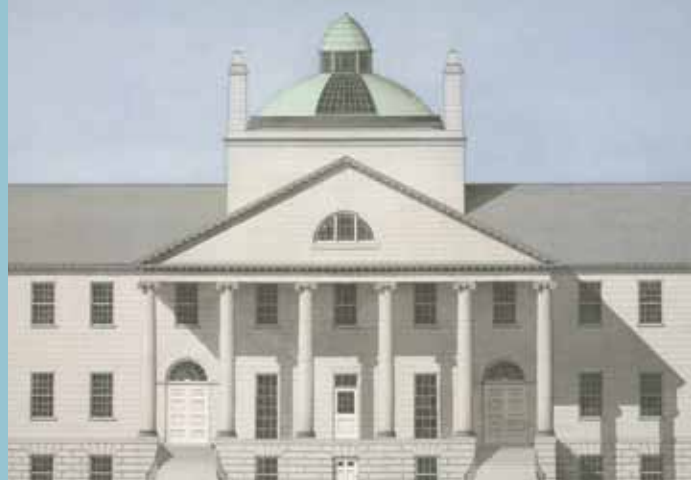
Executive Committee on
RESEARCH
Fostering Innovation at MGH



66th Annual Meeting of the
MGH Scientific Advisory Committee

SAC 2013

Celebration of Science

Next Generation Science at MGH

March 20 & 21, 2013
Simches Auditorium
185 Cambridge Street, 3rd Floor

MGH 1811
RESEARCH Management
Mainstay of MGH Innovation

Contents

Welcome

March, 2013

Welcome to the 66th Annual Meeting of the MGH Scientific Advisory Committee (SAC) on March 20 and 21, 2013. Dr. Richard Lifton has graciously agreed to chair our SAC meeting 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, March 20, followed by an afternoon Research Symposium from 2:00 to 5:00 pm. The outstanding MGH researchers who will be presenting their work in our Symposium this year are the 2013 Howard Goodman Award recipient David Langenau, PhD, and the 2013 Martin Basic and Clinical Research Prize recipients, Leigh Hochberg, MD, PhD, and Michael Talkowski, PhD. We are honored to have two of our distinguished MGH Research Scholars as our scientific keynote speakers, Galit Alter, PhD, and Nir Hacohen, PhD. We will close the first day with a Reception and Colloquium Dinner for invited guests at the Liberty Hotel.

On Thursday, March 21, Dr. Kingston will open the SAC meeting with an ECOR Report. Following this opening, we will turn our attention to presentations by Chiefs from Pathology, Psychiatry, Immunology and the Martinos Center, who will describe some of the remarkable research being conducted across MGH.

Our afternoon sessions will focus on two of the research initiatives that came out of the MGH Strategic Planning Retreat in January. The key initiatives we will explore are:

1. A MGH Research Institute
2. A Translational Medicine Program

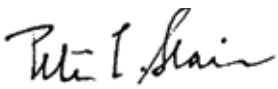
Experience has reaffirmed that we get the most helpful advice and perspective from SAC via open discussion of key issues. To that end, we have structured our program to allow dialogue with our SAC members throughout the program.

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

To maximize the time for discussion during the day, the annual MGH Research Administration Executive Report and Financials for FY12 will be provided in these printed materials in advance of the meeting.

Dr. Kingston plans to highlight some of this information 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 2013 Annual Celebration of Science at MGH

Agenda: Day One, Wednesday, March 20, 2013

11:00 am–1:45 pm, ***Holiday Inn, 15th Floor***

SAC 2013 Poster Session (light lunch available)

2:00 pm–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)

2:15 pm — *2013 Martin Prize for Basic Research*
Reach and grasp by people with tetraplegia using a neurally controlled robotic arm
Leigh R. Hochberg, MD, PhD

2:45 pm — *2013 Martin Prize for Clinical Research*
Sequencing chromosomal abnormalities reveals neurodevelopmental loci that confer risk across diagnostic boundaries
Michael E. Talkowski, PhD

3:15 pm — *Goodman Award*
Fishing for therapies to treat T-cell acute lymphoblastic leukemia
David M. Langenau, PhD

3:45–4:00 pm — **BREAK**

4:00 pm — *Keynote*
INTRODUCTION
Peter L. Slavin, MD

DISSECTING THE NATURE OF PROTECTIVE HUMORAL IMMUNITY
Galit Alter, PhD
2012 MGH Research Scholar, Ragon Institute

HOW THE IMMUNE SYSTEM SEES DNA: DEGRADATION AND DETECTION
Nir Hacohen, PhD
2012 MGH Research Scholar, Rheumatology

6:15–9:00 pm, ***Liberty Hotel, Boston***

Colloquium Reception and Dinner

6:15 pm — **RECEPTION**

7:00 pm — **DINNER AND OPENING WELCOME**
Robert E. Kingston, PhD

7:45 pm — **INTRODUCTION**
Peter L. Slavin, MD

AFTER DINNER REMARKS
Eric S. Lander, PhD
Professor of Systems Biology, Harvard Medical School
Founding Director, the Broad Institute of MIT and Harvard

Agenda: Day Two, Thursday, March 21, 2013

7:30–8:00 am, *Simches 3.120*
SAC MEMBERS BREAKFAST MEETING (Executive Session)

8:00–8:20 am, *Simches 3.110*
WELCOME AND OPENING COMMENTS
Peter L. Slavin, MD, President, Massachusetts General Hospital

8:20–8:45 am
ECOR REPORT 2012
Robert E. Kingston, PhD, Chair, Executive Committee on Research (ECOR)

8:45 am–12:00 pm
DEPARTMENT REPORTS
8:45 am **Pathology, David N. Louis, MD**
9:30 am **Psychiatry, Jerrold F. Rosenbaum, MD**

10:15–10:30 am
BREAK

10:30 am **Rheumatology, Allergy and Immunology, Andrew D. Luster, MD, PhD**
11:15 am **Martinos Center, Bruce R. Rosen, MD, PhD**

12:15–1:15 pm
SERI 2nd Floor
Simches 3.120
LUNCH
SAC Members with small groups of MGH Faculty
ECOR Members, Trustees and Speakers

1:30 pm–4:00 pm, *Simches 3.110*

Next Generation Science at MGH

1:30–1:40 pm
MGH/MGPO 2012–2013 STRATEGIC PLANNING PROCESS: OVERVIEW
Harry W. Orf, Senior Vice President for Research

1:40–2:40 pm
RESEARCH STRATEGIC PLANNING WORKGROUP
- Overview
- Research Institute

***Panel Moderator*:** **Harry W. Orf, PhD, Senior Vice President for Research**
Panelists: **Randy L. Gollub, MD, PhD**
Robert E. Kingston, PhD
Joren C. Madsen, MD, DPhil
Ramnik J. Xavier, MD, PhD

2:40–3:00 pm
BREAK

3:00–4:00 pm
RESEARCH ↔ CLINICAL INTEGRATION WORKGROUP
- Overview
- Translational Medicine Program

Panel Moderator: **Andrea B. Paciello, MHSA**
Panelists: **R. Rox Anderson, MD**
Maurizio Fava, MD
Mason W. Freeman, MD
Frances Toneguzzo, PhD

4:15–4:45 pm, *Simches 3.120*
Executive Session (SAC members only)
4:45–5:00 pm, *Simches 3.120*
Debriefing (SAC members and MGH Leadership)

Goodman & Martin Award Winners

Howard M. Goodman Fellowship 2013

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.

Fishing for therapies to treat T-cell acute lymphoblastic leukemia

David M. Langenau, PhD

Assistant Professor, Department of Pathology

Martin Research Prize 2013 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

Reach and grasp by people with tetraplegia using a neurally controlled robotic arm

Leigh R. Hochberg, MD, PhD

Associate Professor, Department of Neurology

CLINICAL RESEARCH

Sequencing Chromosomal Abnormalities Reveals Neurodevelopmental Loci that Confer Risk across Diagnostic Boundaries

Michael E. Talkowski, PhD

Instructor, Center for Human Genetic Research

Keynote Speakers

Galit Alter, PhD

2012 MGH RESEARCH SCHOLAR

Principal Investigator, Ragon Institute of MGH, MIT and Harvard; Associate Immunologist, Department of Medicine, Massachusetts General Hospital; Associate Professor, Harvard Medical School

The window of opportunity to prevent HIV, TB, and malaria is remarkably short; from the moment the pathogen enters the body to the first cell is infected, due to the fact that once inside a cell, these pathogens have evolved intricate means by which they are able to evade the immunity. Therefore vaccine and/or therapeutic strategies aimed at preventing these infections must act with extreme speed to clear the very first infected cells, and cannot rely on traditional vaccine-induced immune responses thatrequire cellular proliferation, differentiation, and homing to the site(s) of infection. Interestingly, while our innate immune response represents our bodies first line defense against infection, its non-specific nature, diminishes its utility in vaccine design efforts. Yet antibodies represent a critical bridge between the adaptive and innate immune system by providing critical instructions to the innate cells on how an antibody-opsonized complex should be cleared/destroyed. These instructions are conveyed to the innate immune system through a carbohydrate structure/glycan attached to the constant domain of antibodies, which provides a code to innate immune cells that unleashes their anti-microbial activity. Yet, little is known about the mechanism by which this antibody carbohydrate structure is regulated, nor how it can programmed actively through vaccination/ therapeutic approaches to enhance anti-microbial control. Thus the Alter lab focuses on unlocking the key by which the immune system regulates antibody-glycosylation to specifically recruit innate immunity to fight viral infections more aggressively and potentially contribute to the control a wider range of infections, malignancies, and even autoimmune diseases.

Nir Hacohen, PhD

2012 MGH RESEARCH SCHOLAR

Principal Investigator, Center for Immunology and Inflammatory Diseases; Associate Immunologist, Department of Medicine, Massachusetts General Hospital; Associate Professor, Harvard Medical School; Senior Associate Member, Broad Institute of Harvard and MIT

Dr. Hacohen is an immunologist and geneticist focused on dissecting the basic mechanisms of pathogen-sensing by the immune system, pioneering genetic technologies that accelerate the study of the immune system, and deciphering and treating human diseases, especially immune disorders, based on genomic approaches.

The immune system can normally distinguish and respond appropriately to a broad diversity of pathogens that it encounters during a lifetime—including the products of bacteria, fungi, viruses as well as self. Using genomic and proteomic approaches, the Hacohen lab has dissected the basic mechanisms of viral and bacterial sensing, influenza-host interactions, sensing of foreign and self DNA, and the impact of self-DNA on the development of autoimmunity. His group also studies the basis for inter-individual variation in the human immune response in health and disease.

Scientific Advisory Committee 2013

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
Provost
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 2010 through SAC 2013 (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 2010 through SAC 2013 (1st term)

Arthur H. Rubenstein, MBBCh
Executive Vice President
University of Pennsylvania for the Health System
Dean of the School of Medicine
Term: SAC 2010 through SAC 2013 (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 2013

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

Marcus Altfeld, MD, 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‡
Incoming Chief, Department of Medicine
Ex-officio

Dennis A. Ausiello, MD†
Chief, 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

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

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

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

Kurt J. Isselbacher, MD
Honorary Member

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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

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

† Chair Appointment, ‡ Chief's Council

Executive Committee on Research
Officers and Members 2013

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

Susan A. Slaugenhaupt, PhD
Neurology, Molecular Neurogenetics Unit
Elected Representative
January 2011–December 2013

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

Lynda Stuart, MD, PhD
Pediatrics
Elected Representative
January 2011–December 2013

Lynda Stuart, MD, PhD
Pediatrics
Co-Chair, Subcommittee on Review of Research Proposals
Ex-officio

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

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

Deverie Bongard, MBA
Administrative Manager, Molecular Biology
Contributing Member

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

Andrew Chase
Corporate Director, Partners Research Management & Research Finance
Ex-officio

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

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

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

† Chair Appointment, ‡ Chief's Council

Dianne Finkelstein, PhD
Director, Biostatistics Unit
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)
Ex-officio

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

Patricia McCabe
Director, Development for Research
Contributing Member

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

Rebecca Menapace, MBA
Associate Director, Partners Research Ventures & Licensing
Contributing Member

Mary Mitchell
Director, Partners Research Compliance
Contributing Member

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

Steven Niemi, DVM
Director, Animal Welfare Assurance, MGH
Ex-officio

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

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 2013

Harry W. Orf, PhD
SENIOR VICE PRESIDENT FOR RESEARCH

Thanks Rick

As I submit this, my first annual Executive Report to SAC, it is fitting to begin by thanking my predecessor, Rick Bringhurst, for his dedication and leadership. During his tenure, the MGH research enterprise experienced remarkable growth, with total expenditures increasing from $483M in FY05 to $764M in FY11. The opening of the Simches building, the growth and consolidation of the Thematic Centers, the cementing of relationships with the Broad Institute and the Harvard Stem Cell Institute, the reorganization of Partners Research Management, the creation of the Office of Research Career Development, the establishment of the Ragon Institute, and the creation of the MGH Research Scholars Program all occurred on Rick's watch and are among the many accomplishments he can look back on with pride. On behalf of the hospital and its entire research community, thank you, Rick, for all you have done.

The Challenges Ahead

In 2012, the MGH research community continued to grow and remain vigorous and productive across a broad range of basic, translational, and clinical investigations. While the MGH research enterprise continues to thrive, we clearly face significant challenges into the future. Most obvious among these is the negative impact of the continuing stagnation of the NIH budget. In a hospital-based research environment supported principally by the availability of external sponsorship and traditionally heavily reliant upon peer-reviewed NIH support, the trend in NIH funding threatens to destabilize established and highly productive research groups and pose serious threats to the career development of young investigators.

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. We will need to expand our philanthropic efforts, our collaborative relationships with neighboring academic research centers, and our interactions with industry to both replace the loss of traditional federal grant funding and compete successfully for funding redirected toward translational research. I will describe programs and initiatives under development to address these challenges at the end of this report, 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 FY12 were $776M, of which $577M were direct costs and $199M were indirect cost recovery. This represents a 1.6% increase in total research expenditures compared to $764M for the same period in FY11. Submitted proposals increased 16% to 3524 from 3030 in FY11 and new awards were up 12% to 1684 from 1510. Support from direct DHHS funding (which consists mostly of NIH funding), now accounts for 50% of MGH research, down slightly from last year's 51%. Total research expenditures on DHHS-sponsored research in FY12 were $387M, a decrease of 0.8% compared to $390M in FY11. Again in 2012, MGH remains the largest recipient of NIH funding among independent hospitals and 12th nationally for all institutions, up from 13th place in 2011.

ARRA expenditures contributed $20.1M to total research in FY12. From FY09 through FY12, MGH investigators received $143M 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, state/local government, and miscellaneous sponsors, again showed a moderate increase of 4.2%, to $307M in FY12 from $295M in FY11, as investigators have continued to turn to these sources to buffer the constraints on NIH support. "Industry/Corporate" expenditures increased 2.6% to $54M in FY12; this category has experienced large swings in expenditures over the last five years, but the cumulative annual growth rate for FY08–FY12 was 8.6%.

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 2012, MGH and its investigators continued to receive national recognition for their major research contributions. David Altshuler, MD, PhD, and Emery N. Brown, MD, PhD, both received an NIH Transformative R01 Award, and John Higgins, MD, received an NIH New Innovator Award. Biju Parekkadan, PhD, received the Presidential Early Career Award for Scientists and Engineers. Emery N. Brown, MD, PhD, and David T. Scadden Jr., MD, were elected to the American Academy of Arts and Sciences. Jack W. Szostak, PhD, was elected to the American Philosophical Society.

Awards and Recognition: *Hospital*

Research Scholars. As reported last year, 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 2012, the second group of MGH Research Scholars was announced at the hospital's Research Advisory Council (RAC) annual meeting. The eight recipients, three of whom were donor-named, were selected from 96 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 2012 MGH Research Scholars are:

Galit Alter, PhD, Division of Infectious Diseases and the Ragon Institute;

Brian Bacskai, PhD, Department of Neurology *(Phyllis and Jerome Lyle Rappaport Scholar);*

Nicholas Dyson, PhD, MGH Cancer Center *(James and Shirley Curvey Scholar);*

Nir Hacohen, PhD, Center for Immunology and Inflammatory Diseases;

Eng Lo, PhD, MGH Neuroscience Center *(Phyllis and Jerome Lyle Rappaport Scholar);*

Raul Mostoslavsky, MD, PhD, MGH Cancer Center;

Anders Näär, PhD, MGH Cancer Center;

Gary Tearney, MD, PhD, Wellman Center for Photomedicine and the Department of Pathology.

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 2013 recipients for a 2012 publication are Leigh Hochberg, MD, PhD, (Basic Science Award) for his Nature paper entitled, "Reach and grasp by people with tetraplegia using a neurally controlled robotic arm", and Michael Talkowski, PhD, (Clinical Science Award) for his Cell paper entitled, "Sequencing chromosomal abnormalities reveals neurodevelopmental loci that confer risk across diagnostic boundaries."

Goodman Award. The 2013 Howard Goodman Award recipient is David Langenau, PhD, of the MGH Department of Pathology. This Fellowship honors Howard M. Goodman, PhD, 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 annually.

Clinical Research Day. In October 2012, the Clinical Research Program sponsored its tenth annual Clinical Research Day, focusing on "Integrating Genetics into Clinical Medicine." The keynote speaker was James F. Gusella, PhD, Director of the MGH Center for Human Genetic Research, who spoke on, "Genetics: Cycling to Better Care." The day also featured a session where over 230 posters that reflected the increasingly interdisciplinary nature of clinical research across the hospital were presented. The event concluded with a panel discussion, "Integrating Genetics into Clinical Medicine: "Sequencing" the Future of MGH."

Also of note is the new Clinical Research Program website: **http://www2.massgeneral.org/crp/.** It provides new and more efficient tools to help investigators and their study staff more easily navigate the clinical research process and showcases the support available at each stage.

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 approximately 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 FY 2009 and now 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 without increasing the MGH research footprint. The Research Space Management Group has carried out several of the Committee's recommendations, including a greater focus on Indirect Cost (IC) density as an indicator of research space activity. In FY12, overall hospital research IC density improved by 5% over FY11 to $186/NASF, in spite of the fact that there was no significant change in the research footprint. Since the Committee's formation in 2009, IC densities have increased 27% hospital-wide.

Still, demand for research space remains strong. At the start of FY12, RSMG had requests for over 43,000 NASF of additional research space, with approximately 30,000 NASF of these requests for wet lab space. RSMG was able to resolve 62% of these requests throughout the year, accounting for 24,000 NASF total. The remaining unresolved space requests are awaiting space availability along with additional requests for over 45,000 NASF in space received in FY13.

New Projects. RSMG initiated and coordinated numerous projects during the year that helped to further densify MGH research space. In total, RSMG completed 33 minor construction and renovation projects totaling over $2 million and involving more than 8,000 NASF. RSMG currently has 27 projects in process totaling over $28M and covering over 100,000 NASF.

The largest project undertaken in FY12 (and recently completed on time and budget in January, 2013) was the build out of new laboratory space and headquarters at 400 Technology Square in Cambridge for the Phillip T. and Susan M. Ragon Institute. The 60,700 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 BL2 and BL3 mouse vivaria, 12 tissue culture rooms, and a 160-seat conference center with state-of-the-art audiovisual and audio conference capabilities.

Concurrent with completion of the new Ragon Institute space in Cambridge, planning has been underway to renovate and backfill the 20,000 NASF vacated by Ragon in Charlestown. This space includes 37 benches, dry space, and tissue culture space (including BL2+ rooms). RSMG received 18 proposals from 10 departments for this space, requests totaling over 90,000 NASF. The Densification Committee reviewed and discussed the proposals, and working the RSMG, developed three potential scenarios for detailed review. It then selected one scenario with additional modifications to accommodate programs with the greatest need. ECOR and hospital leadership subsequently reviewed and approved the plan in June 2012. In all, seven departments were awarded space and renovations are expected to begin in FY13 and be completed in early FY14.

Finally, RSMG and the Densification Committee have recently begun the process of developing an incentive-based model for space allocation, one that will encourage departments with under-dense space to 'right size' themselves and not horde research space that remains underutilized. The basis of the plan involves giving back to each department/unit a portion of the IC costs it brings in and then charging a space use fee based on the square footage the department/unit occupies. Departments with high space densities would receive more IC funds than they would pay in space fees while under dense departments would see a net cost. Departments at or near the average space research space density would be cost neutral. Work is underway to refine the model, to ensure that departments are not penalized for space being held for new recruits, and to set a time frame for phased implementation. Done thoughtfully and equitably, this model can become an important tool in effectively managing our research space portfolio.

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, Corporate Director 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.

Longitudinal surveys conducted by the MGH Research Administrative Advisory Committee (established in 2009) continue to show steady improvement in quality assessments of PRM and its services and systems over the course of the last four years. Both investigators and administrators report improvement. Even as we see major progress, however, we are aware we still have more work to do to create an environment where investigators are spending less time on administration and more time on science. MGH efforts in this regard are centered on a new Continuous Research Operations Improvement (CROI) program, described below in the 2012 Initiatives section of this report.

In FY12, the PRM management team continued to focus on improving operating efficiency. Key initiatives centered around developing and measuring service benchmarks, realigning work flows to achieve improved turnaround times, increasing transparency, defining responsibilities amongst processes, and improving overall quality of customer service. Opportunities for future work flow enhancements and other operational and financial reporting and tracking improvements were identified and will be primary areas of focus in the upcoming fiscal year. In addition, FY12 placed a greater demand on PRM to help ensure compliance with increased regulatory requirements, most notably new Conflict of Interest rules, on both a Federal and State level.

The PRM team will continue to focus on strengthening overall performance and service to the Partners research community as well as working closely with MGH Research Management on its CROI program. The PRM team is now also working with Dr. Klibanski to better support and promote industry collaborations. Objectives for the coming year include developing measures to prepare for an anticipated decrease in federal funding, dealing with a heightened regulatory environment, and continuing the effort to streamline administrative processes.

Research Ventures and Licensing (RVL)

MGH patent, licensing, venture activity, and associated income continued to grow in 2012.

- Licensing Activity = 196 (+37 – 159 in 2011)
- Material Transfer Agreements = 919 (+292 – 627 in 2011)
- New Disclosures = 324 (+20 – 304 in 2011)
- Patents Filed = 146 (-36 – 182 in 2011)
- Patents Issued = 87 (+2 – 85 in 2011)
- Royalty and Licensing Income = $99.6M (+$6.4M - $93.2M in 2011)

Continued growth is also projected for most categories in 2013 except for royalty income, which is projected to drop approximately 20% due to the expiration of certain patents.

Office for Interactions with Industry (OII)

Navigation of the complex relationship between academic research and the for-profit biomedical sector continues to be a priority for OII. Key accomplishments in 2012 include: 1) the integration of all the separate Partners policies on conflicts of interest and interaction with industry into a single policy document; 2) implementation of revised standards regarding the ban on participating speaking and training presentations paid for by industry; and 3) new policies, processes and systems for compliance with the new (2012) Public Health Service regulations for PHS funded research.

The new PHS regulations place substantial additional compliance burdens on both the hospital and its investigators, including shifting responsibility from the investigator to the hospital for determining whether a relationship exists between an investigator's disclosed financial interest and their research. This change has resulted in a six-fold increase in the number of cases OII reviews! To deal with this increased burden and regulatory complexity, OII has developed new functionality in the electronic disclosure system for submitting financial interests and travel reimbursements, and has delivered new training to over 2600 investigators involved in research.

2012 Initiatives

Remembering For Whom We Work. Listening to your customers is a fundamental tenet of business. Yet, the larger, more complex, and geographically dispersed a support organization gets, the harder it is to retain focus on this basic principle. Remembering that everyone engaged in the conduct of research at MGH is our 'customer', the Research Management office in 2012 established the **MGH Prime Directive for Research Support**: *Focus on the researcher. Further the research mission and bring value to it. Maximize the researcher's time 'at the bench' by eliminating or maximizing the efficiency of their ancillary obligations.*

This directive has served as the guiding principle for establishing a number of initiatives in 2012 to improve communication and better support our research enterprise.

MGH Research Management

Executive Report for SAC 2013

1. Continuous Research Operations Improvement (CROI) Program. 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.

Why do this? In addition to simply being good business practice, a recent survey by the Federal Demonstration Partnership found that PI's spend an average of 42% of their time on administrative activities! Anything we can do to allow our researchers to spend more of their time actually doing research will facilitate scientific discovery, speed the development of medical advances and cures, and improve job satisfaction and retention within the research community.

Our approach to CROI is based on leveraging technology to improve communication and foster a *continuous* improvement process where the status of projects resulting from suggestions are publicly monitored to provide *accountability,* promote *transparency,* and build *trust* between our researchers and those who support them. A complete description of the CROI program—its development, governance, and instructions for use—can be found at our main CROI website: **http://mghresearch.partners.org/ResearchMgmt/CROI.aspx**.

Suggestions received are directed to Working Groups that meet regularly to address the issues presented and work on solutions. They are organized around 13 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. A full listing of the current Working Groups, including the membership and charge of each, can be found on the main CROI website given above.

Three months after launching the program, over 170 suggestions have been received and over two dozen have already 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) developing new job codes for graduate students, undergraduates, and high school interns to streamline their in-processing, payment, and overall integration into the research community; 4) 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]; 5) the creation of a new Research Safety Committee for the hospital; 6) a new pilot email system with dramatically expanded mailbox capacity through automatic archiving and retrieval. A summary of every active suggestion as well as the current status of progress on its resolution can be found on the Suggestion Box website: **http://croi.mgh.harvard.edu/SuggestionBox, which is updated regularly**.

2. Research Help and 'How To' Website. Sometimes, just knowing *where* to go for help is half the battle. Yet, in complex organizations, help resources are often scattered across many departments and websites. To address this concern (and common complaint!), MGH Research Management established a new Research Help and 'How To' website: **http://mghresearch.partners.org/ResearchMgmt/ResearchHelp.aspx**.

On this website, we compiled an alphabetical list, by topic, of the most frequently used information sources—help websites, contact names, phone numbers, and email addresses—to help our researchers quickly find what or who they need. The list is updated and refined constantly from suggestions received from researchers and support staff by the CROI Intranet Working Group.

3. Research Help and 'How To' On Call Line. If a researcher has a problem where they have been unable to find the right person or support department to help using the Help and 'How To' website, if their problem is complicated and they don't know how to get started, or if they have an urgent (but non-emergency) issue, researchers can now call the Research Help and 'How To' on call line at: 617.726.HOW2 (4692). Calls are routed directly to the cell phone of the senior research administrator on duty that week. Personal help and advice is rendered and, as necessary, other staff members are brought in to address the concern.

4. Updated MGH Research Intranet Website. In conjunction with the development of the Research Help and 'How To' website initiative, the CROI Intranet Working Group has done considerable work on the MGH Research Intranet site to 'de-clutter' it, rename headings, and reorganize content to make it more intuitive and user friendly. Additional work continues to be done on the updated site: **http://mghresearch.partners.org/** to bring more features, functionality, and clarity to it.

Renewing Our Commitment to Safety. A concern recognized and now being addressed by Research Management in FY12 is the need to develop a comprehensive safety program for the research community. The current safety structure, where a single research representative sits on the greater MGH Safety Committee, does not provide an adequate mechanism for vital safety information specific to the research community to be communicated effectively to our researchers.

While responsibility for the safety of lab personnel ultimately rests with their PI supervisor, we must ensure that the institution is doing all it can to create a safe work environment and provide PI's and departments with the information and tools necessary to proactively promote safety on a regular basis. In accordance with this goal, we assembled in the summer of 2012 a research safety working group that has pulled together all relevant research safety policies and procedures and assembled them into a comprehensive research safety manual. They completed a similar process for all of the research safety training requirements. The group also developed a Research Safety Committee organizational structure that will assure appropriate representation for all research departments as well as support departments that play a role in safety. Department and unit chiefs have fully supported the creation of this new committee and have all named Departmental Safety Coordinators to serve as their safety liaison and official representative on the committee.

Following a presentation by working group representatives describing this research safety initiative at the January 2012 meeting of the MGH Safety Committee, the Committee officially approved and endorsed the establishment of an MGH Research Safety Committee. Its inaugural meeting is scheduled for April 2013.

MGH Research Management

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Facing the Challenges Ahead: The New Strategic Plan. In early 2012, MGH and MGPO senior management launched a strategic planning effort, encompassing all four aspects of the hospital mission. Phase one of this work culminated in a retreat on April 20, at which senior leaders from across the organization came together to discuss key strategic issues through case presentation and small group sessions. As a result of this effort, six mission-focused workgroups were formed and charged with developing a series of strategies and tactics for their assigned strategic domain. Two such workgroups were formed to address aspects of the research mission, a Research Workgroup whose overarching charge was to organize MGH research for the greatest success and impact in the coming decade, and a Research-Clinical Workgroup to focus specifically on better integrating our research and clinical missions.

The strategies and tactics proposed by these two research workgroups will be presented during the SAC meeting on order to gain feedback on their viability and insight on how best to prioritize them. Therefore, rather then describing each component of the plans in detail here, I will list the key elements of each plan at the end of this section, and provide background for the bases on which they were developed.

As stated earlier, 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. We will need to expand our philanthropic efforts, our collaborative relationships with neighboring academic research centers, and our interactions with industry to both replace the lost of traditional federal grant funding and compete successfully for funding redirected toward translational research. We must find ways to involve both our clinicians and patient community more directly in improving healthcare.

The traditional separation of academia and industry has resulted in generations of innovative biomedical scientists who possess the creativity to develop new therapeutics, devices, and treatments, but who lack seamless access to clinical collaborators and other resources required to turn their discoveries into products that can benefit patients. In order to make our research enterprise competitive, we need to show our investigators the path forward for their promising ideas and to make the necessary resources available to them. We need to show patients the value of participating in clinical trials and in consenting to allow their samples to be used in research. We need to offer industry a formal invitation to explore development opportunities within the hospital by showcasing and expanding our current basic, translational, and clinical capabilities.

The good news is that we already have most of the base assets we need to accomplish these goals and sustain and grow our research enterprise. The bad news is that we haven't adequately organized or supported these assets on an institutional level. Nor have we made them visible to the private sector or even readily accessible to all of our own investigators. We will be successful in the coming decade only if we overcome these challenges now, by developing overarching goals and implementing key strategies to sustain and grow the research enterprise into the next decade. The Research and Research-Clinical Workgroups have done just that.

The Research Workgroup takes as its overarching goal the creation of an MGH Research Institute to become home to broad strategic alliances, increase public visibility, improve and expand relations with industry and external institutions, and provide an internal infrastructure to more directly and effectively support our research community. Within the Research Institute, we propose to implement strategies to:

- Foster and support the growth of team science.
- Solidify the institutional funding base for the research enterprise.
- Optimize use of current research space and prepare for future needs.
- Foster innovation through improved infrastructure, communication, and more efficient use of resources.

To address similar concerns relating to the integration of our clinical and research missions, the Research-Clinical Workgroup developed three key strategies that will:

- Distinguish the MGH by creating a true focus on integrating research and patient care.
- Establish a world-renowned, broad-based "LIFE Registry" to enable MGH investigators to better characterize disease, identify targets for therapy, and enable precision medicine.
- Create the pre-eminent academic medicine translational research program in the nation.

Bringing the strategies of the Research and Research-Clinical Workgroups to realization will require capital investment, modest for some programs and more substantial for others. But, it will also require extensive investments in time and effort, in fostering an even closer relationship between senior management and our scientific leadership, and in assuring our investigators that these initiatives will not constrain their opportunities through centralization, but rather expand them by improving our support infrastructure, increasing our visibility, and integrating their programs into the fabric of a cohesive research enterprise.

Respectfully submitted,

Harry W. Orf, PhD

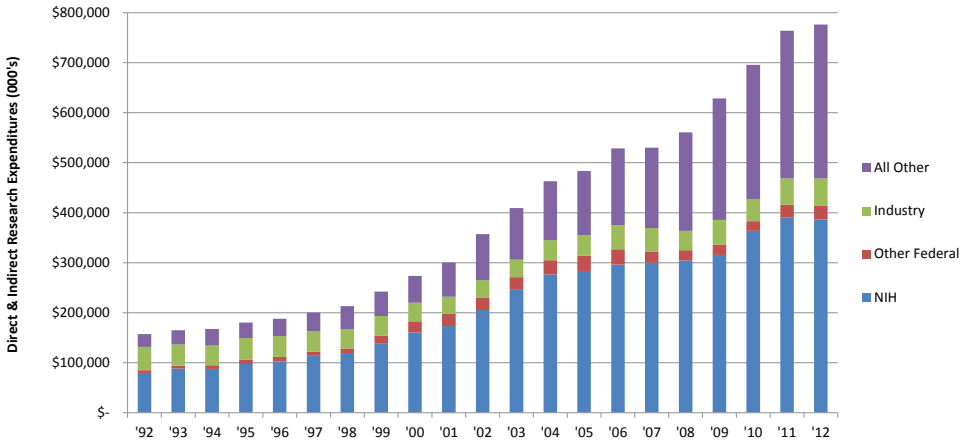
MGH 1811 RESEARCH Management | *Mainstay of MGH Innovation*

MGH Research Management

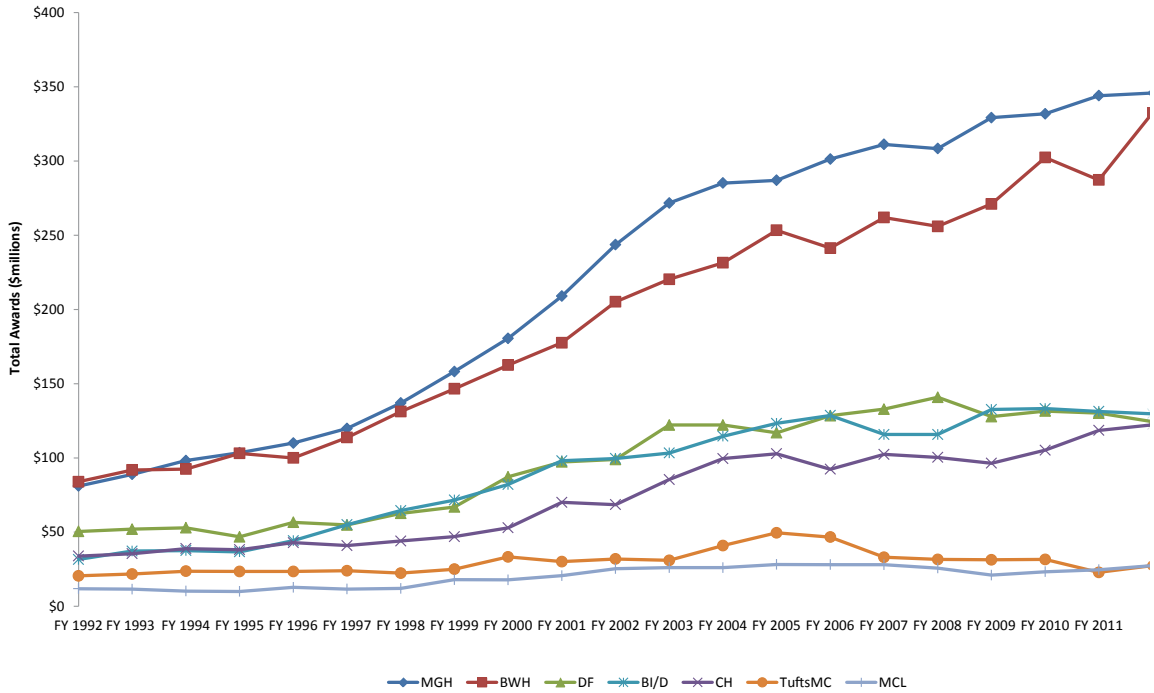
Executive Report for SAC 2013

MGH Research has grown 394% over 20 years to $776 M

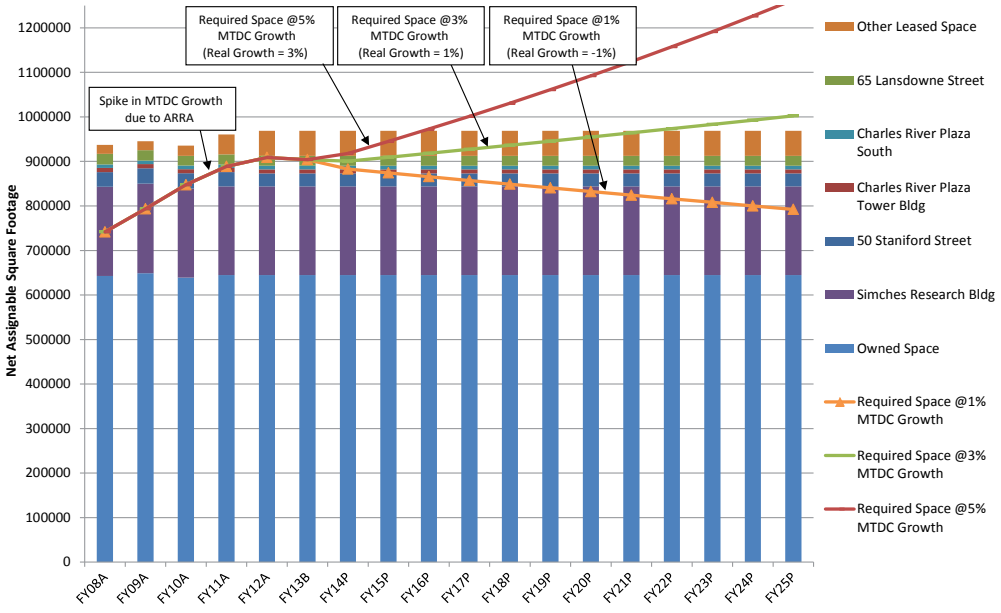
MGH combined research has grown at a compounded annual growth rate of 9.5% between FY97 and FY12. The 5-year moving average annual growth has decreased from 8.3% in FY07 to 6.7% in FY12; the FY11-FY12 growth was 1.6%.



