Fiorina P, Gupta V, Greka A, Burke G, and Mundel P. Abatacept in B7-1 Positive Proteinuric Kidney Disease. *New England Journal of Medicine*. November 8, 2013

From the press release:

"A drug approved for the treatment of rheumatoid arthritis may also turn out to be the first targeted therapy for one of the most common forms of kidney disease, a condition that almost inevitably leads to kidney failure."

Described as one of the greatest scientific findings in nephrology in 25 years in the NEJM editorial titled *"A New Era of Podocyte-Targeted Therapy for Proteinuric Kidney Disease."*

3. Schaldecker T, Kim S, Tarabanis C, Tian D, Hakroush S, Castonguay P, Ahn W, Wallentin H, Heid H, Hopkins CR, Lindsley CW, Riccio A, Buvall L, Weins A, and Greka A. Inhibition of the TRPC5 ion channel protects the kidney filter. Journal of Clinical Investigation. November 15, 2013.

From the press release:
"A group of MGH investigators identified a molecule that plays a key role in the breakdown of the kidney filter, presenting a potential therapeutic target for stopping the type of kidney damage associated with diabetes before it becomes irreversible."

4. Azcutia, V., Routledge, M., Williams, M.R., Newton, G., Frazier W.A., Manica A., Croce K.J., Parkos C.A., Schmider A.B., Turman M.V., Soberman R.J. and Luscinskas F.W. CD47 plays a critical role in T-cell recruitment by regulation of LFA-1 and VLA-4 integrin adhesive functions. Mol Biol Cell. 24; 3358-3368, 2013.

The work describes a distinct pathway that regulates T-cell recruitment in vivo to sites of inflammation. A potential therapeutic target for the treatment of immune-mediated diseases is described as well.

5. Dennis Brown, PhD (Professor of Medicine, HMS) was awarded an Honorary Doctorate of Science by his alma mater, the University of East Anglia, Norwich, UK at a congregation held on Thursday July 18th, 2013. The honor was bestowed in recognition of his contributions to cell biology and physiology.

Palliative Care

Vicki Jackson, MD,MPH

1. Chittenden EH, Anderson WG, Lai CJ, O'Sullivan P. An evaluation of interactive web-based curricula for teaching code status discussions. *J Palliat Med*. 2013 Sep;16(9):1070-3. doi: 10.1089/jpm.2012.0611. Epub 2013 Aug 12.

This publication demonstrated the effectiveness of web based curriculum for teaching residents how to engage in quality discussions of code status. Teaching resuscitation discussions to medical students and residents is time intensive and should be taught by teachers with competence in this area of clinical practice. There are plenty of data that these discussions are often inadequate, and that communication skills training, while time and faculty intensive, improves these conversations. The role of online instruction in teaching communication skills, such as resuscitation discussions, is not established. The study objective was to evaluate the effectiveness of an interactive online curriculum in teaching code status discussions to third-year medical students at one medical school.

2. Jackson VA, Jacobsen J, Greer JA, Pirl WF, Temel JS, Back AL. The cultivation of prognostic awareness through the provision of early palliative care in the ambulatory setting: a communication guide. *J Palliat Med*. 2013 Aug;16(8):894-900. doi: 10.1089/jpm.2012.0547. Epub 2013 Jun 20.

Early, integrated palliative care delivered in the ambulatory setting has been associated with improved quality of life, lower rates of depression, and even prolonged survival. We outline an expert practice that provides a step-wise approach to cultivating prognostic awareness in patients cared for by a palliative care clinician early in the course of the patient's disease. This approach can be used by both novice and more experienced palliative care clinicians.

3. Jacobsen J, Thomas Jd, Jackson VA. Misunderstandings about prognosis: an approach for palliative care consultants when the patient does not seem to understand what was said. *J Palliat Med*. 2013 Jan;16 (1):91-5. doi: 10.1089/jpm.2012.0142. Epub 2012 Dec 12.

This publications articulate the communication techniques used in the delivery of early intervention palliative care. Called in after discussions about prognosis between referring clinicians and patients, palliative care consultants sometimes find that the patient does not seem to understand what the referring clinician believes he or she explained. However, holding a more explicit discussion about prognosis may compromise the palliative care clinician's rapport with both the patient and the referring clinician. We therefore propose a two-part approach to explore apparent prognostic misunderstandings: first, generate a differential diagnosis for why the patient and referring clinician have different reports of what was said, and second, cultivate a partnership with the referring clinician to provide a unified patient care plan.

Pulmonary and Critical Care Division

Benjamin Medoff, MD

1. Tata PR, Mou H, Pardo-Saganta A, Zhao R, Prabhu M, Law BM, Vinarsky V, Cho JL, Breton S, Sahay A, Medoff BD, Rajagopal J. Dedifferentiation of committed luminal epithelial cells into functional stem cells in vivo. Nature. 2013; 503: 218-223. (reviewed in Nature News and Views) Pubmed PMID: 24196716.

This paper by Dr. Jay Rajagopal presents the first rigorous evidence that differentiated epithelial cells can revert into stable and functional stem cells in vivo. This capacity of committed cells to dedifferentiate into stem cells may have a general role in the regeneration of many tissues and in multiple disease states, notably cancer.

2. Farhat MR, Shapiro BJ, Kieser KJ, Sultana R, Jacobson KR, Victor TC, Warren RW, Streicher EM, Calver A, Sloutsky A, Kau D, Posey JE, Plikaytis B, Oggioni MR, Gardy JL, Johnston JC, Rodrigues M, Tang PK, Kato-Maeda M, Borowski ML, Muddukrishan B, Kreiswirth BN, Kurepina N, Galagan J, Gagneux S, Birren B, Rubin EJ, Lander ES, Sabeti P, Murray M. Genomic anlaysis identifies targets of convergent positive selection in drug-resistant Mycobacterium tuberculosis. Nat Genet. 2013 Oct;45(10):1183-9.

Dr. Maha Farhat (Junior Faculty in the Division) published this study. It is the first large scale analysis of whole genome sequences of drug resistant Mycobacterium tuberculosis, and implicates new genes and pathways with drug resistance in this organism.

3. Hariri LP, Villiger M, Applegate MB, Mino-Kenudson M, Mark EJ, Bouma BE, Suter MJ. Seeing beyond the bronchoscope to increase the diagnostic yield of bronchoscopic biopsy. American Journal of Respiratory and Critical Care Medicine. 2013; 187(2): 125-9. PMCID: PMC3570655. * Cover article

Dr Suter's laboratory published a key manuscript in the American Journal of Respiratory and Critical Care Medicine. In this manuscript the authors describe their work in developing robust optical coherence tomography (OCT) interpretation criteria of lung pathology. The ultimate goal of their work is to use OCT as a complementary image guidance tool for improving the diagnostic yield of bronchial biopsy. This body of work is laying the critical foundation necessary prior to the clinical adoption of this promising new technology.

4. Blackwell TS, Tager AM, Borok Z, Moore BB, Schwartz DA, Anstrom KJ, Bar-Joseph Z, Bitterman P, Blackburn MR, Bradford W, Brown KK, Chapman HA, Collard HR, Cosgrove GP, Deterding R, Doyle R, Flaherty KR, Garcia CK, Hagood JS, Henke CA, Herzog E, Hogaboam CM, Horowitz JC, King TE Jr, Loyd JE, Lawson WE, Marsh CB, Noble PW, Noth I, Sheppard D, Olsson J, Ortiz LA, O'Riordan TG, Oury TD, Raghu G, Roman J, Sime PJ, Sisson TH, Tschumperlin D, Violette SM, Weaver TE, Wells RG, White ES, Kaminski N, Martinez FJ, Wynn TA, Thannickal VJ, Eu JP. Future Directions in Idiopathic Pulmonary Fibrosis Research: An NHLBI Workshop Report. *Am J Respir Crit Care Med* 2013; Epub ahead of print Oct 25. PMCID - PMC Journal – in process.

This manuscript is the report of an NIH/NHLBI workshop that Dr. Andrew Tager co-chaired on future research directions in idiopathic pulmonary fibrosis (IPF). The workshop included basic, translational and clinical researchers, along with representatives from the National Heart Lung and Blood Institute, patient advocacy groups, pharmaceutical companies and the Food and Drug Administration. Our goals were to review the current state of IPF research and identify priority areas, opportunities for collaborations and directions for future research. In this manuscript, we made recommendations aimed at coordinating research efforts and accelerating the development of new effective IPF therapies.

Rheumatology, Allergy and Immunology

Andrew D. Luster, MD, PhD

1. Ramirez-Ortiz ZG, Pendergraft WF, Prasad A, Byrne MH, Iram T, Blanchette CJ, Luster AD, Hacohen N, El Khoury J, Means TK. The scavenger receptor SCARF1 mediates the clearance of apoptotic cells and prevents autoimmunity. *Nature Immunology* 2013; 14: 917-926.

Detection and clearance of apoptotic cells is critical for tissue homeostasis. Accumulation of apoptotic cells in tissues causes autoimmune diseases, such as lupus. This study defined a key role for the scavenger receptor SCARF1 in sensing and engulfing apoptotic cells. SCARF1-deficient mice accumulated apoptotic cells in tissues and spontaneously developed a lupus-like autoimmune

disease. This study defined a key mechanism of apoptotic cell clearance and in so doing identified a new therapeutic target for autoimmune diseases.

2. Lee MN, Roy M, Ong SE, Mertins P, Villani AC, Li W, Dotiwala F, Sen J, Doench JG, Orzalli MH, Kramnik I, Knipe DM, Lieberman J, Carr SA, Hacohen N. Identification of regulators of the innate immune response to cytosolic DNA and retroviral infection by an integrative approach. *Nature Immunology* 2013; 14: 179-185.

This study identified key components of the innate immune pathway required for sensing self or foreign DNA. In addition, we use our understanding of the DNA-sensing network to identify and test small molecules that block this pathway, and use these drugs to block the response in cells from patients with Aicardi-Goutieres Syndrome who have severe early autoimmunity due to a hyperactive DNA-sensing pathway.

3. Marangoni F, Murooka TT, Manzo T, Ki EY, Carrizosa E, Elpek, NM, Mempel TR. The transcription factor NFAT exhibits signal memory during serial T cell interactions with antigen presenting cells. *Immunity* 2013; 38: 237-249.

This study used intravital microscopy to visualize, for the first time, the activation and de-activation kinetics of a transcription factor in cytotoxic T cells during their dynamic interactions with antigen-presenting cells in lymph nodes and in tumor tissue. This introduces the use of in vivo imaging to define, at the single cell level, the environmental cues that govern the transcriptional regulation of T cell effector genes and thereby ultimately the outcome of immune responses.

4. Specks U, Merkel PA, Seo P, Spiera R, Langford CA, Hoffman GS, Kallenberg CG, St. Clair EW, Fessler BJ, Ding L, Viviano L, Tchao NK, Phippard DJ, Asare AL, Lim N, Ikle D, Jepson B, Brunetta P, Allen NB, Fervenza FC, Geetha D, Keogh K, Kissin EY, Monach PA, Peikert T, Stegeman C, Ytterberg SR, Mueller M, Sejismundo LP, Mieras K, Stone JH; RAVE-ITN Research Group. Efficacy of remission-induction regimens for ANCA-associated vasculitis. *New England Journal of Medicine* 2013; 369: 417-427.

This study described the long-term results of the RAVE (Rituximab in ANCA-associated Vasculitis) trial, which confirmed that a single course of B-cell depletion therapy with rituximab was as effective as eighteen months of continuous treatment with conventional, chemotherapy-based regimens. On the strength of the RAVE trial alone, rituximab was approved by the US and forty other countries for remission induction in ANCA-associated vasculitis. The RAVE trial opened the way for remission maintenance approaches based on B cell depletion that offer the possibility of long-term, chemotherapy and glucocorticoid-free disease remissions.

Molecular Biology

Bob Kingston, PhD

1. Agarwala V, Flannick J, Sunyaev S; GoT2D Consortium, Altshuler D. "Evaluating empirical bounds on complex disease genetic architecture." Nature Genetics 2013 45:1418-27.

This paper combines large-scale empirical data and computer simulations to address a question of high interest to human genetics and the future of "personalized" or "precision" medicine: what is the architecture underlying the genetic basis of common human diseases. That is, to what extent is the genetic basis of disease due to rare variants of large effect (that might prove highly predictive in the clinic), and to what extent due to many common variants of weak effect. Our paper argues that available data are not yet sufficient to address this question, but pending results from large scale sequencing studies will soon narrow the bounds.

2. Simon, MD, Pinter, S.F., Fang, R., Sarma, K., Rutenberg-Schoenberg, M., Bowman, S.K., Kesner, B.A., Maier, V.K., Kingston, R.E., Lee, J.T. (2013) High-resolution Xist binding maps reveal two-step spreading during X-chromosome inactivation. Nature.Oct 27.

This study uses a high-throughput technique, CHART-seq, to generate a high-resolution chromosomal binding map for the long noncoding RNA, Xist. The binding map demonstrates that Xist RNA spreads along the X-chromosome in a two-step fashion, first targeting active genes before spreading to the rest of the X-chromosome.