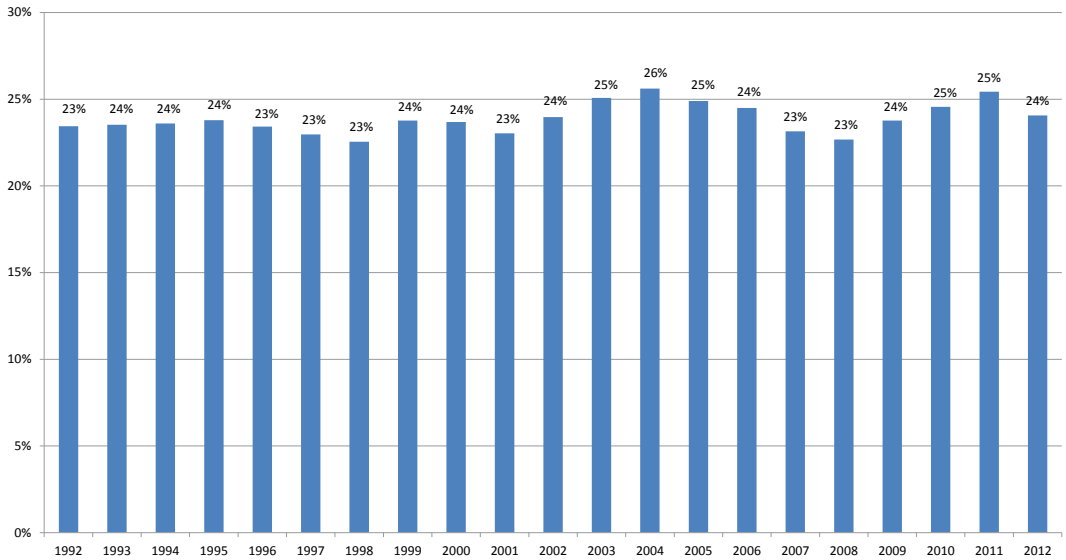
NIH Extramural Awards- Top Local Hospitals
FY 1992 - FY 2012



MGH Space Need Based on MTDC Density



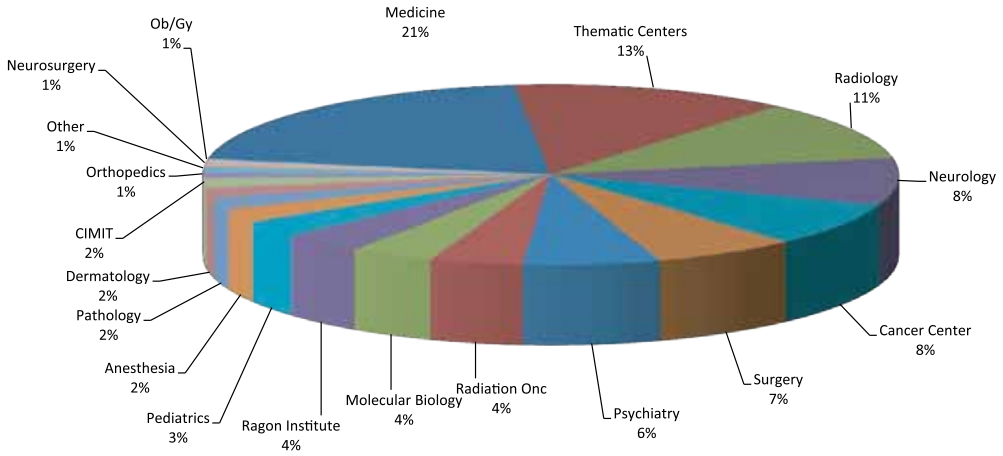
MGH Research Revenue as a Percentage of Total MGH Operating Revenue
FY1992 - FY2012 Actual



MGH Research Management

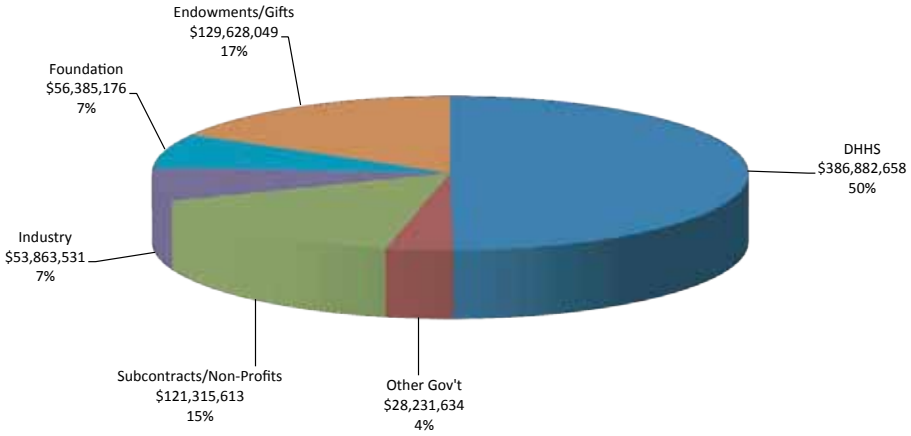
Executive Report for SAC 2013

FY 2012 MGH Research Expenditures
by Department
Direct & Indirect Expenditures $776M



Notes:
• Expenditures include ARRA funding
• Surgery includes Pediatric Surgery, Oral Surgery and Urology
• Other includes Administrative Departments

Massachusetts General Hospital
Total Research Expenditures FY 2012
$776,306,661



Notes:
• DHHS includes ARRA funding
• Other Gov't includes Other Federal and State/Local

MASSACHUSETTS GENERAL HOSPITAL
Science Activity by Sponsor

Type of Activity	Fiscal Year 10/01/11-09/30/12 Direct	Indirect	Total
Federal & State	282,102,729	133,011,563	415,114,291
Non-Federal	294,513,651	66,678,719	361,192,370
Total Expenses FY 12	576,616,380	199,690,281	776,306,661
Analysis of:			
Federal Activity by Sponsor			
DHHS	250,444,801	119,377,290	369,822,091
ARRA	12,092,227	4,968,339	17,060,567
DOD	17,681,044	7,671,055	25,352,099
NASA	288,328	201,954	490,282
NSF	762,956	503,984	1,266,940
DOS	132,529	97,969	230,499
Dept of Veterans' Affairs	20,570	6,714	27,285
Other Federal	165,453	45,447	210,900
Total Other Federal Activity	19,050,880	8,527,124	27,578,004
Subtotal Federal	281,587,908	132,872,753	414,460,662
State	514,820	138,809	653,630
Total State Activity	514,820	138,809	653,630
Total Federal and State	282,102,729	133,011,563	415,114,291
Non-Federal Activity by Sponsor			
Industry	40,243,936	13,619,596	53,863,531
Foundations	51,669,533	4,715,644	56,385,176
Subcontracts/Other Nonprofit	88,852,930	31,543,395	120,396,325
MGH Endowment & Gifts	112,827,964	16,800,085	129,628,049
Total Non-Federal Activity	293,594,363	66,678,719	360,273,082
Total Expenses	575,697,092	199,690,281	775,387,373
Harvard Medical School	919,288	-	919,288
Grand Total	576,616,380	199,690,281	776,306,661

Executive Report for SAC 2013

MASSACHUSETTS GENERAL HOSPITAL
SUMMARY OF DIRECT AND INDIRECT COST SCIENCE ACTIVITY
FY 1989 - FY 2012
(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
Government Grants & Contracts	$415,951	$415,114
Industry	$52,497	$53,864
Foundations	$64,620	$56,385
HMS Grants & Endowments	$1,258	$919
MGH Endowments & Gifts, Subcontracts /Other Nonprofit*	$229,719	$250,024
Total Direct & Indirect Costs	**$764,045**	**$776,307**

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

MASSACHUSETTS GENERAL HOSPITAL
SUMMARY OF ALL DIRECT COST SCIENCE ACTIVITY
FY 1983 - FY 2011
(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
Government Grants & Contracts	$289,838	$281,588
Industry	$40,643	$40,244
Foundations	$59,462	$51,670
HMS Grants & Endowments	$1,258	$919
MGH Endowments & Gifts, Subcontracts /Other Nonprofit*	$182,911	$202,196
Total Direct Costs	**$574,112**	**$576,616**

**2007 MTDC is restated*

**2008 MTDC includes Animal Facility and adjustments*

Center for Faculty Development (CFD) 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 communities respectively.

In 2012 the CFD 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 *75 programs and close to 2,238 faculty, fellows and other professional staff in attendance* at these programs. In addition, 181 individuals (79% of which were faculty, the other 21% were research/clinical fellows and other staff) *visited one of the offices this past year,* the vast majority was for promotion and career advice. One hundred and forty two of these individuals (75% faculty and 25% staff) were seen by CFD Directors/staff, and the other thirty nine individuals came to the office for consults with external consultants relating to difficult conversation scenarios or life coaching. We are excited that this year, the Graduate Student Division (GSD), supported and funded by the Executive Committee on Research, was created effective 12/1. After a thoughtful search process, Thilo Deckersbach, PhD was named its founding director. This office aims to serve the practical needs of graduate students from all academic institutions who are associated with basic and clinical research faculty at MGH and foster a graduate student community at MGH. The goals of the GSD are to serve the basic practical 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: 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: Annual Career Conference Initiative, the New Faculty Orientation, and the status of the Center and its associated offices. This year the CFD added additional faculty members to the Council to leverage cross-departmental experiences.

In the past year the CFD has:

- Facilitated the *third* round of the **MGH Faculty Mentoring Program** with Claflin Distinguished Scholar Award winners with 18 mentoring participants, consisting of three structured training sessions and included creation of an action plan for each mentoring pair. Senior award winners were paired with junior award winners to meet their mentoring objectives. In addition, 89% of the mentoring participants were individually interviewed for feedback. The participant feedback showed the program netted successful matching of pairs, action plans for participants and recommendation to continue the program.
- Consolidated our communications into weekly targeted emails from each office to help streamline our messages to the respective constituencies.
- 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:
    - Continued delivering ACC "Difficult Conversations" training program for faculty who are responsible for giving ACC's as well as other senior leaders. This year both a classroom session was held on 4/26/12 with ~15 faculty members in attendance. This year we also offered individual follow up sessions for faculty who attended a formal session. Eleven faculty members took advantage of the individual sessions and very positive feedback was received.
    - The CFD worked with individual departments over the course of the year to enhance their ACC process and completion status (e.g. Pediatrics (5/8/12, 8/13/12), Radiation Oncology (5/23/12), Psychiatry).
- This year the CFD offered 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. Twenty - eight faculty members attended these coaching sessions.
- Created the **John T. Potts, MD Faculty Mentoring Award** to celebrate good mentorship and help build a "culture of mentoring." John T. Potts, MD was named the first recipient. The call for the next round of nominations went out in 2012 and the winner will be named in 2013.
- Hosted the second annual **New Faculty Orientation** program on 10/14/12 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, David Torchiana, MD, Harry Orf, PhD, Anne Klibanski, MD and Maureen Connelly, MD to name a few. There were approximately 75 new faculty in attendance.
- Hosted a myriad of programs and workshops to help faculty at all stages in their careers:
    - **Academic Career Development:** Sessions were held on 6/4/12, 6/12/12 and 6/20/12 to increase awareness of HMS Promotion Criteria and Areas of Excellence with close to 60 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 2/28/12 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 3/8/12 with approximately 40 faculty members in attendance.

  - **Faculty Development Series:** Multiple sessions were held over the course of the year with more than 250 attendees. E.g. Conflict Management at Work (1/19/12), Nancy J. Tarbell, MD, Faculty Development Lectureship Series (5/2/12), Negotiation Essentials (4/9/12), Dealing with Challenging Negotiation Behaviors (4/9/12) and MGH Faculty Speed Networking Event (2/23/12)
  - Co-sponsored with CFD Offices: A three part career advancement series was held (1/11/12) in conjunction with the Office for Clinical Careers. The sessions focused on crafting the CV narrative, preparing HMS CV and understanding the HMS promotions' process. Approximately 75 faculty members were in attendance. In addition, the Faculty Mentoring Program was held in conjunction with the Office for Women's Careers. These sessions were held 2/8/12, 5/17/12, 12/3/12 and 12/13.

- **Outreach efforts** included meetings with new departmental chairs: Neurology (5/9/12) and Urology (7/25/12); professional development opportunities with Orthopedic Surgery (8/6/12) and HMS New Faculty Orientation (11/1/12 and 11/13/12).
- Collaborated with Consortium of Harvard Affiliated Faculty Development and Diversity Offices (CHADD) to host: **"Building a Culture of Mentors"** a faculty development course for mentors that drew approximately 75 participants from across Harvard hospitals. Keith Miller, PhD from MGH facilitated a break out session on Mentoring Research Fellows at this event held 11/16/12.
- Actively participated on HMS Joint Committee on Status of Women Task Force, Multicultural Affairs Office Advisory Board, and MGH Leadership Academy Curriculum Committee.
- 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 tocontinue to provide networking opportunities for the faculty.
- Continue the ACC initiative by continuing to offer Difficult Conversations training and implementing educationalprograms on conducting the ACC.
- Continue to offer the faculty mentoring program to other departments within the hospital.

Office for Research Career Development (ORCD)

Center for Faculty Developement

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 (numbering over 1000) including administering the MGH Guidelines for Research Fellows and advising the Mass General Postdoctoral Association (MGPA). In 2012, 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. As mentioned in the CFD section above, a new initiative—the Graduate Student Division (GSD)—became effective on December 1st. A faculty director and program manager were recruited in 2012. The next steps for this important office include identifying and quantifying the graduate student constituency at MGH, identifying their needs, creating an advisory structure to help guide the division, and reviewing/restructuring the current transportation program that facilitates access to the HMS quad for graduate students working in MGH laboratories.

In 2012 the ORCD continued to expand efforts to educate junior faculty and research fellows about career options, and instituted a monthly series on the Responsible Conduct of Research (RCR), as part of the Partners institutional RCR education for NIH-funded trainees. The office also developed a new initiative aimed at providing support, resources, and access to MGH research leadership to faculty who have their first R-level NIH grant. This *New Investigator Advancement Initiative* was launched in October 2012.

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 2012, new members were invited to leverage cross departmental knowledge and expertise.

In the past year, the ORCD has:

- Launched the New Investigator Advancement Initiative (NIAI) for MGH faculty who currently hold their first NIH RIevel grant. 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. The 2012 NIAI is comprised of a core group of approximately 15 new PIs who have committed to attend NIAI meetings throughout the academic year. The group met three times in 2012 to discuss: Resources from ORCD and ECOR (10/18/12), the MGH Research Landscape (11/8/12), and Research Integrity (12/6/12). Three additional meetings are planned for 2013.
- Conducted 42 individual **advising meetings** with members of the research community, including 19 faculty and 23 fellows/other research staff. We expect the current funding climate to bring in more faculty over time to reach out for advice on career building, stabilization, and/or career transitions.
- Sponsored the 6th annual **Research Fellows Poster Celebration,** an event to recognize the excellent research being done by our postdoctoral fellows. In 2012 we expanded the event by adding two lectures: the Trends in Biomedical Science Lecture given by Rakesh Jain, PhD, Andrew Werk Cook Professor of Tumor Biology (Radiation Oncology) at HMS and the Director of the Edwin L. Steele Laboratory of Tumor Biology at MGH Cancer Center, and the Research Career Development Lecture was given by Orfeu Buxton, PhD, Assistant Professor, HMS and

Associate Neuroscientist, Brigham and Women's Hospital. Sixtyresearch fellows submitted abstracts and presented posters, and a review committee chose the top twelve posters to receive special recognition and cash prizes. A luncheon following the awards ceremony allowed the winning postdocs an opportunity to network with MGH leaders. This event, attended by MGH President Peter Slavin, was highlighted in the MGH magazine Hotline on 6/8/12.

- Developed a **Career Explorations Series,** to help fellows and junior faculty learn more about careers outside of academia. Programs included: Industry Exploration Program Introduction (3/9/12), Invention Liaison Program Panel Discussion (3/28/12), Careers Away from the Bench Networking Lunch (5/9/12), Preparing for Industry: Resume and Cover Letter Tips (6/7/12). Approximately 130 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 2012 the ORCD offer six hours of RCR training including: Responsible Authorship (1/6/12), Peer Review (2/16/12), Avoiding Research Misconduct (3/23/12), Data Integrity (7/17/12), and Collaborative Science 11/14/12,with approximately 250 researchers in attendance.
- Continued to offer seminars to enhance researchers' **Communications Skills,** including Publishing in the 21st Century (9/12/12) by Martin Frank, President of the American Physiological Society and a thought leader in the publication world, with approximately 80 researchers in attendance. Continued to sponsor and administer **English as a Second Language** classes for the research community, with a total of 123 students enrolled across the spring, summer and fall sessions of 2012. 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** to help guide trainees and junior faculty to funding success. In 2012 the office updated the workshop to include advice from grant administrators as well as faculty, in an expanded 2-part series: The Business of Grant Writing: Advice from Grant Administrators (1/24/12) and Tips for a Successful Grant: Advice from MGH Faculty (2/1/12). Approximately 120 researchers attended these sessions.
- Hosted a **"Yoga for Mindfulness and Resilience at Work"** seminar as part of our work life efforts, with 12 attendees.
- Further expanded the **Industry Exploration Program (IEP):** In collaboration with the Mass BioEd Foundation, we guided an expansion allowing postdocs from other local research institutions to join the IEP. As of December 2012 there were a total of 117 postdocs taking part in the IEP, including 50 MGH postdocs. The IEP is now in its third year of educating research fellows about career options in industry by facilitating group visits to local biotech companies.
- Assisted the MGPA in the administration of the inaugural **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 2012, two research fellow applicants were selected for the $1000 awards.
- Participated in **National Postdoc Appreciation Week** with an Ice Cream Social networking event for research fellows on 9/27/12 to celebrate their contributions to the research community. Approximately 75 research fellows attended this event.
- Continued our successful **Orientation Program** for Research Fellows, now in its fourth year. This program assisted ~ 40 new postdocs during 2012 with small group lunch meetings aimed at communicating information on MGH resources and an introduction to ORCD staff and MGPA postdoc volunteers, on 2/17/12, 4/10/12, 7/10/12 and 10/26/12.

- Modified the **Appointment Extension** process for research fellows who reach the 5-year term limit by requesting departments to provide additional information on the postdoc's recent career plan. In cases of extensions exceeding 7 years, a meeting with the ORCD director may now be required.
- 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.
- 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 2012, the MGPA helped to expand the Industry Exploration Program (IEP, see below), and ran programs on career advancement, (MGPA Annual Membership Meeting, 1/30/12; Introduction to the IEP, 3/9/12, Career Panel Discussion, 11/30/12, communication (the PhD Movie and discussion, 3/20/12, work-life balance (Postdoc Parents Lunch Forum, 2/9/12 and networking (Naturally Obsessed movie and Pub Night, 10/24/12) and co-hosted a mixer with Harvard and MIT post docs, (11/29/12). Approximately 240 post docs attended these programs.

Future Activities:

- Continue to provide programming and advocacy for MGH research faculty, geared toward career development and career satisfaction. As the research funding climate becomes more complex and difficult, it will be crucial to offer strong programs and initiatives that can help faculty achieve funding and research success, maintain and elevate their work and professional satisfaction, and recognize the critical role that they play in the mission of the hospital.
- 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. One such focus might be on developing skills to communicate our science to the public.
- Develop programs and initiatives to guide faculty through the anticipated difficult changes in NIH funding, especially those investigators who may consider career transitions in light of a decrease in research funding. These may include:
    - Contributing to an HR working group to assist researchers in transition due to loss of funding/transition of the laboratory.
- Setting up an internal network to allow lateral transitions within MGH in order to retain highly trained individuals within our research community.
    - Increasing 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 and constituents.
- Continue to clarify and improve the process for granting extensions on the 5-year term limit on the research fellow position.
- Work with the new Graduate Student Division to fulfill the needs of the graduate community at MGH.

Office of Clinical Careers (OCC)

Center for Faculty Development

Theodore A. Stern, MD, Director

The Office for Clinical Careers (OCC) at MGH is 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 (3/20/12 and 9/13/12) 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 (1/12/12 and 5/31/12) 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 three part series covered areas important to teachers: "Enhancing Teaching Skills: Delivering Feedback", "Building an Academic Product" and "Improving Your Presentation Skills". These sessions had approximately 60 faculty in attendance.

Provided programs:

- **Academic Career Advancement:** In conjunction with CFD, a three part career advancement series was held on 1/11/12. The sessions focused on crafting the CV narrative, preparing HMS CV and understanding the HMS promotions' process. Approximately 75 faculty members were in attendance. In addition, the OCC hosted another session "Crafting Your CV Narrative" on 11/29/12 and had 36 faculty in attendance. A new seminar "Drafting Your Chief's Letter" was held on 12/11/12 and approximately 20 faculty members attended.
- **Professional Development:** A two part Scholarly Writing Series on "Case Reports" was held on 6/13 and 6/27 and had ~20 faculty in attendance. The OCC also co hosted a two part Scholarly Writing Seminars Series (3/15/12 and 3/29/12) with Office for Women's Careers. There were 47 faculty members in attendance. In addition, co facilitated Session II of the faculty mentoring program for Claflin Distinguished Scholars.
- **Collaborated** in many of the CFD programs through out the year.
- Participated as a member of Executive Committee on Teaching and Education (ECOTE), to bridge the educational mission of the OCC and ECOTE.
- Provided individual career *advice and counseling*: This year, approximately 80 faculty members have visited the office. These visits covered the promotions process and readiness, career advancement and CV critique.
- The OCC participated in a Neurology department outreach meeting this year. In this meeting on 9/6/12, the Annual Career Conference was discussed with Division Chiefs, to enhance their knowledge. Approximately 20 faculty were in attendance.

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

- Educating 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
- Providing a repository of educator resources by collating existing options (rather than re-inventing the wheel)
- 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 faculty will be given the same opportunity as men faculty to succeed in research and clinical careers at MGH. Through many programs and collaborations, the OWC provides career development resources for women. 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, comprised of administrative and faculty leaders, 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, met two times in 2012, 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 and the Claflin Consultation Initiative.

In the past year, the OWC has:

- 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 (1/26/12, 4/12/12, 11/15/12), and the Faculty Parents Group offered advice from child development experts in a small supportive group setting (3/13/12, 4/25/12, 8/10/12). There were 120 attendees at these sessions.
- Continued the successful annual workshop on **Leadership Strategies for Women Faculty** (5/14/12). The 2012 workshop, "Building Your Leadership Strengths to Influence and Inspire Others," featured HMS Dean Nancy Tarbell as a special guest speaker. Twenty-one 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 Joan Brugge, PhD (4/6/12), and Patricia D'Amore, PhD (12/6/12) with approximately 30 faculty in attendance.
- Collaborated with the Office for Clinical Careers on the **Scholarly Writing** Series on 3/15/12 and 3/29/12. There were 47 faculty members in attendance.

- Ran a full-day Business of Life seminar for women faculty with facilitator Allison Rimm on 7/30/12. 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 2012 session were also able to take advantage of one hour of personal coaching by Ms. Rimm. Twenty eight 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 6/14/12 with 44 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. Twelve applicants were matched with alumnae in 2012, and one of them won a Claflin award. In addition, we hosted a panel discussion (1/10/12) in which two recent Claflin awardees communicated advice and encouragement to potential applicants. Twenty faculty attended, including two who went on to win awards in 2012.
- The OWC outreach included presenting the Claflin Award history and impact to ECOR (9/10/12) and meeting with new department chief: Neurology (5/31/12) to raise awareness of office and its resources and to review women faculty ready for promotion.
- Provided **individual advice and counseling** to women faculty. In 2012, approximately 20 women (18 faculty and 2 post docs) 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 Merit Cudkowicz, MD, Chief of Neurology, titled "From Chemical Engineering to Clinical Department Chair: Lessons Learned as a Woman in Academic Medicine. There were 60 faculty members in attendance at this event.
- Published the eleventh annual **Tribute Book** to celebrate the accomplishments of MGH women faculty.
- Began an in-depth study of gender and HMS faculty promotions. Assisted by MGH administrative fellow Calvin Richardson, we are looking at 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. Preliminary data were presented to the OWC Council and Committee in 2012 and additional analyses are being carried out.
- Collaborated with HR and the Department of Medicine to create additional **lactation room space** to support women faculty and trainees to continue nursing their infants after maternity leave. In 2012, a new lactation space was created in the female on call room on Bigelow 7.
- Explored gender differences in the patent disclosures of MGH faculty. Over the past 10 years, preliminary data show that approximately 12% of patent disclosures have come from women faculty.

- Continued collaborations with the Multicultural Affairs Office and Partners Graduate Medical Education Office regarding residency match data to be able to more accurately capture gender specific data. Participated in 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.
- Collaborate with Partners Research Ventures and Licensing to further explore gender differences in patent disclosures at MGH and develop 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 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 the topics of people management and public image in 2013.
- 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 leader

CONTENTS

Director's Overview of the Clinical Research Program: Year 16

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

A. The 2012 Clinical Research Program Progress Report

What follows is the 16th annual Progress Report of the MGH's Clinical Research Program (CRP). In it, each Unit details its 2012 accomplishments on behalf of the clinical research community. This report is an essential component of our accountability to the MGH for its ongoing investments in one of its franchise missions. These reports not only detail their impressive efforts but also describe the "Lessons Learned" and "Adaptations Planned". Several years ago we added these concluding components to the individual Unit's Progress Reports for two reasons. First, they chronicle the evolution in our collective efforts to serve the clinical research community. Second, they keep our strategic planning dynamic and responsive to the ever-growing complexity of the environment in which our clinical research community operates locally and nationally. Consequently, these components of our annual Progress Report are key to making the CRP's programs as nimble and contemporary as possible as we plan new initiatives to serve our community.

B. Future Institutional Challenges and Opportunities in Clinical Research

As part of the dynamic environment in which we find ourselves, Academic Medical Centers (AMCs) are facing future challenges to their unique societal niches in our nation's healthcare delivery, teaching, research, support of underserved and rare patient populations, and fostering continued innovation in biomedical research. Given that the full magnitude and dimensions of these challenges are still emerging, the question arises whether we should be making a pre-emptive effort to get out ahead of these challenges.

Clearly the CRP's notion of viewing the MGH's vision of a service model in which we view the clinical investigative community as our 'clients' to be served has been validated by several objective measures of the CRP's success as detailed in this report. Building upon the past 16 years of the CRP's successes, the recent efforts to expand this model across the full MGH research infrastructure by Harry Orf, the new Senior Vice President for Research, indicates that the MGH is attempting to leverage this model across all of the other MGH's institutional infrastructure. The first phases of realizing further opportunities to leverage these successes into greater programmatic and optional efficiencies could be achieved by instituting a common geographic co-translocation of other clinical research administrative support services. These include moving the Clinical Research Center (CRC) and the CRP's Administration and Units (Clinical Research Support Office, Biostatistics, Translational Medicine, Clinical Effectiveness, IT, and Education) into a common location where such space is available (like Simches 2). Thus, all MGH's infrastructures supporting clinical research could evolve from their current "cottage industry" mode wherein each views itself as a separate administrative solution to a portion of clinical researchers needs into a newly consolidated, "one stop shopping" service-model. This concept of developing a geographically and functionally unified 'one stop shopping' model is not new nor novel. It was originally proposed by the MGH's Strategic Plan for Clinical Research in 1996 but has never been realized. Such geographic consolidation would represent an important first step that would not only provide a common and more efficient access point for all MGH clinical investigators and their staffs to clinical research administration, it would also rapidly enable two further opportunities for operational efficiencies.

First, such a geographic translocation would enable the institution to issue a parallel mandate to each of these now-adjacent programs to work communally to define and thus implement common administrative procedures based upon the 'best practices' of each. Instituting such novel administrative coherence and streamlining would then allow the building of a common user interface and foster continuous process improvement that could be heavily leveraged.

Second, with such evidence of consolidation and improved efficiency at hand, the MGH could then require all other clinical research supporting services from HMS Catalyst and PHS (Internal Review Board, Partners Clinical Research Office, Research Finance & clinical research billing compliance, etc.) to open and staff 'service outposts' to assist MGH clinical investigators on site via a 'hoteling' arrangement. Depending upon the level of demand for these services, a rotating schedule of "office hours" could be supported. A common service model would be further enhanced by a single website and administrative database. The CRP's new website (http://www2.massgeneral.org/crp/) is designed to be a first step in this direction by supporting the linear workflow of the clinical investigators. As such it is an excellent example of what could be accomplished as our research infrastructure consolidates services to the community.

C. The Time to Change

The MGH has a clear need to streamline the efficiency of all administrative processes in the near future. In clinical research, we are presented with a unique moment to improve our current infrastructure given the need to do this sooner or later. These plans will then set the stage for other programmatic efficiencies that could also occur over time. This moment of opportunity is clearly at hand.

Figure 1: Clinical Trials Expenditures at MGH, FY 92-12

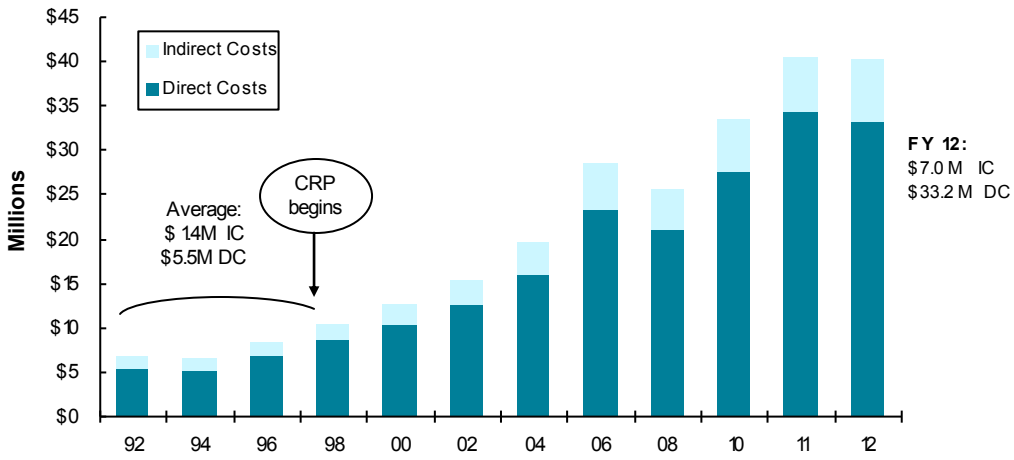
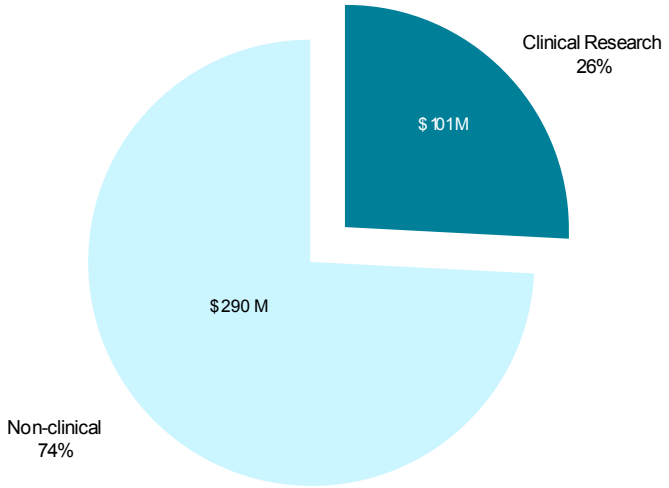


Figure 2: NIH and ARRA $ for Clinical Research in FY 12 - Estimated @ $101M



Enhancement of the Clinical Research Program's Website

Liz Salomon, Ed.M., Project Manager

In 2012, the Clinical Research Program (CRP) felt it essential to revise its website to create a new and more efficient tool to help clinical investigators and their study staff more easily navigate the clinical research process. In undertaking this revision, the CRP sought to provide researchers with faster access to the information, resources and courses necessary to support their work.

The process for this extensive revision of our website was multifold and included: market research, key informant interviews, strategic planning, content creation, website development and release and revision.

The new CRP website (http://www2.massgeneral.org/crp/) was based on Stanford's CTSA website which was modified to fit the needs of the MGH clinical research community. Key informants included the CRP's Director and Faculty and Staff. Their feedback was integrated into the strategic planning that surrounded this website's development. Content creation was managed by the Project Manager and the technical aspects of website development were managed by the CRP Office Manager, augmented by support from the CRP's Information Technology (IT) Unit. The new website was launched on Clinical Research Day 2012 to a very positive response from MGH investigators and study staff. As one investigator wrote: "Really terrific, Bill. I passed it along to all my faculty, especially the young ones. Great for them to have a road map." Since its launch the new CRP website has seen a marked increase in use—a 133% increase in October 2012 over October 2011 visits and a 203% increase in November 2012 over November 2011. The website will continue to be updated on a regular basis and will be revised in response to feedback from the MGH clinical research community.

The next steps in this process include further integration and promotion of new and innovative services offered by the CRP and collaboration with its IT Unit to create an automated recommendation engine that will supply investigators and study staff with service, course and consultancy recommendations based on their individual needs.

Clinical Research Support Office (CRSO)

Andrew A. Nierenberg, MD, Director

GOALS

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

Our goals are to:

- improve the quality, quantity, and safety of clinical research;
- facilitate careers of early career clinical researchers; and
- advance patient care through clinical research.

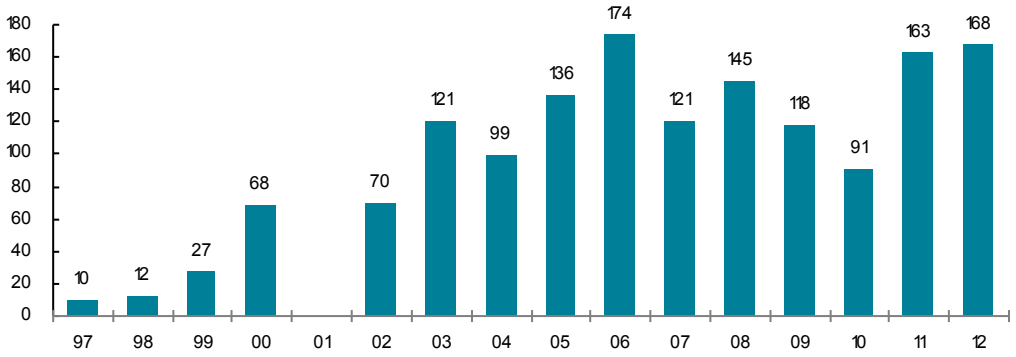
CRSO SERVICES & ACCOMPLISHMENTS

A. Clinical Research Faculty Mentoring with an Emphasis on K Programs

Mentoring MGH's clinical investigators, especially focusing on their early and midcareer development, continues to be a major focus of the CRSO's activities. While the CRSO faculty assumes the lead for the Clinical Research Program (CRP) in these mentoring activities, all CRP

faculty members devote a significant percentage of their efforts on this crucial pipeline activity. In 2012, more than 168 faculty and research fellows reached out to the CRSO (Fig. 1). This number represents a modest increase over the 162 investigators who sought CRSO consultations 2011.

Figure 1: CRSO: PIs Served per Year, 1997 - 2012



Dr. Nierenberg 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. He also reviewed abstracts for Clinical Research Day and presented at CRP-sponsored seminars on grant writing, how to give a presentation, developing careers in clinical investigation. He also developed workshops for junior faculty who are intending to apply for NIH Career Development (K) awards. Dr. Nierenberg also presented seminars or Grand Rounds to the Departments of Emergency Medicine, Anesthesia, and Orthopedic Surgery to discuss the CRP, the CRSO, and the underused NIH K awards, especially the K24 awards for:

i. CRSO Pool of Leasable and Flexible Study Coordinators

Six study coordinators fully trained and funded by the CRP are available to be leased in a flexible fashion by MGH's clinical investigative community to support a wide variety of clinical research projects. This flexible 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.

CRSO coordinators can prepare and track approval of Internal Review Board (IRB) submissions as well as gather and submit various regulatory documents for sponsors as part of study start up. Once a study is underway, CRSO coordinators assist in recruiting study subjects, attending clinic visits, collecting and entering study data, and meeting with sponsor's study monitors. This staff can manage all day-to-day clinical study activities collection and entry, and study close out. In 2012, CRP study coordinators supported 39 individual clinical investigators from 11 departments on 69 individual studies (Fig. 2a & 2b). In addition, a growing number of investigators and study staff are seeking advice and consultations on IRB submissions, either prior to their submission to the IRB or in drafting responses to the IRB's questions, (Fig. 2c)

Fifty two of 168 investigators (30%) used more than one CRSO service including Project Management (PM) support. 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 charges, and other practical interfaces with the Research Management and Financial Departments.

Of the 168 investigators assisted by CRSO faculty, PMs and coordinators, 47% were junior faculty members (instructors and assistant professors), 25.5% were senior faculty (associate professors and professors), 17.5 % were residents and fellows, and 10% were other non faculty professional staff. (Fig. 3)

Figure 2a: Study Coordinators: Projects by Department, 2012

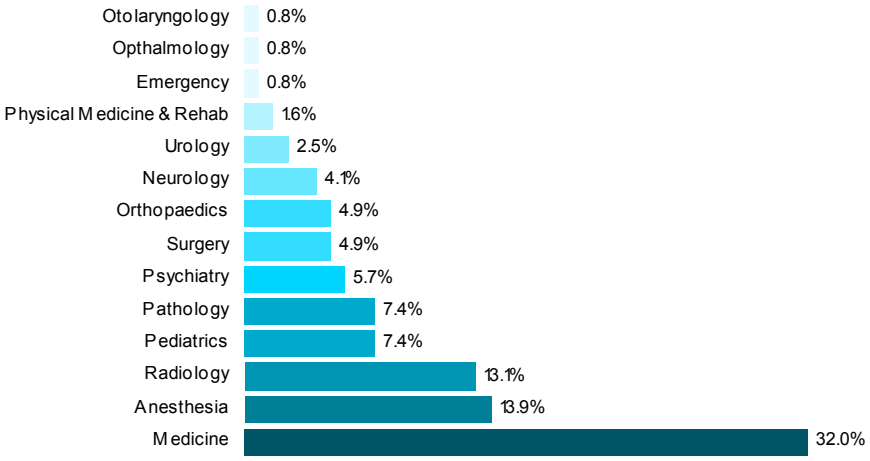


Figure 2b: Study Coordinators: Projects & PIs per Year, 2002 - 2012

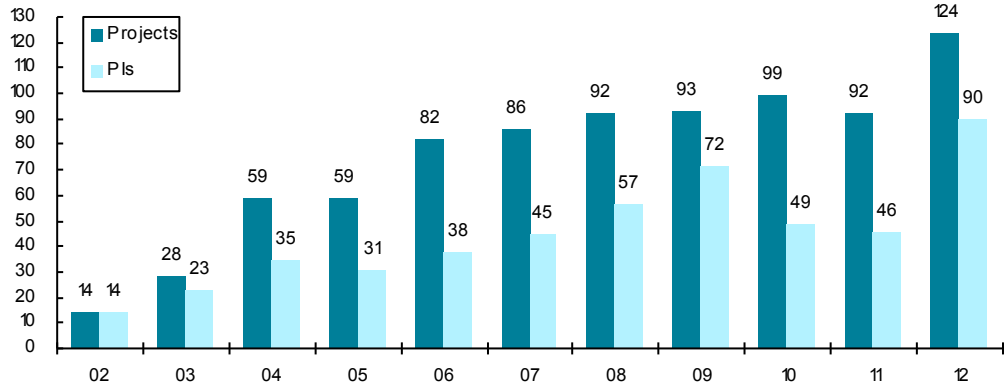


Figure 2c: CRSO: Consulting Hours by Service Type in 2012

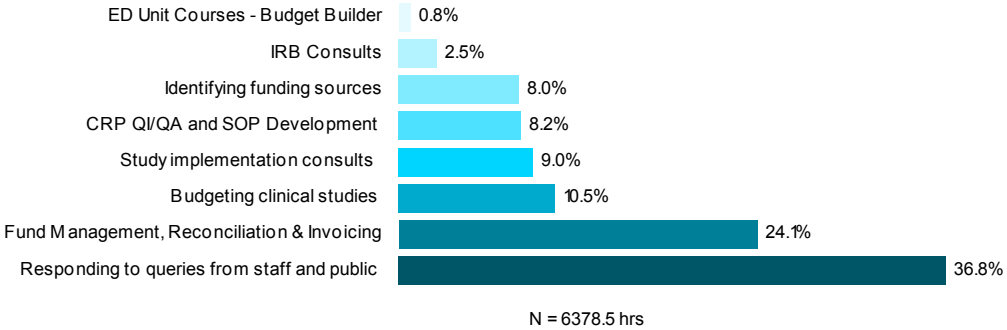
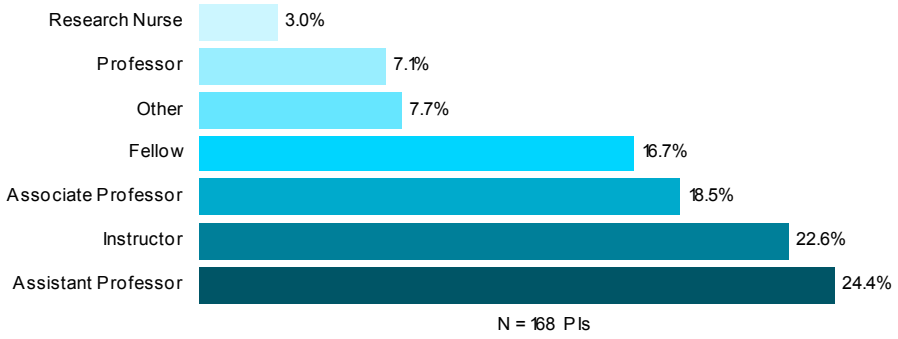


Figure 3: CRSO: PIs Served by Faculty Rank in 2012



B. 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 34 MGH investigators conducting a total of 51 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 out 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.

C. 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.

D. 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. The CRSO also offers interactive workshops specifically for Clinical Investigators applying for an NIH K Awards. These workshops, offered in April and December 2012 and attended by 50 junior faculty and fellows, focus on practical approaches including timelines and grant structure, with an emphasis on the unique requirements of these grants. 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.

E. CRP/CRSO Support of PHS Biorepository for Medical Discovery (PBMD)

Beginning in 2011, CRSO PM's and study coordinators instituted support for the Partners Biorepository for Medical Discovery (PBMD) program in MGH clinics. In 2012, the number of MGH clinics involved in the PBMD program expanded from a single clinic to multiple investigators in multiple clinics throughout MGH. Six Cardiology investigators, the Renal clinic, and the Blood Donor Center are now participating in the program. PMs facilitated start-up activity and rapid implementation of this PHS-wide resource. CRSO study coordinators obtain patient consent, perform phlebotomy, and collect and enter data into the PBMD consent tracking system. In 2012, 1,230 patients provided consent and specimens for the biorepository. In addition, our PM for this project developed monthly reports that will inform the continued expansion of the PBMD throughout the MGH. These management reports detail on a day-by-day and clinic-specific basis total hours involved in interacting with clinic patients, number of patients who provided and declined consent, and administrative support including time associated with IRB and PBMD IT staff interactions related to consent tracking software. Discussions are underway for continued expansion of PBMD in 2013 in several new clinics.