3. EMRE is an essential component of the mitochondrial calcium uniporter complex. Sancak Y, Markhard AL, Kitami T, Kovács-Bogdán E, Kamer KJ, Udeshi ND, Carr SA, Chaudhuri D, Clapham DE, Li AA, Calvo SE, Goldberger O, Mootha VK. Science. 2013 Dec 13;342(6164):1379-82.

A few years ago our lab reported the discovery of the founding molecular components of the mitochondrial calcium uniporter, the major channel that permits calcium entry into mitochondria. In the current paper we report the purification of the uniporter holoholocomplex (uniplex) and used mass spectrometry to identify its components, revealing one new component, called EMRE, that serves to bridge the pore to the regulatory subunit. The full characterization of the complex should enable detailed molecular studies of its mechanism and role in disease.

4. Adamala K and Szostak JW. Non-enzymatic RNA copying inside fatty acid vesicles. Science, 2013; 342:1098-1100.

A fundamental problem standing in the way of the construction of a replicating, evolving protocell is the apparent incompatibility between the high Mg2+ ion requirement of nonenzymatic RNA replication, and the sensitivity of fatty acid based protocell membranes to even low concentrations of Mg2+. In this paper, we show that chelating Mg2+ with citrate protects membranes from disruption by Mg2+ while still allowing RNA template copying to proceed. Based on these observations, we were able to demonstrate nonenzymatic RNA copying inside fatty acid vesicles. This is a major step towards the assembly of a complete model protocell system.

Neurology

Merit E. Cudkowicz, MD, MSc

1. Miller T, Pestronk A, David W, Rothstein J, Simpson E, Appel S, Andres P, Mahoney K, Allred P, Alexander K, Ostrow L, Schoenfeld D, Macklin E, Norris D, Manousakis G, Crisp M, Smith R, Bennett C, Bishop K, Cudkowicz M. An antisense oligonucleotide against SOD1 delivered intrathecally for patients with SOD1 familial amyotrophic lateral sclerosis: a phase 1, randomized, first-in-man study. The Lancet Neurology 2013: May;12(5):435-42.

Mutations in SOD1 cause 13% of familial amyotrophic lateral sclerosis. In the SOD1 Gly93Ala rat model of amyotrophic lateral sclerosis, the antisense oligonucleotide ISIS 333611 delivered to CSF decreased SOD1 mRNA and protein concentrations in spinal cord tissue and prolonged survival. We aimed to assess the safety, tolerability, and pharmacokinetics of ISIS 333611 after intrathecal administration in patients with SOD1-related familial amyotrophic lateral sclerosis.

2. Chen, W.W.*, Balaj, L.*, Liau, L.M., Samuels, M.L., Kotsopoulos, S.K., Maguire, C.A., LoGuidice, L., Soto, H., Garrett, M., Zhu, L.D., Sivaraman, S., Chen, C., Wong, E.T., Carter, B.S., Hochberg, F.H., Breakefield, X.O., Skog, J.: BEAMing and droplet digital PCR analysis of mutant IDH1 mRNA in glioma patient serum and cerebrospinal fluid extracellular vesicles. Molecular Therapy – Nucleic Acids 2:e109, 2013. *These authors contributed equally to this work.

This work reveals the ability to detect mutations in the isocitrate dehydrogenase 1 (IDH1) gene at the mRNA level in vesicles isolated from cerebrospinal fluid of glioma patients. This first-in-the-field mutation detection in brain tumor patients demonstrates the ability to carry out non-invasive monitoring of mutation status, with mutations in IDH1 informing diagnosis, prognosis and treatment paradigms.

3. Kim T, Vidal GS, Djurisic M, William CM, Birnbaum ME, Garcia KC, Hyman BT, Shatz CJ: Human LilrB2 is a beta-amyloid receptor and its murine homolog PirB regulates synaptic plasticity in an Alzheimer's model. Science 2013, 341(6152):1399-1404.

A paper in Science, in collaboration with Carla Shatz of Stanford, revealed a new Amyloid beta interaction protein: Soluble β-amyloid (Aβ) oligomers impair synaptic plasticity and cause synaptic loss associated with Alzheimer's disease (AD). We report that murine PirB (paired immunoglobulin-like receptor B) and its human ortholog LilrB2 (leukocyte immunoglobulin-like receptor B2), present in human brain, are receptors for Aβ oligomers, with nanomolar affinity. The first two extracellular immunoglobulin (Ig) domains of PirB and LilrB2 mediate this interaction, leading to enhanced cofilin signaling, also seen in human AD brains. In mice, the deleterious effect of Aαoligomers on hippocampal long-term potentiation required PirB, and in a transgenic model of AD, PirB not only contributed to memory deficits present in adult mice, but also mediated loss of synaptic plasticity in juvenile visual cortex. These findings imply that LilrB2 contributes to human AD neuropathology and suggest therapeutic uses of blocking LilrB2 function.

4. Chung CY*, Khurana V*, Auluck PK, Tardiff DF, Mazzulli JR, Soldner F, Baru V, Lou Y, Freyzon Y, Cho S, Mungenast AE, Muffat J, Mitalipova M, Pluth MD, Jui NT, Schüle B, Lippard SJ, Tsai LH, Krainc D, Buchwald SL, Jaenisch R, Lindquist S. Identification and Rescue of a-Synuclein Toxicity in Parkinson Patient-Derived Neurons. Science. 2013; *Equal contribution.

This is one of two papers in which we develop a paradigm for identifying and correcting phenotypes in stem cell-derived neurons from patients with neurodegenerative diseases. To establish proof-of-principle we generate induced pluripotent stem cell-derived neurons from Parkinson's disease patients harboring mutations at the alpha-synuclein locus. Critically, we utilize mutation-correction to establish isogenic control cell lines. Our method leverages the power of high-throughput genetic and small molecule screening in a yeast model of alpha-synuclein toxicity to identify early pathologic phenotypes in patient neurons, and genes and small molecules to correct these phenotypes. A target of one such small molecule probe is identified, revealing a new druggable target space for Parkinson's disease.

Neurosurgery

Robert L. Martuza, MD

1. Srinivasan L, Asaad WF, Ginat DT, Gale JT, Dougherty DD, Williams ZM, Sejnowski TJ, Eskandar EN. Action initiation in the human dorsal anterior cingulate cortex. PLoS One. 2013;8(2):e55247.

The cingulate cortex is an enigmatic structure. It has been implicated in error detection, conflict monitoring, and conflict adaption. In these experiments, we studied the role of the cingulate cortex, using the technique described above, in human subjects. We demonstrated that the cingulate seems to play a key role in determining when the solution to a problem is sufficiently clear to initiate an action. Subjects that have an injury to the cingulate cortex react prematurely, before other areas of the brain have had sufficient time to solve a problem. This work ties in nicely with our Nature paper in 2012 which demonstrated that activity in the cingulate cortex reflects different degrees of cognitive difficulty. We now have a coherent model wherein the cingulate cortex monitors the degree of cognitive difficulty, recruits additional brain areas to solve more complex problems, and withholds action until a problem has been solved. This model unifies previously disparate results and provides a basis for understanding cingulate dysfunction in disorders such as obsessive-compulsive disorder and Tourette Syndrome.

2. Cheema TA, Wakimoto H, Fecci PE, Ning J, Kuroda T, Jeyaretna DS, Martuza RL, Rabkin SD.Multifaceted oncolytic virus therapy for glioblastoma in an immunocompetent cancer stem cell model. Proc Natl Acad Sci U S A. 2013 Jul 16;110(29):12006-11

This paper describes a new immunocompetent mouse glioblastoma stem cell tumor model that recapitulates the features of human glioblastoma. This tumor model was used to test an oncolytic herpes simplex virus (oHSV) expressing IL-12, which acted in a multifaceted fashion to inhibit tumor growth; direct oncolysis of glioblastoma stem cells and bulk tumor cells, inhibition of angiogenesis, induced expression of IFNgamma, reduction in tumor infiltrated Tregs, and induction of T-cell mediated anti-tumor activity. These studies provide support for a clinical trial of oHSV-IL12 for glioblastoma.

3. Neuro Oncol. 2014 Jan;16(1):81-91. Epub 2013 Dec 4. IDH1 mutant malignant astrocytomas are more amenable to surgical resection and have a survival benefit associated with maximal surgical resection. Beiko J, 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.

This work demonstrates a >10 year median survival in a cohort of 121 patients with Grade III and IV astrocytic gliomas who are IDH1 mutant and have aggressive surgery, raising the possibility that appropriately tailored surgical and neuro-oncologic management of these patients can lead to survival that dramatically exceeds that of historical glioma cohorts. For this reason, at MGH we now pursue intraop-MRI-guided resections for patients with these tumors.

4. Patel SR, Sheth SA, Martinez-Rubio C, Mian MK, Asaad WF, Gerrard JL, Kwon CS, Dougherty DD, Flaherty AW, Greenberg BD, Gale JT, Williams ZM, Eskandar EN. Studying task-related activity of individual neurons in the human brain. Nat Protoc. 2013 May;8(5):949-57.

In the seminal paper on recording human neurons from awake subjects during surgery. The paper details many of the necessary requirements, including patient safety, stable neuronal recordings, and data analysis. This approach has led to many high impact publications from our group including recent publications in Nature, Nature Neuroscience, Journal of Neuroscience, PLoS One, and Cerebral Cortex.

Obstetrics and Gynecology

Isaac Schiff, MD

1. Rauh-Hain JA, Diver EJ, Clemmer JT, Bradford LS, Clark RM, Growdon WB, Goodman AK, Boruta DM 2nd, Schorge JO, del Carmen MG. Carcinosarcoma of the ovary compared to papillary serous ovarian carcinoma: a SEER analysis. Gynecol Oncol. 2013 Oct; 131(1):46-51.

Our objective was to determine if outcomes of patients with ovarian carcinosarcoma (OCS) differ from women with high-grade papillary serous ovarian carcinoma (HGPSC) when compared by stage as well as to identify any associated clinico-pathologic factors. The Surveillance, Epidemiology, and End Results (SEER) Program data for all 18 registries from 1998 to 2009 was reviewed to identify women with OCS and HGPSC of the ovary. Demographic and clinical data were compared, and the impact of tumor histology on survival was analyzed. Overall, women with OCS had a worse five-year, disease specific survival rate, 28.2% vs. 38.4% ($P < 0.001$). This difference persisted for each FIGO disease stages I–IV, with 5 year survival consistently worse for women with OCS compared with HGPSC. Over the entire study period, after adjusting for histology, age, period of diagnosis, SEER registry, marital status, stage, surgery, radiotherapy, lymph node dissection, and history of secondary malignancy after the diagnosis of ovarian cancer, carcinosarcoma histology was associated with decreased cancer-specific survival.

2. Kulkarni-Datar K, Orsulic S, Foster R, Rueda BR. Ovarian tumor initiating cell populations persist following paclitaxel and carboplatin chemotherapy treatment in vivo. Cancer Lett. 2013 Oct 10; 339(2):237-46.

Recurrent platinum resistant disease following chemotherapy presents a challenge in managing ovarian cancer. Our objective was to assess cancer stem cell populations post treatment. Using tumors derived from genetically defined mouse ovarian cancer cells, we investigated the stem cell properties of residual cells post-chemotherapy. Utilizing CD133 and Sca-1 as markers of candidate cancer stem cell populations, we determined that the relative levels of CD133+ and Sca-1+ cells were unaltered following chemotherapy. CD133+ and Sca-1+ cells exhibited increased stem cell-related gene expression, were enriched in G0/G1-early S phase and exhibited increased tumor initiating capacity, giving rise to heterogeneous tumors. Our findings support the concept that post treatment residual cancer stem cells may contribute to recurrent disease.

3. Young BC, Stanic AK, Panda B, Rueda BR, Panda A. Longitudinal expression of Toll-like receptors on dendritic cells in uncomplicated pregnancy and postpartum. Am J Obstet Gynecol. 2013 Nov 28.

Toll-like receptors (TLRs) are integral parts of the innate immune system and have been implicated in complications of pregnancy. The objective of this study was to prospectively evaluate TLRs 1-9 as expressed on dendritic cells in the maternal circulation at defined intervals throughout pregnancy and postpartum. It was determined that TLRs 1, 7, and 9 were elevated compared with nonpregnant controls with persistent elevation of TLRs 1 into the postpartum period. Concordantly, levels of interleukin-6, interleukin-12, interferon alpha, and tumor necrosis factor alpha increased during pregnancy and returned to levels similar to nonpregnant controls during the postpartum period. The elevated levels of TLRs 1 and interleukin-12 were persistent postpartum, challenging notions that immunologic changes during pregnancy resolve after the prototypical postpartum period.

4. Souter I, Smith KW, Dimitriadis I, Ehrlich S, Williams PL, Calafat AM, Hauser R. The association of bisphenol-A urinary concentrations with antral follicle counts and other measures of ovarian reserve in women undergoing infertility treatments. Reprod Toxicol. 2013 Dec; 42:224-31.