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 2012, RSVP for Health contained over 22,100 registrants, up from 20,500 registered in 2011 (Fig. 4).

Of the 22,100 registrants we have accumulated in RSVP, 14,116 (64 %) are women. Of the 22,100 registrants 16,625 have indicated an interest in participating in studies as healthy volunteers, thus serving 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 2012, MGH investigators used the RSVP database to recruit subjects for 79 individual MGH protocols, up from 60 in 2011. The heaviest users are investigators in the departments of Medicine, Psychiatry, and Radiology.

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 CRP services on junior faculty in recognition of their 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. Since this was an intensively interactive workshop with small groups learning from faculty and K24 awardees, the numbers still had to be

Figure 4: RSVP for Health: Registrants' Demographics

Category	Registrants	
	Count	%
Gender		
Female	14,116	64%
Male	6,922	31%
Not Recorded	1,059	5%
Total	**22,097**	**100%**
Race		
American Indian/Alaskan Native	92	0.4%
Asian	1,036	4.7%
Black or African American	2,759	12.5%
Native Hawaiian/Pacific Islander	69	0.3%
White	14,653	66.3%
Other	942	4.3%
Not Recorded	2,546	11.5%
Total	**22,097**	**100.0%**
Ethnicity		
Hispanic or Latino	1,422	6.4%
Not Hispanic or Latino	14,417	65.2%
Not Recorded	6,258	28.3%
Total	**22,097**	**100.0%**
Age		
<35	10,523	47.6%
36-45	3,168	14.3%
46-65	6,178	28.0%
66+	1,919	8.7%
Not recorded	309	1.4%
Total	**22,097**	**100.0%**
Contact Method		
Email	17,467	79.0%
Post	4,630	21.0%
Total:	**22,097**	**100.0%**

limited. 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 had challenges with the IRB or with managing finances of clinical research. We need to find out the gaps that had occurred and explore methods to prevent such problems from happening in the future. We will need to coordinate preventative measures with Harry Orf's office.

ADAPTATION PLAN

1. Expand specific email notices of available CRP services to clinical researchers who would benefit from the CRSO services to enable better access to this information on the website. Such 'push technology' should enhance serving the individual and varied needs of the MGH's clinical research community.
2. Improve the integration of assistance to young investigators with their mentors and communication with mentors and department chiefs.
3. Continue to encourage department chiefs to consider having Associate Professors in their departments apply for K24 awards.
4. 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.
5. Consider how the CSRO can facilitate early career faculty submitting their first RO1 whether or not they had a K award.

6. Create a dashboard to obtain feedback from mentees and follow up on K award applications, critiques, and those that were not funded as well as those that were. Build the database of critiques to discover patterns and frequently made errors. Build a database of successful K awards to be used as models for applicants. 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.

Clinical Research Education Unit (CREU)

Eric Rosenberg, MD and Janet Hall, 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 their allied healthcare personnel 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, coordinators and study staff, which are foundational and responsive to the ever-changing clinical research landscape. Most recently, the CREU has been capturing these educational offerings for online viewing, thus permitting a learning and operational efficiency that increases the productivity of both the clinical investigative community and our staff.

ACCOMPLISHMENTS

CREU courses are extremely well attended and received. The total number of attendees/online viewers increased yet again in 2012, achieving its highest level since the inception of the program fifteen years ago (Fig. 1). This is a testament to the ongoing need for local educational programs for MGH clinical investigators and their allied healthcare 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.

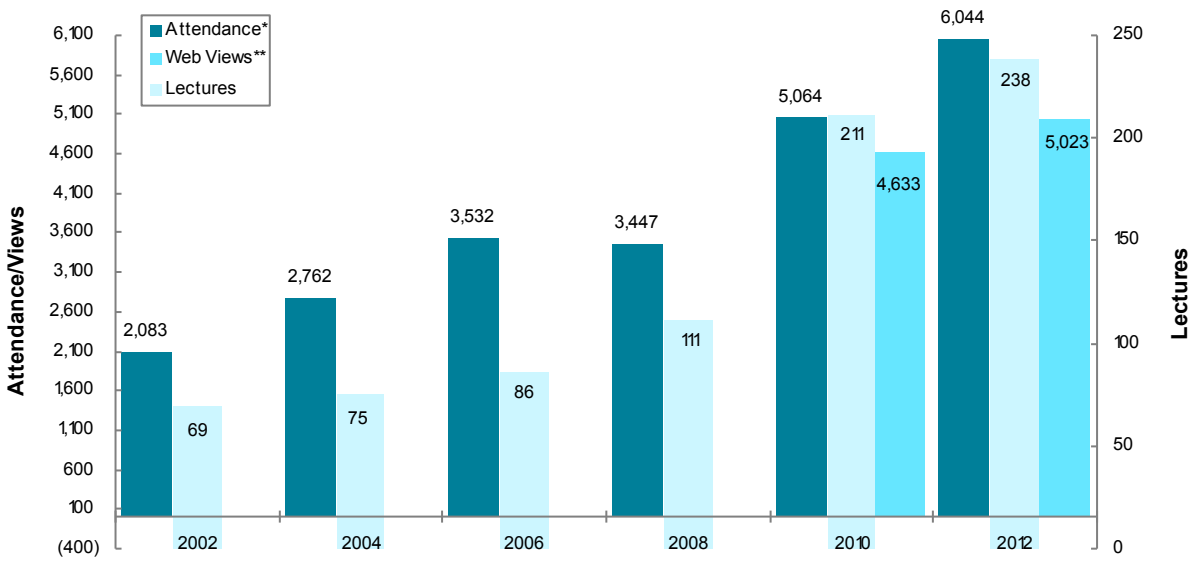
A key focus in 2012 was capturing our expanding online educational programming for the online viewing ease of our customers. Investing time and effort in online education allowed for continued, innovated course development. It also supports clinical investigators and study staff by making courses readily accessible. Online courses launched in 2012 include:

1. ***"Basics of Manuscript Writing for Clinical Researchers"*** This online training reviews the pre-writing phase, the writing phase, and the submission, acceptance and review phase of writing a manuscript.
2. ***"Recruitment and Retention Series: How to Develop a Recruitment Plan"*** This series introduces researchers and study staff to the basics of recruiting, enrolling and retaining study subjects.

A major initiative in 2012 was the development of the Internal Review Board (IRB) Hot Topics Series in collaboration with the Partners Human Research Committee. This series is offered quarterly—the first session was ***"Reporting of Study Results"*** followed by ***"Involving Children in Clinical Research."*** Future sessions will focus on obtaining surrogate consent, research misconduct and deception in clinical research.

Another major accomplishment in 2012 was the development of the CREU's first hybrid course—***"Recruitment and Retention Series."*** As mentioned above the CREU developed an online course focused on the basic concepts of recruiting and retaining study subjects. This online course was supported by two live sessions: (1) ***"Recruitment and Retention Basics from a Coordinators***

Figure 1: Attendance, Web Views and Lectures, 2002 - 2012

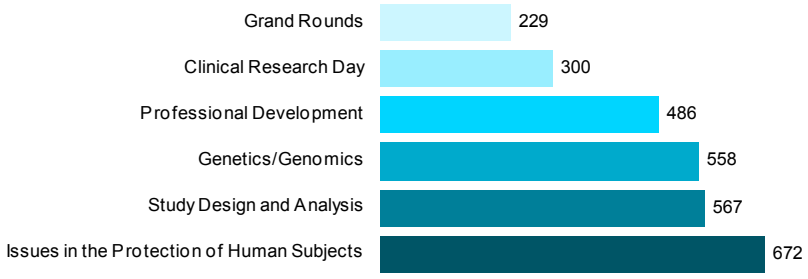


* An attendee is counted once per 'course,' regardless of whether the course is a single lecture or 14 sessions.
** Views are defined as the number of partipants who reviewed a recording of a live course or handout from that course. Multiple online resources available; individuals may overlap.

Perspective"; and (2) ***"Recruiting and Enrolling Minority Subjects into Clinical Trials."*** The final session was a ***"Recruitment Workshop."***

In 2012, 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.

Figure 2: Investigator Courses 2012
Distribution of Attendance per Course Category



Professional Development is a series of courses focused on skill enhancement and growth.

Investigator Program

At the forefront of the CREU's agenda in 2012 was the continued development of courses on cutting-edge topics for clinical investigators (Fig. 2)

The CREU has focused on faculty development and other pipeline issues by developing a core curriculum to support junior investigators in their research careers. The core curriculum consists of 4 courses:

1. ***"Fellows Orientation Part I and Part II"***
2. ***"The Design and Conduct of Clinical Trials"***
3. ***"Basic Biostatistics for Clinical Research"***
4. ***"Applying for an NIH Career Development Award"***
5. ***"Good Clinical Practice and Study Management Basics" (online)***

In addition to this core curriculum, the CREU offers more advanced courses to support clinical investigators in Genetics & Genomics, Clinical Effectiveness (***"Workshop on Study Design: Clinical Effectiveness Research"***) as well as ***"Applied and Problem-Based Biostatistics."***

The courses below were developed in 2012 and are being offered in 2013:

1. ***"Conquering the K: Submitting an NIH Career Development Award"***: Seven session series providing step by step instruction by CRP faculty and K24 awardees on preparing an NIH Career Development award. This was developed in collaboration with the CRSO.
2. ***"Introduction to Survey Research and Design"***: Four session course on survey design, IRB implications, database development, use of social media and analysis. Developed in collaboration with the CRP Clinical Effectiveness Unit.
3. ***"Good Clinical Practices: Introduction and Implementation"***: The Good Clinical Practices (GCP) series is being developed in conjunction with the Partners Human Research Committee and the Quality Improvement Program. The purpose of this course is to provide clinical investigators 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.

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 2,904 attendees in 2012. These educational and community-building opportunities provide study staff with updates on clinical research regulations and operations. The program continues to be one of the CRP's most successful efforts (Fig. 3).

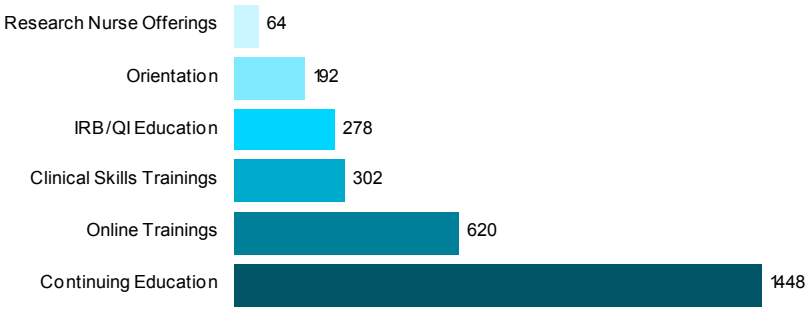
The following courses were new initiatives specifically designed for clinical research coordinators, project managers, research nurses and assistants:

1. ***Clinical Trial Billing Series***: This series included 4 sessions: (1) ***"Introduction to Patient Care Charges and Directing Charges to Research Funds"***; (2) ***"Monitoring, Invoicing and Corrections"***; (3) ***"Clinical Trials with Investigational Devices or Approved Devices with PMS/510K Numbers"***; and (4) ***"Managing Subject Reimbursement and Remuneration."*** This series was developed in collaboration with MGH Research Compliance.
2. ***"Monitor Online Record Access (MORA) Workshops"***: Hands-on, computer-based instruction for using the Monitor Online Record Access Program Developed in-conjunction with MGH Laboratory of Computer Science (LCS).
3. ***StudyTRAX and REDCap Sessions***: These database programs are supported by Partners Research Computing and available to all researchers at MGH. The CREU offers courses which provide instruction for using each program, presenting the advantages and disadvantages of the software depending on study design and hands-on workshops for building and maintaining a database.

The CREU has developed a core curriculum for study staff. The core curriculum for study staff consists of 5 courses:

1. ***"Introduction to Clinical Research" (online)***
2. ***"Orientation Program: Clinical Research Resources at MGH"***
3. ***"IRB/QI Roundtables"***
4. ***"eIRB Hands-On Training"***
5. ***"Good Clinical Practice and Study Management Basics" (online)***
6. ***"Clinical Research Hot Topics Sessions" (monthly)***

Figure 3: Study Staff Courses 2012
Distribution of Attendance per Course Category



In response to departmental requests the CREU developed curriculum tracks to support clinical research coordinator and project manager's educational needs—**Clinical Research Program Training Guide**. This guide outlines the core courses for each job description as well as courses that will promote learning and build skills.

Attendance remained high in 2012 for the CREU's ***Clinical Skills Trainings*** in phlebotomy, ECG and vital signs with 302 attendees.

Figure 4: CME, CEU, and RCR Accredited Courses and Hours 2012

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).

Clinical Research Day

Clinical Research Day continues to be popular at MGH. Clinical Research Day embodies the CRP's efforts to build a viable community of clinical investigators and their allied healthcare 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 in Clinical Research Day remained high with 239 submitted abstracts and 10 team nominations.

The 2012 theme was the application of genetic research into clinical care. James Gusella PhD, Bullard Professor of Neurogenetics, HMS served as the keynote speaker. He captivated the audience with his groundbreaking research on neurogenetics and discussed his vision regarding the impact of genetic research on clinical care. Following Dr. Gusella's keynote address, there was a panel discussion on the integration of genetics into clinical medicine. Leaders in genetic research at MGH 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, considerably higher than having to go the HMS to pursue their education in view of their increasingly tight schedules. There is a continuing need for basic level courses as well as a growing demand for more advanced material for clinical investigators and study staff.
2. **Curriculum.** In 2012, the CREU performed a systematic evaluation of the current curriculum and identified several important gaps. The CREU decided to add continuously required courses to the online compendium to improve availability and allow more time to develop courses to fill these gaps. (See Fig. 7 for full 2012 course listing).
3. **Access.** High attendance at CREU investigator courses in 2012 shows 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, offering continuing education 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. By placing more foundational and unchanging courses online the CREU can 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 a 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.

FUTURE ADAPTATIONS TO THE PROGRAM

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 2013 include: "Basic Elements of Protocol Design and Development," "Critiquing an Article," and "Developing a Hypothesis."
2. The CREU will adapt to ongoing changes in the research environment by continuing to develop, innovate, and create dynamic learning opportunities for study staff.
3. As the research community anticipates a decrease in funding from the NIH, the CREU has developed a series to support junior clinical investigators submitting for an NIH K Award—Conquering the K: Applying for an NIH Career Development Award. This series will assist investigators in preparing a complete, well-written application, which maximizing their chances of being selected to receive a K Award.

Appendix A: CRP Education Unit - Courses and Participation 2012					
Investigator Program	**Attended***	**Faculty**	**Lectures**	**Hours**	**Views****
Study Design and Analysis					
Basic Biostatistics for Clinical Research	217	1	4	6	865
Basic Biostatistics for Clinical Research: Working Sessions	69	1	4	6	188
Applied Biostatistics for Clinical Trials	123	1	4	6	149
Problem-Based Biostatistics for the Clinical Investigator	95	1	4	8	183
Design and Conduct of Clinical Trials	43	18	15	25	NA
Workshop on Study Design: Using MGH Clinical Care Data for Clinical Effectiveness Research	20	8	6	9	154
Genetics/Genomics					
Welcome to the Genetic Code: An Overview of Basic Genetics	102	2	1	2.5	449
Next Generation Sequencing at Harvard: Resources and Applications	212	10	1	6	273
Genetic Literacy: An Intermediate Guide to Understanding the Language and Concepts of Modern Genetic Research	71	3	1	2.25	N/A
A Primer on Complex Trait Genetics: Principles for the Clinical Investigator	80	8	1	6.75	59
Proteomics Nanocourse	93	4	1	4	14
Issues in the Protection of Human Subjects					
Ethics and Clinical Research Protocols	65	1	1	1.5	45
Maintaining Research Subject Privacy and Information Security: What Clinical Researchers Must Know	76	3	1	1.5	43
IRB Issues for the Bench and Desk Scientist (Spring)	44	1	1	1.5	23
What Does the IRB Really Want? How to Write a Human Studies Protocol (Spring)	44	1	1	1.5	41
Reporting Results: Should Subjects Be Told Clinical Research Results?	82	1	1	1.5	18
The Chimeric Brain: Crossing the Boundaries between Species! Scientific, Regulatory and Ethical Implications	58	1	1	1	N/A
IRB Issues for the Bench and Desk Scientist (Fall)	70	1	1	1.5	2
What Does the IRB Really Want? How to Write a Human Studies Protocol (Fall)	66	1	1	1.5	1
Whose Tells the IRB What to Do? The Effects of Case Law on Research Regulations Oversight	60	1	1	1.5	16
Involving Children in Decisions about Research	56	1	1	1.5	14
A Potpourri of FDA Related Issues	51	2	1	1.5	12
Professional Development					
REDCap Programming Training	110	1	16	32	N/A
Applying for an NIH Career Development Award (Spring)	18	8	1	3	154
Recruiting and Enrolling Patients with Disabilities in Clinical Research	21	2	1	1.5	5
Clinical Research Fellows Orientation Part I: Starting Your Clinical Research Career at MGH	22	5	1	2.5	4
MGH Clinical Research Fellows Orientation Part II: Resources for the MGH Clinical Researcher (Summer)	39	15	1	4	50
An Introduction to the Enhanced RPDR Query Tool	90	1	1	1	23
How to Make a Poster	42	1	1	1	135
Advanced RPDR Demonstration	44	1	1	1	3
How to Give a Presentation	80	1	1	1.25	43
Applying for an NIH Career Development Award (Fall)	20	10	1	3	21
Grand Rounds					
Medicine Grand Rounds: *Analytic and Translational Genetics: From Gene Discovery to Impact on Clinical Decision Making*	105	1	1	1	N/A
Medicine Grand Rounds: *Application of Tumor Genetic Analysis for Targeted Cancer Therapy*	87	3	1	1	N/A
Neurology Grand Rounds: *Discovery and Interpretation of Chromosomal Aberrations from Complex Neurodevelopmental Disorders to Prenatal Diagnostics*	37	1	1	1	N/A
Clinical Research Day					
Keynote Address and Panel Discussion	389	8	2	2	N/A
Abstract Submission and Poster Session	239	N/A	N/A	2	N/A
Total, Investigator Program	**3,140**	**129**	**83**	**155**	**2,987**

Appendix A: CRP Education Unit - Courses and Participation 2012

Study Staff Program	Attended*	Faculty	Lectures	Hours	Views**
Orientation					
Navigating Your Way Through Clinical Research at MGH	17	11	1	3	133
Clinical Research Resources at MGH (2)	175	10	4	17	89
Research Nurse Offerings					
Research Nurse Roundtable	64	1	8	8	58
IRB/QI Education					
Amendments and Reporting to the IRB	55	2	3	3	155
Protocol Adherence and Reporting Requirements	33	1	3	3	44
Consent Form Writing	53	3	2	2	166
Informed Consent Process	26	2	2	2	34
New Submissions: Initial Review of Human Subjects Research at Convened Meetings of the IRB	36	3	2	2	104
New Submissions (Part II)	27	1	2	2	32
Continuing Review and Amendments	29	2	2	2	20
Source Documentation	19	2	2	2	31
Clinical Skills Trainings					
ECG training	61	1	9	23	N/A
Phlebotomy	159	2	21	42	N/A
Vital signs training	82	1	10	25	N/A
Continuing Education					
Best Practices for Bio-Specimen Collection and Processing	67	1	1	1	69
ClinicalTrials.gov: Results Reporting	47	2	1	1	42
Budgeting and Tracking for Industry Sponsored Clinical Research & Successfully Managing the Financial Aspects of a Study	57	2	1	1.5	184
Budget Builder Workshops (Winter)	14	1	2	3	77
Understanding and Writing Clinical Research Literature	59	4	3	4.5	188
eIRB Training: A Hands-on Introduction to eIRB	75	1	9	18	17
An Overview of Monitor Online Record Access (MORA)	37	1	1	1	85
Clinical Trial Billing: Charge Capture and Billing Procedures	36	1	1	1	46
Internet Recruitment and Retention: IRB, Security and Web 2.0	64	2	1	1	69
MCA and Budgeting	10	2	1	1	N/A
Clinical Trial Billing: Monitoring Patient Care Charges and Making Corrections	30	1	1	1	17
Publishing Faster: Bridging the Gap Between Electronic Data Capture and the Manuscript Generation Process	51	1	1	1	33
The Principles and Practice of Clinical Research Data Management	58	1	1	1	43
ClinicalTrials.gov: Does Your Study Need Results Reporting?	16	2	1	1	34
Clinical Trial Billing: Clinical Trials with Investigational Devices or Approved Devices with PMA/510K Numbers	17	1	1	1	19
Sponsoring and Managing Multicenter Trials	55	2	2	5	39
See the IRB's QI Checklist: Clinical QI or QI Research? When to Get IRB Review	65	2	1	1	32
Hands-on MORA Training: Managing Monitor Online Record Access	11	1	3	3	15
Budgeting and Tracking Expenses for Industry Sponsored Clinical Research Studies	23	2	1	1.5	11
Budget Builder Workshops (Summer)	11	2	2	3	1
Research Subject Remuneration and Reimbursement: Policy Review and Navigating the Process	106	2	1	1	34
Meet the Protocol Administrators and Managers of the Partners Human Research Office	77	1	1	1	NA
Considering the Research Subject's Perspective	95	1	1	1	15
Using Social Media in Clinical Research	97	1	1	1	30
Cleaning Up After a Problematic Study Coordinator	58	2	1	1	16
Subject Recruitment and Retention	48	3	3	4.5	15
Common Findings by QI at Partners Institutions	36	1	1	1	5
StudyTRAX: Unleashing New Portals	11	1	1	1	NA
StudyTRAX Users Workshop	14	1	1	1	NA
Study Electronic Data Capture: REDCap and StudyTRAX	44	2	1	1	22
StudyTRAX: General Overview	37	1	2	2	5
StudyTRAX Training Session: Survey Research	9	1	1	1	4
StudyTRAX Training Session: Patient Registries	8	1	1	1	2
StudyTRAX Training Session: Clinical Trials	5	1	1	1	1
Online Trainings					
Research Patient Data Registry (RPDR)	31	1	9	0.75	N/A
Good Clinical Practice and Study Management Basics	66	2	4	0.5	N/A
Submitting your Medical Record/Health Information Research Protocol to the IRB	23	1	5	0.75	N/A
IATA Shipping Training for Transportation of Biological Materials and Dry Ice	330	1	5	0.5	N/A
Infection Control Principles and Practice in Clinical Research	68	1	4	0.5	N/A
Introduction to Clinical Research at MGH (online)	85	1	1	0.75	N/A
Basics of Manuscript Writing for Clinical Researchers	17	1	4	0.75	N/A
Total, Study Staff Program	**2,904**	**101**	**155**	**211**	**2,036**
Grand Total	**6,044**	**230**	**238**	**365**	**5,023**

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, and 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 supports seeks to address second translational block issues, i.e. translating evidence from clinical studies into clinical practice. During 2012, 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, 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. In 2012, 13 Departments and 7 Academic Ranks served by the CERU is shown in the Figures below. The 55 consultations were provided to 51 faculty members, 83% of whom were junior investigators.

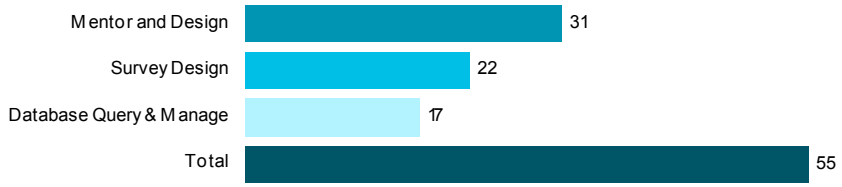
Database Consulting and RPDR support:

These services are provided by Wei He, MPH and Sue Regan, PhD Services include 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.

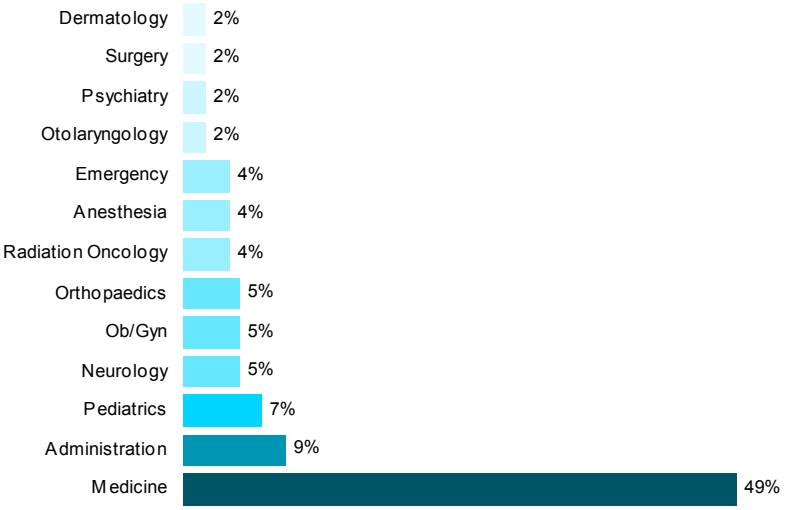
Survey Consultation Service:

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.

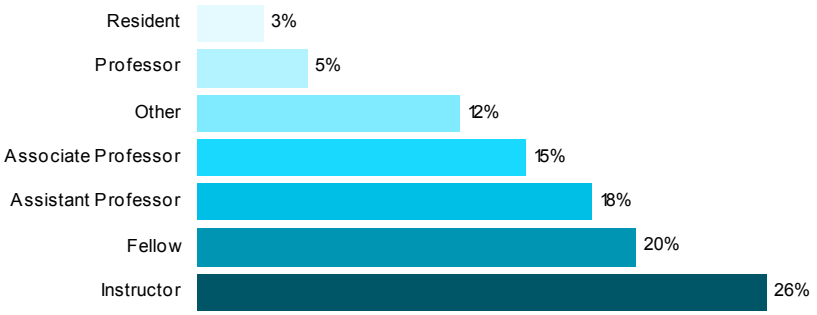
Numbers of CRP CERU Consults, 2012



Distribution of CRP CERU Consults by Department



Distribution of CRP CERU Consults by Academic Rank



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 of Massachusetts General Hospital, Peter Slavin, MD Solicitation and evaluation of research proposals to integrate clinical insights into improved patient care are conducted using an NIH type review and award model. An annual Request For Applications (RFA) for the CIA program announces the intent to support 4–5 hypothesis-driven research projects focusing on the PHS Care Redesign and Patient Affordability Initiatives and Accelerating Improvements in Efficiency Initiative. After five years of success (2005–10), CIA operations were transferred in 2011 to MGH's Department of Quality and Safety and continued under the support of Gregg Meyer, MD, MSc, Senior VP for Quality, The CIA has been an outstanding success for MGH's Clinical Safety and Quality Improvements program.

The 2013 RFA was released at the beginning of December 2012 and will be supported by Dr. 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. Awards support 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 2011–2012 cycle are shown in the Table.

MGH/MGPO Care Redesign & Patient Affordability Research 2012

	PI & Co-Investigators	CIA Project Title	Affiliated Care Redesign Team
1	**Elizabeth Martinez, MD, MHS** Thor Sundt, MD	Building an Infrastructure for Care Improvement in Cardiac Surgery	Coronary Disease: CABG
2	**Linda M Delahanty, MS, RD** Deborah Wexler, MD	Improving Diabetes Outcomes through Lifestyle Changes (IDOLc) Translation Study	Diabetes
3	**Dr. R Sacha Bhatia** Dr. Michael H. Picard Dr. Rory B. Weiner	An Educational Intervention to Reduce Inappropriate Ordering of Thransthoracic Echocardiograms on the General Medicine Service	Coronary Disease: AMI
4	**Andrew Freiberg, MD** Jim Rathnell, MD Bob Dorman, DPT	Total Joint Replacement Accelerated Rehabilitation	Arthoplasty/Total Joint Replacement
5	**Laura Riley, MD** Jeff Ecker, MD	Redesigning Obstetrical Care with a Focus on Induction of Labor	OB/Vaginal delivery

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. In 2011 70% of 23 attendees rated the course Excellent and 27% rated it Good. Admission to the workshop was limited to ensure a low instructor-student ratio. The 2012 curriculum is shown in the Table below.

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.

Date	Session	Content	Format	Required Coursework
Session 1 November 7 3:30pm - 5pm Simches 3.130	***Framing a Testable Hypothesis*** James Meigs, MD, MPH Judy Scheer, SM, RN	**Introduction to Epidemiology:** • Instruction on developing a testable hypothesis from a clinical question. • 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:** 1. Review online training module for medical records IRB submissions. 2. Review required readings (3 articles) **Assignment due for Session 2:** 3. Prepare a written hypothesis to be discussed during the workshop (bring 5 copies).
Session 2 November 14 3:30pm - 5pm Simches 3.130	***Workshop: Developing a Testable Hypothesis*** James Meigs, MD, MPH Anne Thorndike, MD, MPH Clemens Hong, MD	• Developing a testable hypothesis from a clinical question.	Workshop	**Assignments due for Session 3:** 4. Refine your hypothesis. **5.** Prepare &submit your medical records review application to the IRB for review and approval. It must be approved before Session 4.
Session 3 November 28 3:30pm - 5pm Simches 3.130	***Using MGH Clinical Care and Survey Data*** Steve Atlas, MD Clemens Hong, MD	**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.	Lecture & Discussion	**Assignments due for Session 4:** 6. If you have not done so already, prepare and submit your medical records review application to the IRB for review and approval. It must be approved before Session 4. 7. Obtain access to RPDR, complete RPDR online training, and follow instructions on Assignment Sheet for RPDR workshop preparation.
Session 4 December 5 3:30pm - 5pm Simches 3.130	***Hands-On Research Patient Data Registry (RPDR)*** Stacey Duey	**RPDR Computer Lab:** • Create an RPDR query. • Request data using the RPDR data wizard. • Understand the data returned in a query	Workshop: Hands-on Computer Lab	**Assignments due for Session 5:** • Submit an RPDR query • Begin preparing your final project • Review required reading
Session 5 December 12 3:30pm - 5pm Simches 3.130	***Transforming Clinical Care Data into Analytic Datasets*** Sue Regan, Ph.D, Jeanne Triant, MD, MPH	• Transforming RPDR data into analyzable data sets.	Lecture & Case Study	**Assignments due for Session 6:** • Completed final project presentation
Session 6 December 19 3:30pm - 5pm Simches 3.120 Simches 3.130	***Case Presentations*** James Meigs, MD, MPH Anne Thorndike, MD, MPH Clemens Hong, MD	Final project presentations and feedback from preceptors	Case Presentations	

LESSONS LEARNED

After six years, the Clinical Innovation Award Program has become a successful and well-established part of the MGH research and operations mission. In developing the program, the CERU has created an effective mechanism for eliciting high quality proposals in the areas of outcomes and operation research, critical future directions for the MGH. The CERU has generated an institutional environment of research curiosity and collaboration across different departments and between administrators and researchers in these areas that will be crucial for our evolution towards creating a learning environment necessary for our transition to an accountable care organization. Even more importantly, it has demonstrated that even in an operationally intensive, "just do it" environment clinical effectiveness studies can improve care without slowing necessary implementation progress for operations, quality and safety improvement. 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.

ADAPTATION PLAN

CERU adaptations to its support services considered for 2013 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 2012–2013 and on transition to 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 Linked Cohort. The Linked Cohort-PBRN are mirror-image clinical operations-clinical research resources that increasingly serve clinical research goals and hospital quality improvement and patient care efforts.

The MGH CRP CERU intends to help build 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 to position itself well to transition to an ACO and to compete successfully for the increasing federal resources to support CER.

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 primary care junior faculty leaders that are working with residents on practice improvement projects and clinical effectiveness research. This will 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 is now a member of the Massachusetts General Physicians Organization (MGPO) Performance Analysis and Improvement (PAI) publications group. Through this new role, the CERU will support 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. Ultimately the goal is to create a self-supporting model for the MGPO 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.

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 is to:

- improve existing information management resources while attempting to create a broad, new information management infrastructure to support the work of the clinical research community at MGH and PHS;
- 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
- establish ongoing partnerships with clinical researchers to pilot applications and studies with new clinical informatics-based interventions that will create reusable technology platforms for such studies.

ACCOMPLISHMENTS

Our work in 2012 focused principally on building three specific IT solutions targeting different aspects of the clinical research process:

- Clinical Research Program (CRP) Hub—continued development of an online learning management system for clinical research education;
- Monitoring of Online Record Access (MORA)—full implementation of a platform that supports secured and audited clinical data access for clinical research monitors;
- Dynamic Linkage Cohorts—creation and maintenance prospectively of provider patient panels for research or analysis of operations.

In addition, the IT Unit continued to support:

- Clinical trials recruitment web sites—clinicaltrials.partners.org, rsvpforhealth.org

Clinical Research Program Hub—a site for online learning

In 2012, we continued to see increased use of CRP Hub E-Learning courses and we have worked with the CRP Education Unit to add several new, online offerings to the current list of trainings. In concert with E-Learning content and infrastructure improvements, we continued work on the E-portfolio component of CRP Hub. This component allows learners to see their profile preferences, courses taken, courses registered for and evaluation summaries. The collaboration in this area started with the UCLA Computing Technologies Research Lab (CTRL) has started to bear fruit. Via monthly meetings, LCS Hub and UCLA engineers have worked together to upgrade and modernize the Profiles application (originally built at UCLA and used successfully there since 2003) so that it can be used at both the MGH and UCLA clinical/research centers without significant customizations. The continued focus of this work is to synchronize our development code base so that we can better leverage our combined engineering resources to meet shared institutional needs. We ported this first application from a commercial database (Oracle) to the open alternative used at MGH (PostgreSQL) for the CRP Hub. The UCLA team then migrated the Profile application to the latest version of OpenACS. This step allows the two teams to share a code repository from which both teams can extend the application. The collaboratively built application includes Profile and Group management and integration with Pubmed. The application is now being tested on the Hub quality assurance (QA) system.

Hub profiles cover the full range of roles in the MGH clinical research community, including hundreds of study staff and administrator profiles in addition to investigator profiles. There are also MGH investigator profiles in Harvard Catalyst Profiles. We plan to evaluate whether or not Hub investigator profiles can be improved by automatically merging into them investigator profile data from the Catalyst investigator database.

In addition to these E-Learning and profiles improvements, we were able to successfully pilot a new course and attendance tracking application. The tracking application includes badge reading capabilities so that in-person attendance can be tracked with a simple badge swipe at in-person CRP course offerings.

MORA—Monitor Online Record Access

In 2012, we did a phased roll-out of MORA (Monitor Online Record Access), a product developed in collaboration with Partners Research Computing, the MGH Cancer Center, and the cancer research groups at BWH and Dana-Farber. In 2011, a beta version of MORA had been successfully piloted with the Clinical Research Program's study coordinators. After further improvements, in spring of 2012 MORA was made available for use in all appropriate MGH studies. At other points in the year the product was released to Brigham and Women's Partners-IRB reviewed studies.

In summer 2012, we released a significant revision that mitigated the most common complaint coordinators and monitors had provided to us about the product.

In collaboration with the CRP Education Unit, we experimented with a number of different methods of training. We tried both lecture style presentations to large groups and customized hands-on training sessions at individual research sites before settling on the current method. We now offer a monthly "hands-on" laboratory session for clinical research coordinators scheduled by the Education Unit.

The key benefit of MORA is that it eliminates the administrative overhead of traditional methods of monitor clinical data access, which typically involving printing out data, or sitting with the monitor to access data with that individual. It thus enhances clinical research coordinator productivity. To date MORA has been used by 24 sponsor monitors to review 86 MGH research protocols in order to access MGH electronic patient records 422 times. MGH activity represents approximately 14% of the total activity in MORA: the product has received robust acceptance elsewhere within Partners, especially for cancer protocols; 84% of MORA usage has been on protocols where the lead investigator is at Dana-Farber. The MORA team included members of the Information Technology Unit, other LCS staff and members of the CRP Operations and Education units, as well as others from around the network. On December 14 the MORA team was recognized with a Partners in Excellence award in the Partners network team category.

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. Since May 2011, MGH panels have been updated and saved in complete, ready-for-analysis datasets daily. They have been used in the TOP-CARE cancer detection and prevention study, of which Dr. Atlas is the Principal Investigator.

The dynamic linkage cohorts 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 now been adopted as the provider attribution technique used in the Partners Population Health initiative. In the context of rapid deployment of population health initiatives, maintaining a research focus on the methods of derivation for the denominators used in various performance metrics remains essential. Seemingly subtle differences in the specificity of a method of attribution can drive surprising apparent differences in measurement. In addition, the methods of measurement of patient-provider interaction will need to evolve to take into account developments in team-based care under the heading of the patient-centered medical home, and the various electronically mediated methods which patients and providers increasingly use to interact.

Provider attribution research in the context of population health initiatives will help MGH and Partners to operate as an Accountable Care Organization and other risk-based contracts effectively. Ready availability of dynamic linkage cohorts to researchers and analysts allow wise use of the populations they help stratify for research on innovations in the delivery of patient care.

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 robust usage as indicated in Fig. 1.

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

* During 1999-2012 four different technologies for measuring user activity have been used. Figures 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 the level of the last several years.

Research Patient Data Registry (RPDR)

The RPDR project, an innovation developed and driven by the CRP's IT unit, is a successful and now

Figure 2: CRP Information Technology Unit – Patient Recruitment Tool Metrics

• Clinical trials at Partners site sessions/month	
Sessions/month (13% increase from 2011 total)	8,423
• RSVP for Health	
New registrations in 2012 (4% decrease from 2011)	2,379
Cumulative registrants (8% increase from 2011)	22,103
Registrants sent one or more mailings (up 3% from 2011)	19,954

widely deployed as a PHS desktop application collaboration between the Laboratory of Computer Science (LCS) and subsequently PHS's Research Computing Group. It is now mature and has truly remarkable statistics. The RPDR has ~2,900 users throughout the Partners Healthcare System. It is composed of >6 million patients and 1.4 billion coded records from patient encounters, labs and results, and other medical care data. Most importantly, RPDR is one of the cornerstones for i2b2, Partners effort 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.

LESSONS LEARNED

Clinical Research Program Hub

The CRP Hub continues to successfully support our increasing educational demands with the same development and support staff. In addition the expanding code base required incurs maintenance overhead. We are taking a three pronged approach to address this: 1) synchronizing our code base with our UCLA collaborators, 2) introducing automated testing into our workflow so that we can reduce long-term maintenance overhead, and 3) improving our team and engineering processes so that they are better optimized.

It has quickly become clear to us that all three of these have up-front costs that will eventually lead to enhanced efficiencies. We hope to begin reaping the benefits of these investments in the coming year.

MORA

The MORA project had a difficult development history but is now yielding increased efficiencies for those engaged in sponsored research since MORA was fully implemented.

The project taught us some useful lessons that are worth highlighting:

- Implementation across the network of systems that raise significant privacy issues or unique data access risks is complicated by the number of governing bodies whose policies need to be coordinated. “Master policies” at the Partners level that are simply adopted at the Regional Service Organization level would smooth implementation, enable greater understanding of policies by implementers and would tend to reduce, rather than increase the risks.
- Clinical research uses of systems are still not well understood by parts of the organization that have responsibility for administering access to those systems. It is desirable that at least some people in those areas receive a higher degree of training in what occurs in clinical research.

More happily, the project reinforced the lesson already learned that the CRP Education Unit provides a smooth infrastructure for dissemination of information to clinical research coordinators and their training.

Web-based Recruitment Strategies

When Harvard Catalyst was started, the Catalyst program declared support for the nationally funded volunteer registry ResearchMatch. We therefore deemed it appropriate to deemphasize work on RSVP for Health. The theory had been that RSVP for Health was going to become redundant. RSVP for Health has continued to be used; there appears to be negligible recruitment in this geographic area in the ResearchMatch environment. Whether that is because Catalyst has not in fact promoted use of ResearchMatch, or because potential recruits do not in fact find a national recruitment registry appealing is unclear.

We hypothesize that we erred in not realizing that in a sense “all recruitment is local”. For most types of studies of most diseases, subjects seek the local brands; MGH and Partners represent the best brands on offer. We now believe we have undervalued our current product offerings.