Our objective was to assess specific-gravity adjusted urinary BPA (SG-BPA) concentrations prospectively in a cohort of women undergoing infertility treatments. We used regression models to evaluate the association of BPA with antral follicle count (AFC), day-3 serum follicle stimulating hormone levels (FSH), and ovarian volume (OV). BPA, detected in >80% of women, had a geometric mean (±GSD) of 1.6±2.0, 1.7±2.1, and 1.5±1.8µg/L for the women contributing to the AFC (n=154), day-3 FSH (n=120), and OV (n=114) analyses, respectively. There was an average decrease in AFC of 12% (95% CI: -23%, -0.6%), 22% (95% CI: -31%, -11%), and 17% (95% CI: -27%, -6%), in the 2nd, 3rd, and 4th SG-BPA quartile compared to the 1st quartile, respectively (p-trend: <0.001). No association of SG-BPA with FSH or OV was observed. Among women from an infertility clinic, higher urinary BPA concentrations were associated with lower AFC, raising concern for possible accelerated follicle loss and reproductive aging.

Ophthalmology

Joan W. Miller, MD, FARVO

1. Woodward AM, Mauris J, Argüeso P Binding of transmembrane mucins to galectin-3 limits herpesvirus-1 infection of human corneal keratinocytes. J Virol. 2013;87(10):5841-5847.

Epithelial cells lining mucosal surfaces impose multiple barriers to viral infection. At the ocular surface, the carbohydrate-binding protein galectin-3 maintains barrier function by cross-linking transmembrane mucins on the apical glycocalyx. The results of this study show that HSV-1 exploits galectin-3 to enhance virus attachment to host cells and support a protective role for transmembrane mucins under physiological conditions by masking viral entry mediators on the epithelial glycocalyx.

2. Pennock S, Kim D, Mukai S, Kuhnle M, Chun DW, Matsubara J, Cui J, Ma P, Maberley D, Samad A, Van Geest RJ, Oberstein SL, Schlingemann RO, Kazlauskas A. Ranibizumab Is a Potential Prophylaxis for Proliferative Vitreoretinopathy, a Nonangiogenic Blinding Disease. Am J Pathol. 2013; 182(5):1659-70.

Proliferative vitreoretinopathy (PVR) exemplifies a disease that is difficult to predict, lacks effective treatment options, and substantially reduces the quality of life of an individual. Surgery to correct a rhegmatogenous retinal detachment fails primarily because of PVR. Likely mediators of PVR are growth factors in vitreous, which stimulate cells within and behind the retina as an inevitable consequence of a breached retina. This study suggests that available approaches to neutralize VEGF-A (already in use to treat macular degeneration) are prophylactic for PVR, and that anti-VEGF-based therapies may be effective for managing more than angiogenesis- and edema-driven pathological conditions.

3. Sun D, Qu J, and Jakobs TC; Reversible reactivity by optic nerve astrocytes. (2013) Glia, 61(8), 1218-1235

Reactive astrocytes are typically studied in models that cause irreversible mechanical damage to axons, neuronal cell bodies, and glia. This study evaluated the response of optic nerve astrocytes to a mild insult to the nerve. Astrocytes demonstrated reactive remodeling that peaked at three days, showing hypertrophy, process retraction, and simplification of their shape. At no time was there discernible damage to the optic axons, as evidenced by electron microscopy and normal anterograde and retrograde transport. Remarkably, the morphological remodeling was reversible. These findings underscore the plastic nature of reactivity. They show that reactivity can resolve fully if the insult is removed, and show that major damage to neurons is not a mandatory requirement for astrocytes to become reactive.

4. Takeuchi K, Morizane Y, Kamami-Levy C, Suzuki J, Kayama M, Cai W, Miller JW, Vavvas DG. AMP-dependent kinase inhibits oxidative stress-induced caveolin-1 phosphorylation and endocytosis by suppressing the dissociation between c-Abl and Prdx1 proteins in endothelial cells.J Biol Chem. 2013 Jul 12;288(28):20581-91.

Caveolin-1 is the primary structural component of endothelial caveolae that is essential for transcellular trafficking of albumin and is also a critical scaffolding protein that regulates the activity of signaling molecules in caveolae. Phosphorylation of caveolin-1 plays a fundamental role in the mechanism of oxidant-induced vascular hyper permeability. However, the regulatory mechanism of caveolin-1 phosphorylation remains unclear. This study identifies a previously unexpected role for AMPK in inhibition of caveolin-1 phosphorylation under oxidative stress.

Oral and Maxillofacial Surgery

Leonard B. Kaban, DMD, MD

1. Development of a novel buried, automated, continuous distraction device for mandibular lengthening and demonstration that continuous distraction jaw lengthening allows faster distraction rates in a minipig model.

A) Goldwaser BR, Magill J, Papadaki M, Byl M, Kromann R, Yates B, Morency J, Kaban LB, Troulis MJ. Continuous mandibular distraction osteogenesis: a novel device and preliminary results in minipigs. J Oral & Maxillofac Surg 2013 (April) 71:168-177.

B) Peacock ZS, Tricomi BJ, Murphy BA, Magill JC, Kaban LB, Troulis MJ. Automated continuous distraction ostetogenesis may allow faster distraction rates. J Oral & Maxillofac Surg 2013 (June) 71:1073-1084.

Distraction osteogenesis is a commonly used technique for bone lengthening in the craniomaxillofacial region. It allows for bone lengthening and expansion of overlying soft tissue without the need for bone and soft tissue graft harvesting and concomitant donor site morbidity. This is the first study to document that a novel, continuous distraction device, expanding bone automatically and gradually over 24 hours rather than intermittently twice per day, produces bone formation equivalent to or better than standard distraction techniques and at faster distraction

rates. This device developed at MGH and PSI (Physical Sciences Incorporated, North Andover, MA) with NIH funding (NIH-SBIR-4R44DE019047) will potentially revolutionize the field of distraction osteotgenesis.

2. Papadaki M, Kaban LB, Troulis MJ. Endoscopic vertical ramus osteotomy: A long-term prospective study. Int J Oral & Maxillofac Surg 2013 Nov 15 (Epub ahead of print)

Troulis MJ, Kaban LB, (editors) *Minimally Invasive Maxillofacial Surgery*, 2013, People's Medical Publishing House, Shelton, Connecticut, 2013.

The Department of OMFS at MGH, under the leadership of Maria Troulis, has been at the forefront of the development of minimally invasive endoscopic maxillofacial reconstructive surgery. This is the first published prospective study demonstrating the efficacy, safety and excellent outcomes for a minimally invasive endoscopic surgical alternative for correction of a variety of malocclusions and dentofacial deformities involving the lower jaw. In addition, the first textbook on minimally invasive reconstructive OMFS was published this year. As with many other surgical specialties, minimally invasive operations are completely changing day to day practice and improving patient care with equivalent results, reduced morbidity and a quicker return to normal life postoperatively.

3. Kinard BE, Chuang S-K, August M, Dodson TB. How well do we manage the odontogenic keratocyst? J Oral & Maxillofac Surg 2013 (August) 71:1353-1358.

This is the first published study applying appropriate statistical analyses, i.e. survival modeling, to estimate recurrence rates associated with treating odontogenic keratocysts (OKC), common jaw cysts related to impacted teeth. We report a surprisingly high rate of recurrence. It is likely that previous studies underestimated OKC recurrence rates due to inadequate analyses that failed to adjust for the duration of follow-up. The risk of recurrence was comparable between lesions that were enucleated and those that were treated with the less invasive procedure of decompression and stenting. We did not confirm the commonly held belief that the decompression and stenting procedure has recurrence rates lower than enucleation. This may change management of these patients when taking into account the risks and benefits of both treatment options, e.g. length of operation, risk for nerve injury, number of follow-up visits, and need for additional operations.

4. Abramowicz, S, Kim, S, Susarla, HK, Kaban LB. Differentiating arthritic from myofascial pain in children with juvenile idiopathic arthritis: preliminary report. J Oral Maxillofac Surg. 2013 Mar; 71(3):493-6.

Abramowicz S, Susarla HK, Kim S, Kaban LB: Physical findings associated with active temporomandibular joint inflammation in children with juvenile idiopathic arthritis. J Oral Maxillofac Surg. 2013 Oct;71(10):1683-7.

Temporomandibular joint involvement is common in pediatric patients with juvenile idiopathic arthritis producing pain, limitation of motion, condylar resorption, growth restriction and facial asymmetry. Myofascial pain, without synovitis, as a result of muscle hyperactivity and parafunctional habits, may also produce pain and limitation of motion in children. Differentiating between the 2 conditions is important because the management and the consequences are different. These studies specifically address the problem and provide clinicians much needed guidelines for diagnosis and management of these children.

Orthopaedics

Harry Rubash, MD

1. Bragdon CR, Doerner M, Martell J, Jarrett B, Palm H, Malchau H. The 2012 John Charnley Award: Clinical Multicenter Studies of the Wear Performance of Highly Crosslinked Remelted Polyethylene in THA. Clin Orthop Relat Res. 2013 Feb; 471(2):393-402.

This paper, which received the American Hip Society Award in 2012, presented the longest-term clinical outcomes and radiographic wear results of total hip replacement patients having highly crosslinked and melted polyethylene as a bearing surface. This multi-center study of in vivo results of 7-12 years after surgery, being the largest cohort study reported on this topic, and with a range of femoral head sizes, confirmed that the early low wear rates of this new material that was developed at MGH continues into the mid-term follow-up period. In contrast to the high incidence of peri-prosthetic osteolysis reported in previous series with non-cross-linked polyethylene, (up to 37% at 8-10 years follow-up), no incidence of osteolysis was reported in this group of patients.

2. Oral E, Neils AL, Rowell SL, Lozynsky AJ, Muratoglu OK. Increasing irradiation temperature maximizes vitamin E grafting and wear resistance of ultrahigh molecular weight polyethylene. J Biomed Mater Res B Appl Biomater. 2013 Apr; 101(3):436-40.

3. Yang W, Liu X, Choy E, Mankin H, Hornicek FJ, Duan Z. Targeting hedgehog-GLI-2 pathway in osteosarcoma. J Orthop Res. 2013 Mar;31(3):502-9. doi: 10.1002/jor.22230. Epub 2012 Sep 11.

4. Menendez ME, Bot AG, Hageman MG, Neuhaus V, Mudgal CS, Ring D. Computerized adaptive testing of psychological factors: relation to upper-extremity disability. J Bone Joint Surg Am. 2013 Oct 16;95(20):e149.

Otolaryngology

Joseph B. Nadol, Jr., MD

1. "Notch inhibition induces cochlear hair cell regeneration and recovery of hearing after acoustic trauma." Mizutari K, Fujioka M, Hosoya M, Bramhall N, Okano HJ, Okano H, Edge AS. Neuron. 2013 Jan 9;77(1):58-69. PMID: 23312516

Researchers demonstrate for the first time that hair cells can be regenerated in an adult mammalian ear by using a drug to stimulate resident cells to become new hair cells, resulting in partial recovery of hearing in mouse ears damaged by noise trauma. This finding holds great potential for future therapeutic application that may someday reverse deafness in humans.

2. "High intratumor genetic heterogeneity is related to worse outcome in patients with head and neck squamous cell carcinoma." Mroz EA, Tward AD, Pickering CR, Myers JN, Ferris RL, Rocco JW. Cancer. 2013 Aug 15;119(16):3034-42. PMID: 23696076

Researchers demonstrate a new measure of heterogeneity of cells within a tumor that better predicts survival than most traditional risk factors for patients with squamous cell carcinoma of the head and neck. These findings will eventually allow better matching of treatments to individual patients based on this characteristic of their tumors.

3. "Efferent feedback minimizes cochlear neuropathy from moderate noise exposure." Maison SF, Usubuchi H, Liberman MC. J Neurosci. 2013 Mar 27;33(13):5542-52 PMID: 23536069

Researchers found that moderate noise exposure leads to cochlear neuropathy (loss of auditory nerve fibers), which causes difficulty hearing in noisy environments. These findings could eventually lead to screening tests to determine who is most susceptible to hearing loss.

4. "Brief hearing loss disrupts binaural integration during two early critical periods of auditory cortex development." Polley DB, Thompson JH, Guo W. Nat Commun. 2013 Sep 30;4:2547. PMID: 24077484

Researchers found that by inducing brief, reversible hearing loss at key milestones in cortical development, two critical periods after hearing onset regulate the maturations of coordinated binaural sound representations. Their work could eventually lead to a better understanding of which periods in a child's development are most crucial to maintain hearing.

Pathology

David N. Louis, MD

1. Zhu J, Adli M, Zou JY, Verstappen G, Coyne M, Zhang X, Durham T, Miri M, Deshpande V, De Jager PL, Bennett DA, Houmard JA, Muoio DM, Onder TT, Camahort R, Cowan CA, Meissner A, Epstein CB, Shoresh N, Bernstein BE. Genome-wide chromatin state transitions associated with developmental and environmental cues. Cell. 2013 Jan 31;152(3):642-54.

This paper presents a global characterization of the interplay between activating and repressive chromatin structures across different developmental stages and environments. *In vitro* culture is shown to trigger the *de novo* establishment of heterochromatin domains that hinder epigenetic reprogramming during induced pluripotency. The paper also presents a systematic resource of enhancer activity in diverse human tissues – an important resource for human genetics because many disease-associated SNPs appear to act by altering the regulation of cell type-specific enhancers.

2. Wang Y, Velho S, Vakiani E, Peng S, Bass AJ, Chu GC, Gierut J, Bugni JM, Der CJ, Philips M, Solit DB, Haigis KM. Mutant N-RAS protects colorectal cancer cells from stress-induced apoptosis and contributes to cancer development and progression. *Cancer Discov*. 2013 Mar;3(3):294-307.

This study sought to determine the clinically/physiologically relevant conditions under which mutant N-Ras promotes colorectal cancer (CRC) progression and found that mutant N-Ras promoted CRC specifically in the context of inflammation. Mechanistically, N-Ras simultaneously activates canonical MAPK signaling and STAT3 and this work demonstrated for the first time that N-Ras mutation is associated with reduced overall survival in patients with CRC. Studies using a mouse model revealed that cancers expressing mutant N-Ras, unlike those expressing mutant K-Ras, are sensitive to MEK inhibition as a single agent therapy.

3. Chen EY, Dobrinski KP, Brown KH, Clagg R, Edelman E, Ignatius MS, Chen JY, Brockmann J, Nielsen GP, Ramaswamy S, Keller C, Lee C, Langenau DM. Cross-species array comparative genomic hybridization identifies novel oncogenic events in zebrafish and human embryonal rhabdomyosarcoma. *PLoS Genet*. 2013 Aug;9(8):e1003727.

Human cancer genomes are highly complex, making it challenging to identify specific drivers of cancer growth, progression, and tumor maintenance. To bypass this obstacle, this study applied array comparative genomic hybridization (array CGH) to zebrafish embryonal rhabdomyosaroma (ERMS) and utilized cross-species comparison to rapidly identify genomic copy number aberrations and novel candidate oncogenes in human disease. Functional analysis showed important roles for five genes in maintenance of ERMS.

4. Maeder ML, Angstman JF, Richardson ME, Linder SJ, Cascio VM, Tsai SQ, Ho QH, Sander JD, Reyon D, Bernstein BE, Costello JF, Wilkinson MF, Joung JK. Targeted DNA demethylation and activation of endogenous genes using programmable TALE-TET1 fusion proteins. *Nat Biotechnol*. 2013 Dec;31(12):1137-42.

Genome-wide studies have established that cell type-specific patterns of DNA methylation are important for regulating gene expression in both normal development and disease. However, determining the functional significance of specific methylation events has remained challenging, due to the lack of methods for removing such modifications in a targeted manner. This paper described a novel platform for targeted demethylation of any DNA sequence of interest using fusion proteins of customizable transcription activator-like effector (TALE) DNA-binding domains and the TET1 hydroxylase catalytic domain and provided the first direct demonstration that targeted CpG demethylation can lead to substantial increases in endogenous human gene expression. These results define a broadly useful technology platform that can be customized to study the functional significance of DNA methylation marks and for developing targeted therapeutics to re-activate gene expression.

Pediatrics

Ronald E. Kleinman, MD

1.Ganguli K, Meng D, Rautava S, et al. Probiotics Prevent Necrotizing Enterocolitis by Modulating Enterocyte Genes that Regulate Innate Immune-Mediated Inflammation. Am J Physiol Gastrointest Liver Physiol 304: G132–G141, 2013

This work provides the first evidence for a mechanism by which soluble products of probiotic organisms provide cytoprotection in the gastrointestinal tract of humans. In this study we demonstrated that secretions of Bifidobaterium infantis and Lactobacillus acidophilis attenuate the inflammatory response in immature human enterocytes , immature human intestinal xenografts and primary enterocyte cultures of NEC tissue (NEC-IEC), by inducing a maturation of innate immune response genes. Additionally, the secretions of B.infantis, grown individually, are as effective in attenuating intestinal inflammation in immature enterocyte cell culture models as the secretions isolated from B.infantis and L.acidophilus grown together, suggesting that L.acidophilus secretions may protect the immature intestine in ways other than via inflammatory pathways.

2. Khan LA, Zhang H, Abraham N, Sun L, Fleming JT, Buechner M, Hall DH, Göbel V. Intracellular lumen extension requires ERM-1-dependent apical membrane expansion and AQP-8-mediated flux. Nat Cell Biol 2013;15(2):143-156.

This work provides first evidence for water-channel-regulated hydrostatic pressure as a direct morphogenetic force in metazoan tubulogenesis and reveals a novel role for aquaporins in development. The C. elegans single cell excretory canal is a unique in vivo model system to investigate this and the findings have immediate implications for our understanding of vasculogenesis and the development and function of epithelia with secretory and canalicular endomembranes (for instance renal and gastric lumen epithelia), and their respective pathologies.

3. Taveras EM, Gillman MW, Kleinman KP, Rich-Edwards JW, Rifas-Shiman SL. Reducing Racial/ Ethnic Disparities in Childhood Obesity: The Role of Early Life Risk Factors. JAMA Pediatr. 2013:1-7. PMID: 23733179

With funding from NIMHD (R01MD003963; Taveras PI) we have studied the early origins of racial/ ethnic disparities in childhood obesity using data from a pre-birth cohort of mother-infant pairs. Our study in 2010 found substantial racial/ethnic differences in many early life risk factors for obesity not explained by maternal obesity or socioeconomic factors. In this follow up study of the children at mid-childhood, we also found that adjustment for these early life risk factors almost entirely explained the substantial disparities in obesity prevalence observed among white, black, and Hispanic children. Our findings indicate that racial/ethnic disparities in childhood obesity are determined by factors operating in infancy and early childhood.

4.Navaratna D, Fan X, Leung W, Lok J, Guo S, Xing C, Wang X, Lo EH. Cerebrovascular degradation of TRKB by MMP9 in the diabetic brain. J Clin Invest. 2013 Aug 1;123(8):3373-7. doi: 10.1172/JCI65767. Epub 2013 Jul 15

Diabetes elevates the risk for neurological diseases, but little is known about the underlying mechanisms. This study provides the first insights into the mechanisms by which diabetes increases risk for injury to the central nervous system. Brain-derived neurotrophic factor (BDNF) is secreted by microvascular endothelial cells (ECs) in the brain, functioning as a neuroprotectant through the activation of the neurotrophic tyrosine kinase receptor TRKB. In a rat model of streptozotocin-induced hyperglycemia, we found that endothelial activation of MMP9 altered TRKB-dependent trophic pathways by degrading TRKB in neurons. Our findings demonstrate that neuronal TRKB trophic function is ablated by MMP9-mediated degradation in the diabetic brain, disrupting cerebrovascular trophic coupling and leaving the brain vulnerable to injury.

Key Achievements/Publication Highlights for 2013

Psychiatry

Jerrold F. Rosenbaum, MD

1. Castro VM, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, Erb JL, Churchill SE, Kohane IS, Iosifescu DV, Smoller JW, Perlis RH. QT interval and antidepressant use: a cross sectional study of electronic health records. BMJ. 2013 Jan 29;346:f288. doi: 10.1136/bmj.f288.

This study aimed at quantifying the impact of citalopram and other selective serotonin reuptake inhibitors on corrected QT interval (QTc), a marker of risk for ventricular arrhythmia, in a large and diverse clinical population. A cross sectional study using electrocardiographic, prescribing, and clinical data from electronic health records explored the relation between antidepressant dose and QTc. Methadone, an opioid known to prolong QT, was included to demonstrate assay sensitivity. 38,397 adult patients with an electrocardiogram recorded after prescription of antidepressant or methadone between February 1990 and August 2011 were included in the analyses, which examined the relation between antidepressant dose and QTc interval in linear regression, adjusting for potential clinical and demographic confounding variables. For a subset of patients, change in QTc after drug dose was also examined. Dose-response association with QTc prolongation was identified for citalopram (adjusted beta 0.10 (SE 0.04), P<0.01), escitalopram (adjusted beta 0.58 (0.15), P<0.001), and amitriptyline (adjusted beta 0.11 (0.03), P<0.001), but not for other antidepressants examined. An association with QTc shortening was identified for bupropion (adjusted beta 0.02 (0.01) P<0.05). Within-subject paired observations supported the QTc prolonging effect of citalopram (10 mg to 20 mg, mean QTc increase 7.8 (SE 3.6) ms, adjusted P<0.05; and 20 mg to 40 mg, mean QTc increase 10.3 (4.0) ms, adjusted P<0.01). This study confirmed a modest prolongation of QT interval with citalopram, and identified additional antidepressants with similar observed risk. Pharmacovigilance studies using electronic health record data may be a useful method of identifying potential risk associated with treatments.

2. Cross-Disorder Group of the Psychiatric GWAS Consortium.* Genome-wide analysis identifies loci with shared effects on five major psychiatric disorders. *The Lancet,* 2013 Apr 20;381(9875):1371-9. *Jordan Smoller, MD, Sc.D. is Corresponding author and chair of the Writing Group.

This study is the largest genome-wide analysis of psychiatric disorders to date (total N = 61,220) and identified 4 loci that confer risk across five child- and adult-onset disorders included in the Psychiatric GWAS Consortium (PGC): autism spectrum disorder, ADHD, bipolar disorder, major depressive disorder and schizophrenia. In addition, aggregate polygene risk score analysis demonstrated cross-disorder sharing of common genetic risk factors. Using pathway analyses, we identified a specific biological pathway—voltage-gated calcium channel signaling—as contributing to the pathogenesis of multiple psychiatric disorders, supporting the value of pursuing this pathway as a therapeutic target for psychiatric disease. The study thus provides the first genome-wide evidence that individual and aggregate molecular genetic risk factors are shared across five psychiatric disorders that are treated as distinct categories in clinical practice. As such, it provides evidence relevant to psychiatry's goal of moving beyond descriptive syndromes toward an etiologically-informed nosology.

3. Lau, E. F., Gramfort, A., Hämäläinen, M. S., & Kuperberg, G. R. Automatic semantic facilitation in anterior temporal cortex revealed through multimodal neuroimaging. The Journal of Neuroscience. 2013; 33(43): 17174-17181.

This study is the first to use three multimodal neuroimaging techniques—electroencephalography (EEG), magnetoencephalography (MEG), and functional magnetic resonance imaging (fMRI)—to show when and where the brain automatically uses context to extract meaning from words: within the left anterior superior temporal cortex within 300ms after word onset. The findings have widespread implications for understanding how the extraction of meaning from language can potentially break down in a number of developmental and acquired neuropsychiatric disorders, including schizophrenia, autism spectrum disorders, dyslexia, stroke and dementias.

4. Roffman JL, Lamberti JS, Achtyes ES, Galendez GC, Raeke LH, Silverstein NJ, Smoller JW, Hill M, Goff DC. Randomized multicenter investigation of folate plus B12 supplementation in schizophrenia. JAMA Psychiatry 70:481-489, 2013.

This multi-site, randomized, placebo-controlled clinical trial of folic acid and vitamin B12 supplementation in schizophrenia demonstrated promise for treating negative symptoms, a debilitating aspect of the disorder that does not respond to conventional antipsychotic medications. Treatment response varied based on the presence of functional genetic variants in the folate metabolic pathway, a finding with implications for personalized medicine. A related MRI study demonstrated that active treatment improved prefrontal function and resulted in increased cortical thickness. This work was honored with the hospital-wide Outcomes Research Award at MGH Clinical Research Day on October 3, 2013.

Radiation Oncology

Jay Loeffler, MD

1) M Snuderl et al. Targeting placental growth factor/neuropilin 1 pathway inhibits growth and spread of medulloblastoma. *Cell* 152: 1065–1076 (2013).

Medulloblastoma is the most common malignant brain tumor of childhood. Surgery and chemoradiation are curative in some but not all cases, and are associated with devastating treatment-related sequelae. This landmark study revealed that targeting tumor–stromal interactions mediated by PlGF/Neuropilin 1 pathway could block tumor growth and progression in multiple medulloblastoma subtypes. This discovery may revolutionize medulloblastoma therapy by integrating anti-PlGF therapy in existing treatment protocols. This approach will be tested later this year in a planned phase II trial as part of a collaborative effort between the MGH Hospital for Children and other children hospitals.

This paper was highlighted in Nature Reviews Cancer, Cancer Discovery and New England Journal of Medicine.

2) R Samuel et al. Generation of functionally competent and durable engineered blood vessels from human induced pluripotent stem cells. *PNAS* 110:12774-9 (2013).

This is the first demonstration of engineering functional blood vessels from human iPS cells that were durable for more than 9 months. This article was highlighted by the NIH Director, the New England Journal of Medicine, and BBC News.

3) KE Emblem, et al. Vascular architecture imaging identifies patient responders to anti-angiogenic therapy. *Nature Medicine* 19:1178-1183 (2013).

This landmark study revealed the first imaging biomarker that can identify brain tumor patients who would benefit from antiangiogenic therapy. This article was highlighted by Nature Reviews Cancer and Nature Reviews Clinical Oncology.

4) V Chauhan, et al. Angiotensin inhibition enhances drug delivery and potentiates chemotherapy by decompressing tumor blood vessels. *Nature Communications* 4: 2516 (2013).

This landmark study revealed that widely prescribed angiotensin blockers are capable of "normalizing" the extracellular matrix, opening compressed tumor vessels, and improving the delivery and efficacy of molecular and nanomedicine. This finding offers new hope for improving treatment in highly fibrotic tumors that have dismal prognosis and has led to a clinical trial at MGH on losartan and chemotherapy in pancreatic ductal adenocarcinomas (NCT01821729). A patent based on this finding was licensed by a start-up company (XTuit).