ADAPTATIONS PLANNED

Establishing a strategic position in clinical research informatics in the era of eCare

The Information Technology Unit is based in the Laboratory of Computer Science (LCS) in the Department of Medicine, a unit with a deep history in pioneering developments in health care informatics, and a long history of “innovation in place” in clinical systems. The advent of eCare,

for all its planned benefits, will prevent a certain kind of tightly integrated clinical system innovation at which the Laboratory has proven itself adept, and which has enabled several CRP-supported research innovations that have gained clinical acceptance (including the HIV FastTrack implementation alluded to above).

The Laboratory therefore needs to reposition itself within the institution. Four aspects of the Laboratory's developing strategy are:

- Becoming a center of expertise and service in the development of applications at the edge of the core enterprise system that will augment and amplify the benefits of the core system
- Developing new partners and clients for LCS clinical research informatics
- Building on unique platforms and leveraging the current client base
- Adopting a research about clinical research approach

Edge system development. 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. While there will be numerous differences in detail, the relationship between the LCS systems and the Epic system will be quite similar to the relationship LCS-built systems now have to PHS IS-built systems. The new areas of expertise that necessarily must be cultivated at LCS will have significant application to clinical research service support. For instance, the potential future migration of MORA to continue to work once eCare clinical functionality is implemented will depend on use of the Epic clinical data services.

Developing new partners and clients for LCS clinical research informatics. As the LCS role as a provider of core clinical systems is reduced, LCS will be pursuing new opportunities in clinical research informatics based on a model of adding value around the core vendor-supplied system. Some base needs will be "generic—most of these will increasingly be met by offerings from Partners Research Computing. The CRP Information Technology Unit role will increasingly come as a "solutions provider," that can supply essential expertise in coordinating the capture of clinical and research data within realistic patient and provider workflow. While some core platform work can be supported by the CRP investment, the scope of the work required will often involve seeking additional funding via new client and partner relationships, a few of which are currently under negotiation. One specific example is the potential for a new patient-generated data capture tool called Sprout to efficiently capture patient questionnaire information for use in clinical notes and research. This potential will be explored in collaboration with the Lurie Center, a funded and active center for Autism Spectrum Disorder treatment and research, where an LCS faculty member has an appointment.

Building on unique platforms for web-based patient recruitment

As discussed above, we believe that with the intention of avoiding duplication of service, we undervalued RSVP for Health and, to a degree, clinicaltrials.partners.org. At the same time, rsvpforhealth.partners.org and clinicaltrials.partners.org need to be brought in line with developments in social media and widespread use of mobile computing, and reframed within a strategy that explicitly puts subject recruitment in the context of partnership with the public in support of clinical research. Significantly, this will involve developing strategies and tools for using social media to, in effect, recruit the public to publicize MGH-branded trials.

What is required to implement this idea exceeds current resources. Consequently, in the coming year we will be working to develop partnerships and new initiatives that will help us modernize our toolkit for driving subject recruitment.

Continued coordination with Partners Research Computing

The MORA project has been a complicated but successful partnership with Partners Research Computing. Coordinating offerings with Research Computing will be important as both groups seek to respond to the changing systems environment at the institution.

Research about clinical research

To both sharpen our concepts and help create the intellectual scaffolding for leadership in clinical research informatics, we will formulate research studies around key initiatives. Example areas calling for disciplined study include a comparison of why individuals might prefer enrollment in ResearchMatch to RSVP for Health (or the reverse), measurement of the efficacy of electronic direct-to-monitor training in MORA compared to the current "train the trainer" method used, and measurement of the efficacy of the new tool Sprout in eliciting usable research data from patients in the context of normal clinical workflow.

Improving the HUB platform through collaboration and improved techniques

In respect to our collaboration plans with UCLA, we plan to adapt our version control systems used for our software development to facilitate sharing with UCLA and other partners long term. We have also invested in setting up a testing framework using the industry-standard automated software testing program, Selenium with the goal of reducing maintenance overhead. We are sharing this work with UCLA as well. As we roll out both the Profiles work and the badge-reader based attendance tracking system in the new year we plan to use them as test cases for our new functional testing framework. As part of our efforts to improve the Profiles application we will be refining the groups support so it can be adapted to meet both CRP course-sign-up and reporting needs. In addition, we will use these profiles and groups enhancements to make course recommendations to our end users based on similarity scores. Finally, we plan to streamline our processes in order to move more quickly and iterate faster so we can support more users with less. We will continue our monthly meetings with external partners and bi-monthly meetings with the CRP Education Unit, but we will be implementing modern software project management methodologies (e.g. agile management, which includes an iterative method of determining requirements in a highly flexible and interactive manner).

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.

COLLABORATIVE RESOURCES

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. 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 Center for Human Genetic Research (CHGR) is a trans-disciplinary research center devoted to human genetics and encompassing scientists and laboratories from numerous 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.

ACCOMPLISHMENTS

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 genetic research 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 2012 GGU Grand Rounds Series is illustrated in Fig. 1.

Figure 1: 2012 Grand Rounds

Medical Grand Rounds

March 22

Analytic and Translational Genetics: From Gene Discovery to Impact on Clinical Decision Making
Mark J. Daly, Ph.D., Chief, Analytic and Translational Genetics Unit, MGH, Associate Professor of Medicine, HMS, MGH, Senior Associate Member, Co-Director, Program in Medical and Population Genetics, Broad Institute of Harvard and MIT

May 24

Application of Tumor Genetic Analysis for Targeted Cancer Therapy
Leif William Ellisen, M.D., Ph.D., MGH Cancer Center, Anthony John Iafrate, M.D., Ph.D., Director, Center for Integrated Diagnostics, and David N. Louis, M.D., Pathologist-in-Chief, MGH

October 11

Genetics: Cycling to Better Care
James F. Gusella, Ph.D., Bullard Professor of Neurogenetics, HMS, Director, Center for Neurofibromatosis and Allied Disorders, HMS, Director, Center for Human Genetic Research, MGH

Neurology Grand Rounds

October 25

Discovery and Interpretation of Chromosomal Aberrations from Complex Neurodevelopmental Disorders to Prenatal Diagnostics
Michael Talkowski, Ph.D., Instructor in Neurology, HMS, Assistant in Genetics, MGH

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".

The GGU expanded its curriculum in 2012 by adding a new course, **Next Generation Sequencing at Harvard: Resources and Applications**. This course, which was co-sponsored by the Translational Genetics and Bioinformatics Program of the Harvard Catalyst, was extremely well-received.

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. We will continue to focus on the needs of MGH clinical investigators as we create the 2012 curriculum are actively working with the Harvard Catalyst education group to expand the MGH's broad educational courses in genetics and genomics to the entire Harvard community. Fig. 2 lists the 2012 GGU courses and faculty.

Figure 2: 2012 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 – 102
  Faculty included: *Susan Slaugenhaupt, Ph.D., Jordan Smoller, M.D., M.Sc.*

- **"Next Generation Sequencing at Harvard: Resources and Applications"**
  This course included an introductory lecture on next-generation sequencing methodologies, lectures on scientific applications, and presentations by seven facilities performing next-gen sequencing. The goal was to provide attendees with fundamental knowledge of this important tool, and the information needed to access sequencing facilities.
  Attendees – 212
  Faculty included: *Niall Lennon, Ph.D., Heidi Rehm, Ph.D., Paul Van Hummelen, Ph.D., Mike Talkowski, Ph.D., Mark Borowsky, Ph.D., Vance Morgan, Ph.D., Claire Reardon, Jane Wilkinson, Matthew Meyerson, M.D., Ph.D., Oliver Hofmann*

- **"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 – 71
  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 – 80
  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.*

- **"Proteomics Nanocourse"**
  This nanocourse introduced fundamental language and concepts including basic concepts of mass spectrometry, sample preparation, quantitative proteomics, protein-protein interaction networks, post-translational modifications, proteomics data analysis, proteomic biomarker discovery and validation, translational introduction of diagnostic and prognostic biomarkers into the clinic, proteomics approaches to understand basic disease mechanisms and to identify potential novel drug targets, as well as applications for personalized medicine.
  Attendees – 93
  Faculty included: *Towia Libermann, Ph.D., Jarrod Marto, Ph.D., Hanno Steen, Ph.D., Steve Carr, Ph.D.*

Figure 3: Course Attendee's Academic Rank

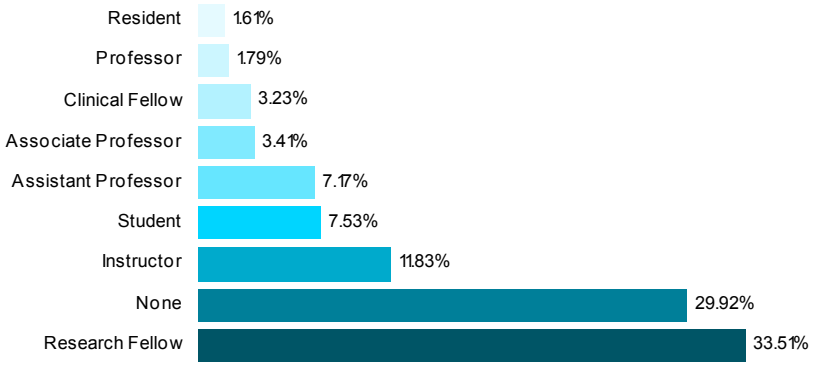
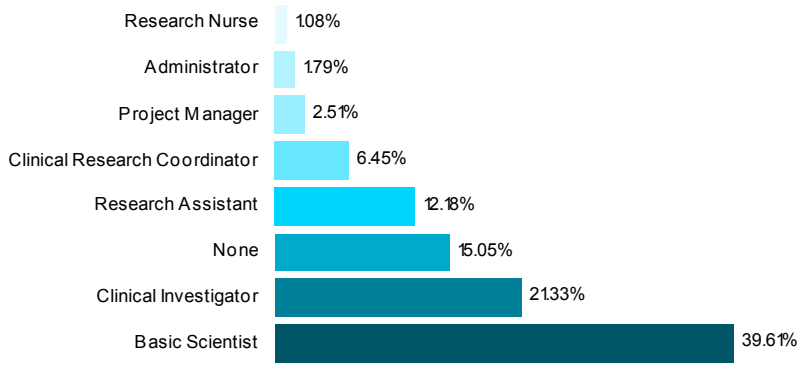


Figure 4: Course Attendee's Research Role



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

Consultations to Investigators

One of the GGU's primary 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 2012, twelve MGH investigators received consultations through joint efforts of the Genetics and Genomics Unit and the Harvard Catalyst. Investigators came from the following departments, centers, or units: Cardiology, Cutaneous Biology Research Center, Dermatology, Ragon Institute of MGH, MIT, and Harvard, Infectious Disease, Pathology, Pediatrics, Orthopedics, Urology, Neurology, Gastrointestinal Unit, and Molecular Biology. In May of 2012, the Harvard Catalyst discontinued its consultation services. Moving forward the GGU will continue to provide this important resource for the MGH community.

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 and is in the process of submitting an application for renewal of the educational program. 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 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 2012, we had over 450 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.

3. 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.

4. 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.

   In 2013, we will pilot recording all of our courses for online posting to increase availability and access to the MGH clinical research community.
3. 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.

   "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.

   "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.
4. 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.
5. 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 Internal Review Board.

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 played the lead role in working with the Partners IRB to streamline its process for review of protocols for novel therapeutics. The success of the TMU-led pilot program led the Director of the Partners Office of Human Studies (OHS), Dr. Pearl O'Rourke, to re-evaluate the way in which the IRB was reviewing protocols in the therapeutics arena, particularly those involving multi-center trials. The OHS is now in the process of convening a new working group tasked with exploring more generalized solutions to speed IRB reviews of time-sensitive protocols. Some of the options being considered are outsourcing certain protocols to independent IRBs and/or the creation of a special ad hoc review committee. The TMU will participate in this task force. The TMU also worked extensively with the Partners OHS to provide detailed insights into how external contract research facilities function and how MGH PI's might safely and productively engage in clinical research at these sites. The TMU has played 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 led to the formation of multiple committees empanelled to provide novel strategic input to the hospital in areas affecting all of its missions. A subcommittee on translational medicine was formed and Dr. Freeman asked to lead that group in providing insights on advancing the translational research activities of the hospital. The committee has reported its strong recommendations to enhance the translational environment at the MGH and these will be reviewed at a Strategic Planning retreat in January, 2013 for potential implementation next year. This Strategic Plan outlines a bold and far-reaching vision for translational research that seeks to diversify support for such activities in the face of concerns over the NIH's ability to fund this line of work.
- The TMU was a major contributor to a collaborative grant involving multiple Harvard institutions that was assembled in the fall of 2012 in response to an RFA from the NHLBI requesting applications to create a therapeutic and diagnostic development program in disease areas germane to that institute. Dr. Loscalzo at the Brigham is the PI of the grant and Dr. Freeman is one of five faculty members, including Dr. Loscalzo, who are slated to serve on the Executive Committee of the program, should it be funded. The grant award represents funding of up to $24 million dollars for translational research over the next 7 years and will be reviewed in March 2013.

- The TMU provided consultative services to a variety of MGH investigators in 2012, a partial list of which is highlighted below to indicate the kind of services TMU provides.
  a. Dr. Xiaying Wang had an NHLBI grant funded to develop an annexin-conjugated TPA molecule that could be used to treat acute strokes. He did not have a manufacturing and quality control plan in place and the TMU worked out a process that was endorsed by the NHLBI and enabled him to maintain funding of a grant of ~ $6m dollars.
  b. Ed Ryan of Infectious Disease has generated a concept for developing a cholera vaccine that required extensive FDA discussions concerning the components of the vaccine. The TMU has spent several months of effort on this program with Dr. Ryan enabling it to move forward with regulatory endorsement.
  c. Robert Ackerman of Neurology received guidance on the development of a Phase 1 human research protocol involving PET and MRI imaging.
  d. Dr. Martin Yamush sought out the TMU's help in developing a regulatory strategy for the use of a perfusate that could be used for organ donations.
  e. Other investigators from GI, Dermatology, and Surgical transplantation have been assisted by the TMU via preparations of sections of grants, filing of IND's, or reviews of proposals that needed budgetary, regulatory, or other scientific input.
- 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 2b clinical trial in 300 patients. The success of the trial has led to a commitment from the biotech sponsor, Theracos Inc, to proceed to phase 3. The latter program will entail trials of this new drug in over 3,000 patients. This effort represents one of the most sophisticated and complex drug development programs ever undertaken by an academic translational medicine group.
- Dr. Freeman co-directs the Harvard-wide translational medicine course that was held again on the Longwood campus in June 2012. 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 taught in the summer 2012 Clinical Fellows Orientation to Clinical Research at MGH.

LESSONS LEARNED

- Translational research is clearly emerging as one of the critical determinants of the future of those academic medical centers poised to do this research like the MGH. The critical mass of basic investigators, longitudinal patient care, and clinical investigators that are required for translation to occur are becoming defining issues for leading centers proceeding into the future.
- The TMU is finding that investigators need considerable support for their translational research across a wide spectrum of issues ranging from data management tools to regulatory advice. The demand for this input is increasing and the TMU is challenged to provide sufficient help in all areas, given its limited personnel. This has prompted the inclusion of specific support staff requests in the proposed Translational Medicine Center strategic plan.

- The Introduction to Translational Medicine course that has been presented the past three years via the Harvard Catalyst program is a very popular and effective didactic training experience. However, translational research requires hands-on training programs akin to medical residency education. To achieve this, a translational medicine program with supported fellowships needs to be put in place.

ADAPTATION PLANNED

- The growth strategy of the TMU has been to embed its activities in grant proposals in a number of different arenas. The year 2013 will see multiple grants in which the TMU is embedded and vetted by the NIH. Successful acquisition of some of these grant awards will significantly strengthen the TMU.
- The magnitude of the MGH commitment to a new and expanded translational research center should be addressed in the Strategic planning process that is currently underway. This should bring clarity on the scope of the role the TMU will be asked to play in coming years.

Biostatistics Unit

Dianne Finkelstein, PhD, Director

GOALS

The broad goal of the Clinical Research Program'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 any Internal Review Board-approved MGH investigator in the study design for their clinical research grant applications prior to submission;
- Support data analysis for their studies after funding is obtained;
- Guide them in their selection of the appropriate biostatistical methodology and interpretation of data for papers intended for submission to journals; and
- Support the Clinical Research Program's educational mission via individual, onsite consultations, a Biostatistics Lecture Series, and individual tutorials in collaboration with the Education Unit.

ACCOMPLISHMENTS

A. Overview of Principal Activities:

In addition to the Unit Chief, 6 faculty PhD members from the MGH"s Biostatistics Center participate in these Clinical Research Program (CRP) activities including D. Schoenfeld, H. Lee, D. Hayden, E. Macklin, H. Zheng, and B. Healy. This pool of onsite MGH biostatisticians provides the full spectrum of expertise to match the equally broad and growing spectrum of needs of the MGH clinical research community.

Since its inception 16 years ago, it has been the CRP's policy to offer free initial consultations of 4–6 hours to all MGH clinical investigators planning any Internal Review Board (IRB) approved human study. Dr. Lee, Assistant Professor of Medicine and Director of the CRP's Biostatistical Consulting Laboratory, personally triages each initial consultative inquiry for statistical assistance, taking into consideration the specific nature of the investigator's need and matching it to both the specific in house biostatistical expertise and time required.

The Unit also offers both formal lecture series in biostatistics and selective biostatistics work shops 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 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. Figures 1–4 break this Unit's work down by Faculty Rank (Fig.1), Department (Fig. 2), Nature of Project (Fig. 3), and Hours by faculty (Fig. 4).

The Unit also maintains and supports the MGH's institutional platform of common statistical IT packages, advanced statistical software including SAS, STATA, Power and Sample Size, and RedCap, all connected to Partners Network in addition to other high capacity computing tools (workstations and a protected network system). This 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

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 for the onsite use of clinical investigators that enables them to work under the direct supervision of the faculty. Computer programmers and staff research assistants aided the faculty consultations. This computing lab supports the formal course work of the Biostatistics Unit and was used by 50 researchers who received consultation for sessions averaging one hour in length. This volume decreased by 50% (one per week) compared to that of the previous year (n=112), a decline possibly due to the expansion of our course curriculum to include more computational software and examples in the formal didactic components of our CRP program. Until two years ago Dr. Healy would do about 30–40 consultations for investigators in his course. Investigators continue to meet with him within his extended office hour in the lab. In addition, the Catalyst program also offered consultations to some of those investigators.

B. Education:

Drs. Finkelstein and Hayden delivered 2 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.

C. Individual Consultations:

The CRP supported 50 (compared to 36 in the previous year) initial consultations directed to this Unit exclusively from the CRP office. The majority of these consultations were with MGH's junior investigators (Instructors, Assistant Professors, or Fellows, generally functioning in collaboration with senior faculty). We also supported senior investigators at the Associate Professor and Professor levels, and others such as residents, medical students, research associates, and research nurses (see Figures 1 & 2). These consultations involved study design or analysis advice for manuscript preparation, handling statistical considerations during IRB submissions, and education on special statistical method topics (see Figure 3). A total of 209 hours (see Figures 4, 5, and 6) (compared to 134 hours in the previous year) were spent for these consultations.

Figure 1: Percent of Projects by Faculty Ranks

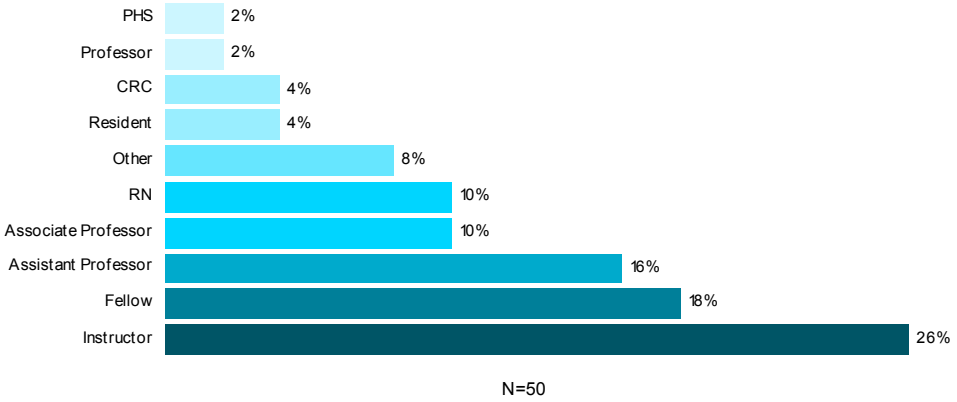


Figure 2: Percent of Projects by Department Specialty

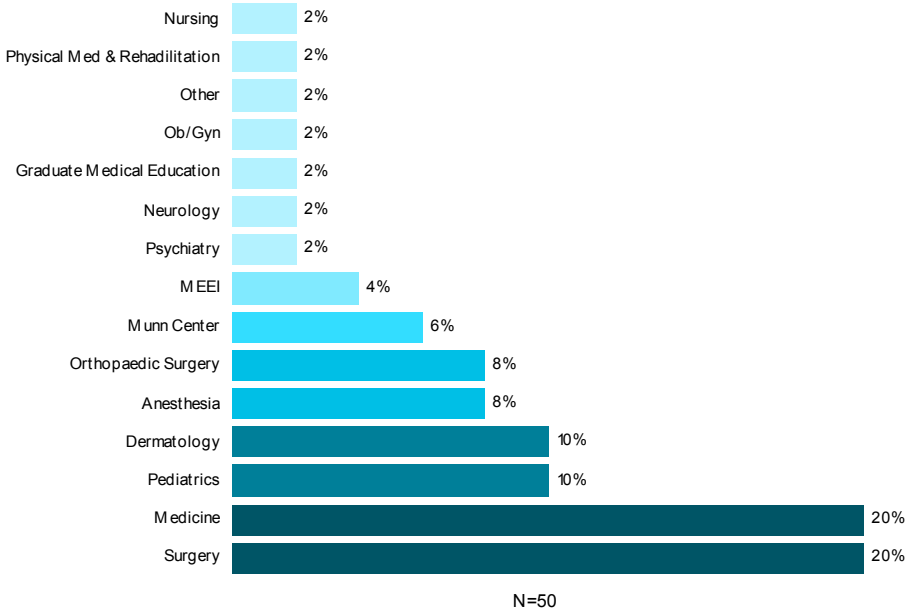


Figure 3: Percent of Projects by Project Types

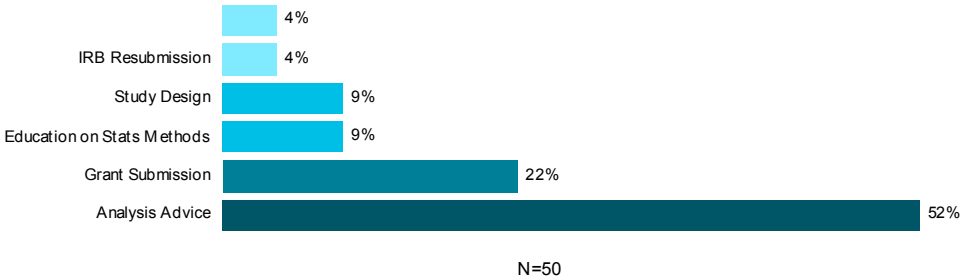


Figure 4: Project Hours by Faculty Ranks

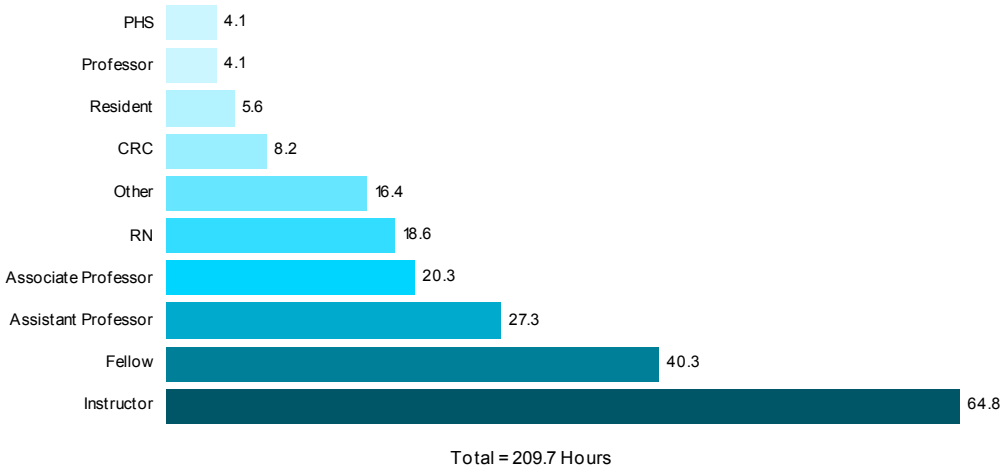


Figure 5: Project Hours by Department Specialty

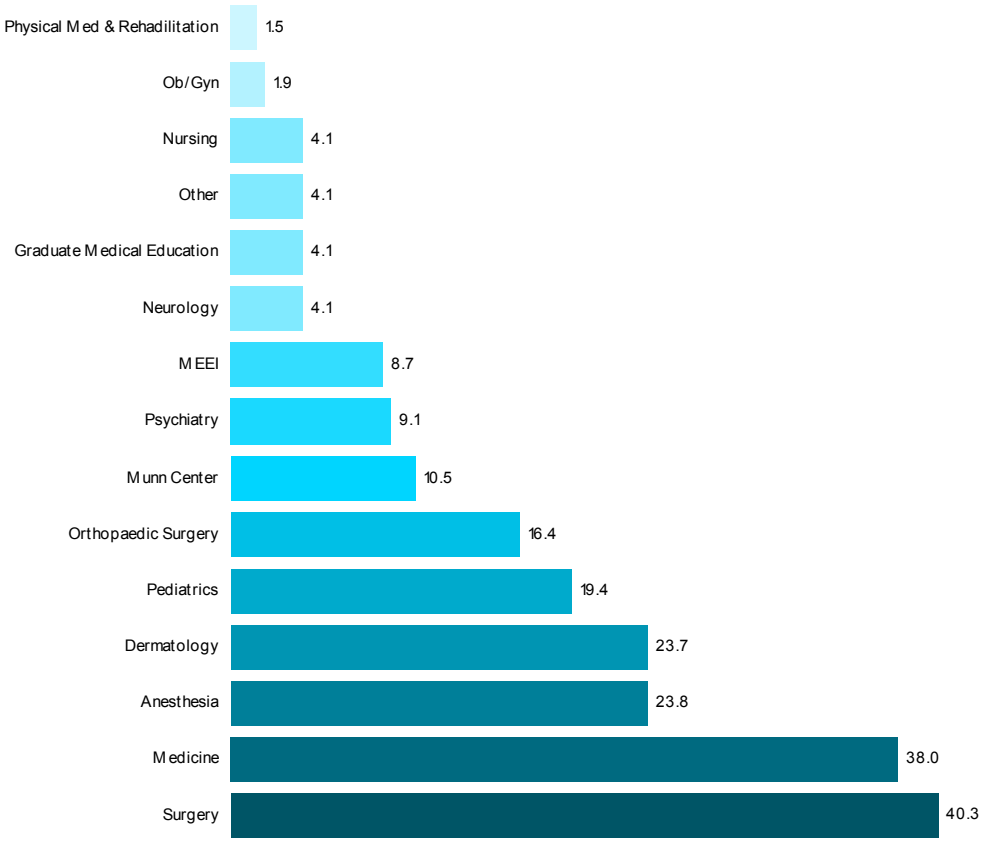
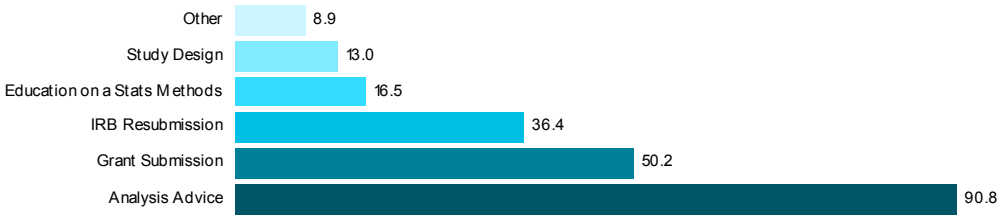


Figure 6: Project Hours by Project Types



In addition to these individual consultations, the Unit conducted consultations with 49 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 increased volume compared to the last year (27 PIs). These consultations were qualitatively similar and included discussions on study design, contributing the statistical considerations to the application, and committing a portion of their time to the grant research if it was funded. If the grant is funded, the MGH statistician can then shift a portion of their activities to new personnel to make their time available to the new project. This shift may require 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 because of the overlap between these two services which are somewhat redundant in populations served, nature of problems discussed, and time spent. 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 faculty and staff of other CRP Units and programs who are assisting clinical investigators more broadly and collaboratively within the CRP structure with other aspects of their individual projects (such as IRB submission, budget preparations, grant submissions, mentoring etc), Thus the CRP efforts are tightly coordinated by the CRP program to provide as much of 'one stop shopping' as possible. This attempt at integration is unique to the CRP's service model approach. Second, both the educational milieu and technological support for the biostatistics support services offered by the CRP is onsite which lends itself to relationship building over time. Thus, courses and computer lab services that are offered by CRP statisticians and are available onsite at the MGH and at times convenient for physician scientists with complex patient care and clinical responsibilities stand in contrast to Catalyst courses and much of their support programs which reside solely at the Longwood campus and are available during the daytimes only. Finally, CRP statisticians working with investigators during the preparations of their individual grant applications are then available to commit their time to the eventual execution of the grant and research effort as members of the research team. (This is again 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 and integration of support provided by the 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 and distinguish these efforts from the Catalyst supported functions.

LESSONS LEARNED

From Consulting Activities: Locality Matters. A crucial function of the CRP's Biostatistical Unit's programs is to provide MGH's clinical investigative community with fully integrated, local statisticians who are interactive collaborators and/or co-investigators on their grants. These goals afford a full spectrum of services that then not only support the submission but also the execution of these proposals through 'up front" consulting activities and then 'back end support by the Biostatistical Unit and laboratory serially over time. 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 clinical investigators of the MGH. During the year, the Biostatistics Unit offered PhD or MA statistician support (from 5–50% FTE) in this 'back end' support fashion to several investigators in the MGH, including Drs. James Perrin (Pediatrics), Andrew Nierenberg (Psychiatry), Donna Felsenstein (Infectious Disease), and Kenneth Freedberg (Infectious Disease/MPEC).

From the educational mission: The Need is Expanding: The annual CRP Basic Biostatistics Course enrolled >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 integrate 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 these elements have not only become crucial but are now required components of NIH programs such as 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 our Unit's educational offerings in collaboration with the CRP's Education Unit in the coming year. 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 new service also includes standing a statistical computing and consult lab in dedicated space contiguous to the Biostatistics Unit. There is also an interest in providing additional online lectures and tools to allow investigators to learn statistics at their own timing and pace as the CRP's Education Unit has been doing for the past several years. In many ways, the Biostatistical Lectures are ideally suited to this program which could great reduce the future educational burden at least but also perhaps allow it to expand to newer areas in need of such support such as Genetics and Genomics.

ADAPTATION PLANNED

Unfortunately, many MGH investigators still submit grant proposals with insufficient statistical input and support. As can be expected, these are typically much less successful than those with proper biostatistical input. Hence, it would be useful if the MGH could establish a new mechanism whereby some biostatistical review could be inserted into the grant submission process, allowing at least 2–4 weeks prior to submission. The initial focus of such an expansion of support would be to examine in details those grants that are applying to the MGH's bridge funding to improve the return 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 its submission to the granting agency might ensure that their study designs are compatible with research goals might streamline use of valuable IRB committee time. 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, which is providing increased visibility of Biostatistics at the MGH.

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, 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 Department works with ECOR, 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 requirements.

The Department strives to improve and coordinate processes for planning, allocation, and renovation of research space through 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 aims to improve and coordinate processes for planning, allocation, and renovation of research space.

RSMG compiles annual departmental surveys of research space utilization and reviews the results with Department/Center Chiefs or Program Directors to anticipate changing space needs and to develop plans for meeting future research space requirements.

The Research Space Management Group is responsible for developing and ensuring adherence to safeguards designed to prevent loss, damage, or theft of all research equipment valued at $1500 and above. This entails the maintenance of the Research Equipment Inventory Database as well as responsibility for the identification, management, and disposition of research equipment.

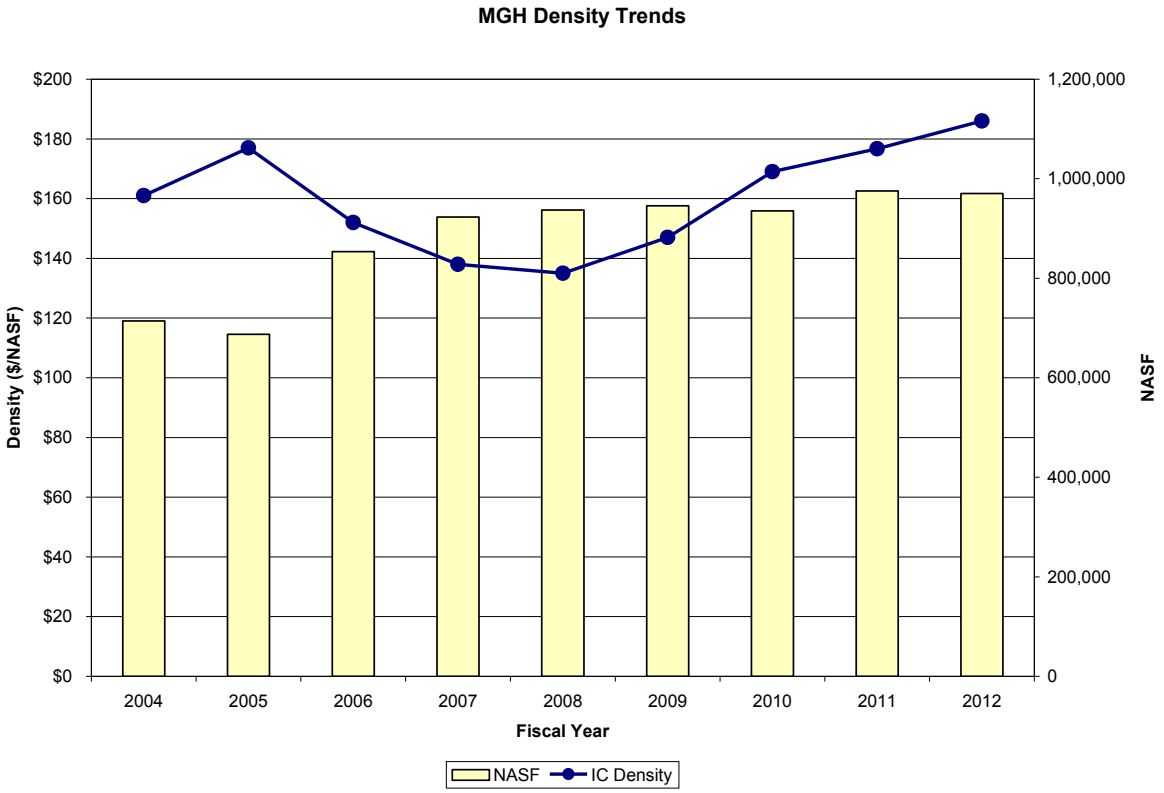
RSMG manages research facilities on both the main campus and in the Charlestown Navy Yard. RSMG operations staff is on call 24/7 to troubleshoot pressing lab issues. The RSMG facilities team also manages the Research Support Services Core in order to provide essential services to research groups in a cost-effective and efficient manner.

Staffing

The RSMG staff worked hard to make FY12 a success. The Department experienced one staff transition over the past year. Trevor Higgins, Senior Space Analyst, resigned to pursue a growth opportunity with the Partners Planning and Construction Office. Trevor was a three year veteran of RSMG and his contributions will be missed. RSMG is working with Human Resources to identify qualified candidates for the position.

FY12 Successes

ECOR's Research Densification Committee continued to provide guidance on matters relating to optimizing utilization of existing MGH research space during FY12. Committee membership includes senior leadership from MGH Research Departments, the Senior Vice President of Research, 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 FY12, overall hospital research IC density improved by 5% over FY11 to $186/NASF. MGH's research footprint did not change significantly in FY12. Since the Committee's original formation in fiscal year 2009, IC densities have increased 27% hospital-wide.

RSMG initiated and coordinated numerous projects during the year that helped to further densify MGH research space. In total, RSMG completed 33 construction and renovation projects totaling over $2 million and involving more than 8,000 NASF. RSMG currently has 27 projects in process totaling over $28M and covering over 100,000 NASF.

In order to accommodate the increased demand for dry research space, MGH renovated 1,600 NASF in the Simches Building to create additional computational space for the Center for Human Genetic Research. RSMG also converted 400 NASF of underutilized conference area space on the fourth floor of Building 149 to office space for GI research, and 200 NASF of underutilized space on the second floor of Building 149 to office space for Psychiatry. RSMG also helped negotiate temporary allocations in Building 149 to provide additional space for Neurology and the Wellman Center for Photomedicine.

There were also several successes in densifying wet lab space during FY12. Renovations in Building 149 for the Department of Radiology's 3T Skyra Magnet are nearing completion. RSMG renovated approximately 7,000 NASF on the main campus for the expansion of the Wellman Center for Photomedicine's optical and diagnostic imaging laboratories. RSMG also facilitated correction activities such as humidity and air issues in CCM facilities and satellite animal areas, and energy saving initiatives such as hospital-wide fume hood replacements.

We expect all of these projects will contribute to bolstering hospital IC density during 2013 and allow these innovative and valuable research programs to grow and flourish.

Space Requests
At the start of fiscal year 2012, RSMG received requests for over 43,000 NASF of additional research space; approximately 30,000 NASF of these requests were for wet lab space and over 13,000 NASF of these requests were for dry space. RSMG was able to resolve 62% of these requests throughout the year, accounting for 24,000 NASF total. The remaining unresolved space requests are awaiting space availability. To date, RSMG has received over 45,000 NASF in space requests for FY13.

Survey Activity
In 2012, RSMG analysts completed 52 special reports involving 3 Thematic Centers, 6 Departments, and 1 other research entity, which totaled 309,041 square feet. RSMG staff provided eleven comprehensive annual space surveys which detailed current space and staff, and analyzed departmental funding and metrics over multiple years. The information provided quantitative data for use as a tool in current and future space planning decisions by Department and Thematic Center Chiefs. Numerous financial summaries and density analyses were sent to administrators in Thematic Centers, Departments, and Units throughout the year. RSMG staff also prepared monthly Institutional density reports.

Space Management System Database Development
Throughout fiscal year 2012, RSMG continued its collaboration with Partners Real Estate and Facilities and Brigham and Women's Hospital on a redesign of the Space Management System (SMS) database. The project scope is managed by the Partners IS Research Applications Group. User interface testing is scheduled to begin in January 2013 with development scheduled for completion in July 2013. The original system was designed and implemented by MGH's RSMG in 2001, and adopted by BWH in 2005. The new system will be an enterprise version, capable of use by all Partners entities with research activities.

Research Capital Equipment
In 2012, RSMG received information on 2,284 newly purchased pieces of capital equipment. RSMG reviewed each item to determine if it met eligibility criteria for inclusion in the Research Equipment Inventory Database; 677 items were deemed eligible items. These items, which can be situated in any MGH building where research occurs, were located and tagged following which detailed data about the equipment was entered into the database.