Ragon Institute of MGH, MIT & Harvard

Bruce Walker, MD, Director

1. Ragon Institute Kendall Square Opening complete with facilities for BLS3 work on HIV and TB

The primary goal of the Ragon Institute is to employ collaborative, cross-disciplinary, and transformative science to develop an effective HIV vaccine, with a long-term vision to harness the immune system to prevent and cure human disease. We envision a future where physical scientists, engineers, basic immunologists, vaccinologists, and clinicians work together to cure, manage, and prevent infectious and inflammatory diseases, cancers and autoimmune diseases. In keeping with this vision, we have established a new physical facility in Kendall Square complete with the capacity for BSL3 work on HIV and TB. Providing an integrated research portfolio in the Boston area is of great importance to developing new approaches to HIV-TB clinical care and to understanding immunoregulation of HIV-TB co-infection.

2. Ranasinghe S, Cutler S, Davis I, Lu R, Soghoian DZ, Qi Y, Sidney J, Kranias G, Flanders MD, Lindqvist M, Kuhl B, Alter G, Deeks SG, Walker BD, Gao X, Sette A, Carrington M, Streeck H. Association of HLA-DRB1-restricted CD4$^+$ T cell responses with HIV immune control. Nat Med. 2013 Jul; 19(7):930-3.

Given the poorly defined role of HLA class II-restricted CD4+ T cell responses to HIV immune control we found distinct stratifications in the effect of HLA-DRB1 alleles on HIV viremia, with HLA-DRB1*15:02 significantly associated with low viremia and HLA-DRB1*03:01 significantly associated with high viremia. Notably, a subgroup of HLA-DRB1 variants linked with low viremia showed the ability to promiscuously present a larger breadth of peptides with lower functional avidity when compared to HLA-DRB1 variants linked with high viremia. Our data provide systematic evidence that specific HLA-DRB1 alleles exhibit a considerable impact on the control of HIV replication, an effect that seems to be mediated primarily by the protein specificity of CD4+ T cell responses to HIV Gag and Nef.

3. Ackerman ME, Crispin M, Yu X, Baruah K, Boesch AW, Harvey DJ, Dugast AS, Heizen EL, Ercan A, Choi I, Streeck H, Nigrovic PA, Bailey-Kellogg C, Scanlan C, Alter G. Natural variation in Fc glycosylation of HIV-specific antibodies impacts antiviral activity. J Clin Invest. 2013 May 1;123(5):2183-92.

While the induction of a neutralizing antibody response against HIV remains a daunting goal, data from both natural infection and vaccine-induced immune responses suggest that it may be possible to induce antibodies with enhanced Fc effector activity and improved antiviral control via vaccination. In aiming to define the natural glycoforms associated with robust Fc-mediated antiviral activity we demonstrate that spontaneous control of HIV and improved antiviral activity are associated with a dramatic shift in the global antibody-glycosylation profile toward agalactosylated glycoforms. These glycoforms were associated with enhanced Fc-mediated reduction of viral replication and enhanced Fc receptor binding and suggest that B cell programs tune antibody glycosylation actively in an antigen-specific manner, potentially contributing to antiviral control during HIV infection.

4. Li C, Toth I, Zur Wiesch J, Pereyra F, Rychert J, Rosenberg ES, van Lunzen J, Lichterfeld M, Yu XG. Functional characterization of HLA-G+ regulatory T cells in HIV-1 infection. Plos Pathogens 2013 Jan;9(1):e1003140.

Regulatory T cells (Tregs) represent a specialized subpopulation of T lymphocytes that may modulate spontaneous HIV-1 disease progression by suppressing immune activation or inhibiting antiviral T cell immune responses. Here, we show that non-classical HLA-G-expressing CD4 Treg are highly susceptible to HIV-1 infection and significantly reduced in persons with progressive HIV-1 disease courses, with the proportion of HLA-G$^+$ CD4 and CD8 T cells being inversely correlated to markers

of HIV-1 associated immune activation. Mechanistically, this corresponded to an increased ability of HLA-G$^+$ Treg to reduce bystander immune activation suggesting that the loss of these cells during advanced HIV-1 infection may contribute to immune dysregulation and HIV-1 disease progression.

Surgery

Keith D. Lillemoe, MD

Burns and Surgery, Science, and Bioengineering

Ronald G. Tompkins, MD, ScD

1. Division of Surgery, Science, and Bioengineering

The Department of Surgery's newly formed Division of Surgery, Science, and Bioengineering is a dynamic enterprise that promotes the development of new approaches to healthcare delivery and personalized medicine, minimally invasive therapies, as well as a myriad of new technologies such as re-engineered organs, smart nano-pharmaceuticals and nanodiagnostics, and living cell-based microfabricated devices for diagnostics, therapeutics, high-throughput drug screening, and basic and applied biomedical investigation. It is this type of far-reaching research and its translation that will potentiate our basic science discoveries, bringing them to their full potential. Thus, the new Division provides a unique and robust environment that pursues excellence, embraces risk, and strives to have global impact in an unfettered fashion enabling research and development initiatives that can be applied to meet the nation's major health science and technology challenges.

2. Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker HV, Xu W, Richards DR, McDonald-Smith GP, Gao H, Hennessy L, Finnerty CC, López CM, Honari S, Moore EE, Minei JP, Cuschieri J, Bankey PE, Johnson JL, Sperry J, Nathens AB, Billiar TR, West MA, Jeschke MG, Klein MB, Gamelli RL, Gibran NS, Brownstein BH, Miller-Graziano C, Calvano SE, Mason PH, Cobb JP, Rahme LG, Lowry SF, Maier RV, Moldawer LL, Herndon DN, Davis RW, Xiao W, Tompkins RG; Inflammation and Host Response to Injury, Large Scale Collaborative Research Program. Genomic responses in mouse models poorly mimic human inflammatory diseases. Proc Natl Acad Sci U S A. 2013 Feb 26;110(9):3507-12. Epub 2013 Feb 11. PMCID: PMC3587220

The results presented in this article demonstrate a lack of correlation between human inflammatory diseases and the mouse models used ultimately to create drugs to treat these diseases. The publication provides an extensive database and analysis to reconsider the limitations of murine models in human disease and calls into question the limitation of relying upon murine models to mimic far more complex human diseases. The article suggests "humanizing" mouse models and more reliance on actual patient data to study human disease in humans.

3. Ozkumur E, Shah AM, Ciciliano JC, Emmink BL, Miyamoto DT, Brachtel E, Yu M, Chen PI, Morgan B, Trautwein J, Kimura A, Sengupta S, Stott SL, Karabacak NM, Barber TA, Walsh JR, Smith K, Spuhler PS, Sullivan JP, Lee RJ, Ting DT, Luo X, Shaw AT, Bardia A, Sequist LV, Louis DN, Maheswaran S, Kapur R, Haber DA, Toner M. Inertial focusing for tumor antigen-dependent and -independent sorting of rare circulating tumor cells. Sci Transl Med. 2013 Apr 3;5(179):179ra47. PMCID: PMC3760275.

The rarity of circulating tumor cells (CTCs) in the blood of cancer patients has required development of highly specialized technologies for their isolation. CTC isolation approaches have traditionally involved multiple batch processing steps, resulting in substantial loss of CTCs. This article describes a microfluidic cell capture platform (CTC-iChip) that is capable of sorting rare CTCs from whole blood at 10 million cells/second.

4. Saeidi N, Meoli L, Nestoridi E, Gupta NK, Kvas S, Kucharczyk J, Bonab AA, Fischman AJ, Yarmush ML, Stylopoulos N. Reprogramming of intestinal glucose metabolism and glycemic control in rats after

gastric bypass. Science. 2013 Jul 26;341(6144):406-10. PubMed PMID: 23888041. PMCID: in process

A team of researchers from the Massachusetts General Hospital Center for Engineering in Medicine (MGH-CEM), Boston Children's Hospital, and Shiners Hospital for Children has identified a novel mechanism for resolution of diabetes following weight loss surgery. One of the main and unexpected finding in the study was that the intestine undergoes a profound metabolic and physiological remodeling that leads to extensive cellular proliferation requiring significant amounts of glucose to fuel these events. These findings are expected to provide novel targets for development of less-invasive anti-diabetic therapies.

Cardiac Surgery

Thoralf M. Sundt, MD

1. Delayed Tolerance in Non-Human Primate Heart Allograft Recipients

We have developed the first successful protocol to induce delayed tolerance in nonhuman primate heart allograft recipient using bone marrow and donor kidney cotransplantation. By successfully delaying recipient conditioning and bone marrow transplantation until four months after organ transplantation, we have demonstrated that tolerance can be extended to recipients of cadaveric heart allografts. Modifications of this protocol could be applied to human heart transplant recipients.

2. Booher AM. Isselbacher EM. Nienaber CA. Trimarchi S. Evangelista A. Montgomery DG. Froehlich JB. Ehrlich MP. Oh JK. Januzzi JL. O'Gara P. Sundt TM. Harris KM. Bossone E. Pyeritz RE. Eagle KA. IRAD Investigators. The IRAD classification system for characterizing survival after aortic dissection. American Journal of Medicine. 126(8):730.e19-24, 2013 Aug. PMC ID: 23885677

The classification of aortic dissection into acute versus chronic is based on survival estimates of patients treated decades before modern diagnostic and treatment modalities were available. Based on data from the International Registry of Aortic Dissection (IRAD), we developed a new classification of aortic dissection which may provide clinicians with a more precise method of characterizing the interaction of time, dissection location, and treatment type with survival.

3. Di Eusanio M. Patel HJ. Nienaber CA. Montgomery DM. Korach A. Sundt TM. Devincentiis C. Voehringer M. Peterson MD. Myrmel T. Folesani G. Larsen M. Desai ND. Bavaria JE. Appoo JJ. Kieser TM. Fattori R. Eagle K. Di Bartolomeo R. Trimarchi S. Patients with type A acute aortic dissection presenting with major brain injury: should we operate on them? Journal of Thoracic & Cardiovascular Surgery. 145(3 Suppl):S213-21.e1, 2013 Mar. PMC ID: 23410778

The management strategy remains controversial for patients presenting with type A acute aortic dissection with cerebrovascular accident or coma. Using observational data from the International Registry for Acute Dissection, we found that although brain injury at presentation adversely affects hospital survival of patients with type A acute aortic dissection, the patients selected to undergo surgery demonstrated improved late survival and frequent reversal of neurologic deficits.

4. Madariaga ML, Michel SG, Tasaki M, Villani V, La Muraglia II GM, Sihag S, Gottschall J, Farkash EA, Shimizu A, Allan JS, Sachs DH, Yamada K, Madsen JC. Induction of Cardiac Allograft Tolerance Across a Full MHC barrier in Miniature Swine by Donor Kidney Co-transplantation. American Journal of Transplantation 2013:10:2558-66.

We have tested the effect of cotransplanting an allogeneic heart and kidney from the same MHC-mismatched donor and demonstrated that kidney-induced cardiac allograft tolerance (KICAT) can be observed across the clinically relevant full MHC histocompatibility barrier. Elucidating the renal element(s) responsible for KICAT could provide mechanistic information relevant to the induction of tolerance in recipients of isolated heart allografts as well as other tolerance-resistant organs.

Center for Laryngeal Surgery and Voice Rehabilitation

Steven M. Zeitels, MD, Chief

Robert E. Hillman, PhD, Co-Director/Research Director

1. John C. Wain and Steven M. Zeitels: Aortic Homograft Reconstruction of Laryngotracheal Stenosis

Recently, we have employed cadaveric cryopreserved homograft aorta (CCHA) to successfully treat laryngotracheal stenosis in a series of 4 patients. This demonstrated that transplanting human cadaveric cryopreserved homograft aorta provides the airway surgeon with a reliable and conceptually-novel reconstructive option for patients with complex laryngotracheal stenosis. The success in this pilot series allowed for optimal voice and aerodigestive function. CCHA retains a number of assets as a laryngotracheal airway substrate including the: 1.mechanical properties of the soft-tissue graft as a scaffold, 2. lack of graft immunogenicity, 3. practical incorporation of the aortic homograft into local soft tissues, and 4. ease of surgical handling of the graft.

2. A.D. Fiedman, R.E. Hillman, T. Landau-Zemer, J.A. Burns, S.M. Zeitels (2013). Voice Outcomes for Photoangiolytic KTP Laser Treatment of Early Glottic Cancer. Annals of Otology, Rhinology & Laryngology 122.

Surgery and radiotherapy routinely provide high cure rates in treating early glottic cancer. Therefore, key metrics for success are optimal voice outcome and preservation of future cancer treatment options. In this study, pretreatment and posttreatment voice outcome data were obtained for 92 patients (64 with T1 cancer and 28 with T2 cancer) who underwent 532-nm KTP laser treatment of early glottic cancer. Results demonstrated that KTP laser treatment significantly improved postoperative vocal function in patients with early glottic cancer. Furthermore, radiotherapy was preserved as an oncological treatment option.