Audit Type	Audit Success
Equipment purchased with Federal and Non-Federal sources valued at $1500 - $4999	97%
Equipment purchased through Federal Contracts valued at $5000 or greater	100%
Equipment purchased with Federal sources valued at $5000 and greater	100%
Equipment purchased with Federal and Non-Federal sources valued at $5000 or greater	99%
Equipment categorized as Category N (Due-Diligence)	100%
Equipment purchased with Non-Federal sources valued at $5000 or greater	99%

Research Space Management Group

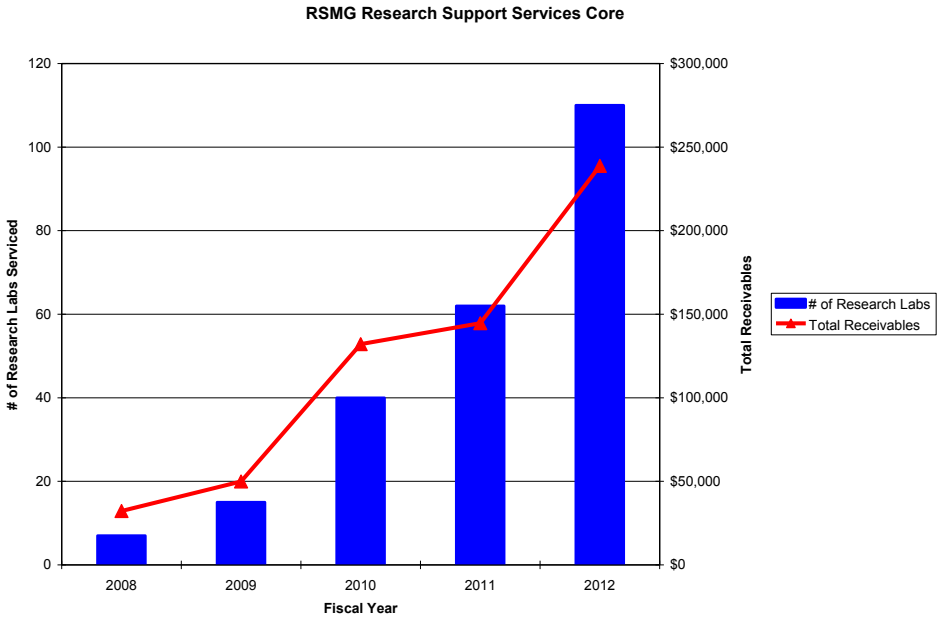
Program Review 2012

RSMG conducts annual statistical "mini-audits" to validate equipment records maintained in the Research Equipment Inventory Database. These audits provide RSMG, Research Management, Research Finance, Capital Accounting, and 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 2012; a total of 601 pieces of equipment were randomly selected. Total population size of equipment eligible for audit was 3,721; 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. Research Support Services Core

RSMG's Research Support Services Core underwent further expansion in 2012. The Core is a break-even operation designed to provide essential services to researchers at a reasonable cost, such as centralized CO2, glass washing, autoclaving, copier services, and cable TV. The Research Support Services Core provides services to laboratories in the Simches Research Center, the MGH Main Campus, and Building 149.

The number of laboratories utilizing the glass washing, autoclaving, cable TV, CO2, and photocopier services increased in fiscal year 2012 to 110 labs. Total receivables increased by 10% from $144,685 (FY2011) to $238,764 (FY12).



Looking Ahead to 2013

An anticipated flat or reduced NIH budget is likely to present continued challenges for MGH's research enterprise, as alternate funding resources are sought with lower indirect cost recovery rates. Although MGH research activity was bolstered throughout 2010 and 2011 due to increased NIH funding through the American Reinvestment and Recovery Act, the expiration of this funding did not impact hospital-wide densities. Overall, IC densities increased in FY12. The Densification Committee continues to explore various methods by which to identify opportunities to densify the current research space configuration to maximize the institution's research capacity and indirect cost recovery.

In FY12, renovations continued 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 60,700 square foot facility will include 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 will also include a mouse vivarium, 12 tissue culture rooms, and a 160 seat conference center with state of the art audio-visual and audio-conference capabilities. Construction is substantially complete and relocations will occur in January 2013.

RSMG, in collaboration with the Densification Committee, initiated a formal planning process in order to backfill the 20,000 NASF of research space that the Ragon Institute will vacate in Building 149. This space includes 37 benches, dry space, and tissue culture space (including BL2+ rooms). RSMG received 18 proposals from 10 departments for this space; the requests totaled approximately 90,000 NASF. The Densification Committee reviewed and discussed the proposals, and from these discussions, RSMG developed 3 potential scenarios for review and comment. The Densification Committee selected one scenario with additional modifications to accommodate programs with greatest need; ECOR and hospital leadership approved the plan in June 2012. Seven departments were awarded space and renovations are expected to occur in FY13 and FY14.

We expect continued success in these initiatives for FY13 due in part to the professionalism and dedication of RSMG staff.

- Nancy Hanafin, Supervisory Analyst
- Denise Adan, CAD/CAFM Specialist, Asset Management, and Special Projects
- Lauren Barsanti, Training Manager and Special Projects
- Norah Chen, Senior Space Analyst
- Patricia Frederico, Research Operations and Facilities Manager
- Meghan Hennelly, Office Coordinator
- Wendy Hobbs, Senior Space Analyst
- Yoel Jimenez, Asset Analyst
- Jeanne Kotelly, Research Operations and Facilities Manager
- Carmen Lilley, Research Technician

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 MGH Transplantation Biology Research Center manages a breeding herd of 450 uniquely inbred miniature swine in Grafton, MA for allogeneic and xenogeneic organ transplant protocols.

The MGH Institutional Animal Care and Use Committee (IACUC) governs 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 SRAC before the requisite animals can be ordered and experiments begun. Currently, there are more than 900 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 eight staff veterinarians (seven of whom are board-certified in laboratory animal medicine or veterinary clinical pathology).

Notable CCM R& D activities include 1) a collaborative brain imaging study with MGH Psychiatry and Radiology to compare the neurocircuitry of human maternal attachment to human pet attachment, and 2) development of expanded capabilities in the CCM Comparative Clinical Pathology Laboratory particularly involving novel and mico-volume blood and urine testing options for various laboratory animal species.

The Multicultural Affairs Office

Program Review 2012

Elena B. Olson, JD, Executive Director

Background:

In 1992, Dr. Winfred Williams founded the Office for Minority Health Professions to address the issue of increasing the number of URM trainees at MGH, principally in the Department of Medicine. In 2000, the office was renamed the Multicultural Affairs Office (MAO), to reflect its evolution into a Hospital-and community-wide resource that works with virtually all departments at MGH. In late 2006, MAO was restructured with the support of MGH President Peter Slavin. As part of this restructuring, a multi-disciplinary advisory board co-chaired by Drs. Williams and Slavin, and comprised of chiefs of service, hospital and MGPO leadership, trustees, an HMS Dean, as well as senior faculty underrepresented in medicine (URM), was created to provide advice and assistance with the strategic direction of the office. MAO's staff includes an Executive Director, as well as 2 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.

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 research at MGH. In light of this mission, MAO has three broad-based objectives:

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

Accomplishments:

1. OVERALL: ENGAGEMENT OF LEADERSHIP/DEPARTMENTS

- Four 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 this past year that all 19 clinical departments became fully engaged. Currently, 12 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 specific 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, one of which established the Diversity Leaders group. 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 20th 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 was established in 2006, merging two existing mentorship programs—the Hispanic Medical Students Mentorship Program founded in 2000 and the Black Health Organization Mentorship Program founded in 2005. It 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. In 2000, MAO began to actively provide 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 year, 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 2011-12 recruitment season and hosted a total of 11 receptions, which gave minority 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 2012, 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, 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:

- See Alumni Reunion information above.
- 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, 25 awards have been granted and 94% 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.
- Held fourth annual Award Recognition Ceremony honoring 2012 MFDA recipients and including a poster presentation of the prior MFDA winners (2003-2011).
- 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.
- 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. 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. Education and Research

- 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 Outreach

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:

- 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.
- Complete DOM pilot on Teamwork and Communication, and expand focus on other Departments.

The MAO Staff:

Administrative Full-Time Staff:

Elena Olson, JD, *Executive Director*

Klara Bustamante, *Staff Assistant*

Part-Time Faculty Staff:

Winfred Williams, MD, *Co-Chair, Advisory Board*

Alexy Arauz, MD, MPH, *Associate Director*

Joseph Betancourt, MD, MPH, *Program Director for Multicultural Education*

Rhonda Bentley-Lewis, *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 2012 as will be evident 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 is actively building its 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

Gary Ruvkun won the Dr. Paul Janssen Award for Biomedical Research from Johnson & Johnson for the co-discovery of microRNAs.

Jack Szostak was appointed Professor of Chemistry and Chemical Biology, Faculty of Arts and Sciences, Harvard University.

Research Programs

AUSUBEL LABORATORY

My laboratory uses genetic, genomic, and chemical approaches to investigate the molecular basis of microbial pathogenesis and host innate immunity in the model nematode *Caenorhabditis elegans* and the reference plant *Arabidopsis thaliana*. We are particularly interested in elucidating those aspects of pathogenesis and host defense that are similar irrespective of the pathogen and the host. The rationale for studying both Arabidopsis and *C. elegans* is that mechanisms underlying bacterial (and fungal) pathogenesis and the host innate immune response are similar in plants and animals and that the plant and nematode projects are synergistic. For example, our expertise with the Arabidopsis defense response led directly to the hypothesis that *C. elegans* indirectly recognizes *P. aeruginosa* ToxA protein, the subject of a recent 2012 paper in *Cell Host & Microbe*. We are focusing on common features of immune signaling in plants and animals including the fact that both plants and animals respond to microbe-associated molecular patterns (MAMPs). Working on both *C. elegans* and Arabidopsis has injected a lot of energy into the lab and I plan on continuing both projects for the foreseeable future.

Select Publications

McEwan DL, Kirienko NV, Ausubel FM Host Translational Inhibition by Pseudomonas aeruginosa Exotoxin A Triggers an Immune Response in Caenorhabditis elegans. Cell Host Microbe.;11(4):364-74 (2012)

Feinbaum RL, Urbach JM, Liberati NT, Djonovic S, Adonizio A, Carvunis AR, Ausubel FM Genome-Wide Identification of Pseudomonas aeruginosa Virulence-Related Genes Using a Caenorhabditis elegans Infection Model. PLoS Pathog. ;8(7):e1002813 (2012)

Pukkila-Worley R, Feinbaum R, Kirienko NV, Larkins-Ford J, Conery AL, Ausubel FM Stimulation of Host Immune Defenses by a Small Molecule Protects C. elegans from Bacterial Infection. PLoS Genet.;8(6):e1002733 (2012)

Pukkila-Worley R, Ausubel FM Immune defense mechanisms in the Caenorhabditis elegans intestinal epithelium. Curr Opin Immunol.;24(1):3-9 (2012)

FREEMAN LABORATORY/TRANSLATIONAL MEDICINE GROUP (TMG)

The programs in TMG are diverse and include re-purposing of existing molecules toward an academically identified new target or disease (e.g., bevacizumab treatment of respiratory papillomatosis), the generation of new vaccines for cholera, and the development of a novel oral anti-diabetic agent.

The TMG has been working with the hospital administration to put forth a plan to create a Translational Medicine Institute at MGH. This plan focuses on the creation of a laboratory of human investigation in which novel therapeutic molecules and devices would be tested in patients to assess early signals of safety and efficacy.

CCIB

Select Publications

Best SR, Friedman AD, Landau-Zemer T, Barbu AM, Burns JA, Freeman MW, Halvorsen YD, Hillman RE, Zeitels SM Safety and dosing of bevacizumab (avastin) for the treatment of recurrent respiratory papillomatosis. Ann Otol Rhinol Laryngol. 2012;121(9):587-93 (2012)

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HUNG LABORATORY

The increasing prevalence of antibiotic resistance among clinically important pathogens is a growing threat, outpacing the development of antibiotics with new mechanisms of action. *Pseudomonas aeruginosa*, an important clinical pathogen with increasing antibiotic resistance, encodes one of the largest sets of two-component signaling (TCS) systems known in bacteria and is thought to use these to coordinate the transition between growth in the external environment and in a human host, including the transition from acute to chronic infection lifestyles. We have identified several novel TCS not previously known to play a role in acute infection by screening a comprehensive set of *P. aeruginosa* mutants in 58 TCS sensor kinases in a new vertebrate model of acute infection. We identified kinB, phoR, bqsS, and copS as being required for full virulence in *Danio rerio* (zebrafish) embryos as well as gacS and retS, which have previously been shown to be required for infection in other models. We found that while KinB is required for acute infection, it signals non-canonically, independent both of its cognate response regulator, AlgB, and of its kinase activity.

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Stanley SA, Schmidt Grant S, Kawate T, Iwase N, Shimizu M, Wivagg C, Silvis M, Kazyanskaya E, Aquadro J, Golas A, Fitzgerald M, Dai H, Zhang L, Hung DT Identification of novel inhibitors of M. tuberculosis growth using whole cell based high-throughput screening. ACS Chem Biol. (2012)

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Barczak AK, Gomez JE, Kaufmann BB, Hinson ER, Cosimi L, Borowsky ML, Onderdonk AB, Stanley SA, Kaur D, Bryant KF, Knipe DM, Sloutsky A, Hung DT RNA signatures allow rapid identification of pathogens and antibiotic susceptibilities. Proc Natl Acad Sci U S A. (2012)

JOUNG LABORATORY

Rapid advances with zinc finger nucleases (ZFNs) and transcription activator-like effector nucleases (TALENs) have transformed our ability to make targeted gene modifications in a wide variety of organisms and cell types. Tools and techniques for making ZFN- or TALEN-mediated alterations are becoming well refined and broadly distributed. Over the past three years we have developed publicly available protocols, reagents, and software for engineering ZFNs and TALENs and have used these methods to generate customized nucleases for endogenous genes in plants, zebrafish, mice, and human somatic and pluripotent stem cells. As a result, today almost any investigator can knock out their genes of interest using these resources. Despite the importance of mutational analysis for understanding gene function, targeted sequence alterations represent only one tool for biological research. To understand gene function completely, methods for controlling gene expression both spatially and temporally would

CCIB

provide powerful tools. Engineered zinc finger and transcription activator-like effector repeat DNA-binding domains have the potential to contribute to all of these areas and to thereby further the suite of customizable tools available to the biomedical research community.

Select Publications

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Joung JK, Sander JD TALENs: a widely applicable technology for targeted genome editing. Nat Rev Mol Cell Biol. (2012)

Reyon D, Khayter C, Regan MR, Joung JK, Sander JD Engineering Designer Transcription Activator—Like Effector Nucleases (TALENs) by REAL or REAL-Fast Assembly. Curr Protoc Mol Biol. 2012;Chapter 12:Unit12.15 (2012)

Reyon D, Tsai SQ, Khayter C, Foden JA, Sander JD, Joung JK FLASH assembly of TALENs for high-throughput genome editing. Nat Biotechnol. (2012)

Ramirez CL, Certo MT, Mussolino C, Goodwin MJ, Cradick TJ, McCaffrey AP, Cathomen T, Scharenberg AM, Joung JK Engineered zinc finger nickases induce homology-directed repair with reduced mutagenic effects. Nucleic Acids Res. (2012)

RUVKUN LABORATORY

We have identified a number of genes via genetic analysis and RNA interference gene inactivations that act as protein coding cofactors for the function of miRNAs and siRNAs in *C. elegans*. Some of these proteins were identified in genetic screens for decrease in miRNA function, some in genetic screens for decrease in siRNA function, and some in genetic screens for increase in siRNA function. We have also identified the target small RNAs that mediate these functions by deep RNA sequencing of selected mutant strains.

From a combination of genetic analyses and RNAi screening, we have discovered hundreds of gene inactivations and mutations that promise to reveal the neuroendocrine circuit through which *C. elegans* fat storage set points are determined. Because RNAi does not as potently target neurons, we have also configured classical genetic screens for low fat storage and high fat storage mutations. Some of the 80 mutants in our current collection store extraordinarily high levels of fat under all conditions tested whereas others have defects in the mobilization of fat induced by starvation or drug treatments.

Select Publications

Shore DE, Carr CE, Ruvkun G Induction of cytoprotective pathways is central to the extension of lifespan conferred by multiple longevity pathways.PLoS Genet;8(7): e1002792 (2012)

Phillips CM, Montgomery TA, Breen PC, Ruvkun G MUT-16 promotes formation of perinuclear Mutator foci required for RNA silencing in the C. elegans germline. Genes Dev. (2012) Zhang C, Montgomery TA, Fischer SE, Garcia SM, Riedel CG, Fahlgren N, Sullivan CM, Carrington JC, Ruvkun G The Caenorhabditis elegans RDE-10/RDE-11 Complex Regulates RNAi by Promoting Secondary siRNA Amplification. Curr Biol. (2012) Zhang C, Ruvkun G New insights into siRNA amplification and RNAi. RNA Biol.;9(8): (2012)

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Melo JA, Ruvkun G Inactivation of Conserved C. elegans Genes Engages Pathogen- and Xenobiotic-Associated Defenses. Cell;149(2):452-66 (2012)

Shi Z, Ruvkun G The mevalonate pathway regulates microRNA activity in Caenorhabditis elegans. Proc Natl Acad Sci U S A;109(12):4568-73 (2012)

Wu X, Shi Z, Cui M, Han M, Ruvkun G Repression of Germline RNAi Pathways in Somatic Cells by Retinoblastoma Pathway Chromatin Complexes. PLoS Genet.;8(3) (2012)

SEED LABORATORY

We have assembled a large collection of human cDNA expression plasmids from various commercial and public repository sources. Using an automated transfection process, we introduce DNA from each plasmid individually into cells in culture, and evaluate the resulting changes in expression of a reporter plasmid either cointroduced with the cDNA or stably integrated into the target cell genome. In this manner we can evaluate the activity of close to 70% of known human cDNAs. Screens carried out using this approach have revealed a number of interesting candidates with activity in pathways of high current interest, including those inducing apoptotic or autophagic programs or eliciting NF-kB, p53, STAT3, SMAD, PPARα/γ, or type I interferon transcriptional responses. The screens can be carried out either for activating factors, that induce an increase in the activity of a reporter, usually luciferase, under the control of the appropriate transcriptional element, or for inhibitory factors, that diminish the level of transcription of the reporter gene. In the latter case it is necessary to control for genes that have cytotoxic action, such as those that promote apoptosis. The cDNAs known to have cytotoxic action have been cataloged and are typically not pursued if they are uncovered in the course of an inhibitory screen. In the next three years we plan to use this system to continue to identify new components of the p53 and PPAR pathways. We also plan to supplement this type of gene discovery activity by the implementation of forward genetic screens in haploid embryonic stem cells created by parthenogenetic activation of oocytes and cultivation of the resulting haploid or partially haploid embryos to the blastocyst stage.

Select Publications

Wang X, Spandidos A, Wang H, Seed B PrimerBank: a PCR primer database for quantitative gene expression analysis, 2012 update. Nucleic Acids Res. 2012;40(Database issue):D1144-9 (2012)

Zhou L, Kawate T, Liu X, Kim YB, Zhao Y, Feng G, Banerji J, Nash H, Whitehurst C, Jindal S, Siddiqui A, Seed B, Wolfe JL STAT6 phosphorylation inhibitors block eotaxin-3 secretion in bronchial epithelial cells. Bioorg Med Chem.;20(2):750-8 (2012)

Freeman J, Kriston-Vizi J, Seed B, Ketteler R A High-content Imaging Workflow to Study Grb2 Signaling Complexes by Expression Cloning. J Vis Exp.;(68) (2012)

Cho JL, Roche MI, Sandall B, Brass AL, Seed B, Xavier RJ, Medoff BD Enhanced Tim3 Activity Improves Survival after Influenza Infection. J Immunol. (2012)

SHEEN LABORATORY

Innate Immunity is the most ancient and evolutionarily conserved central defense system that distinguishes host-self from non-self microbial pathogens in plants, animals and humans. It provides the first line of inducible defense against infectious diseases and underlies the prevention of constant and omnipresent microbial invasion. A key function of innate immunity is the detection of microbe-associated molecular patterns (MAMPs, such bacterial flagellin) by pattern recognition receptors and the launch of appropriate defense responses. Recent discoveries have revealed remarkable convergent evolution in the recognition of diverse MAMPs by leucine-rich-repeat receptors and the activation of multiple MAPK cascades in plants, animals and humans. Despite the universal and essential

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involvement of MAPK cascades in mediating MAMP signaling in plants, worms, flies, mammals and humans, the molecular mechanisms underlying the intertwined signaling webs remain mostly elusive due to the complexity of functional redundancy, mutant lethality and shared components in distinct signaling pathways. The goal of this research project is to establish a regulatory framework for convergent MAMP signaling using Arabidopsis thaliana as a model system.

Select Publications

Xiong Y, Sheen J Rapamycin and glucose-target of rapamycin (TOR) protein signaling in plants. J Biol Chem.;287(4):2836-42 (2012)

Lee H, Chah OK, Plotnikov J, Sheen J Stem Cell Signaling in Immunity and Development. Cold Spring Harb Symp Quant Biol. (2012)

Boudsocq M, Sheen J CDPKs in immune and stress signaling. Trends Plant Sci. (2012)

Niu Y, Sheen J Transient expression assays for quantifying signaling output. Methods Mol Biol;876:195-206 (2012)

Lee H, Khatri A, Plotnikov JM, Zhang XC, Sheen J Complexity in Differential Peptide-Receptor Signaling: Response to Segonzac et al. and Mueller et al. Commentaries. Plant Cell. (2012)
Li JF, Sheen J DNA purification from multiple sources in plant research with homemade silica resins. Methods Mol Biol.;862:53-9 (2012)

Liu KH, McCormack M, Sheen J Targeted parallel sequencing of large genetically-defined genomic regions for identifying mutations in Arabidopsis. Plant Methods. ;8(1):12 (2012)

STUART LABORATORY

Infectious diseases represent a major burden on healthcare resources. In addition, the emergence of antibiotic resistant bacterial strains and concerns of bioterrorism have increased the need to understand the normal defense mechanisms that combat pathogens. Phagocytosis, the process of cellular engulfment of microbes into a newly formed membrane-limited organelle, the 'phagosome', is an essential component of the innate immune defense system. It directs bacteria into a highly hydrolytic and acidic environment, the mature phagolysosome, which limits replication and destroys the engulfed organism. An additional component of host defense is inflammatory signaling, which is triggered by pattern recognition receptors (PRRs), including the transmembrane Toll-like receptors (TLRs)

and the cytosolic NOD-like receptors (NLRs). We have observed that certain pathogens, such as S. aureus, exhibit absolute dependence upon the phagosome to initiate immune activation: signaling cannot be triggered from the cell surface and bacteria must be delivered into a mature phagolysosome for induction of the proinflammatory cytokine response. We hypothesize that for these pathogens the phagosome plays an active and essential role in sensing and coordinating innate immune signaling by both TLRs and NLRs.

Select Publications

Sokolovska A, Becker CE, Stuart LM Measurement of Phagocytosis, Phagosome Acidification, and Intracellular Killing of Staphylococcus aureus. Curr Protoc Immunol. ; Chapter 14:Unit14.30 (2012)

Lacy-Hulbert A, Stuart LM Penetration Resistance: PKR's Other Talent. Immunity. ; 36(5): 695-6 (2012)

Luhachack LG, Visvikis O, Wollenberg AC, Lacy-Hulbert A, Stuart LM, Irazoqui JE EGL-9 Controls C. elegans Host Defense Specificity through Prolyl Hydroxylation-Dependent and -Independent HIF-1 Pathways. PLoS Pathog;8(7) (2012)

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Perez B, Paquette N, Païdassi H, Zhai B, White K, Skvirsky R, Lacy-Hulbert A, Stuart LM Apoptotic cells can deliver chemotherapeutics to engulfing macrophages and suppress inflammatory cytokine production. J Biol Chem. (2012)

SZOSTAK LABORATORY

The principle goal of this research is to improve our understanding of the origin of cellular life on earth, and of the potential for life to arise on other planets. The effort is focused on the laboratory synthesis of simple protocells that are able to reproduce and adapt through evolution. In the next three years we hope to achieve two objectives: 1) to develop a complete model protocell in which both the nucleic acid genome and the cell membrane are capable of indefinite cycles of replication, and 2) to study potential pathways for the transition from primitive to modern cell membranes.

Select Publications

Budin I, Debnath A, Szostak JW Concentration-driven growth of model protocell membranes. J Am Chem Soc. (2012)

Zhu TF, Adamala K, Zhang N, Szostak JW Photochemically driven redox chemistry induces protocell membrane pearling and division. Proc Natl Acad Sci U S A. (2012)

Powner MW, Zheng SL, Szostak JW Multicomponent assembly of proposed DNA precursors in water. J Am Chem Soc. (2012)

Szostak JW Attempts to define life do not help to understand the origin of life.

J Biomol Struct Dyn.;29(4):599-600 (2012)

Zhang N, Zhang S, Szostak JW Activated ribonucleotides undergo a sugar pucker switch upon binding to a single-stranded RNA template. J Am Chem Soc.;134(8):3691-4 (2012)

Guillen Schlippe YV, Hartman MC, Josephson K, Szostak JW In Vitro Selection of Highly Modified Cyclic Peptides That Act as Tight Binding Inhibitors. J Am Chem Soc. (2012)

TOMPKINS LABORATORY

Severe trauma not only remains a major cause of hospitalization and morbidity, but is also the leading cause of death in individuals under the age of 45. The frequency of post-trauma infections, sepsis, and MSOF remain all too frequent due, in large part, to the heterogeneity of the host immune response to severe trauma, and the inability to accurately identify patients who have immunological abnormalities early after admission and who are therefore at high risk of complicated outcomes. Our overarching hypothesis has been that early changes in the human blood leukocyte transcriptome (<12-24 hrs) after severe blunt trauma can be used to identify patients who will have an adverse clinical outcome, and who ultimately may benefit from intervention therapies targeting innate and adaptive immune responses.

Based on our analysis of severe blunt trauma patients enrolled in the 'Inflammation and the Host Response to Injury' Program, we have proposed that a large proportion of patients who would generally meet the inclusion criteria for a study of severely injured patients are not in need of immunomodulatory therapy and are unlikely to benefit from such therapies (IFNγ, β-glucan or immunoglobulin). In contrast, there exists a subset of patients who will have a protracted clinical course, and would benefit from interventional therapies with biological-response modifiers. Inclusion of the former patients in such a clinical trial who would either not benefit or might be harmed by such therapies has made it extremely difficult to identify the beneficial effects of these interventions in the latter subset of patients who would be responsive to these therapies. We believe that this failure to identify those patients a priori who may actually benefit from intervention ('personalized

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therapies') is one reason that clinical trials in trauma and sepsis have failed. Therefore, it is absolutely essential that a rapid prognostic be developed and used to prospectively identify those severely injured patients who would be good candidates for the immunomodulatory intervention. The overall goal of the proposed clinical trial would be to determine whether administration of IFNγ will alter the clinical trajectory in a subgroup of severely injured patient identified by a prognostic indicator based on a genomic signature likely to have an adverse clinical outcome and who would benefit from such therapies.

Select Publications

Carter EA, Paul KW, Barrow SA, Fischman AJ, Tompkins RG
Previous burn injury predisposes mice to lipopolysaccharide-induced changes in glucose metabolism. J Burn Care Res.;33(5):683-9 (2012)

Weber JM, Sheridan RL, Fagan S, Ryan CM, Pasternack MS, Tompkins RG
Incidence of Catheter-Associated Bloodstream Infection After Introduction of Minocycline and Rifampin Antimicrobial-Coated Catheters in a Pediatric Burn Population. J Burn Care Res.;(2012)

XAVIER LABORATORY

The overall goal in the laboratory is to discover and understand the function of important mediators and effectors involved in innate (autophagy, pathogen-containing vacuole) and adaptive (T cell activation) immunity. Of particular interest are the cellular components and regulatory networks that interact dynamically within temporal, spatial and patho-physiological contexts of innate immunity. We are pursuing integrative systems approaches that closely couple genome-wide experimentation with high-throughput assays (RNAi and cDNA screens) and computational methods. Using these approaches, we are interested in addressing the following questions:

What are the mechanisms by which autophagy regulates innate and adaptive immunity?
What are the roles of NOD/LRR domains in sensing microbial effectors?
How are innate immune pathways dysregulated in mucosal immunity?
The adaptive immunity program focuses on the elucidation of signal transduction pathways coordinated by the CARMA/Dlg family of scaffold proteins.

Crohn's disease and ulcerative colitis are debilitating inflammatory diseases of the gastrointestinal tract collectively known as inflammatory bowel diseases (IBD). Among complex diseases, genetics has been particularly successful in the identification of genes for IBD with recent efforts in genome-wide association studies bringing the total number of genes to more than 100. These studies have highlighted the significance of the relationship between intracellular responses to microbes and the regulation of adaptive immunity in the pathogenesis of IBD.

With the rapid progress in human genetics it has become clear that a major challenge in the study of complex genetic traits is to determine how disease genes and their corresponding alleles exert their influences on the biology of health and disease. Our lab focuses on applying novel genomic, genetic, and chemical biology approaches to gain insights into the function of genetic variants underlying common inflammatory diseases and to explore the potential for reversing the effects of susceptibility alleles.

Select Publications

Conway KL, Goel G, Sokol H, Manocha M, Mizoguchi E, Terhorst C, Bhan AK, Gardet A, Xavier RJ
p40phox Expression Regulates Neutrophil Recruitment and Function during the Resolution Phase of Intestinal Inflammation. J Immunol. (2012)

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Kuballa P, Nolte WM, Castoreno AB, Xavier RJ Autophagy and the immune system. Annu Rev Immunol.;30:611-46 (2012)

Smeekens S, Ng A, Kumar V, Johnson MD, Plantinga TS, van Diemen C, Arts P, Verwiel ETP, Gresnigt MS, Fransen K, van Sommeren S, Oosting M, Cheng S-C, Joosten LAB, Hoischen A, Kullberg B-J, Scott WK, Perfect JR, van der Meer JWM, Wijmenga C, Netea M, Xavier RJ. Functional genomics identifies type 1 interferon pathway as central for host defense against *Candida albicans*. Natuer Communications (2012) (in press—DOI: 10, 1038/ncomms2343)

Huett A, Heath RJ, Begun J, Sassi SO, Baxt LA, Vyas JM, Goldberg M, Xavier RJ. The LRR- and RING-domain protein LRSAM1 is an E3 ubiquitin ligase crucial for ubiquitin-dependent autophagy of intracellular *Salmonella* Typhimurium. Cell Host & Microbe; Dec 13:12(6):778-790 (2012)

CORE ACTIVITIES

The CCIB DNA Core regularly explores new offerings to facilitate bench science in the hospital and academic community. The DNA core would like to implement a plasmid validation service, which will provide complete annotated plasmid sequences with a reasonable price and turnaround. Pilot studies have to date been promising, but plasmids with internal repeat structures remain a challenge to interpret because of the typically short read length provided by the current generation of high throughput sequencing instrumentation. The DNA core may also attempt to pilot a service based on forward genetics using haploid murine ES cells. An effort in the Seed lab is presently exploring project feasibility.

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 2012, building upon the genome-wide definition of common normal human genetic variation, both sequence and dosage differences, and extending rapidly to rare variation through advances in 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, monoclonal antibody production, confocal microscopy, genotyping, DNA sequencing, bioinformatics), 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.

2012 PROGRESS:

CHGR faculty had another successful year, completing the Center's formal 5 year review with very complimentary comments from the reviewers concerning our past and ongoing successes, and a request that we develop a strategic plan to support continued excellence. We demonstrated in the review our progress across all portions of the genetic research cycle, involving various aspects of human genetics and a range of clinical disciplines, progress that is reflected in a publication rate that increased almost 20% from 2011 to more than 315 papers in FY2012. . In particular, many advances were enabled by the increasing implementation of next-generation sequencing technology which is rapidly becoming the primary technological strategy for most genetic/genomic analysis. The increasing need prompted us to add sequence-based bioinformatics services to our shared capabilities for CHGR faculty. 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 more than 55 representing a wide range of departments and disciplines. Our cooperative, collaborative, interdisciplinary approach garnered the Team Award at MGH Clinical Research Day last year and five of the top winners this year involved investigators from CHGR.

Notably, one of our Faculty, David Altshuler, won the prestigious Stern Award from the American Society of Human Genetics in the past year. Over the past year, FY12 also saw the promotion of both Katherine Sims and Jonathan Rosand to full Professor in Neurology, the initiation of full Professor appointments for Susan Slaugenhaupt and Jordan Smoller, the recruitment of Daniel MacArthur

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and Benjamin Neale to the Analytical and Translational Genetics Unit and the recruitment of Rakesh Karmacharya to the Psychiatric and Neurodevelopmental Genetics Unit. In discussion with Merit Cudkowicz, new Chief of Neurology, we have also initiated promotion to Assistant Professor of two Instructors in Neurology, Inh-Sik Seong, an expert in protein biochemistry, and Jong-Min Lee, an investigator accomplished in both molecular and computational genetics.

Overall, the CHGR remains very strong and well funded, with ~$37 million in grant funding ($28.9M direct/ $8.3M indirect), supporting the research of 310 investigators and staff (including 101 classified as "non-employees" as they are paid by outside fellowships and student awards). In addition, we continued to extend our mission through other basic and clinical investigators at the MGH, as we increased our Associate Faculty to more than 55 scientists, representing a wide range of disciplines and departments. We are currently engaged in our strategic planning process to set the course for the next several years.

Selected Notable Publications:

Bick AG, Calvo SE, Mootha VK. Evolutionary diversity of the mitochondrial calcium uniporter. Science. 2012; 336:886. PMID: 22605770.

Chiang C, Jacobsen JC, Ernst C, Hanscom C, Heilbut A, Blumenthal I, Mills RE, Kirby A, Lindgren AM, Rudiger SR, McLaughlan CJ, Bawden CS, Reid SJ, Faull RL, Snell RG, Hall IM, Shen Y, Ohsumi TK, Borowsky ML, Daly MJ, Lee C, Morton CC, MacDonald ME, Gusella JF, Talkowski ME. Complex reorganization and predominant non-homologous repair following chromosomal breakage in karyotypically balanced germline rearrangements and transgenic integration. Nat Genet. 2012; 44:390-7. PMID: 22388000.

Jain M, Nilsson R, Sharma S, Madhusudhan N, Kitami T, Souza AL, Kafri R, Kirschner MW, Clish CB, Mootha VK. Metabolite profiling identifies a key role for glycine in rapid cancer cell proliferation. Science. 2012; 336:1040-4. PMID: 22628656.

James MF, Stivison E, Beauchamp R, Han S, Li H, Wallace MR, Gusella JF, Stemmer-Rachamimov AO, Ramesh V. Regulation of mTOR complex 2 signaling in neurofibromatosis 2-deficient target cell types. Mol Cancer Res. 2012; 10:649-59. PMID: 22426462.

Jostins L, Ripke S, Weersma RK, Duerr RH, McGovern DP, Hui KY, Lee JC, Schumm LP, Sharma Y, Anderson CA, Essers J, Mitrovic M, Ning K, Cleynen I, Theatre E, Spain SL, Raychaudhuri S, Goyette P, Wei Z, Abraham C, Achkar JP, Ahmad T, Amininejad L, Ananthakrishnan AN, Andersen V, Andrews JM, Baidoo L, Balschun T, Bampton PA, Bitton A, Boucher G, Brand S, Büning C, Cohain A, Cichon S, D'Amato M, De Jong D, Devaney KL, Dubinsky M, Edwards C, Ellinghaus D, Ferguson LR, Franchimont D, Fransen K, Gearry R, Georges M, Gieger C, Glas J, Haritunians T, Hart A, Hawkey C, Hedl M, Hu X, Karlsen TH, Kupcinskas L, Kugathasan S, Latiano A, Laukens D, Lawrance IC, Lees CW, Louis E, Mahy G, Mansfield J, Morgan AR, Mowat C, Newman W, Palmieri O, Ponsioen CY, Potocnik U, Prescott NJ, Regueiro M, Rotter JI, Russell RK, Sanderson JD, Sans M, Satsangi J, Schreiber S, Simms LA, Sventoraityte J, Targan SR, Taylor KD, Tremelling M, Verspaget HW, De Vos M, Wijmenga C, Wilson DC, Winkelmann J, Xavier RJ, Zeissig S, Zhang B, Zhang CK, Zhao H; International IBD Genetics Consortium (IIBDGC), Silverberg MS, Annese V, Hakonarson H, Brant SR, Radford-Smith G, Mathew CG, Rioux JD, Schadt EE, Daly MJ, Franke A, Parkes M, Vermeire S, Barrett JC, Cho JH. Host-microbe interactions have shaped the genetic architecture of inflammatory bowel disease. Nature. 2012; 491:119-24. PMID: 23128233.

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Lee JM, Gillis T, Mysore JS, Ramos EM, Myers RH, Hayden MR, Morrison PJ, Nance M, Ross CA, Margolis RL, Squitieri F, Griguoli A, Di Donato S, Gomez-Tortosa E, Ayuso C, Suchowersky O, Trent RJ, McCusker E, Novelletto A, Frontali M, Jones R, Ashizawa T, Frank S, Saint-Hilaire MH, Hersch SM, Rosas HD, Lucente D, Harrison MB, Zanko A, Abramson RK, Marder K, Sequeiros J, MacDonald ME, Gusella JF. Common SNP-based haplotype analysis of the 4p16.3 Huntington disease gene region. Am J Hum Genet. 2012; 90: 434-44. PMID: 22387017.

Lee JM, Ramos EM, Lee JH, Gillis T, Mysore JS, Hayden MR, Warby SC, Morrison P, Nance M, Ross CA, Margolis RL, Squitieri F, Orobello S, Di Donato S, Gomez-Tortosa E, Ayuso C, Suchowersky O, Trent RJ, McCusker E, Novelletto A, Frontali M, Jones R, Ashizawa T, Frank S, Saint-Hilaire MH, Hersch SM, Rosas HD, Lucente D, Harrison MB, Zanko A, Abramson RK, Marder K, Sequeiros J, Paulsen JS; PREDICT-HD study of the Huntington Study Group (HSG), Landwehrmeyer GB; REGISTRY study of the European Huntington's Disease Network, Myers RH; HD-MAPS Study Group, MacDonald ME, Gusella JF; COHORT study of the HSG. CAG repeat expansion in Huntington disease determines age at onset in a fully dominant fashion. Neurology. 2012; 78: 690-5. PMID: 22323755.

Lee PH, Perlis RH, Jung JY, Byrne EM, Rueckert E, Siburian R, Haddad S, Mayerfeld CE, Heath AC, Pergadia ML, Madden PA, Boomsma DI, Penninx BW, Sklar P, Martin NG, Wray NR, Purcell SM, Smoller JW. Multi-locus genome-wide association analysis supports the role of glutamatergic synaptic transmission in the etiology of major depressive disorder. Transl Psychiatry. 2012; 2:e184. PMID: 23149448.

Neale BM, Kou Y, Liu L, Ma'ayan A, Samocha KE, Sabo A, Lin CF, Stevens C, Wang LS, Makarov V, Polak P, Yoon S, Maguire J, Crawford EL, Campbell NG, Geller ET, Valladares O, Schafer C, Liu H, Zhao T, Cai G, Lihm J, Dannenfelser R, Jabado O, Peralta Z, Nagaswamy U, Muzny D, Reid JG, Newsham I, Wu Y, Lewis L, Han Y, Voight BF, Lim E, Rossin E, Kirby A, Flannick J, Fromer M, Shakir K, Fennell T, Garimella K, Banks E, Poplin R, Gabriel S, DePristo M, Wimbish JR, Boone BE, Levy SE, Betancur C, Sunyaev S, Boerwinkle E, Buxbaum JD, Cook EH Jr, Devlin B, Gibbs RA, Roeder K, Schellenberg GD, Sutcliffe JS, Daly MJ. Patterns and rates of exonic de novo mutations in autism spectrum disorders. Nature. 2012; 485:242-5. PMID: 22495311.

Perlis RH, Iosifescu DV, Castro VM, Murphy SN, Gainer VS, Minnier J, Cai T, Goryachev S, Zeng Q, Gallagher PJ, Fava M, Weilburg JB, Churchill SE, Kohane IS, Smoller JW. Using electronic medical records to enable large-scale studies in psychiatry: treatment resistant depression as a model. Psychol Med. 2012; 42: 41-50. PMID: 21682950.

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Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet. 2012; 380: 572-80. PMID: 22607825.

Center for Regenerative Medicine

Center Overview

CRM

David T. Scadden, MD, Director

The Center for Regenerative Medicine is dedicated to understanding how tissues are formed and may be repaired. Our primary goal is to develop novel therapies to regenerate damaged tissues and overcome debilitating chronic disease. The success of this effort requires a cohesive team of scientists and clinicians with diverse areas of expertise, but with a shared mission and dedication to the larger goal. 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 direction for CRM is drawn from four sources—its membership and director, its Recruitment Committee, its recently-formed Scientific Advisory Board and a group of lay leaders composing the Innovation Fund Steering Committee. It has now initiated two clinical trials based on results from the laboratories of CRM.

Investigators within the Center include:

Andrew Brack, PhD, Assistant Professor of Medicine
The Brack lab's interests lie at the interface between adult stem cell biology and tissue regeneration. 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 consists of 4 Postdoctoral Fellows (PhDs), 1 PhD students, and 1 research technician. The lab is supported by 2 NIH R01, Sanofi-Aventis, the Harvard Stem Cell **Institute, the Muscular Dystrophy Association and the Ellison Foundation.**

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 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 laboratory consists of 1 postdoctoral fellow and 1 technician. His research is funded by Roche Pharmaceuticals and an NIH U01.