3. D. D. Mehta, M. Zañartu, S. W. Feng, H. A. Cheyne II, R. E. Hillman. Mobile voice health monitoring using a wearable accelerometer sensor and a smartphone platform. IEEE Transactions on Biomedical Engineering, 59(11), 3090–3096.

This paper reports on the NIH-funded development of a new, versatile, and cost-effective clinical tool for unobtrusive ambulatory monitoring of vocal function that utilizes a neck-placed miniature accelerometer and Smartphone (with custom-designed app) to collect data on daily voice use for up to an entire week. This new technology is expected to improve the clinical assessment of many common voice disorders that are believed to be caused by vocal abuse/misuse because current assessment procedures rely on patient self-report that is subjective and notoriously unreliable. The new system was also featured in an article published in the fall 2013 edition of NIH Medline Plus.

4. M. Zañartu, J. C. Ho, D. D. Mehta, R. E. Hillman, and G. R. Wodicka, (2013) "Subglottal impedance-based inverse filtering of speech sounds using neck surface acceleration", IEEE Trans. Audio Speech Lang. Proc., 21(9), pp. 1929-1939. DOI: 10.1109/TASL.2013.2263138 link.

This paper describes a model-based inverse filtering approach for the accurate, non-invasive estimation of the aerodynamic source of sound that is generated by the larynx during voice production. The approach, referred to as subglottal impedance-based inverse filtering (IBIF), takes as input the signal from a lightweight accelerometer placed on the skin over the extrathoracic trachea and yields estimates of the modulated airflow that is produces sound as the vocal cords vibrate during voice production. The proposed method further advances the use of the neck surface acceleration signal for ambulatory assessment of vocal function and for other ambulatory applications in speech communication.

Key Achievements/Publication Highlights for 2013

Codman Center for Clinical Effectiveness

Matthew Hutter, MD, Director

David Shahian, MD, Associate Director

1. Carroll JD, Edwards FH, Marinac-Dabic D, Brindis RG, Grover FL, Peterson ED, Tuzcu EM, Shahian DM, Rumsfeld JS, Shewan CM, Hewitt K, Holmes DR, Jr., Mack MJ. The STS-ACC transcatheter valve therapy national registry: a new partnership and infrastructure for the introduction and surveillance of medical devices and therapies. J Am Coll Cardiol 2013; 62:1026-1034.

This paper describes a completely new paradigm for FDA surveillance of medical devices using registries developed by professional societies rather than industry. It is hoped that the concepts described in this paper can be used in a broad array of applications under FDA jurisdiction.

2. Jacobs JP, O'Brien SM, Shahian DM, Edwards FH, Badhwar V, Dokholyan RS, Sanchez JA, Morales DL, Prager RL, Wright CD, Puskas JD, Gammie JS, Haan CK, George KM, Sheng S, Peterson ED, Shewan CM, Han JM, Bongiorno PA, Yohe C, Williams WG, Mayer JE, Grover FL. Successful linking of the Society of Thoracic Surgeons Database to Social Security data to examine the accuracy of Society of Thoracic Surgeons mortality data. J Thorac Cardiovasc Surg 2013; 145:976-983.

This paper addresses a major limitation of most current clinical data registries--they typically collect only in-hospital or 30-day outcomes. As early outcomes improve and lengths of stay decrease, it will be important to focus more on long term outcomes such as survival. By linking with various governmental and commercial claims registries, this can be done efficiently and at much lower cost. However, privacy concerns must be recognized, as these linkages do require the use of identifiers at some stage.

3. Shahian DM, He X, Jacobs JP, Rankin JS, Peterson ED, Welke KF, Filardo G, Shewan CM, O'Brien SM. Issues in quality measurement: target population, risk adjustment, and ratings. Ann Thorac Surg 2013; 96:718-726.

Healthcare report cards abound, but many are methodologically flawed. This paper describes three fundamental yet often neglected issues in provider profiling. Using real world data, it illustrates the implications of failing to correctly apply basic profiling principles.

4. Loehrer AP, Song Z, Auchincloss HG, Hutter MM. Massachusetts health care reform and reduced racial disparities in minimally invasive surgery. JAMA Surg 2013;148(12):1116-1122.

The 2006 Massachusetts health care reform expanded insurance to over 97% of residents and served as a model for the federal Affordable Care Act. Little is known as to how expanding health insurance coverage impacts well documented disparities in health care, including the utilization of minimally invasive surgical approaches for appendectomy and cholecystectomy. Authors examined Massachusetts and six control states, to evaluate for changes in the probability of receiving laparoscopic surgery. Non-white patients in Massachusetts and control states were significantly less likely to receive laparoscopic surgery prior to the 2006 reform. After reform, racial disparities in minimally invasive surgery decreased and were no longer significant in Massachusetts while disparities persisted in control states. Our findings provide optimistic evidence for the potential impact of expanded insurance coverage on racial disparities in surgical care delivery.

General/GI Surgery

David Rattner, MD

1. Sahora K, Mino-Kenudson M, Brugge W, Thayer SP, Ferrone CR, Sahani D, Pitman MB, Warshaw AL, Lillemoe KD, Fernández-del Castillo C. Branch duct intraductal papillary mucinous neoplasms: does cyst size change the tip of the scale? A critical analysis of the revised international consensus guidelines in a large single-institutional series. Annals of Surgery 2013; 258:466-75.

This study represents the largest single-institution cohort of branch duct IPMNs, which are potential precursors of pancreatic cancer, and directly addresses the controversy regarding safety of non-operative management. It shows this is safe.

2. Kaliannan K, Hamarneh SR, Economopoulos KP, Nasrin Alam S, Moaven O, Patel P, Malo NS, Ray M, Abtahi SM, Muhammad N, Raychowdhury A, Teshager A. Mohamed MM, Moss AK, Ahmed R, Hakimian S, Narisawa S, Millan JL, Hohmann E, Warren HS, Bhan AK, Malo MS, Hodin RA. Intestinal alkaline phosphatase prevents metabolic syndrome in mice. Proc Natl Acad Sci USA, 2013 Apr 23;110(17):7003-8.

This study describes a novel discovery in which a gut enzyme supplement is used to prevent the metabolic syndrome, including obesity, diabetes, fatty liver, etc. This is the first time that inflammatory factors in the intestinal tract are targeted to prevent the systemic problem of the metabolic syndrome. The work represents a paradigm shift in regard to the way in which this disease can be treated and if successfully translated to the bedside could improve the lives of millions of people.

3. Sylla P, Bordeianou LG, Berger D, Han KS, Lauwers GY, Sahani DV, Sbeih MA, Lacy AM, Rattner DW. A pilot study of natural orifice transanal endoscopic total mesorectal excision with laparoscopic assistance for rectal cancer. 2013. Surg Endosc, 27(9):3396-405.

In 2013, we published the results of our pilot study demonstrating the preliminary safety of efficacy of NOTES transanal total mesorectal excision (TME) with laparoscopic assistance in the management of resectable node-negative rectal cancer in 5 eligible patients. This pilot study was supported by a CIMIT grant awarded to Dr. David Rattner in 2008, as well as from the MGH Cancer Center Thematic Priority Grant awarded to Dr. Sylla in 2009. This trial is the culmination of experimental work conducted by our MGH NOTES team since 2007.

Laboratory for Tissue Engineering and Organ Fabrication

Joseph Vacanti, MD

1. Bichara DA, Pomerantseva I, Zhao X, Zhou L, Kulig KM, Tseng A, Kimura AM, Johnson MA, Vacanti JP, Randolph MA, Sundback CA. Successful Creation of Tissue-Engineered Autologous Auricular Cartilage in an Immunocompetent Large Animal Model. Tissue Eng Part A. 2013 Oct 4. [Epub ahead of print]

The objectives of this study were to demonstrate engineered autologous auricular cartilage in the immunologically aggressive subcutaneous environment of an immunocompetent animal model, and to determine the impact of in vitro culture duration of chondrocyte-seeded constructs on the quality of neocartilage maturation in vivo. The quality of cartilage engineered in sheep decreased with prolonged in vitro culture time. Superior cartilage formation was demonstrated after 2 weeks of in vitro culture; the neocartilage quality improved with increased implantation time. Autologous auricular cartilage was successfully engineered in the subcutaneous environment of an ovine model using expanded chondrocytes seeded on a fibrous collagen scaffold after a 2-week in vitro culture period.

2. Cervantes TM, Bassett EK, Tseng A, Kimura A, Roscioli N, Randolph MA, Vacanti JP, Hadlock TA, Gupta R, Pomerantseva I, Sundback CA.Design of composite scaffolds and three-dimensional shape analysis for tissue-engineered ear. J R Soc Interface. 2013 Jul 31;10(87):20130413.

We have previously demonstrated that a titanium wire framework within a composite collagen ear-shaped scaffold helped to maintain the gross dimensions of the engineered ear after implantation, resisting the deformation forces encountered during neocartilage maturation and wound healing. The ear geometry was redesigned to achieve a more accurate aesthetic result when implanted subcutaneously in a nude rat model. A non-invasive method was developed to assess size and shape changes of the engineered ear in three dimensions. These quantitative shape analysis results have identified opportunities to improve shape fidelity of engineered ear constructs.

3. Kulig KM, Luo X, Finkelstein EB, Liu XH, Goldman SM, Sundback CA, Vacanti JP, Neville CM. Biologic properties of surgical scaffold materials derived from dermal ECM.Biomaterials. 2013 Jul;34(23):5776-84.

Surgical scaffold materials are available from several companies and are unique products manufactured by proprietary methodology. A significant need exists for a more thorough understanding of scaffold properties that impact the early steps of host cell recruitment and infiltration.In this study, a panel of in vitro assays was used to make direct comparisons of several similar, commercially-available materials: Alloderm, Medeor Matrix, Permacol, and Strattice. Differences in the materials were detected for both cell signaling and scaffold architecture-dependent cell invasion. Our results indicate that both biologic and structural properties need to be carefully assessed in the considerable ongoing efforts to develop new uses and products in this important class of biomaterials.

4. Song JJ, Guyette JP, Gilpin SE, Gonzalez G, Vacanti JP, Ott HC. Regeneration and Experimental Orthotopic Transplantation of a Bioengineered Kidney. Nature Medicine 2013 May;19(5):646-51. doi: 10.1038/nm.3154. Epub 2013 Apr 14.

End organ failure is the leading health care challenge in the Western World with organ transplantation as the only potentially curative therapy currently available. However, its outcomes are limited by donor organ shortage and the side effects of harsh immunosuppressive treatments. Dr. Ott's invention of whole organ decellularization and the application of this novel technology to generate functional recellularized tissues is truly paradigm shifting. Having previously reported on the generation of a functional rodent heart and lungs (in Nature Med. 2008 and 2010, respectively) this latest manuscript describes the application of this technology to kidney regeneration. With this unique approach, the native organ's architecture is preserved, so that the resulting graft can be transplanted just like a donor kidney and connected to the recipient's vascular and urinary systems. If this technology can be scaled to human-sized grafts, patients suffering from renal failure who are currently waiting for donor kidneys or who are not transplant candidates could theoretically receive new organs derived from their own cells.

Pediatric Surgery

Allan Goldstein, MD

Pediatric Surgical Research Laboratories, Patricia K. Donahoe, MD, Director

1. Miraoui H, Dwyer AA, Sykiotis GP, Plummer L, Feng B, Beenken A, Pers TH, Dworzynski P, Durrani S, Keefe K, Niedziela M, Raivio T, Crowley WF jr, Seminara SB, Quinton R, Hughes VA, Ozata M, Kumanov P, Yialamas MA, Hall JE, Vliet GV, Chanoine JP, Rubenstein J, Mohammadi M, Tsai P, Sidis Y, Lage K* and Nelly Pitteloud N*. Mutations in FGF17, IL17RD, DUSP6, SPRY4, and FLRT3 are identified in individuals with congenital hypogonadotropic hypogonadism. *These authors contributed equally. Am J Hum Genet 2013;92:725-743.

By combining sequencing and network-based approaches to the interpretation of genetic data, we were able to identify an expanded FGF receptor signaling network that is disrupted in disorders of human reproduction.

2. Belkind-Gerson J, Carreon A, Benedict LA, Steiger C, Pieretti A, Nagy N, Dietrich J, Goldstein AM. Nestin-expressing cells in the gut give rise to enteric neurons and glial cells. Neurogastroenterology & Motility 2013;25:61-69.

We successfully isolated and expanded in vitro a population of neuronal progenitor cells capable of giving rise to neurons following transplantation into aneural colon in vivo. The progenitor cells were isolated from intestinal mucosa, which is readily accessible endoscopically in humans. This study lays the groundwork for using the gut mucosa as an autologous source for cell-based therapies to treat neurointestinal diseases.

3. Pepin D, Hoang M, Nicolaou F, Hendren K, Benedict LA, Sosulski A, Al-Moujahed A, Vavvas D, Donahoe PK. A novel albumin leader sequence substitution enhances production, cleavage, and potency of recombinant Mullerian inhibiting substance. Technology Journal, Vol 01, Issue 01, September 2013

Modified human Mullerian Inhibiting Substance (hMIS) cDNA constructs produced more homobeneous and more potent MIS for pharceutical scale up. These same constructs transfected into AAV9 vectors and delivered as single injection gene therapy inhibits human ovarian cancer cells xenotransplanted models and blocks ovarian folliculogenesis, indicating that hMIS can function as a universal contraceptive. These findings led to four patents being submitted.

4. Pieretti AC, Ahmed AM, Roberts JD, Kelleher CM. A novel in vitro method to study alveologenesis. Am J Resp Cell Mol Bio 2013 (e-pub ahead of print Sept 25)

This manuscript describes and validates the first in vitro model of postnatal lung alveolarization. This innovative methodology will greatly facilitate the study of lung diseases in newborns.

Plastic and Reconstructive Surgery

William G. Austen, Jr., MD

1. Dougherty M, Kamel G, Grimaldi M, Gfrerer L, Shubinets V, Ethier R, Hickey G, Cornell RA, Liao EC. Distinct requirements for wnt9a and irf6 in extension and integration mechanisms during zebrafish palate morphogenesis. Development. 2013 Jan; 140(1):76-81.

Dr. Liao's laboratory focuses on the molecular events of craniofacial development using the zebrafish as a model. Development of the palate in vertebrates involves cranial neural crest migration, convergence of facial prominences and extension of the cartilaginous framework. Dysregulation of palatogenesis results in orofacial clefts, which represent the most common structural craniofacial birth defects. Detailed analysis of zebrafish palatogenesis revealed distinct mechanisms of palatal morphogenesis: extension, proliferation and integration. In this report, his laboratory shows that wnt9a is required for palatal extension, wherein the chondrocytes form a proliferative front, undergo morphological change and intercalate to form the ethmoid plate. Meanwhile, irf6 is required specifically for integration of facial prominences along a V-shaped seam. This work presents a mechanistic analysis of palate morphogenesis in a clinically relevant context.

2. Cetrulo CL Jr, Torabi R, Scalea JR, Shimizu A, Leto Barone AA, Gillon BC, Tasaki M, Leonard DA, Cormack TA, Villani V, Randolph MA, Sachs DH, Yamada K. Vascularized composite allograft transplant survival in miniature Swine: is MHC tolerance sufficient for acceptance of epidermis? Transplantation. 2013 Dec 15;96(11):966-74.

Dr. Cetrulo and his colleagues in the Division of Plastic and Reconstructive Surgery performed their first hand transplant in October 2012. Although the surgery is a technical success, the patient will remain on systemic immunosuppression for the remainder of his life. Dr. Cetrulo's laboratory focuses on developing strategies to achieve immune tolerance to vascularized composite tissue allografts (hands, face, etc.) that would preclude the use of life-long immunosuppression. Previous

work in Massachusetts General Hospital miniature swine, which had accepted class I-mismatched kidneys long-term after 12 days of high-dose cyclosporine A, uniformly accepted donor-major histocompatibility complex (MHC)-matched kidneys without immunosuppression. However, these tolerant kidney recipients rejected donor MHC-matched split-thickness skin grafts by day 25, without changes in renal graft function or antidonor in vitro responses. Dr. Cetrulo's group has now tested whether this "split tolerance" would also be observed for the primarily vascularized skin of vascularized composite allografts (VCAs) added to animals that were conditioned by long-term tolerance to kidney allografts. All tissues of a VCA are accepted long-term on animals tolerant of class I-mismatched kidneys, with the exception of epidermis, the survival of which is markedly prolonged compared with split-thickness skin grafts. Exposure of tolerant animals to second donor-matched kidneys before VCA increases the longevity of the VCA epidermis, suggesting an increase in the immunomodulatory mechanisms associated with tolerance of the kidney. Understanding the mechanisms of tolerance to the various component tissues of VCAs will lead to clinical strategies for eliminating life-long immunosuppression for patients receiving hand or face allotransplants.

3. Reish RG, Damjanovic B, Austen WG Jr, Winograd J, Liao EC, Cetrulo CL, Balkin DM, Colwell AS. Infection following implant-based reconstruction in 1952 consecutive breast reconstructions: salvage rates and predictors of success. Plast Reconstr Surg. 2013 Jun;131(6):1223-30.

Few studies address salvage rates for infection in implant-based breast reconstruction. An understanding of success rates and clinical predictors of failure may help guide management. A retrospective analysis of multisurgeon consecutive implant reconstructions from 2004 to 2010 was performed. Salvage with intravenous antibiotics and implant exchange was successful in 37.3 percent of patients. Smoking, irradiation, chemotherapy, and mastectomy skin necrosis were predictors for developing infection. Patients with a higher white blood cell count at admission and methicillin-resistant S. aureus were more likely to fail implant salvage. There was no association with time interval to tissue expander insertion and secondary explantation.

4. Lee JH, Kirkham JC, McCormack MC, Nicholls AM, Randolph MA, Austen WG Jr. The effect of pressure and shear on autologous fat grafting. Plast Reconstr Surg. 2013 May;131(5):1125-36.

Fat grafting has become routine in plastic surgery because of low donor-site morbidity, a low complication rate, and fast recovery time. The optimal technique, however, has yet to be defined. Two critical variables are pressure and shear, both defined as force divided by area. In this study, the authors examined the effect of pressure and shear on human fat grafts in a nude mouse model. Higher aspiration pressures up to -0.83 atm did not affect fat graft viability in vivo. Positive pressure up to 6 atm also did not affect fat graft viability. The degree of shear stress, which is a function of flow rate, did significantly affect fat graft viability. Fat grafts injected slowly with low shear stress significantly outperformed fat injected with high shear stress. These data suggest that shear stress is a more important variable regarding fat graft viability than pressure.

Surgical Oncology

Kenneth K. Tanabe, MD

1. Rocco laboratory

The Rocco laboratory published this year a novel way to measure intratumor heterogeneity from next-generation tumor DNA sequencing data, technology that is expected to enter clinical practice in the next few years. Dr. Rocco and his colleagues then used this measure as a biomarker to show that higher intratumor heterogeneity is related to shorter overall survival in head and neck squamous cell carcinoma. This success formed the basis for obtaining a 3 year supplement to his ongoing NIH-sponsored clinical study of oropharyngeal squamous cell carcinoma, to allow prospective evaluation of this biomarker in a homogeneously treated cohort of patients in new collaborations with Drs. Todd Golub and Gaddy Getz of

the Broad Institute. This work is expected soon to provide an important addition to methods for choosing patients for clinical trials of de-intensified therapy, and ultimately to help guide the choice of personalized therapy. A patent application for this process has also been submitted.

2. Tanabe and Fuchs laboratories

The Tanabe and Fuchs laboratories in collaboration have demonstrated that hepatocellular carcinoma (HCC) can be prevented in animal models of cirrhosis by inhibiting the receptor for EGF (EGFR) using an inhibitor already approved by the FDA for cancer treatment. Of equal importance, not only does the inhibitor effectively prevent HCC in preclinical models, it also reverses the process of cirrhosis. These effects on liver cirrhosis are traditionally monitored by histologic examination of liver specimens. And in another scientific advance, in collaboration with MGH investigators they have demonstrated that the extent of liver fibrosis can be monitored non-invasively using MRI and molecular probes developed at MGH that bind to collagen deposition in the liver. These discoveries are now applied to patients. A clinical trial designed to determine the effects of EGFR inhibition on cirrhosis in patients with HCC has been approved by the NCI and will be initiated in 2014.

3. Soldano Ferrone laboratory

The Soldano Ferrone laboratory has identified a novel mechanism of acquired and intrinsic BRAF inhibitor resistance. We demonstrate that Sonic Hedgehog (Shh) pathway activation mediated by PDGFR-alpha (PDGFRa) up-regulation caused BRAF inhibitor resistance in vitro and in vivo. In addition our data defined novel combinatorial strategies to overcome the Shh/PDGFRa mediated resistance both in vitro and In vivo. The PDGFRa inhibitors sunitinib, imatinib and crenolanib as well as the novel Shh inhibitor LDE225 overcome the BRAF inhibitor resistance in vitro and in vivo. The clinical relevance of these data is indicated by the association of PDGFRα up-regulation in melanoma matched biopsies of BRAF-I +/- MEK inhibitor treated patients with shorter time to disease progression and lower tumor regression. These findings suggest that monitoring patients for early PDGFRα up-regulation will facilitate the identification of those who may benefit from the treatment with BRAF-I in combination with clinically approved PDGFRα or Shh inhibitors.

4. Yu M, Bardia A, Wittner BS, Stott SL, Smas ME, Ting DT, Isakoff SJ, Ciciliano JC, Wells MN, Shah AM, Concannon KF, Donaldson MC, Sequist LV, Brachtel E, Sgroi D, Baselga J, Ramaswamy S, Toner M, Haber DA, Maheswaran S. Circulating Breast Tumor Cells Exhibit Dynamic Changes in Epithelial and Mesenchymal Composition. Science 2013; 339:580-84.

This work demonstrates the plasticity exhibited by breast tumor cells shed into the blood, defined as circulating tumor cells (CTCs). Breast CTCs change cell fates quite rapidly and in response to treatment.

Thoracic Surgery

Douglas J. Mathisen, MD

1. Izar B, Sequist L, Lee M, Muzikansky A, Heist RS, Iafrate AJ, Dias-Santagata D, Mathisen DJ, Lanuti M. Impact of EGFR mutation status on outcomes in patients with resected stage I NSLC. Ann Thorac Surg. 2013 Sep;96(3):962-8.

In this study we sought to identify the pure prognostic role of EGFR mutation in patients with completely resected stage I NSCLC who received no adjuvant therapy. Completely resected stage I EGFR mutation-positive NSCLC patients have a significant survival advantage compared with EGFR wild-type patients. Mutation of the EGFR gene is a positive prognostic marker in completely resected stage I NSCLC.

2. Tapias LF, Mino-Kenudson M, Lee H, Wright C, Gaissert HA, Wain JC, Mathisen DJ, Lanuti M. Risk factor analysis for the recurrence of resected solitary fibrous tumours of the pleura: a 33-year experience and proposal for a scoring system. Eur J Cardiothorac Surg. 2013 Jul;44(1):111-7.

Surveillance after resection of solitary fibrous tumours of the pleura (SFTP) remains undefined. This study reviews our experience with surgical treatment of SFTP to determine the specific risk factors to predict recurrence. Surgical treatment of SFTP remains the primary curative therapy with low perioperative morbidity and mortality. A new scoring system was constructed on common clinical and histological characteristics and predicted all recurrences when retrospectively applied to our study cohort. The score may be used to assess prognosis and to guide postoperative surveillance. If validated in a larger population, selected patients with excellent prognosis may not require surveillance imaging. In contrast, patients with scores predictive of disease recurrence may be selected for the study of adjuvant therapy and frequent surveillance imaging.

3. Elizabeth Gilpin S1, Guyette JP1, Gonzalez G1, Ren X1, Asara JM1, Mathisen DJ1, Vacanti JP2, Ott HC3. Perfusion decellularization of human and porcine lungs: Bringing the matrix to clinical scale.J Heart Lung Transplant. 2013 Oct 26. pii: S1053-2498(13)01511-8. doi: 10.1016/j.healun.2013.10.030.

Organ engineering is a theoretical alternative to allotransplantation for end-stage organ failure. Whole-organ scaffolds can be created by detergent perfusion via the native vasculature, generating an acellular matrix suitable for recellularization with selected cell types. We aimed to up-scale this process, generating biocompatible scaffolds of a clinically relevant scale. Rat, porcine, and human lungs were decellularized by detergent perfusion at constant pressures. Collagen, elastin, and glycosaminoglycan content of scaffolds were quantified by colorimetric assays. Proteomic analysis was performed by microcapillary liquid chromatography tandem mass spectrometry. Extracellular matrix (ECM) slices were cultured with human umbilical vein endothelial cells (HUVEC), small airway epithelial cells (SAEC), or pulmonary alveolar epithelial cells (PAECs) and evaluated by time-lapse live cell microscopy and MTT (3-[4,5-dimethylthiazol-2-yl]-2,5-diphenyltetrazolium bromide) assay. Whole-organ culture was maintained under constant-pressure media perfusion after seeding with PAECs. Rat lungs were decellularized using: (1) sodium dodecyl sulfate (SDS), (2) sodium deoxycholate (SDC), or (3) 3-[(3-cholamidopropyl)dimethylammonio]-1-propanesulfonate (CHAPS). Resulting scaffolds showed comparable loss of DNA but greatest preservation of ECM components in SDS-decellularized lungs. Porcine (n = 10) and human (n = 7) lungs required increased SDS concentration, perfusion pressures, and time to achieve decellularization as determined by loss of DNA, with preservation of intact matrix composition and lung architecture. Proteomic analysis of human decellularized lungs further confirmed ECM preservation. Recellularization experiments confirmed scaffold biocompatibility when cultured with mature cell phenotypes and scaffold integrity for the duration of biomimetic culture. SDS-based perfusion decellularization can be applied to whole porcine and human lungs to generate biocompatible organ scaffolds with preserved ECM composition and architecture.