Nabeel El-Bardeesy,PhD, Assistant Professor of Medicine (Cancer Center) (Affiliate)
The Bardeesy Laboratory focuses on understanding the genetic program for PDAC 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, 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 research interests are directed towards 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.

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 consists of 5 Postdoctoral Fellows (PhDs), 1 Clinical Fellow, 4 PhD students, 2 undergraduates and a lab manager/ research technician. Konrad also supports a .5 FTE staff assistant. The Hochedlinger lab is supported by 2 NIH R01, 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 consists of 6 Postdoctoral Fellows (1 MD/5 PhD), 2 undergraduate students and 1 technician. The Rajagopal lab is funded by internal funds, the Cystic Fibrosis Foundation, the Harvard Stem Cell Institute, 2 NIH R21s, Massachusetts Eye and Ear Infirmary and DOD.

Eric Liao, MD, PhD, Assistant Professor of Medicine (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. Dr. Liao's lab is currently comprised of 5 postdoctoral fellows, an aquatics facility manager, and 1 technician. The Liao lab is funded by the Plastic Surgery Education Foundation, The March of Dimes Foundation, The Harvard Stem Cell Institute, the American Surgical Association 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 consists of 3 postdoctoral fellows and 1 research technician. 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) (Affiliate)
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 (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 consists of 5 postdoctoral Fellows, 4 staff scientist, a Clinical Fellow, a MD student, a Clinical Research Coordinator and a Research Technician. 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.

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Amar Sahay, PhD, Assistant Professor of Medicine (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 made up of 4 postdoctoral fellows, 1 clinical fellow, 1 MD student, 1 undergraduate student and 1 research technician. The Sahay lab is currently funded by an NIH R00, the Ellison Medical Foundation and an internal funding.

Shobha Vasudevan, PhD, Assistant Professor of Medicine (Cancer Center)
Dr. Vasudevan's lab is investigating the mechanisms of gene expression regulation of cancer associated genes 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 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 consists of 4 postdoctoral fellows and 1 research technician. 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 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. The Vacanti lab consists of 3 senior Scientists, 1 Instructor/Resident in Cardiothoracic Surgery, 1 research Technologist and 2 research technicians.

David Scadden, MD, Gerald and Darlene Jordan Professor of Medicine, Professor and co-chair Department of Stem Cell and Regenerative Biology
The Scadden laboratory focuses on the hematopoietic stem cell and its microenvironment or niche. The Scadden lab covers 2 campuses, that of the Simches Research Building and the newly outfitted Fairchild Building on the Campus of Harvard University. The Scadden lab is consists of 20 post-doctoral fellows including 12 PhDs, 3 MDs and 5 MD, PhDs. Also in the laboratory are 5 undergraduate students working on their thesis. The lab is affiliated with the HSCI, Broad Institute and the Cancer Center. It is funded by the NIH (R01s, U01s), The Ellison Medical Foundation, The Harvard Stem Cell Institute, Glaxo-Smith Kline, Anchor Therapeutics. Postdoctoral fellows in the lab are funded by the Alex Lemonade Stand Foundation, Leukemia and Lymphoma Society, International Society of Hematology, American Society of Hematology, the NIH (K, Ts, Proton Beam, R03), The Canadian Institute of Health Research, the Government of Lebanon, Bullock Wellman Foundation, Leukemia Research Foundation, the American Association of Neurology, and internal funding (ECOR).

Recruitment Activities:

CRM began with just three members and is currently at 15 faculty. The Center is currently recruiting for 1 new junior faculty candidates and expects to add one or two new members in the course of the next year. The Center is currently undertaking a nationwide search to recruit a faculty member at the level of Assistant Professor.

Dr. Jenna Galloway is the newest recruit to the CRM. Dr. Galloway is the most recent faculty recruit to the MGH CRM. Dr Galloway's primary research interests are directed towards understanding

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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.

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 of FAS and the Howard Hughes Medical Institute. 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 also serving as Co-chair of the recently formed Department of Stem Cell and Regenerative Biology (SCRB) of Harvard University, the first department between faculties in Harvard's history. Several CRM faculty have and will continue to 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 has 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.

The junior faculty has also used the opportunities of the CRM collaborations to their advantage. All junior faculty that have come to the Center have participated in this program offered by the HSCI. Most recently, the Flow Cytometry core was awarded another 3 years of funding. This core is essential to the research of many at the Center for Regenerative Medicine.

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.

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.

Public Policy:

CRM has played a role in the development of policies regarding human embryonic stem cell research within Partners and in efforts with HSCI.

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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 bi-monthly lab seminars which shares the research being down within the CRM community.

The Center has also formed a unique 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 students through this program.

Philanthropic Support:

CRM, the MGH Development Office and CRM's eleven member 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:

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David Scadden, MD

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CSB

Ralph Weissleder, MD, PhD, Director

(report prepared 12/03/12)

The mission of the Center for Systems Biology (CSB) is to analyze how biological 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 153 employees, including 32 faculty.

Investigator Labs at the Center for Systems Biology

Bernstein, Bradley, MD, PhD, Associate Professor of Pathology
The Bernstein laboratory applies high-throughput sequencing-based technologies to the genome-wide characterization of both human and mouse chromatin structure. The long-term goal of the work is to achieve a systems level understanding of chromatin regulation during development, and of how chromatin mis-regulation contributes to human disease.

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.

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

Lin, Herbert, 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, Assistant Professor of Radiology
The research interests of the Nahrendorf laboratory are focused on imaging molecular processes during the healing phase following myocardial infarction. The targets imaged are innate immune cells, particularly monocytes and macrophages, which have been shown to be key players in conditions such as cardiovascular disease. 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, Assistant 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 (particularly as they relate to disease genes) at many levels, from nanoparticle molecular imaging, to systems biology analysis of patient cells, to the use of patient Electronic Medical Records (EMR) for data mining and analytics.

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 strategies such as 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 2012

CSB faculty have published approximately 130 articles over the last year and over 350 articles over the last 3 years. Of those published in 2012, several have appeared in *Nature* journals as well as in other high profile journals such as *Science, Science Translational Medicine* and *The Proceedings of the National Academy of Sciences*. Selected publications from each laboratory are highlighted below (for full listings please see: http://csb.mgh.harvard.edu/publications):

BERNSTEIN LABORATORY

- The ENCODE Project Consortium. An integrated encyclopedia of DNA elements in the human genome. **Nature** 2012; 489:57-74. The article describes the discovery of new insights into the regulation of human genes, and their organization within the genome. Bernstein is the primary investigator of a production center at the MGH/Broad Institute for the ENCODE consortium.
- Abdel-WahabO, Adli M, Saunders LM, Gao J, Hricik T, Shih AH, Pandey S, Patel J, Chung YR, Koche R, Perna F, Zhao X, Taylor JE, Park CY, Carroll M, Melnick A, Nimer SD, Jaffe JD, Aifantis I, Bernstein BE* and Levine RL*. ASXL1 mutations promote myeloid transformation through loss of PRC2-mediated gene repression. **Cancer Cell** 2012; 22:180-93. (*corresponding author)
- Ku M, Jaffe JD, Koche RP, Rheinbay E, Endoh M, Koseki H, Carr SA, Bernstein BE. H2A.Z landscapes and dual modifications in pluripotent and multipotent stem cells underlie complex genome regulatory functions. **Genome Biol** 2012; 13:R85.
- Ryan RJH, Bernstein BE. Genetic events that shape the cancer epigenome. **Science** 2012; 336:1513-4

BRETON LABORATORY

- Ruan YC, Shum WW, Belleannee C, Da Silva N, and Breton S. ATP secretion in the male reproductive tract: essential role of CFTR. **The Journal of Physiology** 2012; 590: 4209-4222. The article describes the discovery that CFTR, the protein that is mutated in cystic fibrosis, is involved in the regulation of ATP release from epithelia cells in the epididymis. Defective ATP signaling in this organ might contribute to dysfunction of the male reproductive tract associated with CFTR mutations.
- Wagner CA, Mohebbi N, Uhlig U, Giebisch GH, Breton S, Brown D, and Geibel JP. Angiotensin II stimulates H-ATPase activity in intercalated cells from isolated mouse connecting tubules and cortical collecting ducts. **Cell Physiol Biochem** 2011; 28: 513-520.
- Brown D, Bouley R, Paunescu TG, Breton S, and Lu HAJ. New insights into the dynamic regulation of water and acid-base balance by renal epithelial cells. **Am J Physiol Cell Physiol** 302: C1421-1433, 2012.
- Krapf D, Ruan YC, Wertheimer EV, Battistone MA, Pawlak JB, Sanjay A, Pilder SH, Cuasnicu P, Breton S, and Visconti PE. cSrc is necessary for epididymal development and is incorporated into sperm during epididymal transit. **Developmental Biology** 369: 43-53, 2012.
- Kim JK, Vinarsky V, Wain JC, Zhao R, Jung K, Choi J, Lam A, Pardo-Saganta A, Breton S, Rajagopal J, and Yun SH. *In vivo* imaging of tracheal epithelial cells in mice during airway regeneration. American journal of respiratory cell and molecular biology, 2012: *in press.*

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BROWN LABORATORY

- Hennings, J. C., Picard, N., Hübner, A. K., Stauber, T., Maier, H., Brown, D., Jentsch,T. J., Vargas, R., Eladari, D. and Hübner, C. A mouse model for distal renal tubular acidosis reveals a previously unrecognized role of the V-ATPase a4 subunit in the proximal tubule. **EMBO Mol. Medicine**, 4: 1057-1071, 2012. We generated a new mouse model deficient in a subunit of the vacuolar H+ATPase that shows an unexpected defect in proximal tubule function that is related to some cases of human Fanconi syndrome.
- Chen, Y., Rice, W., Gu, Z., Li, J., Huang, J., Brenner, M. B., Van Hoek, A., Xiong, J., Gundersen, G. G., Norman, J. C., Hsu, V. W., Fenton, R. A., Brown, D., and Lu, H. A. J. Novel function of aquaporin 2 in promotion cell migration and epithelial morphogenesis. **J. Am. Soc. Nephrol.** 23: 1506-1517, 2012. The identification of a transmembrane water channel (aquaporin 2) as an integrin binding protein that plays a key role in cell migration and kidney tubule morphogenesis.
- Brown, D., Bouley, R., Paunescu, T. G., Breton, S., and Lu, H. A. New insights into the dynamic regulation of water and acid/base balance by renal epithelial cells. **Am. J. Physiol.** 302: C1421-C1433, 2012.
- Yui, N., Lu H. A. J , Bouley, R., and Brown. D. AQP2 is Necessary for Vasopressin and Forskolin Mediated Filamentous Actin Depolymerization in Renal Epithelial Cells. **Biology Open** 1, 101-108, 2012.
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HIGGINS LABORATORY

- Wood DK, Soriano AO, *Mahadevan L, *Higgins JM, Bhatia SN. A biophysical marker of severity in sickle cell disease. **Science Translational Medicine** 2012;4(123):123ra26 (*Co-corresponding authors). Describes the discovery of a biophysical biomarker (the rheodynamics of blood samples in a microfluidic system) capable of predicting the risk of complications in sickle cell patients better than any other currently known biomarker.
- Grover WH, Bryan AK, Diez-Silva M, Suresh S, Higgins JM, Manalis SR. Measuring single-cell density. **Proc Natl Acad Sci U S A**. 2011;108(27):10992-10996.
- Ersoy I, Bunyak F, Higgins JM, Palaniappan K. Coupled edge profile active contours for red blood cell flow analysis. **Proceedings of the EEE Symposium on Biomedical Imaging** (ISBI) (2012) 748-751.
- Kim Y, Dasari RR, Higgins JM, Suresh S, Park Y. Anisotropic light scattering of individual sickle red blood cells. **Journal of Biomedical Optics Letters.** 2012 Apr; 17(4).

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CHARLES LIN LABORATORY

- Wang K, Liu T-M, Wu J, Horton NG, Lin CP*, Xu C*. Three-color femtosecond source for simultaneous excitation of three fluorescent proteins in two-photon fluorescence microscopy. **Biomedical Optics Express** 2012; 3:1972–1977. (*corresponding authors). Describes the development of a new compact fiber laser source for simultaneous two-photon excitation of multiple fluorescent proteins
- Park D, Spencer JA, Koh BI, Kobayashi T, Fujisaki J, Clemens TL, Lin CP, Kronenberg HM, Scadden DT. Endogenous bone marrow MSCs are dynamic, fate-restricted participants in bone maintenance and regeneration. **Cell Stem Cell** 2012; 10(3):259-72.
- Zhang L, Alt C, Li P, White RM, Zon LI, Wei X, Lin CP. An Optical Platform for Cell Tracking in Adult Zebrafish. **Cytometry Part A** 2012; 81:176-82.

HERBERT LIN LABORATORY

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- Gutierrez OM, Sun CC, Chen W, Babitt JL, Lin HY. Statement of concern about a commercial assay used to measure soluble hemojuvelin in humans. **Am J Nephrology**, 2012, In Press.

NAHRENDORF LABORATORY

- Dutta P*, Courties G*, Wei Y, Leuschner F, Gorbatov R, Robbins CS, Iwamoto Y, Thompson B, Carlson AL, Heidt T, Majmudar MD, Lasitschka F, Etzrodt M, Waterman P, Waring MT, Chicoine AT, van der Laan AN, Niessen HWM, Piek JJ, Rubin BB, Butany J, Stone JR, Katus HA, Murphy SA, Morrow DA, Sabatine MS, Vinegoni C, Moskowitz MA, Pittet MJ, Libby P, Lin CP, Swirski FK, Weissleder R, Nahrendorf M. Myocardial infarction accelerates atherosclerosis. **Nature.** 2012;487(7407):325-9. Describes the discovery that myocardial infarction enhances atherosclerosis via interactions between the sympathetic nervous system and the bone marrow.
- Swirski FK, Nahrendorf M. Leukocyte regulation of atherosclerosis and myocardial infarction. **Science 2012.** *In press.*
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PITTET LABORATORY

- Cortez-Retamozo V, Etzrodt M, Newton A, Rauch PJ, Chudnovskiy A, Berger C, Ryan R, Iwamoto Y, Marinelli B, Gorbatov R, Forghani R, Novobrantseva TI, Koteliansky V, Figueiredo JL, Chen JW, Anderson DG, Nahrendorf M, Swirski FK, Weissleder R, Pittet MJ. Origins of tumor-associated macrophages and neutrophils. **Proc Natl Acad Sci U S A.** 2012;109:2491. Describes the discovery that cancers can instigate the development of tumor-promoting immune responses away from the tumor stroma by acting on hematopoietic stem cells and macrophage progenitor cells.
- Etzrodt M, Cortez-Retamozo V, Newton A, Zhao J, Ng A, Wildgruber M, Romero P, Wurdinger T, Xavier RJ, Geissmann F, Meylan E, Nahrendorf M, Swirski FK, Baltimore D, Weissleder R, Pittet MJ. Regulation of monocyte functional heterogeneity by miR-146a and Relb. **Cell Reports.** 2012;1:317
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SHAW LABORATORY

- Cohen KS, Cheng S, Larson MG, Cupples LA, McCabe EL, Wang YA, Ngwa JS, Martin RP, Klein RJ, Hashmi B, Ge Y, O'Donnell CJ, Vasan RS, Shaw SY* and Wang TJ*. Circulating CD34+ progenitor cell frequency is associated with clinical and genetic factors. **Blood.** 2012; in press. Describes the identification of genetic loci and clinical factors that contribute to the number of circulating CD34+ cells, a population of stem/progenitor cells that are widely used clinically in hematopoietic stem cell transplants.
- Ananthakrishnan AN, Cai T, Savova G, Cheng SC, Chen P, Guzman Perez R, Gainer VS, Murphy SN, Szolovits P, Xia Z, Shaw SY, Churchill S, Karlson EW, Kohane I, Plenge RM, Liao KP. Improving Case Definition of Crohn's Disease and Ulcerative Colitis in Electronic Medical Records Using Natural Language Processing: a Novel Informatics Approach. **Inflammatory Bowel Disease.** 2012; *in press.*
- Epa VC, Burden FR, Tassa C, Weissleder R, Shaw S, Winkler DA. Modeling biological activities of nanoparticles. **Nano Lett.** 2012;12:5808-12.
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STONE LABORATORY

- Wang H, Smith RN, Spooner AE, Isselbacher EM, Cambria RP, MacGillivray TE, Stone JH, Stone JR. Giant cell aortitis of the ascending aorta without signs or symptoms of systemic vasculitis is associated with elevated risk of distal aortic events. **Arthrit. Rheum.** 2012; 64:317-319.
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- Stone JR. Pathology of myocardial infarction, coronary artery disease, plaque disruption, and the vulnerable atherosclerotic plaque. **Diag. Histopathol.** 2012; 18:478-483.
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SWIRSKI LABORATORY

- Rauch PJ, Chudnovskiy A, Robbins CS, Weber GF, Etzrodt M, Hilgendorf I, Tiglao E, Figueiredo JL, Iwamoto Y, Theurl I, Gorbatov R, Waring MT, Chicoine AT, Mouded M, Pittet MJ, Nahrendorf M, Weissleder R, Swirski FK. 2012. Innate response activator B cells protect against microbial sepsis. **Science** 2012; 335 (6068): 597-601. Describes the discovery of the innate response activator (IRA) B cell, a new cell that appears to be important in polymicrobial sepsis
- Robbins CS, Chudnovskiy A, Rauch PJ, Figueiredo JL, Iwamoto Y, Gorbatov R, Etzrodt M, Weber GF, Ueno T, van Rooijen N, Mulligan-Kehoe MJ, Libby P, Nahrendorf M, Pittet MJ, Weissleder R, Swirski FK. 2012. Extramedullary hematopoiesis generates Ly-6C high monocytes that infiltrate atherosclerotic lesions. **Circulation** 2012; 125:364-74.
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WEISSLEDER LABORATORY

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CSB

PLATFORM LEADERS

Bioimaging Platform (Vinegoni, Nahrendorf):

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Chemical Biology Platform (Mazitschek, Keliher, Hilderbrand, McCarthy):

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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 16 active projects.

GRANTS
The CSB currently has 62 active grants and approximately 24 pending grants. New and noteworthy grants include:

- U54 HG006991(PI: Bernstein): "Expanding the catalog of chromatin regulatory elements in the human genome". Successfully obtained the next round of ENCODE funding, which will allow the center to continue and expand its efforts in identifying and characterizing functional elements in the human genome.
- 2P01CA069246-15A1: Project 2 - Experimental Therapeutics and BioMonitoring for Brain Tumors (PI: Weissleder).
- 1DP2DK098087-01: Systems Biology of *In Vivo* Human Blood Cell Populations (PI: John Higgins) Sept. 28, 2012–August 31, 2017.
- 1R01HL113156: Magnetic Nanosensors for Biomedical Analyses of Microvesicles (PI: Hakho Lee/Weissleder). April 1st 2012–March 31st 2017.
- 1R01 HD069623: Role of epididymal dendritic cells in male reproductive function (PI Da Silva): August 12 2011–May 31 2012.
- 1R01DK096586-01: Cell Biology of Vasopressin-induced water channels (PI: Dennis Brown). September 20 2012–August 31 2016.
- R21DK092619: Fam49b on the structure and function of glomerular filtration apparatus (PI: Jenny Lu) September 1 2012–August 31 2013.

CSB

- Young Investigator Award (Nephcure Foundation): Characterization of Fam49b interacting proteins and their role in modulating actin cytoskeleton reorganization and trafficking of slit diaphragm proteins in podocytes (PI: Jenny Lu). July 19 2012–October 31 2015.
- Interim support R01 (MGH ECOR): Study of the novel role of AQP2 on cell migration and epithelial morphogenesis (PI: Jenny Lu). September 1 2012–August 31 2013.
- Foundation Award: Partha Dutta. July 1st 2012–June 6th 2014.
- Novartis contract; Targeting IL-1beta in cardiovascular disease (PI: Filip Swirski, Matthias Nahrendorf). September 1 2012–September 1 2013.
- Siemens contract; EMR-based Predictive Analytics in type 2 diabetes (PI: Stan Shaw).

Awards, Nominations and Promotions

- Promotions to Professor: Sylvie Breton, PhD
- Promotions to Associate Professor: James Stone, MD, PhD; Bradley Bernstein MD, PhD
- Promotions to Assistant Professor: Jenny Lu, MD, PhD (Dennis Brown laboratory).
- Bradley Bernstein, MD, PhD was the recipient of the 2012 MGH Martin Prize for Basic Research
- John Higgins, MD was the recipient of a 2012 NIH Director's New Innovator Award.
- Dennis Brown, PhD received the 2012 Joseph B. Martin Dean's Award for Leadership in the Advancement of Women at Harvard Medical School and Harvard School of Dental Medicine.
- Dennis Brown, PhD was appointed Director of the MGH Office for Research Career Development.
- Jodie Babitt, MD, was the recipient of the 2012 MGH Howard Goodman Fellowship.
- Sylvie Breton, PhD was the 2012 recipient of the highly prestigious "Research Award" from the Society for the Study of Reproduction.
- Sylvie Breton, PhD was one of the 2011 recipients of the MGH scholar program.
- Alt Clemens, PhD (Charles Lin laboratory) won the 2012 Pascal RoI Award for Best Paper in Ophthalmic Technologies at the SPIE Photonics West, BiOS conference in San Francisco for his paper entitled "*In vivo* quantification of microglia dynamics with a scanning laser ophthalmoscope in a mouse model of focal laser injury".

R. Rox Anderson, MD, Director
www.massgeneral.org/wellman

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 over 200 research personnel among 13 interactive laboratories. We are intellectually diverse, pursuing basic questions and technology solutions for problems in many different organ systems. Cancer, coronary artery disease, infection, trauma and immunity are prevalent themes. We are technology leaders for in vivo microscopy; tissue imaging and spectroscopy; light-activated drug treatments; novel optical reporter molecules; laser surgery; and integration of these with other technologies. We are a nucleus of the MIT-Harvard H.S.T. program, and work openly with many other universities. The Wellman Center delivers its mission in practice—to improve people's lives.

Center Highlights for 2012

GROWTH & SUPPORT

- WCP grew by ~20%, to 230 people, including 30 full-time faculty and 16 affiliated faculty.
- Research expenditures were $28.3 million, a 20% increase over 2011.
- Research revenues were $30.6 million (includes IP revenues), a 25% increase over 2011.
- 39 new research awards were made to Wellman Center faculty from NIH, DOD, industry, and NSF respectively; there are 92 currently active research grants at WCP.
- WCP fosters and actively supports photomedicine research throughout MGH. There are ~70 substantial collaborations in progress between WCP and other researchers at MGH / HMS.
- A new research core for Computation was added in 2012.
- Adequate nearby space is our #1 challenge. This year, WCP spent $2.4M renovating ~3000 s.f. of old laboratories in the Thier, Bartlett Hall and Bartlett Extension buildings, which should be operational in early 2013 but does not add any net space. Working with the MGH Research Space Management Group, WCP may open laboratories in CNY and potentially other sites, and is considering all options.

FACULTY PROMOTIONS AND NEW FACULTY

- WCP now includes 5 Professors, 8 Associate Professors, and 6 Assistant Professors.
- In 2012, there were 2 promotions to Assistant Professor.
- 2 new Instructors joined WCP.

INNOVATION & TECHNOLOGY TRANSFER

Moving discoveries and innovations all the way into medical practice is central to our mission, brings scientists and clinicians together, and creates new opportunities. Wellman now accounts for several of MGH's top 10 patents (based on royalty income). Working with the Partners RVL office, we re-invest a sizable portion of this limited IP income to provide core services that emphasize high-quality translational research. About 30 discoveries and inventions now in the WCP "pipeline" are well beyond the proof-of-concept stage, moving toward clinical applications. During 2012:

- The recently-established Translational Research Core led by Gabriela Apiou became very active.
- 23 new invention disclosures were filed.
- 56 new US patents applications were filed.

Wellman Center for Photomedicine

Center Overview

WCP

- 26 new US patents were issued, and 35 patents were issued from other countries.
- Wellman Center inventions generated total MGH royalties of ~ $19.3M during 2012.
- A dozen start-up companies are founded upon WCP inventions. Several of them achieved pivotal FDA approvals for biomedical devices during 2012.

EDUCATION

- WCP offers competitive support for graduate students, research and clinical fellowships
- 20 graduate and 11 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.
- 2012 marked the 10th year of Wellman's Summer Institute in Biomedical Optics, led by Andy Yun PhD. Twelve undergraduate students enrolled.
- WCP hosted two international educational programs
    - o 3 graduate students enrolled in the Tokyo University summer exchange program (7th year), supported by a large grant to the University of Tokyo. MGH is one of 4 collaborating institutes for graduate student summer training.
    - o 6 undergraduate students from KAIST University (Korea) majoring in electrical, chemical, mechanical engineering and the biological sciences.

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 2012, two Bullock Fellowships were awarded for research to begin in 2013. The fellows will study new strategies for rapid optical assessment of coagulopathies (M. Tripathi PhD in Seemantini Nadkarni's laboratory), and esophageal imaging by a unique capsule-shaped microscope (M. Gora PhD in Gary Tearney's laboratory).

Some Research Highlights of 2012

WCP faculty published 120 peer-reviewed research papers in 2012. Some selected publications:

ROX ANDERSON LABORATORY

Sakamoto FH, Doukas AG, Farinelli WA, Tannous Z, Shinn M, Benson S, Williams GP, Gubeli JF 3rd, Dylla HF, Anderson RR. Selective photothermolysis to target sebaceous glands: theoretical estimation of parameters and preliminary results using a free electron laser. Lasers Surg Med. 2012 Feb;44(2):175-83.

The pathophysiology of acne depends on an active sebaceous gland, which is part of the hair follicle apparatus. Laser hair removal was invented at WCP, using pulses of light absorbed by melanin to selectively heat and irreversibly damage the hair-producing part of hair follicles. This paper reports that a similar strategy using optical pulses at wavelengths preferentially absorbed by CH2 bonds in sebum lipids, can selectively heat and damage sebaceous glands in intact human skin. A superconducting free-electron laser at the Jefferson National Accelerator was used to obtain the appropriate wavelength and pulse structure.

BRETT BOUMA LABORATORY

Vakoc BJ, Fukumura D, Jain RK, Bouma BE. Cancer imaging by optical coherence tomography: preclinical progress and clinical potential. Nat Rev Cancer. 2012. PMCID: PMID: 22475930.

WCP

This publication describes an optical technique for imaging the microstructure, vascular and lymphatic network within and surrounding tumors. Quantitative assessment of the tumor microenvironment permits an understanding of phenomena such as angiogenesis, and the opportunity for longitudinal studies of response to existing and novel therapies for cancer.

CONOR EVANS LABORATORY

Klein OJ, Bhayana B, Park Y, Evans CL. ***In vitro* optimization of EtNBS-PDT against hypoxic tumor environments with a tiered, high content, 3D model optical screening platform.** *Mol Pharm*. 2012 Nov 5;9(11):3171-82.

This publication introduces an in vitro therapeutic screening approach based on high-content imaging of naturally hypoxic, three-dimensional ovarian cancer models. Using a small library of photoactive compounds, the 3D imaging screen was able to identify optimal regimens against hypoxic cellular environments, and could prove to be a powerful tool for image-guided therapeutic planning.

MICHAEL HAMBLIN LABORATORY

Xuan W, Vatansever F, Huang L, u Q, Xuan Y, Dai T, Ando T, Xu T, Huang YY, Hamblin, MR. Transcranial low-level laser therapy improves neurological performance in traumatic brain injury in mice: effect of treatment repetition reginmen. PLoS ONE, 2012.

Shows that transcranial near-infrared low level laser therapy (LLLT) can improve neurological function, and reduce lesion size in a mouse model of traumatic brain injury (TBI) caused by controlled cortical impact. Shows for the first time that neuroprogenitor cells are induced in the brain in response to LLLT for TBI. Shows a biphasic dose response for treatment repetitions with 3 daily laser treatments being better than either 1 or 14.

CHARLES LIN LABORATORY

Wang K, Liu T-M, Wu J, Horton NG, Lin CP*, Xu C*. Three-color femtosecond source for simultaneous excitation of three fluorescent proteins in two-photon fluorescence microscopy. Biomedical Optics Express 2012; 3:1972–1977. (*corresponding authors)

In collaboration with Chris Xu at Cornell, we have developed a compact fiber laser source with spectral and temporal characteristics that are tailored for simultaneous two-photon excitation of multiple fluorescent proteins. This work is important because the new laser source will significantly expand the capability of two photon microscopy for deep tissue imaging.

SEEMANTINI NADKARNI LABORATORY

Z. Hajjarian, S. Nadkarni, “Evaluating the Viscoelastic Properties of Tissue from Laser Speckle Fluctuations,” Scientific Reports 2012; 2:316.

The fine motions of tissue can be measured by laser light scattering, which presumably relate to important mechanical functions, hemodynamics, drug uptake, and other properties. This manuscript establishes a strong correlation between viscoelastic index obtained from Laser speckle rheology, and viscoelastic modulus obtained from conventional mechanical testing, for both tissue models ($r = 0.79$, $p < 0.0001$) and tissue ($r = 0.88$, $p < 0.0001$) specimens.

ROBERT REDMOND LABORATORY

Ni T, Senthil-Kumar P, Dubbin K, Aznar-Cervantes SD, Datta N, Randolph MA, Cenis JL, Rutledge GC, Kochevar IE, Redmond RW. Lasers Surg Med. 2012 Oct;44(8):645-52. doi: 10.1002/lsm.22066. Epub 2012 Aug 21

Photochemical sealing of a electrospun silk mat around the tendon repair site provides considerable benefit in Achilles tendon repair. Adhesions to surrounding tissues are significantly reduced and the

WCP

silk wrap adds strength to the repair in the early post-surgical period. This new technique has the potential to facilitate earlier mobilization of the joint and considerable improvement in functional recovery.

GARY TEARNEY LABORATORY

Tearney GJ, Regar E, Akasaka T, et. al. Consensus standards for acquisition, measurement, and reporting of intravascular optical coherence tomography studies: A report from the international working group for intravascular optical coherence tomography standardization and validation. **J Am Coll Cardiol**. 2012;59:1058-1072.

This paper describes the output of the International Working Group for IVOCT Standardization and validation—a two year effort from over 250 investigators to describe standards on how to utilize IVOCT and interpret IVOCT images. It is a key step towards disseminating this technology for widespread clinical use.

HENSIN TSAO LABORATORY

Njauw CN, Kim I, Piris A, Gabree M, Taylor M, Lane AM, DeAngelis MM, Gragoudas E, Duncan LM, Tsao H. Germline BAP1 inactivation is preferentially associated with metastatic ocular melanoma and cutaneous-ocular melanoma families. PLoS One. 2012;7(4):e35295. doi: 10.1371/journal.pone.0035295. Epub 2012 Apr 24. PubMed PMID: 22545102; PubMed Central PMCID: PMC3335872.

This manuscript codifies a new melanoma syndrome which we designated cutaneous/ocular melanoma, atypical melanocytic proliferations and other internal neoplasms (common syndrome). We also characterized the contribution of germline bap1 mutations to this syndrome and showed that carriers are predisposed to metastatic ocular melanoma.

BENJAMIN VAKOC LABORATORY

Siddiqui, MS and Vakoc BJ. Optical-domain subsampling for data efficient depth ranging in Fourier-domain optical coherence tomography. Optics Express 20:17398-17951 (2012)

This is an early report of a new technical approach to optical coherence tomography (OCT). This approach solves one of the key limitations of OCT by allowing long-range imaging with practical computational and electronic hardware. As a result, this approach could form the basis for expanding the clinical utility of OCT.

MEI WU LABORATORY

Chen X., D. Shah, G. Kositratna, D. Manstein, R. R. Anderson, and M. X. Wu. 2012. Facilitation of transcutaneous drug delivery and vaccine immunization by a safe laser technology. J.Control Release. 159(1):43-51

The article describes potential for both needle-free delivery and additive-free adjuvantation of various protein-based vaccines. Delivery of vaccines via ablative laser-generated microchannals, significantly boosts vaccination response while reducing skin irritation, and potentially eliminating the need for contaminated sharps. An integrated, safe, more effective and more cost-effective vaccination system may result.

ANDY YUN LABORATORY

Kim JK, Lee WM, Kim P, Choi M, Jung K, Kim S, Yun SH. Fabrication and operation of GRIN probes for in vivo fluorescence cellular imaging of internal organs in small animals. **Nature Protocols** 2012;7:1456-1469.

This paper describes how to build and use high-resolution miniature endoscopes to visualize fluorescent cells and molecular events in live mice. Images from it were selected as Cover Art.

CONTENTS

Key Achievements/Publication Highlights for 2012

Anesthesia, Critical Care and Pain Medicine

Jeanine Wiener-Kronish, MD, Chief

1. Lewis LD, Weiner VS, Mukamel, EA, Donoghue JA, Eskandar EN, Madsen JR, Anderson WS, Hochberg LR, Cash SS, Brown EN, Purdon PL. Rapid fragmentation of neuronal networks at the onset of propofol-induced unconsciousness. Proc Natl Acad Sci USA. (in press) http://www.pnas.org/content/early/2012/11/02/1210907109.abstract

The neurophysiological mechanisms by which anesthetic drugs cause loss of consciousness are poorly understood. In this study, the authors found that the onset of slow oscillations is a neural correlate of propofol-induced loss of consciousness, marking a shift to cortical dynamics in which local neuronal networks remain intact but become functionally isolated in time and space.

2. Buys ES, Raher MJ, Kirby A, Mohd S, Baron DM, Hayton SR, Tainsh LT, Sips PY, Rauwerdink KM, Yan Q, Tainsh RET, Shakartzi HR, Stevens C, Decaluwé K, Rodrigues-Machado MDG, Malhotra R, Van de Voorde J, Wang T, Brouckaert P, Daly MJ, and Bloch KD. Genetic modifiers of hypertension in soluble guanylate cyclase a1-deficient mice. Journal of Clinical Investigation 2012;122(6):2316-25

Studies in mice deficient in the nitric oxide (NO)-regulated and cGMP-generating enzyme soluble gunaylate cyclase (sGC) illustrate that sGC signaling has gender-specific cardiovascular effects. Using linkage analysis in mice, the authors identified quantitative trait loci linked to mean arterial pressure (MAP) in the context of sGC deficiency, and identified the renin-angiotensing-aldosterone system as a blood pressure-modifying mechanism in a setting of impaired NO/cGMP signaling.

3. Hatcliff J, King A, Lee I, MacDonald A, Fernando A, Robkin M, Vasserman E, Weininger S, Goldman JM. Rationale and architecture principles for medical application platforms. In: Proceedings from the IEEE/ACM Third International Conference on Cyber-Physical Systems (ICCPS); 2012: 3-12.

This paper presents the clinical safety/effectiveness and economic motivations for medical application platforms (MAPs), and describes key characteristics of MAPs that are guiding the search for appropriate technology, regulatory, and ecosystem solutions. It includes an overview of the Integrated Clinical Environment (ICE)—one particular architecture for MAPs, and the Medical Device Coordination Framework—a prototype implementation of the ICE architecture.

4. Kim H, Chen L, Lim G, Sung B, Wang S, McCabe MF, Rusanescu G, Yang L, Tian Y, Mao J. Brain indoleamine 2,3-dioxygenase contributes to the comorbidity of pain and depression. J Clin Invest. 2012 Aug 1;122(8):2940-54. doi: 10.1172/JCI61884. Epub 2012 Jul 2.

Pain and depression are frequently comorbid disorders, but the mechanism underlying this association is unknown. In this study, the authors revealed an IDO1-mediated regulatory mechanism underlying the comorbidity of pain and depression and suggested a new strategy for the concurrent treatment of both conditions via modulation of brain IDO1 activity.

Cancer Center

Daniel A. Haber, MD, PhD, Chief, Cancer Center
David P. Ryan, MD, Chief, Hematology Oncology

1. Garnett, Edelman, Heidorn et al, Systematic identification of genomic markers of drug sensitivity in cancer cells. Nature: 483, 570-5 2012

In a major collaboration between the MGH Cancer Center and the Welcome Trust Sanger Institute in the UK, the MGH Center for Molecular Therapeutics led by Dr. Cyril Benes published a landmark study of cancer drug sensitivity profiles across ~600 cancer cell lines. The study correlated both genetic and expression biomarkers of response and resistance to novel targeted agents, defining the landscape of cancer drug sensitivity, and setting the stage for early phase clinical trials based on previously unknown gene/drug interactions.

2. Yu, Ting et al., RNA Sequencing of pancreatic circulating tumour cells implicates Wnt signaling in metastasis. Nature, 487: 510-3, 2012

Using innovative approaches to isolating circulating tumor cells (CTCs) in the bloodstream of patients with pancreatic cancer and characterizing them using next generation RNA sequencing, the group led by Daniel Haber, Shyamala Maheswaran and Mehmet Toner RNA identified aberrant activation of the Wnt pathway in CTCs, showing that it provides anti-anoikis signals that enhance the survival of epithelial cells in the circulation. Inhibitors of the non-canonical Wnt pathway kinase TAK1 abrogated this effect, raising the possibility of targeting survival pathways used by circulating metastatic precursor cells.

3. Chen et al. A murine lung cancer co-clinical trial identifies genetic modifiers of therapeutic response. Nature 483: 613-7, 2012

A team codirected by Jeff Engelman developed a "co-clinical trial", testing genotype-directed therapies in a mouse model matched to human lung cancer. The response of KRAS-mutant lung cancer to a MEK inhibitor was correlated with the presence or absence of genetic mutations in p53 and LKB1, two genes that are commonly disrupted in human lung cancer. The impact of these mutations on drug response were then matched with human trials of similar agents.

4. Flaherty et al., Improved survival with MEK inhibition in B-RAF mutated melanoma, NEJM, 367: 107-14, 2012 and Flaherty et al, Combined B-RAF and MEK inhibition in melanoma with B-RAF V600 mutations. NEJM, 367: 1694-703, 2012b

Following up on his seminal study of B-RAF inhibitors in the treatment of metastatic melanoma (Flaherty et al, NEJM, 2010), Keith Flaherty led international trials of novel regimens in this disease. First, his team demonstrated that a MEK inhibitor is effective in treating B-RAF-mutant melanoma (Flaherty, et al, NEJM 2012a), and then he showed that the combination of a B-RAF and a MEK inhibitor is considerably more effective than either regimen alone. This study has changed the standard of care for B-RAF-mutant melanoma and points to the important benefit of targeting an oncogenic pathway using two inhibitors that together can block the feedback loops that contribute to acquired drug resistance.

Key Achievements/Publication Highlights for 2012

CIMIT

John A. Parrish, MD, Director

1. EIS as an "EKG for the Brain": Portable Point-of-Care Detection of Acute Traumatic Brain Injury (PIs: Michael H Lev, MD and Giorgio Bonmassar, PhD)

Currently there is no portable, non-invasive monitoring device capable of detecting ischemic stroke or intracranial hemorrhage. Computed tomography (CT) and magnetic resonance imaging (MRI), the first line modalities for such diagnosis, are limited in their battlefield and sport field availability. The main goal of this project is to develop a system for rapid point-of-care detection, assessment, and monitoring of acute brain injury using Electrical Impedance Spectroscopy (EIS), an advance on "passive" electroencephalogram (EEG) recording. EIS relies on non-invasive measurement and modeling of the conduction of minute electrical currents through the head, across a spectrum of frequencies. Early results are very promising and demonstrate high sensitivity and specificity of EIS in distinguishing normal from pathologic brain.

2. Novel home monitoring approaches to insomnia diagnosis and treatment (PI: Matt Bianchi, MD, PhD)

Insomnia is a common but poorly understood disorder. This CIMIT funded project is developing novel home monitoring technologies to study sleep using simple wearable devices to monitor the quantity and quality of sleep in patients with insomnia over a week or more of their home routine. In comparing this objective data with each patient's subjective sense of how long and how well they slept, this team has identified three important features of insomnia: 1) patients with insomnia often under-estimate how much they are sleeping ("misperception"), 2) some patients show the misperception pattern every night (which we consider a "trait" they have), 3) some patients show variable amounts of misperception, which can be considered a "state" factor, meaning it is malleable and holds potential insights into predictive factors and/or points of intervention. One of the devices designed by our team, a tee-shirt with embedded fabric sensors, finished early validation studies for quantifying sleep-wake stages, as well as a breathing problem called sleep apnea. This washable, comfortable, accurate device holds immense promise for advancing the diagnosis and treatment of the two most common sleep disorders: insomnia and sleep apnea.

3. Rapid Screening of MRSA-colonized Patients in the Ambulatory Setting (PI: David Hooper, MD)

For patients with a history of Methicillin-resistant Staphylococcus aureus (MRSA), the Centers for Disease Control mandates routine contact precautions (CP). Implementation of CP results in cohorting patients with similar precautions status (i.e., two MRSA+ male patients in a semi-private room), placement in a private room, or allowing a second bed in a semi-private room to go unoccupied. CPs disrupt workflow, impose excess costs, and contribute to patient flow bottlenecks that affect care throughout. While data suggest that the majority of individuals clear MRSA colonization spontaneously, there are currently no guidelines for when CP should be discontinued. This project is implementing rapid MRSA screening with PCR in the ambulatory setting, using a novel alert system which queries the Partners Clinical Data Repository (CDR) to identify eligible patients in real-time, allowing results processing in under two hours and subsequent discontinuation of CP. The project aims to improve patient care across clinical environments, lower costs, and increase work-flow efficiency.

Dermatology

David E. Fisher, MD, PhD, Chief

1. Hu B, Castillo E, Harewood L, Ostano P, Reymond A, Dummer R, Raffoul W., Hoetzenecker W., Hofbauer GF, Dotto, GP. Multifocal epithelial tumors and field cancerization from loss of mesenchymal CSL signaling. Cell. 2012 Jun 8;149(6):1207-20.

Field cancerization is a clinical condition of major significance, resulting in frequent multiplicity and recurrence of epithelial cancers. Genetic and epigenetic changes of the epithelium have been implicated as likely primary determinants, while alterations of the underlying mesenchyme have received relatively little attention. In their paper, Hu et al., found that loss of Notch signaling in the mesenchymal / fibroblast compartment of skin can play an equally important primary role in field cancerization, with implications that may extend to the many other organs in which this process occurs.

2. Mitra D, Morgan A, Wang J, Hoang MP, Lo J, Guerrero CR, Lennerz JK, Mihm MC, Wargo JA, Robinson KC, Devi SP, Vanover JC, D'Orazio JA, McMahon M, Bosenberg MW, Haigis KM, Haber DA, Wang Y, Fisher DE. An ultraviolet-radiation-independent pathway to melanoma carcinogenesis in the redhair-fairskin background. Nature. 2012 Nov 15;491(7424):449-53.

This manuscript examines a mouse model of melanoma arising in the redhair-fairskin genetic background. The work reports the discovery that red pigment promotes melanoma formation even in the absence of UV radiation. The mechanism involves mutagenesis arising from reactive oxygen species generated as a consequence of red pigment biosynthesis.

3. Zhang J, Jackson AF, Naito T, Dose M, Seavitt J, Liu F, Heller EJ, Kashiwagi M, Yoshida T, Gounari F, Petrie HT and Georgopoulos K. Harnessing of the nucleosome remodeling deacetylase complex controls lymphocyte development and prevents leukemogenesis. Nat Immunol 2012; 13 (1) 86-94.

Loss in Ikaros DNA binding activity from the Nucleosome remodeling Deacetylase complex in lymphocytes causes a local increase in both chromatin remodeling and histone deacetylation resulting in repression of the associated lymphoid-specific genes. Importantly, a redistribution of the NuRD complex to transcriptionally poised non-Ikaros gene targets, involved in growth and metabolism, is followed by their induction. Our data supports a model by which a developmental regulator such as Ikaros functions not only by targeting but also by restricting the activity of epigenetic regulators. This restriction is exerted both locally by preventing access to chromatin in the vicinity of Ikaros binding sites at lymphoid specific genes and globally by preventing epigenetic factor distribution to non-lineage (non-Ikaros) networks.

4. Ritprajak P, Hayakawa M, Sano Y, Otsu K, Park JM. Cell type-specific targeting dissociates the therapeutic from the adverse effects of protein kinase inhibition in allergic skin disease. Proc Natl Acad Sci USA. 2012 Jun 5;109(23):9089-94.

This study utilized cell-selective delivery of an anti-inflammatory protein kinase inhibitor by using conditional gene knockout mouse lines lacking the protein kinase in several different cell types. The effects of interfering with an inflammatory signaling pathway were therapeutic or adverse depending on the targeted cell type. These findings highlight a dilemma in targeted molecular therapy, yet also suggest cell selective drug delivery as a potential solution for improving therapeutic index.

Key Achievements/Publication Highlights for 2012

Emergency Medicine

Alasdair K. Conn, MD, Chief

1. Brouwers, H.B., Biffi, A., Ayres, A.M., Schwab, K., Cortellini, L., Romero, J.M., Rost, N.S., Viswanathan, A., Greenberg, S.M., Rosand, J., Goldstein, J.N. Apolipoprotein E Genotype Predicts Hematoma Expansion in Lobar Intracerebral Hemorrhage. Stroke, 2012 June; 43(6): 1490-5.

This manuscript was the first to use genetics to examine the vascular pathophysiology underlying ongoing bleeding following the initial development of intracerebral hemorrhage. It has traditionally been quite difficult to study the basic mechanism of vessel rupture and continued bleeding, but this analysis highlighted a new approach to studying this critical process. It was published with an accompanying editorial highlighting its impact.

2. Camargo CA Jr, Ganmaa D, Frazier AL, Kirchberg FF, Stuart JJ, Kleinman K, Sumberzul N, Rich-Edwards JW. Randomized trial of vitamin D supplementation and acute respiratory infection in Mongolia. Pediatrics 2012; 130: e561-e567. PMID: 22908115.

The investigators performed a randomized, double-blinded, placebo-controlled trial on the effect of vitamin D supplementation on risk of acute respiratory infections in Mongolian children. In this population with low baseline levels of vitamin D during winter, vitamin D supplementation halved the risk of acute respiratory infections (OR 0.50, 95% CI 0.28-0.88).

3. Wilcox SR, Bittner EA, Elmer J, Seigel TA, Nguyen NT, Dhillon A, Eikermann M, Schmidt U. Neuromuscular blocking agent administration for emergent tracheal intubation is associated with decreased prevalence of procedure-related complications. Crit Care Med. 2012 Jun;40(6):1808-1813. PMID:22610185.

Although rapid sequence intubation with neuromuscular blockade is the standard of care in the Emergency Department, this technique has not been otherwise widely adopted. Some Intensivists and Anesthesiologists performing emergent airway management for hospitalized patients out of the OR have remained concerned that routine use of neuromuscular blockade in emergent intubations could lead to increased complications, including death. Investigators prospectively recorded data for all emergent, out of OR intubations at MGH and UCLA. We found that the use of neuromuscular blockade significantly reduced the rates of intubation-related complications. This paper is the first to demonstrate that neuromuscular blockade is beneficial in hospitalized patients, as it has been shown to be in Emergency Department patients.

4. Hoffmann, U., Truong, Q.A., Schoenfeld, D.A., Chou, E.T., Woodard, P.K., Nagurney, J.T., Pope, J.H., Hauser, T.H., White, C.S., Weiner, S.G, Kalanjian, S., Mullins, M.E., Mikati, I., Peacock, W.F., Zakroysky, P., Hayden, D., Goehler, A., Lee, H., Gazelle, G.S., Wiviott, S.D., Fleg, J. and Udelson, J.E.; ROMICAT-II Investigators. Coronary CT Angiography versus Standard Evaluation in Acute Chest Pain. N England Journal of Medicine 2012 July 26; 367 (4):299-308, DOI: 10.1056/NEJMoa12.

This multicenter randomized controlled trial in which the Emergency Department (ED) of the MGH played a central role compared the effectiveness of alternative strategies to rule out myocardial ischemia in ED patients presenting with chest pain. It demonstrated that the use of cardiac CT angiography compared to traditional risk-stratification tests led to shorter ED lengths-of-stay and cost-effective use of resources. It was accompanied by an editorial and was widely quoted in the media.

Imaging (formerly called Radiology)

James H. Thrall, MD, Chief

ATHINOULA A. MARTINOS CENTER FOR BIOMEDICAL IMAGING

BRUCE ROSEN, MD, PhD, DIRECTOR

1. Wedeen VJ, Rosene DL, Wang R, Dai G, Mortazavi F, Hagmann P, Kaas JH, Tseng WY. The geometric structure of the brain fiber pathways. Science. 2012 Mar 30;335(6076):1628-34. Erratum in: Science 2012 May 11;336(6082):670.

This landmark paper, which describes the grid-like structure of fiber pathways in the human brain, has given the first clear indication of the validity of the grid structure thesis in the human brain. This work is also important because it demonstrated the performance of the Martinos Center's 3T "Connectom" scanner, a unique MRI system with high-performance gradient coil specifically engineered for high-resolution diffusion imaging studies of human brain connectivity, in support of the large, multi-site Human Connectome Project. Since it was published in March 2012, this article has received worldwide coverage in the scientific and popular media, and has been featured in more than 3,000 news stories.

2. Polasek M, Fuchs BC, Uppal R, Schühle DT, Alford JK, Loving GS, Yamada S, Wei L, Lauwers GY, Guimaraes AR, Tanabe KK, Caravan P. Molecular MR imaging of liver fibrosis: a feasibility study using rat and mouse models. J Hepatol. 2012; 57:549-55.

Liver fibrosis and its end stage, cirrhosis, represent the final common pathway of virtually all chronic liver diseases. While fibrosis can be identified and quantified using biopsy, repeated biopsy is not a practical solution for monitoring disease progression or response to therapy. This article demonstrates that MRI with a type I collagen-targeted probe can distinguish liver fibrosis in two animal models of disease. This molecular MR imaging technique, alone or in combination with other MRI techniques, offers the potential of directly imaging collagen and non-invasively staging liver fibrosis.

CARDIAC MR PET CT PROGRAM

UDO HOFFMANN, MD, MPH, DIRECTOR

1. Subramanian S*, Tawakol A*, Burdo TH, Abbara S, Wei J, Vijayakumar J, Corsini E, Abdelbaky A, Zanni MV, Hoffmann U, Williams KC, Lo J, Grinspoon SK. Arterial inflammation in patients with HIV. JAMA. 2012 Jul 25;308(4):379-86.

This proof of concept study suggests that inflammation is increased in HIV patients despite a compromised immune system. It demonstrates increased inflammation in the arterial wall as shown by FDG PET as compared to age and sex matched non-HIV patients. These findings could explain the increased burden of coronary artery disease, especially non-calcified and high risk plaque and subsequent increased cardiovascular adverse events.

2. Hoffmann U, Truong QA, Schoenfeld DA, Chou ET, Woodard PK, Nagurney JT, Pope JH, Hauser TH, White CS, Weiner SG, Kalanjian S, Mullins ME, Mikati I, Peacock WF, Zakroysky P, Hayden D, Goehler A, Lee H, Gazelle GS, Wiviott SD, Fleg JL, Udelson JE; ROMICAT-II Investigators. Coronary CT angiography versus standard evaluation in acute chest pain. N Engl J Med. 2012 Jul 26;367(4):299-308.

This NIH funded multicenter randomized trial compares the efficiency of CCTA first as compared to standard of care as a diagnostic strategy to evaluate and triage patients presenting with acute chest pain to the ED. The results demonstrate both the benefits and the risks of cardiac CT in this population. It shows that CCTA is a save and efficient early triage tool which leads to fast discharge of the majority of patients. It also demonstrates that CCTA is a more sensitive test to detect CAD than SOC, leads to better separation of patients who do and who do not have CAD. On the other hand CCTA leads to more diagnostic testing, especially ICA and interventions PCI.

CENTER FOR ADVANCED MEDICAL IMAGING SCIENCES

GEORGES EL FAKHRI, PhD, DIRECTOR

1. Chun SY, Reese T, Ouyang J, Guerin B, Catana C, Zhu X, Alpert N, and El Fakhri G. MRI-Based Nonrigid Motion Correction in Simultaneous PET/MRI. J Nucl Med 2012; 53: 1284-1291 (Featured Cover August issue).

This paper reports the validation and first results of simultaneous quantitative PET-MR imaging using an integrated scanner to compensate for respiratory and cardiac motion in oncologic whole-body PET-MR. Tagged MR studies were performed simultaneously as dynamic listmode PET studies were acquired to yield dramatic and significant improvement in signal to noise ratio (166-276%) when quantitating tumor activity and detecting small lesions compared to traditional PET-CT.

2. Alpert N, Fang Y, El Fakhri G. Single-scan Rest/Stress Imaging 18F-labeled flow tracers—Theory and Simulation Studies. Med. Phys. 2012;39: 6609-6620.

This article reports a novel measurement strategy to obtain both rest and stress blood flow during a single, relatively short, scan session. This is a major departure from conventional 2-day imaging protocol and the innovation of this method is to treat the rest-stress scan as a single entity in which the myocardial blood flow parameters change due to pharmacological challenge. Myocardial blood flow was accurately and precisely estimated from a single-scan rest/stress study. By accounting for the time-dependence of the kinetic parameters, the proposed models achieved good accuracy and precision (5%) under different vasodilators and different ischemic states.

CENTER FOR MOLECULAR IMAGING RESEARCH

RALPH WEISSLEDER, MD, DIRECTOR

1. McCarthy JR, Sazonova IY, Erdem SS, Hara T, Thompson BD, Patel P, Botnaru I, Lin CP, Reed GL, Weissleder R, Jaffer FA Multifunctional nanoagent for thrombus-targeted fibrinolytic therapy. Nanomedicine (Lond). 2012;7(7):1017-28.

This study reports on a new thrombolytic nanoagent targeted to a component of thrombi known as activated factor XIII (FXIIIa). The thrombus-targeted nano-fibrinolytic agent was synthesized using a magnetofluorescent crosslinked dextran-coated iron oxide nanoparticle platform, conjugated to recombinant tissue PA (tPA). Treatment of thromboembolism using this nanoagent was demonstrated both in vitro and in vivo.

2. Forghani R, Wojtkiewicz GR, Zhang Y, Seeburg D, Bautz BR, Pulli B, Milewski AR, Atkinson WL, Iwamoto Y, Zhang ER, Etzrodt M, Rodriguez E, Robbins CS, Swirski FK, Weissleder R, Chen JWDemyelinating Diseases: Myeloperoxidase as an Imaging Biomarker and Therapeutic Target. Radiology. 2012;263(2):451-60

This study found that myeloperoxidase (MPO) may be a key mediator of myeloid inflammation and tissue damage in the murine model of multiple sclerosis known as experimental autoimmune encephalomyelitis (EAE). MPO inhibition was accompanied by decreased demyelination and lower inflammatory cell recruitment in the brain. MPO inhibition also significantly reduced the severity of clinical symptoms and improved survival in mice with EAE. MPO thus represents a promising therapeutic target, and/or imaging biomarker, for demyelinating diseases as well as potentially for other diseases in which MPO is implicated.

INSTITUTE FOR TECHNOLOGY ASSESSMENT

SCOTT GAZELLE, MD, PhD, DIRECTOR

1. Pandharipande, P, Eisenberg J, Lee RJ, Gilmore M, Turan E, Singh S, Kalra MK, Liu B, Kong CY, Gazelle GS. Patients with Testicular Cancer Undergoing CT Surveillance Demonstrate a Pitfall of Radiation-Induced Cancer Risk Estimates: The Timing Paradox. Radiology, 2012.

This study demonstrated an important limitation of lifetime radiation-induced cancer risk metrics in the setting of testicular cancer surveillance; in particular, their failure to capture the delayed timing of radiation-induced cancers relative to cancers that are related to tumor recurrence (and might therefore be missed if CT scanning was not performed). The research involved using a Markov simulation model to estimate outcomes in patients with testicular cancer who underwent CT surveillance after orchiectomy. Life expectancy losses and lifetime mortality risks due to testicular cancer and radiation-induced cancers were compared. The analysis demonstrated that lifetime mortality risks due to testicular cancer were slightly greater than lifetime mortality risks from radiation-induced cancers; however, life expectancy losses due to testicular cancer were more than three times greater than life expectancy losses due to radiation-induced cancers.

2. Knudsen A, Hur C, Gazelle GS, Schrag D, McFarland EG, Kuntz KM. Rescreening of Persons with a Negative Colonoscopy Result: Results from a Microsimulation Model. Annals of Internal Medicine, 2012; 157:611-620.

The study used a microsimulation model to assess the comparative effectiveness and costs of colonoscopy versus other rescreening strategies in patients after an initial negative colonoscopy. The study found that rescreening strategies based on fecal occult blood testing or CT colonography provide similar benefits compared to a strategy of rescreening with colonoscopy, but with fewer complications and at a lower cost.

Key Achievements/Publication Highlights for 2012

NEUROPROTECTION RESEARCH LABORATORY

ENG LO, PhD, DIRECTOR

1. Guo S, Zhou Y, Xing C, Lok J, Som AT, Ning MM, Ji X, Lo EH. The vasculome of the mouse brain. PLOS One 2012; 7:e52665.

Brain microvessels are not just inert pipes but comprise an endocrine organ that actively releases signals into and receives signals from the neuronal parenchyma. We mapped gene expressions in mouse cerebral endothelium and showed that the brain vasculome (1) is unique and different from vasculomes in heart and kidney, (2) contains active signaling networks, (3) is linked with GWAS-identified genes for stroke, Alzheimer's disease and Parkinson's disease, and (4) contains many potential biomarkers from plasma protein databases.

2. Hayakawa K, Pham LD, Katusic ZS, Arai K, Lo EH. Astrocytic high-mobility group box 1 promotes endothelial progenitor cell-mediated neurovascular remodeling during stroke recovery. Proc Natl Acad Sci USA 2012; 109:7505-7509.

Crosstalk between the brain and systemic responses in blood may play critical roles during recovery after stroke and brain injury. We show that reactive astrocytes can release a damage-associated molecular-pattern molecule called high-mobility-group-box-1 (HMGB1) that promotes endothelial progenitor cell (EPC)-mediated neurovascular remodeling during stroke recovery. in vivo validation of this compound is now proceeding in a NINDS U01 program.

NEUROVASCULAR RESEARCH LABORATORY

CENK AYATA, MD, DIRECTOR

1. Eikermann-Haerter K, Lee JH, Yuzawa I, Liu CH, Zhou Z, Shin HK, Zheng Y, Qin T, Kurth T, Waeber C, Ferrari MD, van den Maagdenberg AM, Moskowitz MA, Ayata C. Migraine mutations increase stroke vulnerability by facilitating ischemic depolarizations. Circulation. 2012 Jan 17;125(2):335-45.

Optical and magnetic resonance imaging, and electrophysiological recordings in transgenic mouse models for familial hemiplegic migraine type 1 indicate that glutamatergic hyperexcitability in migraine renders the brain more susceptible to ischemic depolarizations. As a result, the minimum critical level of blood flow required for tissue survival (i.e., viability threshold) is elevated, and infarction ensues even in mildly ischemic tissues. This represents a paradigm shift in search of a mechanism for increased stroke risk in migraineurs, and radically differs from those previously postulated based on clinical data alone.

Medicine

Dennis A. Ausiello, MD, Chief, MGH Medical Services

BIOSTATISTICS CENTER

DIANNE FINKELSTEIN, PhD, DIRECTOR

1. Udo Hoffmann, MD, MPH, Quynh A. Truong, MD, MPH, David A. Schoenfeld, PhD, Eric T. Chou, MD, Pamela K. Woodard, MD, John T. Nagurney, MD, MPH, J. Hector Pope, MD, Thomas H. Hauser, MD, MPH, Charles S. White, MD, Scott G. Weiner, MD, MPH, Shant Kalanjian, MD, Michael E. Mullins, MD, Issam Mikati, MD, W. Frank Peacock, MD, Pearl Zakroysky, BA, Douglas Hayden, PhD, Alexander Goehler, MD, PhD, Hang Lee, PhD, G. Scott Gazelle, MD, MPH, PhD, Stephen D. Wiviott, MD, Jerome L. Fleg, MD, and James E. Udelson, MD for the ROMICAT-II Investigators; Coronary CT Angiography versus Standard Evaluation in Acute Chest Pain; N Engl J Med 2012; 367:299-308

This paper reports research that was done under two RO1 grants (one to Udo Hoffmann for the clinical coordinating center and one to David Schoenfeld for the data coordinating center) and establishes that CCTA is a safe and efficient early triage tool for patients presenting with chest pain at the Emergency Department enabling quick and direct discharge of the majority of patients initially deemed at low to intermediate likelihood of acute chest pain and will likely have far reaching effects on clinical practice.

2. Paul E Goss, IE Smith, J O'Shaughnessy, B Eijlertsen, M Kaufmann, F Boyle, A U Buzdar, P Fumeleua, W Gradishar, M Martin, B Moy, M Piccart-Gebhart, K Pritchard, D Lindquist, Yanin Charvari-Guerra, G Akton, E Rappold, LS Williams, Dianne M Finkestein on behalf of the TEACH investigators; Adjuvant lapatinib for women with early-stage HER2-positive breast cancer: a randomized, controlled, phase 3 trial; Lancet Oncology 2012.

This paper reports the results of a placebo-controlled trial of over 3000 women worldwide, who were previously treated with adjuvant chemotherapy, but were trastuzumab-naïve, and entered the trial any time after diagnosis. Although the primary comparison on DFS was only marginally significant (p=.053), when the analysis was restricted to patients who were HER2-positive on central fluorescence in-situ hybridization review, there was a marginally significant benefit (p=.04) on DFS for patients who received lapatanib.

3. Mandel M, Mercier F, Eckert B, Chin P, Betensky RA. (2012). Estimating time to disease progression comparing transition models and survival methods - an analysis of multiple sclerosis data; Biometrics.

This article reports an analysis that aims to quantify the effect of fingolimod, an oral treatment for relapsing remitting multiple sclerosis (MS), on disability progression. The standard approach utilizes survival analysis methods, which may be problematic for MS studies that assess disability at only a few time points and include as a cardinal feature both relapses and remissions. Instead, a Markov transition model is proposed that uses all available transition data for analysis of time to progression and provides a description of the short-term effect of treatment and other covariates on the disability process.

4. 157. Lee BL, Liedke PE, Barrios CH, Simon SD, Finkelstein DM, Goss PE, Breast cancer in Brazil: present status and future goals.Lancet Oncol. 2012 Mar;13(3):e95-e102.

This paper summarizes the status of breast cancer prevention and care in Brazil. It is an important evaluation of the status of this health issue in the emerging world and the impact of public health insurance initiatives. It represents the first of many publications arising from the global cancer research program under Dr. Paul Goss of MGH Cancer Center.

CARDIOLOGY

WILLIAM DEC, JR., MD, CHIEF

1. Voight BF, Peloso GM, Orho-Melander M, Frikke-Schmidt R, Barbalic M, Jensen MK, Hindy G, Hólm H, Ding EL, Johnson T, Schunkert H, Samani NJ, Clarke R, Hopewell JC, Thompson JF, Li M, Thorleifsson G, Newton-Cheh C, Musunuru K, Pirruccello JP, Saleheen D, Chen L, Stewart A, Schillert A, Thorsteinsdottir U, Thorgeirsson G, Anand S, Engert JC, Morgan T, Spertus J, Stoll M, Berger K, Martinelli N, Girelli D, McKeown PP, Patterson CC, Epstein SE, Devaney J, Burnett MS, Mooser V, Ripatti S, Surakka I, Nieminen MS, Sinisalo J, Lokki ML, Perola M, Havulinna A, de Faire U, Gigante B, Ingelsson E, Zeller T, Wild P, de Bakker PI, Klungel OH, Maitland-van der Zee AH, Peters BJ, de Boer A, Grobbee DE, Kamphuisen PW, Deneer VH, Elbers CC, Onland-Moret NC, Hofker MH, Wijmenga C, Verschuren WM, Boer JM, van der Schouw YT, Rasheed A, Frossard P, Demissie S, Willer C, Do R, Ordovas JM, Abecasis GR, Boehnke M, Mohlke KL, Daly MJ, Guiducci C, Burtt NP, Surti A, Gonzalez E, Purcell S, Gabriel S, Marrugat J, Peden J, Erdmann J, Diemert P, Willenborg C, König IR, Fischer M, Hengstenberg C, Ziegler A, Buysschaert I, Lambrechts D, Van de Werf F, Fox KA, El Mokhtari NE, Rubin D, Schrezenmeir J, Schreiber S, Schäfer A, Danesh J, Blankenberg S, Roberts R, McPherson R, Watkins H, Hall AS, Overvad K, Rimm E, Boerwinkle E, Tybjaerg-Hansen A, Cupples LA, Reilly MP, Melander O, Mannucci PM, Ardissino D, Siscovick D, Elosua R, Stefansson K, O'Donnell CJ, Salomaa V, Rader DJ, Peltonen L, Schwartz SM, Altshuler D, Kathiresan S. Plasma HDL cholesterol and risk of myocardial infarction: a mendelian randomisation study. Lancet. 2012 Aug 11; 380(9841):572-80. Epub 2012 May 17. Erratum in: Lancet. 2012 Aug 11; 380(9841):564. PMCID: PMC3419820.

In countless observational epidemiological studies, a higher concentration of high-density lipoprotein (HDL) cholesterol in plasma has been associated with a lower risk of myocardial infarction (MI). In this important study, the hypothesis was tested as to whether individuals who carry HDL cholesterol-boosting gene variants are protected from risk for MI. The key and unexpected finding was that patients who carried HDL-cholesterol-boosting variants had the same risk of MI as those who did not carry these variants. These results suggest that some means of raising HDL cholesterol may not lower MI risk in humans and question the conventional wisdom that high HDL cholesterol causally protects against MI.

2. Ahfeldt T, Schinzel RT, Lee YK, Hendrickson D, Kaplan A, Lum DH, Camahort R, Xia F, Shay J, Rhee EP, Clish CB, Deo RC, Shen T, Lau FH, Cowley A, Mowrer G, Al-Siddiqui H, Mahrendorf M, Musunuru K, Gerszten RE, Rinn JL, Cowan CA. Programming human pluripotent stem cells into white and brown adipocytes. Nature Cell Biology. 2012;14(2):209-19.

The utility of human pluripotent stem cells as a tool for understanding disease and as a renewable source of cells for transplantation therapies is dependent on efficient differentiation protocols that convert these cells into relevant adult cell types. Here we report the robust and efficient differentiation of human pluripotent stem cells into adipocytes using inducible expression of the gene PPARG2. These pluripotent stem cell-derived adipocytes retained their identity independent of transgene expression, could be maintained in culture for several weeks, expressed mature markers, and exhibited mature functional properties such as lipid catabolism. This study thus establishes novel high fidelity models of human cardiometabolic diseases for basic investigation and drug screening.

3. Cheng S, Rhee EP, Larson MG, Lewis GD, McCabe EL, Shen D, Palma MJ, Roberts LD, Dejam A, Souza AL, Deik AA, Magnusson M, Fox CS, O'Donnell CJ, Vasan RS, Melander O, Clish CB, Gerszten RE, Wang TJ. Metabolite profiling identifies pathways associated with metabolic risk in humans. Circulation 2012; 125(18):2222-31. .

Although metabolic risk factors are known to cluster in individuals who are prone to developing diabetes mellitus and cardiovascular disease, the underlying biological mechanisms remain poorly understood. To acquire a more detailed understanding of the biochemical pathways, we applied high-throughput metabolite profiling to samples from individuals from the Framingham Heart Study. We observed that the presence of metabolic risk factors (including obesity, insulin resistance, high blood pressure, and dyslipidemia) was significantly associated with variation in metabolites not previously implicated in cardiometabolic disease. By demonstrating the feasibility and utility of biochemical profiling in large clinical samples, and by placing our data in a publicly available database, our work can serve as a resource for future studies of cardiovascular and metabolic diseases for the broader investigative community

4. Ellinor PT, Lunetta KL, Albert CM, Glazer NL, Ritchie MD, Smith AV, Arking DE, Müller-Nurasyid M, Krijthe BP, Lubitz SA, Bis JC, Chung MK, Dörr M, Ozaki K, Roberts JD, Smith JG, Pfeufer A, Sinner MF, Lohman K, Ding J, Smith NL, Smith JD, Rienstra M, Rice KM, Van Wagoner DR, Magnani JW, Wakili R, Clauss S, Rotter JI, Steinbeck G, Launer LJ, Davies RW, Borkovich M, Harris TB, Lin H, Völker U, Völzke H, Milan DJ, Hofman A, Boerwinkle E, Chen LY, Soliman EZ, Voight BF, Li G, Chakravarti A, Kubo M, Tedrow UB, Rose LM, Ridker PM, Conen D, Tsunoda T, Furukawa T, Sotoodehnia N, Xu S, Kamatani N, Levy D, Nakamura Y, Parvez B, Mahida S, Furie KL, Rosand J, Muhammad R, Psaty BM, Meitinger T, Perz S, Wichmann HE, Witteman JC, Kao WH, Kathiresan S, Roden DM, Uitterlinden AG, Rivadeneira F, McKnight B, Sjögren M, Newman AB, Liu Y, Gollob MH, Melander O, Tanaka T, Stricker BH, Felix SB, Alonso A, Darbar D, Barnard J, Chasman DI, Heckbert SR, Benjamin EJ, Gudnason V, Kääb S. Meta-analysis identifies six new susceptibility loci for atrial fibrillation. Nat Genet. 2012 Apr 29. doi: 10.1038/ng.2261. [Epub ahead of print] PMID: 22544366.

In this manuscript published on behalf of the AFGen Consortium, the authors identified six novel genetic loci for atrial fibrillation. These loci included cardiac transcription factors, ion channels and signaling molecules. This work will provide the foundation for future studies on the mechanism of atrial fibrillation.

DIABETES UNIT

JOSEPH AVRUCH, MD, CHIEF

1. Blood glucose control in type 1 diabetes with a bihormonal bionic endocrine pancreas. Russell SJ (Diabetes Unit), El-Khatib FH, Nathan DM (Diabetes Unit), Magyar KL, Jiang J, Damiano ER. Diabetes Care. 2012 Nov;35(11):2148-55. doi: 10.2337/dc12-0071.

A bihormonal bionic endocrine pancreas driven by a continuous glucose monitor was evaluated in type 1 diabetics in experiments lasting more than two days and including six high-carbohydrate meals and exercise as challenges to glycemic control. The overall mean PG was 158 mg/dL, with 68% of PG values in the range of 70-180 mg/dL. During 192 h of nighttime control, mean PG was 123 mg/dL, with 93% of PG values in the range of 70-180 mg/dL and only one episode of mild hypoglycemia (minimum PG 62 mg/dL). These results justify a trial testing a wearable version of the system under free-living conditions.

2. Intensification of diabetes medication and risk for 30-day readmission. Wei NJ (Diabetes Unit), Wexler D (Diabetes Unit), Nathan DM (Diabetes Unit), Grant RW. Diabet Med. 2012 Nov 5. doi: 10.1111/dme.12061. [Epub ahead of print]

Optimization of glycemic control is a primary measure of the efficacy and quality of care. This study examined whether in-hospital diabetes regimen intensification could be accomplished in patients with poorly controlled glycaemia and its impact on 30-day risk for unplanned readmission/emergency department admission, a major driver of hospital associated costs. Among medicine service patients with baseline HbA(1c) = (8%), glucose therapy intensification was associated with a significantly decreased early readmission risk (adjusted odds ratio 0.33, 95% CI 0.12-0.88, P = 0.03) and lower post-discharge HbA(1c), mean decrease (sd): 1.8 (2.4)% vs. 0.6 (1.4)%, P < 0.01. These findings support the safety and durable impact of diabetes regimen optimization during hospital admission.

3. Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. Scott RA and 213 coauthors. Nat Genet. 2012;44:991-1005. doi: 10.1038/ng.2385. PMID:22885924

Jose Florez (Diabetes unit), Claudia Langenberg, Erik Ingelsson, Inga Prokopenko, Inês Barroso and colleagues perform large-scale association analyses using the Metabochip to gain further insights into the genetic architecture of glucose regulation. They identify 38 new loci influencing 1 or more glycemic traits and show that many of these loci also modify risk of type 2 diabetes. Such data from GWAS and complimentary approaches and further improve our biological understanding of glycemic control and the etiology of diabetes.

4. Molecular diagnosis of infantile mitochondrial disease with targeted next-generation sequencing. Calvo SE, Compton AG, Hershman SG, Lim SC, Lieber DS, Tucker EJ, Laskowski A, Garone C, Liu S, Jaffe DB, Christodoulou J, Fletcher JM, Bruno DL, Goldblatt J, Dimauro S, Thorburn DR, Mootha VK(Diabetes unit). Sci Transl Med. 2012;4(118):118ra10. doi: 10.1126/scitranslmed.3003310. PMID:22277967

Next-generation sequencing of the mitochondrial DNA (mtDNA) and exons of ~1000 nuclear genes encoding mitochondrial proteins was performed in 42 unrelated infants with clinical and biochemical evidence of mitochondrial oxidative phosphorylation disease. Firm diagnoses were enabled in 10 patients (24%) who had mutations in genes previously linked to disease. Thirteen patients (31%) had mutations in nuclear genes not previously linked to disease. The pathogenicity of two such genes, NDUFB3 and AGK, was supported by complementation studies and evidence from multiple patients, respectively. The results underscore the potential and challenges of deploying NGS in clinical settings.

ENDOCRINOLOGY

HENRY M. KRONENBERG, MD, CHIEF

1. Fernandez-Rebollo, E., Maeda, A., Reyes, M., Turan, S., Frohlich, L. F., Plagge, A., Kelsey, G., Juppner, H. & Bastepe, M. Loss of XLalphas (extra-large alphas) imprinting results in early postnatal hypoglycemia and lethality in a mouse model of pseudohypoparathyroidism Ib. Proc Natl Acad Sci U S A, 2012; 109: 6638-43. PMCID: PMC3340037

Pseudohypoparathyroidism, type 1b is a mysterious human disorder in which the renal proximal tubule does not respond properly to parathyroid hormone and patients develop hypocalcemia. The disease is caused by deletions in the GNAS locus that cause imprinting abnormalities that lead to poor expression of the a subunit of the Gs signaling protein in the proximal tubule. Here Fernandez-Rebollo, for the first time, have generated an animal model of this disease. This model will now allow the investigators to unlock the mystery of Gs regulation by tissue-specific imprinting.

2. Fulzele, K., Krause, D. S., Panaroni, C., Saini, V., Barry, K. J., Liu, X., Lotinun, S., Baron, R., Bonewald, L., Feng, J. Q., Chen, M., Weinstein, L. S., Wu, J. Y., Kronenberg, H. M., Scadden, D. T. & Divieti Pajevic, P. Myelopoiesis is regulated by osteocytes through Gsalpha-dependent signaling. Blood, 2012. Nov 16 [Epub ahead of print]

The osteocyte is the most abundant, but least understood cell in bone. Here, Fulzele et al, for the first time, show that osteocytes regulate hematopoiesis. When the signaling protein, Gsa is ablated specifically from osteocytes in mice, the mice develop a dramatic increase of myeloid cells (white blood cells) in their bone marrow, blood, and spleen. This expansion can be mimicked with cultured bone and marrow and in this setting, G-CSF is essential for the activity. Thus, through increasing G-CSF, the mutant osteocytes drive expansion of white blood cells.

3. Mitchell DM, Regan S, Cooley MR, Lauter KB, Vrla MC, Becker CB, Burnett-Bowie SA, Mannstadt M. Long-Term Follow-Up of Patients with Hypoparathyroidism. J Clin Endocrinol Metab. 2012 Oct 5. [Epub ahead of print]

The authors surveyed the current care of people with primary hyperparathyroidism in the Partners system. They document a surprisingly high number of patients with diminished renal function and kidney stones in this group. Previously, treatment of this disease with oral calcium and calcitriol was viewed as quite safe and effective. These discouraging results mandate the exploration of novel therapies for this uncommon disease.

4. Song, L., Liu, M., Ono, N., Bringhurst, F. R., Kronenberg, H. M. & Guo, J. Loss of wnt/beta-catenin signaling causes cell fate shift of preosteoblasts from osteoblasts to adipocytes. J Bone Miner Res, 2012; 27: 2344-58. PMCID: PMC3474875

The authors use genetic tricks to mark cells early in the osteoblast lineage in intact mice. They then ask whether cells already committed to the osteoblast lineage can leave that lineage and become fat cells. They report that when signaling through the wnt pathway is blocked in these cells by knocking out the ß -catenin gene, then a fairly large fraction of osteoblastic cells become fat cells. They conclude that ongoing wnt signaling is required even after cells are committed to the osteoblast lineage to keep them on that track. Thus, osteoblast differentiation is less reversible than previously realized.

GASTROINTESTINAL UNIT

RAMNIK XAVIER, MD, CHIEF

1. Liao X, Lochhead P, Nishihara R, Morikawa T, Kuchiba A, Yamauchi M, Imamura Y, Qian Z, Baba Y, Shima K, Meyerhardt JA, Giovannucci E, Fuchs CS, Chan AT,*† Ogino S*† (co-corresponding and co-senior authors). Aspirin use, PIK3CA mutation, and colorectal cancer survival. N Engl J Med. 2012 Oct 25;367(17):1596-606.

Dr. Chan and colleagues demonstrated that among patients with colorectal cancer, use of aspirin after diagnosis is associated with improved survival among patients with PIK3CA-mutated tumors. In contrast, patients with PIK3CA wild-type tumors did not have a significant survival benefit. These findings extended their previous report (Chan et al. JAMA 2009) that showed that aspirin is associated with better survival, especially among PTGS-2 (COX-2) positive tumors and validate experimental data that demonstrate a confluence of the COX-2 and PIK3CA pathways that are fundamental to colorectal carcinogenesis. They also underscored the potential for PIK3CA mutation to serve as a potential predictive biomarker for adjuvant aspirin therapy in colorectal cancer.

2. Ding Q*, Lee YK*, Schaefer EAK* Peters DT, Kim K, Veres A, Kuperwasser N, Meissner TB, Hendriks WT, Trevisan M, Gupta RM, Motola DL, Moisan A, Freisen M, Schinzel RT, Xia F, Tang A, Wann A, Ahfeldt T, Daheron L, Zhang F, Rubin LL, Peng LF, Chung RT, Musunuru K and Cowan CA (*co-first authors). Cell Stem Cell . 2012 Dec 12; eprint ahead of publication.

Dr. Chung's group, working together with Dr. Musunuru and Cowan's group, have used a novel genome editing technology (TALEN) to generate a stable complete ApoB100 knockout hepatocyte cell line. This cell line supports HCV replication poorly, but reintroduction of exogenous ApoB100 partially restores HCV replication. Together, these data indicate that apoB-100 is integral to the HCV viral lifecycle and that APOB-targeting therapeutics (e.g., mipomersen) may have efficacy in treating HCV-infected patients.

3. Smeekens S, Ng A, Kumar V, Johnson MD, Plantinga TS, van Diemen C, Arts P, Verwiel ETP, Gresnigt MS, Fransen K, van Sommeren S, Oosting M, Cheng S-C, Joosten LAB, Hoischen A, Kullberg B-J, Scott WK, Perfect JR, van der Meer JWM, Wijmenga C, Netea M, Xavier RJ. Functional genomics identifies type 1 interferon pathway as central for host defense against Candida albicans. Nature Communications 2012 (in press—DOI: 10.1038/ncomms2343).

In this study, Dr. Xavier's group examined human antifungal defense mechanisms in the context of the pathogen Candida albicans, which causes mucosal and systemic infections especially in immunocompromised hosts. By integrating transcriptional analysis with functional genomics, Dr. Xavier et al demonstrated an unexpected role for genes in the type I interferon pathway in host defense against Candida.

4. Huett A, Heath RJ, Begun J, Sassi SO, Baxt LA, Vyas JM, Goldberg M, Xavier RJ. The LRR- and RING-domain protein LRSAM1 is an E3 ubiquitin ligase crucial for ubiquitin-dependent autophagy of intracellular Salmonella Typhimurium. Cell Host & Microbe, 2012 Dec 13;12(6):778-790.

This paper provided mechanistic insight into antibacterial autophagy, a degradative process that serves a critical role in the removal of intracellular bacteria such as Salmonella. Here Dr. Xavier's group identified LRSAM1 as the E3 ubiquitin ligase crucial for ubiquitin-dependent autophagy of Salmonella. This work characterizes LRSAM1 as a novel antibacterial sensor that mediates target selection for the autophagy pathway and defends the cytoplasm from invasive bacteria.