4. Matthay MA, Anversa P, Bhattacharya J, Burnett BK, Chapman HA, Hare JM, Hei DJ, Hoffman AM, Kourembanas S, McKenna DH, Ortiz LA, Ott HC, Tente W, Thébaud B, Trapnell BC, Weiss DJ, Yuan JX, Blaisdell CJ. Cell therapy for lung diseases. Report from an NIH-NHLBI workshop, November 13-14, 2012. Am J Respir Crit Care Med. 2013 Aug 1;188(3):370-5. doi: 10.1164/rccm.201303-0522WS.

The National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health convened the Cell Therapy for Lung Disease Working Group on November 13-14, 2012, to review and formulate recommendations for future research directions. The workshop brought together investigators studying basic mechanisms and the roles of cell therapy in preclinical models of lung injury and pulmonary vascular disease, with clinical trial experts in cell therapy for cardiovascular diseases and experts from the NHLBI Production Assistance for Cell Therapy program. The purpose of the workshop was to discuss the current status of basic investigations in lung cell therapy, to identify some of the scientific gaps in current knowledge regarding the potential roles and mechanisms of cell therapy in the treatment of lung diseases, and to develop recommendations to the NHLBI and the research community on scientific priorities and practical steps that would lead to first-in-human trials of lung cell therapy.

Transplant Surgery

James F. Markmann MD, PhD

1. Kawai T, Sachs DH, Sykes M, Cosimi AB: HLA-mismatched renal transplantation without maintenance immunosuppression. New Engl J Med. (Letter to the Editor). 2013; 368: 1850-1852.

This report summarizes the long-term results (> 10 yrs) and ongoing success of our clinical tolerance induction trials which were the first in the world to be initiated.

2. Schuetz C, Dong N, Smoot E, Elias N, Schoenfeld DA, Markmann JF, Yeh H. HCC patients suffer less from geographic differences in organ availability. Am J Transplant 2013 Nov;13(11):2989-95. PMID: 24011291.

This work continues to investigate the details of the geographic variation in liver donor organ availability and its impact on the outcome of liver transplant recipients. The work makes a strong case for changes in allocation policy to better prioritize patients at greatest risk and to expand the areas of organ distribution to gain equity across the US.

3. Lee S. Yamada Y, Tonsho M, Boskovic S, Nadazdin O, Schoenfeld D, Cappetta K, Atif M, Smith RN, Cosimi AB, Benichou G, Kawai T: Alefacept promotes immunosuppression-free renal allograft survival in nonhuman primates via depletion of recipient memory T cells. Amer J Transplant. 2013. 12: 3223-3229.

This report documents a new approach to achieving tolerance using a novel anti-LFA-1 molecule.

Transplantation Biology Research Center

Joren C. Madsen, MD, DPhil, & Laurence A. Turka, MD

1. Zhang R, Huynh A, Whitcher G, Chang J, Maltzman JS, Turka LA. An obligate cell-intrinsic function for CD28 in Tregs. J Clin Invest. 2013 Jan 2. PMCID: PMC3561819

A subset of lymphocytes known as regulatory T cells is important for preventing autoimmunity and promoting the survival of organ transplants. This work defines a new pathway important for the survival and function of these cells, with implications for the design and use of new immunosuppressive protocols.

2. Okumi M, Scalea JR, Gillon BC, Tasaki M, Villani V, Cormack T, Hirakata A, Shimizu A, Sachs DH, Yamada K. The induction of tolerance of renal allografts by adoptive transfer in miniature swine. Am J Transplant. 2013 May; 13(5):1193-202. PMCID: PMC3671754

This paper describes the transfer of tolerance from one highly inbred swine to another without immunosuppression, by renal transplantation of a kidney and peripheral blood cells from a tolerant animal. It represents the first report of adoptive transfer of tolerance in a large animal model and was made possible by the derivation of highly inbred MGH miniature swine through a selective breeding program.

3. Cetrulo CL Jr, Torabi R, Scalea JR, Shimizu A, Leto Barone AA, Gillon BC, Tasaki M, Leonard DA, Cormack TA, Villani V, Randolph MA, Sachs DH, Yamada K. Vascularized composite allograft transplant survival in miniature Swine: is MHC tolerance sufficient for acceptance of epidermis? Transplantation. 2013 Dec 15; 96(11):966-74. PMCID: In process

We show that all tissues of a vascularized composite allograft (VCA) except epidermis are accepted long-term on animals tolerant of class-I mismatched kidneys. The survival of epidermis is markedly prolonged compared to split thickness skin grafts, but is not indefinite. Exposure of tolerant animals to second donor-matched kidneys prior to VCA increases the longevity of the VCA epidermis, suggesting an increase in the immunomodulatory mechanisms associated with tolerance of the kidney. These data have important implications in achieving tolerance of face and hand transplants.

4. Tasaki M, Shimizu A, Hanekamp I, Torabi R, Villani V, Yamada K*. The protective effects of Rituximab against early development of proteinuria in pig-to-baboon xeno kidney transplantation. J Am Soc Nephrol. 2013 in press.

Although one of major obstacles in xenogeneic kidney transplant is post-transplant proteinuria, the underlying mechanisms of this complication have not been defined. To elucidate this mechanism in xenotransplantation, we examined the role of SMPDL-3b on post-transplant proteinuria. In our GalT-KO renal transplant model, we found that Rituximab treatment prevented in vitro damage to pig podocytes as well as the early development of proteinuria following xenogeneic GalT-KO KTx in baboons. Notably, treatment with Rituximab correlated inversely with the level of SMPDL-3b expression suggesting that the drug has a protective effect. This is the first mechanistic study to examine the effects of Rituximab treatment on proteinuria in xenotransplantation.

Trauma, Emergency Surgery and Surgical Critical Care

George Velmahos, MD

1. Van der Wilden GM, Velmahos GC, D'Andrea KJ, Jacobs L, DeBusk MG, Adams CA, Gross R, Burkott B, Agarwal S, Maung AA, Johnson DC, Gates J, Keely E, Michaud Y, Charash WE, Winchell RJ, Desjardins SE, Rosenblatt MS, Gupta S, Gaeta M, Chang Y, de Moya M. Successful nonoperative management of the most severe blunt renal injuries. A multicenter study of ReCONECT. Arc Surg 2013;148:924-31.

The latest study from the very successful collaborative of the Research Consortium of New England Centers for Trauma (ReCONECT), which is founded and led by the MGH trauma team. In this article the collaborative explored the nonoperative management of severe blunt kidney injuries and found it safe and effective.

2. Kasotakis G, Duggan M, Li Y, O'Dowd D, Baldwin K, de Moya M, King DR, Alam HB, Velmahos GC. Optimal pressure of abdominal gas insufflation for bleeding control in a severe swine splenic injury model. J Surg Res, 2013;184(2):931-6.

The latest in the series of articles on the value of abdominal insufflation to stop exsanguination from severe abdominal organ injuries. Our group evaluated different pressures and a new portable abdominal insufflating device which can be used in the prehospital environment.

3. Zhao T, Li Y, Baoling L, Liu Z, Chong W, Deperalta DK, Velmahos GC, Alam HB. Novel pharmacologic treatment attenuates septic shock and improves long term survival. Surgery 2013;154:206-13.

One more article on the effectiveness of histone deacetylase inhibitors. After the extensive experience with hemorrhagic shock animal models, our group explored this pharmacologic treatment in models of septic shock and found it to be similarly beneficial

4. Duggan M, Rago A, Sharma U, Zugates G, Freyman T, Busold R, Caulkins J, Pham Q, Chang Y, Mejaddam A, Beagle J, Velmahos G, de Moya M, Zukerberg L, Ng TF, King DR. Self-expanding polyurethane polymer improves survival in a model of noncompressible massive abdominal hemorrhage. J Trauma 2013;74:1462-7.

The second article documenting the effects of a self-expanding foam which can be injected into the abdomen to control abdominal bleeding. This project, which is supported by the DOD, aims to create a method of prehospital bleeding control after intracavitary injuries.

Vascular and Endovascular Surgery

Richard P. Cambria, MD

1. Albadawi H, Haurani MJ, Oklu R, Trubiano J, Laub P, Yoo HJ , Watkins MT. Differential effect of zoledronic acid on human vascular smooth muscle cells, J. Surg. Res. Nov 8 2013 Jun 15;182(2):339-46.

In this publication, our laboratory has shown for the first time that human vascular smooth muscle cell proliferation can be modulated by zoledronic acid. To date only animal models (rat and rabbit) have shown that zoledronic acid, commonly used in humans to treat malignancies and osteoporosis, can also inhibit the development of intimal hyperplasia. Intimal Hyperplasia is the leading cause for failure of open and endovascular interventions in humans. These in vitro data with human cells provides crucial ongoing rationale for using this agent as a potential in vivo therapeutic agent to ameliorate intimal hyperplasia in humans.

2. Conrad MF, Boulom V, Mukhopadhyay S, Garg A, Patel VI, Cambria RP. Progression of Asymptomatic Carotid Stenosis Despite Optimal Medical Therapy. J of Vasc Surg. 2013 Jul 58;(1):128-35.

This manuscript was presented at the New England Society of Vascular Surgery in October of 2012. It reviews the ability of medical management (aspirin/statin therapy) to prevent disease progress or symptom development in patients with moderate (50-69%) carotid artery stenosis. Our data indicate that medical therapy, even "optimal" medical therapy, failed to halt the progression of disease to severe or very severe (>70%) carotid stenosis. This is an important first step in determining if medical therapy will effectively prevent stroke in patients with severe asymptomatic carotid stenosis. This publication refuted the often-championed position that modern medical therapy will control asymptomatic carotid stenosis.

3. Lancaster RT, Conrad MF, Patel VI, Cambria M, Ergul EA, Cambria RP. Further Experience with Distal Aortic Perfusion and Motor Evoked Potential Monitoring in the Management of Extent I-III Thoracoabdominal Aneurysms. J Vasc Surgery 2013; 58:283-290.

This manuscript was presented by Dr Lancaster at the New England Society of Vascular Surgery where he was awarded the Darling prize for the best paper. This is a continuation of our extensive experience with thoracoabdominal aneurysm repair. The present study provides further evidence that distal aortic perfusion with continuous monitoring of motor-evoked potentials in order to guide selective reimplantation of intercostal arteries is a useful adjunct in the repair of extent I-III TAA. Specifically, this operative strategy yields lower rates of perioperative mortality and permanent spinal cord injury. Accordingly, it is the preferred method for the open repair of extent I-III TAA.

4. Patel VI, Ergul E, Conrad MF, Gravereauz E, Schermerhorn ML, Schanzer A, Goodney PP, Cambria RP. Aneurysm Sac Enlargement Independently Predicts Late Mortality in Patients Treated with EVAR. J of Vasc Surgery 2013;57:(5)87S-88S.

This Vascular Study Group of New England paper report on 1642 EVAR patients. At one year after surgery, AAA sac enlargement was noted in 8% of the cohort; such enlargement was associated with significant reduction in late survival.

Urology

Michael L. Blute, Sr., MD

1. Blute, M. Comprehensive molecular characterization of clear cell renal cell carcinoma. Cancer Genome Atlas Nature. 2013 Jul 4;499(7456):43-9.

Genetic changes underlying clear cell renal cell carcinoma include alterations in genes controlling cellular oxygen sensing (e.g. VHL) and the maintenance of chromatin states (e.g. PBRM1). More than 400 tumors were analyzed using different genomic platforms. Nineteen significantly mutated genes were identified. Aggressive renal cancers showed modifications of the metabolic pathways which correlated with tumor stage and severity offering new opportunities for management and therapy.

2. Wu CL, Schroeder BE, Ma XJ, Cutie CJ, Wu S, Salunga R, Zhang Y, Kattan MW, Schnabel CA, Erlander MG, McDougal WS. Development and validation of a 32-geneprognostic index for prostate cancer progression. Proc Natl Acad Sci U S A. 2013 Apr 9;110(15):6121-6.

The accurate determination of the risk of cancer recurrence is an important unmet need in the management of prostate cancer. Patients and physicians must weigh the benefits of currently available therapies vs. the potential morbidity of different treatments. A gene expression signature, prognostic for prostate-specific antigen (PSA) recurrence, was identified through a bioinformatics analysis of the expression of 1,536 genes in malignant prostate tissue from a training cohort of consecutive patients treated with radical prostatectomy. The 32-gene signature identified here functioned as a robust prognostic marker for disease recurrence. This assay may aid in treatment strategy after surgery and has the potential to impact decision making at time of prostate biopsy before selection for any treatment.

3. American Urological Association Research Scholar Grantee

Urologic Oncology Fellow—Dr. Mark Preston

Title of Project: The Association between Finasteride and High-grade or Lethal Prostate Cancer

Mentors: Dr. Aria Olumi (MGH) and Dr. Loreli Mucci (HSPH)

Publication: JAMA Int Med (In-Press)

In a very competitive application process, Dr. Mark Preston was selected as the American Urological Association Research Scholar for the academic year 2013-14. During his research time, Dr. Preston has demonstrated significant productivity in research activity. Most notably, his project will be published in the journal JAMA Internal Medicine. Using a cohort with 448,803 person-years of follow-up, the research demonstrated that chemoprevention with 5-alpha reductase inhibitors (5ARI) was protective against low and moderate risk prostate cancer. However, in contrast to previously published reports, Dr. Preston's work demonstrated that 5ARI use was not associated with developing high-grade or lethal prostate cancer.