GENERAL MEDICINE UNIT

KENNETH L. MINAKER, MD, CHIEF

1. Atlas SJ, Ashburner JM, Chang Y, Lester WT, Barry MJ, Grant RW. Population-based Breast Cancer Screening in a Primary Care Network. Am J Manag Care 2012;18:821-9. PMID: 23286611

This study examined long-term outcomes of a novel population management health information technology system for preventive breast cancer screening. The study presented 2-year follow-up results after a 1-year cluster randomized trial of practices within the MGH primary care network. We found that population-based informatics systems can enable sustained increases in mammography screening rates beyond rates seen with office-based visit reminders.

2. Scott RA, Lagou V, Meigs JB, Teslovich TM, Florez JC, Langenberg C, Ingelsson E, Prokopenko I, Barroso I. Large-scale association analyses identify new loci influencing glycemic traits and provide insight into the underlying biological pathways. Nat Genet. 2012 Sep;44(9):991-1005. PMID: 22885924

Dr. Meigs international collaborations are leading to ever-increasing knowledge of diabetes and diabetes-related genetics. This paper and a companion paper bring to >120 the number of unique genetic loci where common variants are associated with diabetes-related quantitative traits (like fasting glucose) or type 2 diabetes risk.

3. Thorndike AN, Sonnenberg L, Riis J, Barraclough S, Levy DE. A 2-phase labeling and choice architecture intervention to improve healthy food and beverage choices. American Journal of Public Health. 2012:102:527-533. PMCID: PMC3329221.

Using insights from behavioral economics we assessed whether a 2-phase labeling and choice architecture intervention would increase sales of healthy food and beverages in a large hospital cafeteria. Phase 1 was a 3-month color-coded labeling intervention (red = unhealthy, yellow = less healthy, green = healthy). Phase 2 added a 3-month choice architecture intervention that increased the visibility and convenience of some green items. At baseline (977,793 items, including 199,513 beverages), 24.9% of sales were red and 42.2% were green. Sales of red items decreased in both phases ($P < .001$), and green items increased in phase 1 ($P < .001$). The largest changes occurred among beverages. Red beverages decreased 16.5% during phase 1 ($P < .001$) and further decreased 11.4% in phase 2 ($P < .001$). Green beverages increased 9.6% in phase 1 ($P < .001$) and further increased 4.0% in phase 2 ($P < .001$). Bottled water increased 25.8% during phase 2 ($P < .001$) but did not increase at 2 on-site comparison cafeterias ($P < .001$). A color-coded labeling intervention improved sales of healthy items and was enhanced by a choice architecture intervention.

4. Volandes AE, Paasche-Orlow MK, Mitchell SL, El-Jawahri A, Davis AD, Barry MJ, Hartshorn KL, Jackson VA, Gillick MR, Walker-Corkery ES, Chang Y, López L, Kemeny M, Bulone L, Mann E, Misra S, Peachey M, Abbo ED, Eichler AF, Epstein AS, Noy A, Levin TT, Temel JS. J Clin Oncol. 2012 Dec 10. [Epub ahead of print Dec 10, 2012] PMID:23233708

This study assessed a novel video decision support tool to improve cardiopulmonary resuscitation (CPR) decision making for patients with cancer using a randomized controlled trial. Participants in the control arm (n = 80) listened to a verbal narrative describing CPR and the likelihood of successful resuscitation. Participants in the intervention arm (n = 70) listened to the identical narrative and viewed a 3-minute video depicting a patient on a ventilator and CPR being performed on a simulated patient. The primary outcome was participants' preference for or against CPR measured immediately after exposure to either modality. 47% of patients had lung or colon cancer. In the control arm, 38 participants (48%) wanted CPR, 41 (51%) wanted no CPR, and one (1%) was uncertain. In contrast, in the intervention arm, 14 participants (20%) wanted CPR, 55 (79%) wanted no CPR, and 1 (1%) was uncertain (unadjusted odds ratio, 3.5; 95% CI, 1.7 to 7.2; $P < .001$). Mean knowledge scores were higher in the intervention arm ($P < .001$), and 93% were comfortable watching the video. Participants with advanced cancer who viewed a video of CPR were less likely to opt for CPR than those who listened to a verbal narrative.

Key Achievements/Publication Highlights for 2012

INFECTIOUS DISEASES

STEPHEN B. CALDERWOOD, MD, CHIEF

1. Johnson RA, Uddin T, Aktar A, Mohasin M, Alam MM, Chowdhury F, Harris JB, Larocque RC, Kelly Bufano M, Yu Y, Wu-Freeman Y, Leung DT, Sarracino D, Krastins B, Charles RC, Xu P, Kovác P, Calderwood SB, Qadri F, Ryan ET. Comparison of immune responses to the O-specific polysaccharide and lipopolysaccharide of Vibrio cholerae O1 in Bangladeshi adult patients with cholera. Clin Vaccine Immunol. 2012 Nov;19(11):1712-21. doi: 10.1128/CVI.00321-12. Epub 2012 Sep 19.

This report characterizes polysaccharide responses in patients with cholera. Immunity against cholera is serogroup specific, and serogroup specificity is defined by the O-specific polysaccharide. Despite this, analysis of OSP responses in patients with cholera has not previously been performed. In a collaborative effort with researchers at NIDDK and ICDDRB-Bangladesh, we performed such an analysis. This knowledge critically informs cholera vaccine development programs.

2. Fixen KR, Janakiraman A, Garrity S, Slade DJ, Gray AN, Karahan N, Hochschild A, Goldberg MB. A genetic reporter system for positioning of proteins at the bacterial pole. mBio. 2012. 3(2): pii: e00251-11 doi: 10.1128/mBio.00238-11.

The mechanisms that underlie protein localization are incompletely understood, in part because of the paucity of methods that allow saturation screening for mutants in which protein localization is altered. This paper is significant because it describes a genetic reporter assay that enables screening of bacterial populations for changes in localization of proteins within the bacterial cytoplasm. The utility of the system in identifying factors required for proper localization of the Shigella autotransporter protein IcsA to the pole of rod-shaped bacteria was demonstrated by the identification of a conserved cell division protein as being required for positioning of IcsA and other autotransporters to this site within the bacterial cell.

3. Tam JM, Mansour MK, Khan NS, Yoder NC and Vyas JM. Use of fungal derived polysaccharide-conjugated particles to probe Dectin-1 responses in innate immunity. Integrative Biology, 2012, 4, 220–227.

Generation of the initial immune response to pathogenic fungi by the immune system requires recognition of key moieties founds on the fungal cell wall. This structure is complex and dynamic in nature, rendering the ability to determine the relative contribution of individual cell wall components to the immune response difficult. To overcome this, we have designed synthetic fungal like particles which retain the same size and shape of C. albicans, but is composed of a single, homogenous polysaccharide derived from the fungal cell wall. This paper describes that this fungal like particle triggers release of inflammatory cytokines from macrophages and provides important proof of concept to this approach to dissect the host response against fungal pathogens.

4. Huang Y, Yuan J, Righi E, Kamoun WS, Ancukiewicz M, Nezivar J, Santosuosso M, Martin JD, Martin MR, Vianello F, Leblanc P, Munn LL, Huang P, Duda DG, Fukumura D, Jain RK, Poznansky MC. Vascular normalizing doses of antiangiogenic treatment reprogram the immunosuppressive tumor microenvironment and enhance immunotherapy. Proc Natl Acad Sci U S A. 2012 Oct 23;109(43):17561-6.

Collaborative paper with Dr. Rakesh Jain on combining anti-VEGF therapy with a cancer vaccine to maximize an anti-tumor effect in two models of breast cancer published in PNASUS. This work demonstrated that an optimum dose of a VEGF inhibitor in combination with a cancer vaccine results in significant improvements in survival in both a spontaneous and viral model of breast cancer in mice. These findings are directly applicable to clinical studies where high doses of VEGF inhibitor have been less than efficacious and there is now an attempt to discover combinatorial therapeutic approaches that involve VEGF inhibition and immunotherapy. Our work provides the first indication that this might be possible. While VEGF inhibition normalizes intratumoral vessels, the immunotherapeutic approach augments anti-tumor T cell infiltration and function within the tumor.

MOLECULAR ENDOCRINOLOGY

JOEL F. HABENER, MD, CHIEF

1. Weight loss peptide increases basal energy expenditure in obese mice.

A pentapeptide given to diet-induced obese mice increases basal oxygen consumption independently of food intake and physical activity. This energy burning peptide acts directly on mitochondria and is in pre-clinical development as a potential novel, and unique weight loss drug for the treatment of obesity and associated metabolic syndrome.

2. Liu Z, Stanojevic V, Brindamour LJ, Habener JF. GLP1-derived nonapeptide GLP1(28-36)amide protects pancreatic beta-cells from glucolipotoxicity. J Endocrinol. 2012; 213:143-154

A nonapeptide derived from the C-terminus of the glucoincretin hormone GLP-1 protects insulin-producing beta cells in the pancreas from oxidative stress imparted by elevated glucose levels (glucotoxicity). The peptide enters beta cells and targets to mitochondria where it maintains mitochondrial membrane potential by inhibiting the opening of the mitochondrial permeability transition pore caused by oxidative stress. Thereby, the nonapeptide inhibits cytochrome C release, activation of the intrinsic apopotosis pathway, and promotes and prolongs beta cell survival.

3. Habener JF, Stanojevic V. Alpha-cell role in beta-cell generation and regeneration. Islets. 2012; 4:188-198

This article critically reviews the current evidence and models for the participation of the alpha cells in the neogenesis and transdifferentiation into insulin-producing beta cells in the pancreatic islets of Langerhans. Alpha cells are endowed with an unusual plasticity in their innate capacity to de-differentiate into stem-like cells and re-differentiate into beta cells. One model of beta cell regeneration involves the production of the chemokine, stromal cell-derived factor 1, by injured beta cells, and its paracrine actions on adjacent alpha cells that results in the production of glucagon-like peptide-1, a potent growth and survival factor for beta cells.

NEPHROLOGY

M. AMIN ARNAOUT, MD, CHIEF

1. CCDC103 mutations cause primary ciliary dyskinesia by disrupting assembly of ciliary dynein arms. Panizzi JR, Becker-Heck A, Castleman VH, Al-Mutairi DA, Liu Y, Loges NT, Pathak N, Austin-Tse C, Sheridan E, Schmidts M, Olbrich H, Werner C, Häffner K, Hellman N, Chodhari R, Gupta A, Kramer-Zucker A, Olale F, Burdine RD, Schier AF, O'Callaghan C, Chung EM, Reinhardt R, Mitchison HM, King SM, Omran H, Drummond IA. Nature Genetics 2012 May 13; 44(6): 714-9

Cilia motility defects cause primary ciliary dyskinesia, a disorder affecting 1:15,000-30,000 births. Cilia motility requires the assembly of multisubunit dynein arms that drive ciliary bending. Despite progress in understanding the genetic basis of PCD, mutations remain to be identified for several PCD-linked loci. Here we show that the zebrafish cilia paralysis mutant schmalhans (smh(tn222)) encodes the coiled-coil domain containing 103 protein (Ccdc103), a foxj1a-regulated gene product. We also show that Ccdc103 acts as a dynein arm attachment factor that causes primary ciliary dyskinesia when mutated.

2. Metabolite profiling identifies pathways associated with metabolic risk in humans. Cheng S, Rhee EP, Larson MG, Lewis GD, McCabe EL, Shen D, Palma MJ, Roberts LD, Dejam A, Souza AL, Deik AA, Magnusson M, Fox CS, O'Donnell CJ, Vasan RS, Melander O, Clish CB, Gerszten RE, Wang TJ. Circulation. 2012 May 8;125(18):2222-31. Epub 2012 Apr 11.

Although metabolic risk factors are known to cluster in individuals who are prone to developing diabetes mellitus and cardiovascular disease, the underlying biological mechanisms remain poorly understood. Using metabolic profiling, we identified circulating metabolites not previously associated with metabolic traits. Experimentally interrogating one of these pathways demonstrated that excess glutamine relative to glutamate, resulting from exogenous administration, is associated with reduced metabolic risk in mice.

3. Repulsive guidance molecule (RGM) family proteins exhibit differential binding kinetics for bone morphogenetic proteins (BMPs). Wu Q, Sun CC, Lin HY, Babitt JL PLoS One. 2012;7(9):e46307.

This paper demonstrates that members of the RGM family of BMP co-receptors exhibit preferential binding for distinct subsets of BMP ligands. Relative to other RGMs, RGMC/ hemojuvelin (mutations of which cause juvenile hemochromatosis) has the highest affinity for BMP6, consistent with the important physiologic role of hemojuvelin-mediated BMP6 signaling in regulating systemic iron homeostasis.

4. The nuclear membrane leukotriene synthetic complex is a signal integrator and transducer. Bair, A.M., Turman, M.V., Vaine, C.A., Panetierri, Jr., R.A., and Soberman, R.J. Mol. Biol. Cell. 2012; 23, 22 4456-4464 (2012), PMID: 23015755

Leukotrienes are bioactive signaling molecules generated in myeloid cells from arachidonic acid that initiate and amplify innate and adaptive immunity. We have identified how a single structure, the multiprotein leukotriene synthetic complex (previously discovered by our laboratory), integrates and transduces extracellular signals on the nuclear membrane of neutrophils to generate the chemotactic lipid LTB4. Not only does this work establish a molecular basis for how cells transduce signals via bioactive lipids, but also lays the groundwork for developing therapies based on the disruption of specific low-affinity transient interactions between proteins.

NEUROENDOCRINE

ANNE KLIBANSKI, MD, CHIEF

1. Subramanian S, Tawakol A, Burdo TH, Abbara S, Wei J, Vijayakumar J, Corsini E, Abdelbaky A, Zanni MV, Hoffmann U, Williams KC, Lo J*, Grinspoon SK*. Arterial inflammation in patients with HIV. JAMA. 2012; 308(4):379-86.*Contributed equally.

The prevalence of cardiovascular disease, including MI and acute coronary syndrome, is increased in HIV-infected patients. This study is the first to demonstrate increased arterial inflammation in HIV-infected patients, and utilizes PET-FDG to assess for the presence of subintimal macrophage activation. The increased activation was most significantly associated with markers of systemic macrophage activation, suggesting new mechanisms and potential treatment strategies for subclinical atherosclerosis related to immune activation in HIV-infected patients.

2. Lawson EA, Holsen LM, Santin M, Meenaghan E, Eddy KT, Becker AE, Herzog DB, Goldstein JM, Klibanski A. Oxytocin secretion is associated with severity of disordered eating psychopathology and insular cortex hypoactivation in anorexia nervosa. J Clin Endocrinol Metab. 2012; 97(10):E1898-908.

Animal data suggest that oxytocin is involved in appetite regulation. This is the first study in humans to demonstrate the relationships between oxytocin, food-motivation neurocircuitry using functional magnetic resonance imaging (fMRI) and disordered eating psychopathology assessement. Oxytocin secretion was associated with the severity of disordered eating psychopathology in anorexia nervosa and using a food-related fMRI paradigm, was associated with hypoactivation of food motivation neurocircuitry in women with active anorexia nervosa and those who had recovered weight. These data suggest that oxytocin has appetite-regulating functions in humans, and dysregulation in anorexia nervosa may contribute to symptoms of disordered eating.

3. Colao A, Petersenn S, Newell-Price J, Findling JW, Gu F, Maldonado M, Schoenherr U, Mills D, Salgado LR and Biller BMK on behalf of the Pasireotide B2305 Study Group. A 12-month phase III study of pasireotide in Cushing's disease. N Engl J Med. 2012; 366:914-24.

Cushing's disease is associated with high morbidity and mortality and there is no approved tumor targeted therapy. Human corticotroph tumors express somatostatin receptors and pasireotide has a unique, somatostatin-receptor-binding profile, with high binding affinity for somatostatin-receptor subtype 5. In this multi-center randomized placebo controlled trial, cortisol and corticotropin secretion decreased, and clinical signs and symptoms of Cushing's disease diminished in a significant number of patients. These data supports the potential use of pasireotide as a targeted treatment for Cushing's disease.

4. Fazeli PK, Bredella MA, Freedman L, Thomas BJ, Breggia A, Meenaghan E, Rosen CJ, Klibanski A. Marrow fat and preadipocyte factor-1 levels decrease with recovery in women with anorexia nervosa. J Bone Miner Res. 2012 Apr 16. [Epub ahead of print].

Anorexia nervosa is a state of self-induced chronic starvation. Despite low levels of subcutaneous and visceral adipose tissue in anorexia nervosa, levels of marrow adipose tissue are elevated. This study demonstrates that in women who have recovered from anorexia nervosa, levels of marrow adipose tissue are comparable to those of healthy controls. This study suggests that marrow adipose tissue may be more sensitive to nutritional changes that other fat depots and gives us insight into the potential role of marrow adipose tissue in energy homeostasis.

PULMONARY AND CRITICAL CARE

BENJAMIN D. MEDOFF, MD, CHIEF

1. Cho JL, Roche MI, Sandall B, Brass AL, Seed B, Xavier RJ, Medoff BD. Enhanced Tim3 Activity Improves Survival After Influenza Infection. J Immunol. 2012 Sep 15;189(6):2879-89. PMID:22875804

This study demonstrated that the counter-regulatory protein Tim3 modulates T cell activity and inflammation in a mouse model of influenza infection. Specifically, the studies demonstrated that Tim3 activation led to decreased CD3zeta phosphorylation in response to TCR stimulation. This signaling defect was associated with decreased cytokine production by T cells and decreased cytotoxicity. Finally, the experiments demonstrated that enhanced Tim3 activity improved morbidity and mortality in a murine model of influenza.

2. Mak RH, Alexander BM, Asomaning K, Heist RS, Liu CY, Su L, Zhai R, Ancukiewicz M, Napolitano B, Niemierko A, Willers H, Choi NC, Christiani DC. A single-nucleotide polymorphism in the methylene tetrahydrofolate reductase (MTHFR) gene is associated with risk of radiation pneumonitis in lung cancer patients treated with thoracic radiation therapy. Cancer. 2012 Jul 15;118(14):3654-65. doi: 10.1002/cncr.26667. Epub 2011 Dec 5. PubMed PMID: 22144047; PubMed Central PMCID: PMC3312983

This study examined the association between functional single-nucleotide polymorphisms in candidate genes from oxidative stress pathways and risk of radiation pneumonitis (RP) in patients treated with thoracic radiation therapy for locally advanced lung cancer. This study showed an association between MTHFR (Folate meatabolism) genotype and risk of clinically significant RP. Further study of MTHFR-related pathways may provide insight into the mechanisms behind RP, and provide potential target for pharmacological intervention.

3. Ranieri VM, Thompson BT, Barie PS, Dhainaut JF, Douglas IS, Finfer S, Gårdlund B, Marshall JC, Rhodes A, Artigas A, Payen D, Tenhunen J, Al-Khalidi HR, Thompson V, Janes J, Macias WL, Vangerow B, Williams MD; PROWESS-SHOCK Study Group. Drotrecogin alfa (activated) in adults with septic shock. N Engl J Med. 2012 May 31;366(22):2055-64. doi: 10.1056/NEJMoa1202290. Epub 2012 May 22. PubMed PMID: 22616830

Dr. Thompson was the Co-PI and corresponding author on this international RCT that demonstrated no effect of an approved yet controversial treatment for severe septic shock; recombinant human activated protein C. This RCT led to the global withdrawal of this treatment from the market and has prompted a reexamination of both our current conceptual model of human sepsis and our approach to clinical trials for severe sepsis

4. Mou H, Zhao R, Sherwood R, Ahfeldt T, Lapey A, Sicilian L, Izvolsky K, Musunuru K, Cowan C, Rajagopal J. Generation of multipotent lung and airway progenitors from mouse ESCs and patient-specific Cystic Fibrosis iPSCs. Cell Stem Cell 2012, 10: 385-387.

Deriving lung progenitors from patient-specific pluripotent cells is a key step in producing differentiated lung epithelium for disease modeling and transplantation. By mimicking the signaling events that occur during mouse lung development, we generated murine lung progenitors in a series of discrete steps. We then adapted this strategy to produce disease-specific lung progenitor cells from human Cystic Fibrosis induced pluripotent stem cells (iPSCs), creating a platform for dissecting patient-specific human lung disease.

REPRODUCTIVE ENDOCRINOLOGY

WILLIAM F. CROWLEY, MD, CHIEF

1. Avbelj Stefanija M, Jeanpierre M, Sykiotis GP, Young J, Quinton R, Abreu AP, Plummer L, Au MG, Balasubramanian R, Dwyer AA, Florez JC, Cheetham T, Pearce SH, Purushothaman R, Schinzel A, Pugeat M, Jacobson-Dickman EE, Ten S, Latronico AC, Gusella JF, Dode C, Crowley WF Jr, Pitteloud N. An ancient founder mutation in PROKR2 impairs human reproduction. Hum Mol Genet. 2012

Oct 1;21(19):4314-24. doi:10.1093/hmg/dds264. Epub 2012 Jul 5. PubMed PMID: 22773735; PubMed Central PMCID: PMC3441126.

This article identifies a unique loss of function mutation in the Prokineticin 2 Receptor that causes Isolated GnRH Deficiency (IGD)and reproductive failure. Whereas all previous mutations in the genes causing IGD have been private mutations. However, the L173R mutation described in this article has been seen in several population and appears to occur on a single haplotype demonstrating its founder nature. Moreover, the small size of this haplotype (124kb) demonstrates that is nearly 9,000k years old. The heterozygous advantage of this mutation may well related to the ability to extinguish reproductive competency during environmental stress such as malnutrition, migrations, seasonal breeding and stress as seen in women with hypothalamic amenorrhea.

2. Gianetti E, Hall JE, Au MG, Kaiser UB, Quinton R, Stewart JA, Metzger DL, Pitteloud N, Mericq V, Merino PM, Levitsky LL, Izatt L, Lang-Muritano M, Fujimoto VY, Dluhy RG, Chase ML, Crowley WF Jr, Plummer L, Seminara SB. When genetic load does not correlate with phenotypic spectrum: lessons from the GnRH receptor (GNRHR). J Clin Endocrinol Metab. 2012 Sep;97(9):E1798-807. doi: 10.1210/jc.2012-1264. Epub 2012 Jun 28. PubMed PMID: 22745237; PubMed Central PMCID: PMC3431570.

The central message of the Gianetti paper is that in genetics, exceptions to the rule can lay the foundation for future gene discovery. As shown in Gianetti et al, mutations in GNRHR are relatively common causes of hypogonadotropic hypogonadism, occurring in about 4% of patients. Receptor function in patients harboring biallelic mutations (one on each allele) in GNRHR appears to correlate with the phenotypic spectrum of GnRH deficiency. However, patients harboring monoallelic mutations (one allele only) in GNRHR demonstrate a paradoxically wider spectrum of GnRH deficient states (mild to severe). This suggests the presence of yet to be identified genetic and/or non-genetic factors that work in combination with the mutated GNRHR allele to produce reproductive phenotypes.

3. Welt CK, Styrkarsdottir U, Ehrmann DA, Thorleifsson G, Arason G, Gudmundsson JA, Ober C, Rosenfield RL, Saxena R, Thorsteinsdottir U, Crowley WF, Stefansson K. Variants in DENND1A are associated with polycystic ovary syndrome in women of European ancestry. J Clin Endocrinol Metab. 2012 Jul;97(7):E1342-7. doi: 10.1210/jc.2011-3478. Epub 2012 Apr 30. PubMed PMID: 22547425; PubMed Central PMCID: PMC3387396.

Polycystic ovary syndrome is a complex, heritable disorder that results in infertilty and an increased risk for endometrial hyperplasia, type 2 diabetes and other cardiovascular risk factors. The manuscript reports an association between a genetic variant in DENND1A and risk for polycystic ovary syndrome in women of European ancestry. The variant was previously identified in a genome-wide association study in Han Chines women. The gene, which was not previously known to play a role in polycystic ovary syndrome pathophysiology, may play a role in the hypothalamic overactivity common in the syndrome.

4. Shaw ND, Butler JP, McKinney SM, Nelson SA, Ellenbogen JM, Hall JE. Insights into Puberty: The Relationship between Sleep Stages and Pulsatile LH Secretion. J Clin Endocrinol Metab. 2012 Nov;97(11):E2055-62. doi: 10.1210/jc.2012-2692. Epub 2012 Sep 4. PubMed PMID: 22948756; PubMed Central PMCID: PMC3485602.

During the early stages of puberty, the rise in gonadotropin-releasing hormone (GnRH) and luteinizing hormone (LH) is initially restricted to sleep. The current study demonstrates that it is deep sleep, rather than sleep in general, that is specifically associated with LH pulse initiation, suggesting that deep sleep may play a role in the control of puberty.

RHEUMATOLOGY, ALLERGY & IMMUNOLOGY

ANDREW D. LUSTER, MD, PhD, CHIEF

1. Murooka TT, Deruaz M, Marangoni F, Seung E, Vrbanac VV, von Andrian UH, Tager AM, Luster AD, Mempel TR. HIV-infected T cells are migratory vehicles for local and systemic viral dissemination. Nature 2012; 490: 283-287.

This highly innovative study brought together two cutting-edge technologies, multiphoton intravital imaging and humanized mice, to visualize HIV infection and the spread of HIV infection in human cells in lymph nodes in vivo for the very first time. Contrary to previously held beliefs, this study revealed that HIV-infected T cells continue to migrate after infection and that HIV spreads not through the release of free virus into the circulation, but instead relies on the ability of infected T cells to carry the infection out of the lymph node to other tissues to establish a systemic infection.

2. Groom JR, Richmond J, Murooka TT, Sorensen EW, Sung JH, Bankert K, von Andrian UH, Moon JJ, Mempel TR, Luster AD. CXCR3 receptor-ligand interactions in the lymph node optimize CD4+ T helper 1 differentiation. Immunity 2012; 37: 1091-1103.

Differentiation of naive CD4+ T cells into T helper (Th) cells is a defining event in adaptive immunity. This study demonstrated that the (Th1) cell-associated chemokine receptor CXCR3 plays a crucial role in promoting cell-cell interactions and guiding intralymph node movements of activated T cells that promote differentiation toward an interferon-g-producing Th1 cell phenotype. Using a newly developed dual chemokine fluorescent reporter transgenic mouse, this study demonstrated that this movement depended on expression of two CXCR3 ligands in distinct lymph node compartments.

3. Sadik CD, Kim ND, Iwakura Y, Luster AD. Neutrophils orchestrate their own recruitment in murine arthritis through C5aRr and Fc?R signaling. Proc Natl Acad Sci USA 2012; 109: E177-85.

Neutrophil recruitment into the joint is a hallmark of inflammatory arthritides, including rheumatoid arthritis. This study demonstrated that C5aR and Fc?Rs work in sequence to initiate and sustain neutrophil recruitment in vivo. Specifically, C5aR activation of neutrophils was required for LTB4 release and early neutrophil recruitment into the joint, whereas Fc?R engagement upon neutrophils induced IL-1ß release and subsequent neutrophil-active chemokine production, ensuring continued inflammation.

4. 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 2012; in press.

This study performed an integrative analysis of DNA-sensing by the immune system. Using an approach that combines mass spectrometry, RNAi and drug discovery, this study identified many new components of the DNA-**sensing pathway and small molecules that can be used to modulate the pathway, with potential applications to treatment of autoimmune disease such as lupus.**

Molecular Biology

Robert E. Kingston, PhD, Chief

1. Hu, Z., Hom, S., Kudze, T., Tong, X.J., Choi, S., Aramuni, G., Zhang, W., and Kaplan, J.M. (2012). Neurexin and neuroligin mediate retrograde synaptic inhibition in C.elegans. Science 337, 980-984.

Characterization of the function of three genes linked to autism. Mutations in three genes linked to Autism (Neurexin, Neuroligin, and MEF-2) were shown to regulate the kinetics of neurotransmitter release. Post-synaptic Neurexin (NX) and pre-synaptic Neuroligin (NL) mediated a retrograde synaptic signal that inhibited neurotransmitter release. Retrograde inhibition was induced by mutations that inactivated a muscle microRNA (miR-1) and was abolished by mutations inactivating the transcription factor MEF-2, a miR-1 target. NX and NL selectively inhibit fusion of a subpopulation of synaptic vesicles (SVs) that mediate slow release, most likely via changes in Tomosyn, an inhibitor of SV exocytosis. These studies resonate with previous work showing that mouse triple knockouts lacking NL1-3 also have prolonged synaptic responses, indicating that NL regulation of synaptic response kinetics is conserve.

2. McEwan, D.L., N.V. Kirienko, and F.M. Ausubel (2012) Host translational inhibition by Pseudomonas aeruginosa Exotoxin A triggers an immune response in Caenorhabditis elegans via translational inhibition. Cell Host & Microbe 11:364-374.

Pathogenesis mechanism. The mechanism by which intestinal epithelial cells recognize that they are under pathogen attack is poorly understood. The work in this paper demonstrates that the intestinal epithelial cells in the model nematode C. elegans recognize the bacterial pathogen Pseudomonas aeruginosa at least in part by using a cellular surveillance system that monitors the effects of bacterial toxins, in this case a toxin that blocks protein synthesis. This is one of the first clear examples in an animal that pathogens can be recognized not only by highly conserved pathogen-encoded molecules such as LPS and peptidoglycan, components of the bacterial cell wall, but by the deleterious effects they have on host cell.

3. Jain M, Nilsson R, Sharma S, Madhusudhan N, Kitami T, Souza A, Kafri R, Kirschner MW, Clish CB, Mootha VK. Metabolite profiling reveals a key role for glycine in rapid cancer cell proliferation. Science 2012: 336(6084): 1040-44.

Metabolic vulnerability in cancer cells. Metabolic profiling was used to study global metabolic flux in the NCI-60 collection—a richly annotated collection of diverse cancer cell lines. Rapidly proliferating cancer cells were found to have an unexpected appetite for the amino acid glycine, that appears to be fulfilled either through utilization of glycine in the media, or through its mitochondrial biosynthesis. The work identifies a new metabolic vulnerability of rapidly proliferating cancer cells. Importantly, the work also identifies the mitochondrial 1-carbon/folate pathway as a potential target for cancer.

4. Melo, JA and G. Ruvkun. 2012. Inactivation of essential cellular pathways stimulates microbial avoidance behavior, drug detoxification, and pathogen defense-related responses in C. elegans. Cell, Apr 13;149(2):452-66.

Animal poison and bacterial pathogen surveillance pathways and human disease. Genetic analysis of the C. elegans response to natural toxins and to pathogenic bacteria has led to the idea that animal cells interpret that a bacterial attack is occurring with induction of non-feeding behaviors and drug detoxification responses. Viewing many diseases through the prism of this newly discovered system allows a reinterpretation of a variety of disorders from other branches of medicine as aberrant responses to toxins and bacteria, as many of the regulatory factors identified in C. elegans are conserved in humans. Core cellular processes in humans are proposed to be under constant surveillance, with disruption of these processes by a mutation, a drug, or a pathogen-encoded toxin inducing coordinated responses. The analysis reported in this work reveals components of this newly discovered drug/toxin surveillance pathway as well as the endocrine systems that spread the detoxification signal systemically. In a sense, this work aims to explain the molecular basis of feeling sick.

Neurology

Merit E. Cudkowicz, MD, Chief

1. Vassoler FM, White SL, Schmidt HD, Sadri-Vakili G, Pierce RC. Nat Neurosci. 2013 Jan;16(1):42-7. doi: 10.1038/nn.3280. Epub 2012 Dec 16.

Our findings from this study demonstrate that exposure to cocaine alters gene expression by modifying the epigenome in the brain as well as the germline and can be inherited.

2. de Calignon A, Polydoro M, Suárez-Calvet M, William C, Adamowicz DH, Kopeikina KJ, Pitstick R, Sahara N, Ashe KH, Carlson GA, Spires-Jones TL, Hyman BT. Propagation of tau pathology in a model of early Alzheimer's disease. Neuron. 2012 Feb 23;73(4):685-97.

In this paper we describe a mechanism whereby neurofibrillary tangles "spread" throughout the cortex, suggesting the means by which patients with Alzheimer's disease progress and, by implication, a target that might stop progression.

3. Hochberg, L.R., Bacher, D., Jarosiewicz, B., Masse, N.Y., Simeral, J.D., Vogel, Haddadin, S., Liu, J., Cash S.S., van de Smagt, P., and Donoghue, J.P. Reach and grasp by people with tetraplegia using a neurally controlled robotic arm. Nature 2012; 485: 372-375.

In this paper, two people with tetraplegia used the investigational, intracortical BrainGate system to reach and grasp with a neurally-controlled robotic arm, simply by thinking about the movement of their own hand. One of the participants, a 58 year old woman with a brainstem stroke, used the system to pick up and drink from a thermos of coffee. This was first time in the nearly 15 years since her stroke that she was able to serve herself a beverage solely of her own volition.

4. Comparison of 30-day mortality models for profiling hospital performance in acute ischemic stroke with vs without adjustment for stroke severity. Fonarow GC, Pan W, Saver JL, Smith EE, Reeves MJ, Broderick JP, Kleindorfer DO, Sacco RL, Olson DM, Hernandez AF, Peterson ED, Schwamm LH. JAMA. 2012 Jul 18;308(3):257-64. doi: 10.1001/jama.2012.7870. PMID: 22797643 [PubMed -indexed for MEDLINE]

This study evaluated two different methods for ranking stroke quality of care at US hospitals from best to worst based on the rate at which Medicare patients died in the 30 days after they were admitted to the hospital. Medicare has similar measures for heart failure, heart attack and pneumonia, based on data hospitals submit for payment byMedicare. This method can be easily applied to all US hospitals, but it doesn't include a measure of stroke severity which is known to be the most important predictor of death in stroke patients. Thereforethe methods to adjust the rankings to account for who is at greatestrisk of dying might be flawed, and this could lead to wrongly labeling a high performing hospital as a low performer, or vice versa.

Key Achievements/Publication Highlights for 2012

Neurosurgery

Robert L. Martuza, MD, Chief

1. Sheth S, Mian M, Patel S, Asaad W, Williams Z, Dougherty D, Bush G, Eskandar E. Human Dorsal Anterior Cingulate Neurons Mediate Behavioral Adaptation. Nature. 2012 Aug 9;488(7410):218-21.

This work used a multi-disciplinary approach, involving functional MRI, neuronal recordings, and behavioral analysis, to study an enigmatic but important part of the brain called the cingulate gyrus. The work demonstrated that the cingulate gyrus is critical in recruiting different parts of the brain to solve problems with varying degrees of difficulty.

2. Shanechi MM, Hu RC, Powers M, Wornell GW, Brown EN, Williams Z. Neural population partitioning and a concurrent brain-machine interface for sequential motor function. Nature Neurosci. 2012 Nov;15(12):1715-22. doi: 10.1038/nn.3250.

This paper demonstrates a novel population partitioning structure within the primate premotor cortex that allows new and added information to be held in working memory with surprisingly little degradation. This insight is used to develop a new type of brain-machine interface that can decode full motor sequences prior to movement and then execute them as desired, thus also providing extremely fast and accurate performances.

3. Bonmassar, G, Lee, SW, Freeman, DK, Polasek, M, Fried, SI, Gale, JT. Microscopic magnetic stimulation of neural tissue. Nature Comm. 2012 Jun 26;3:921. PubMed PMID: 22735449.

This paper demonstrates that the flow of current through very small coils can generate a magnetic field strong enough to activate neurons. This finding is significant for several reasons. First, the size of the coil is smaller than that of the leads used in existing DBS systems. Thus, the possibility arises that micro-coil based magnetic stimulation could be used as an alternative to existing DBS systems. This is highly attractive as the new technology could overcome some of the side effects associated with DBS, e.g. incompatibility with MRI. Second, the size of the coil allows the study of precise interactions between magnetic stimulation and neural tissue. This therefore has the potential to elucidate the mechanisms associated with TMS; such mechanisms have remained elusive despite considerable efforts.

Obstetrics and Gynecology

Isaac Schiff, MD, Chief

1. White YAR, Woods DC, Takai Y, Ishihara O, Seki H, Tilly JL. Oocyte formation by mitotically active germ cells purified from ovaries of reproductive age women. Nature Medicine 2012; 18: 413–421 (cover article, highlighted by a News & Views Commentary and a Nature Podcast).

This study describes a new method for the purification of female germline or oogonial (oocyte-producing) stem cells from the ovaries of adult mice and of reproductive age women, and a complete characterization of the purified cells before and after ex vivo expansion. For the mouse cells, generation of fertilization competent eggs following intraovarian transplantation into recipient females was demonstrated among many other endpoints. In parallel, the human ovary-derived oocyte precursor cells were shown to generate new oocytes, which initiate follicle formation, after injection into adult human ovarian cortical tissue that was xenografted into mouse hosts. This work opens the door for intensive investigations into the potential clinical utility of human female germline stem cells for improving fertility in women whose fertility has been compromised by aging or insults.

2. Rauh-Hain JA, Rodriguez N, Growdon WB, Goodman AK, Boruta DM, Horwitz NS, del Carmen MG, Schorge JO. Primary debulking surgery versus neoadjuvant chemotherapy in stage IV ovarian cancer. Annals of Surgical Oncology 2012; 19: 959–966.

The standard of care treatment for women with stage IV ovarian cancer has historically been primary debulking surgery (PDS). This report provides clinical outcomes data in support of a shift away PDS toward neoadjuvant chemotherapy with interval debulking surgery (NACT-IDS). Of 242 women diagnosed with stage IV ovarian cancer, 176 underwent PDS and 45 underwent NACT-IDS, whereas the remaining 21 were treated with chemotherapy only. Retrospective analysis indicated that NACT-IDS for advanced ovarian cancer resulted in higher rates of complete resection to no residual disease, less morbidity and equivalent overall survival compared to PDS.

3. Imudia AN, Awonuga AO, Kaimal AJ, Wright DL, Styer AK, Toth TL. Elective cryopreservation of all embryos with subsequent cryothaw embryo transfer in patients at risk for ovarian hyperstimulation syndrome reduces the risk of adverse obstetric outcomes: a preliminary study. Fertility & Sterility 2012; doi: 10.1016/j.fertnstert.2012.08.060 (released September 28).

Ovarian hyperstimulation syndrome in female patients undergoing assisted reproduction are more likely to have small for gestational age (SGA) infants and preeclampsia (gestational hypertension and proteinuria), both of which represent major obstetric complications. In this study, outcomes were monitored in 52 women with elevated peak estrogen levels during controlled ovarian hyperstimulation, 32 of which underwent fresh embryo transfer (ET) and the remaining 20 underwent elective cryopreservation of all embryos with subsequent cryothaw-ET at a later date. Women who underwent elective cryopreservation of all embryos and subsequent cryothaw-ET were statistically less likely to deliver SGA infants and develop preeclampsia. These preliminary findings support the possibility that obstetric complications commonly linked to ovarian hyperstimulation syndrome may be at least partially offset by embryo cryopreservation and cryothaw-ET when the patient's hormonal milieu is more balanced.

4. Nehra D, Le HD, Fallon EM, Carlson SJ, Woods DC, White YAR, Pan AH, Guo L, Rodig SJ, Tilly JL, Rueda BR, Puder M. Prolonging the female reproductive lifespan and improving egg quality with dietary omega-3 fatty acids. Aging Cell 2012; 11: 1046–1054.

Advanced maternal age in women is tied to decreased egg quality and poor fertility, even with the use of assisted reproductive technologies. In this investigation, mice with lifelong consumption of a diet rich in omega-3 fatty acids exhibited a prolongation of natural reproductive lifespan and significant improvements in egg quality as the animals aged. The beneficial effects of omega-3 fatty acids on egg quality were also observed in female mice that were fed standard diets until just before reproductive compromise, at which time the diet was acutely enriched with omega-3 fatty acids. In comparison, excess omega-6 fatty acids in the diet were found to produce the opposite outcomes. These data support that omega-3 fatty acids might provide an effective and practical strategy for slowing ovarian aging and maintaining egg quality in women at advanced maternal ages.

Ophthalmology

Joan W. Miller, MD, Chief

1. Patricia A. D'Amore, PhD, MBA, FARVO is named Schepens Eye Research Institute Director of Research

Following an international search, Patricia D'Amore, PhD, MBA, FARVO on November 1, 2012 was named Director of Research at Schepens Eye Research Institute. Dr. D'Amore is Professor of Ophthalmology and Pathology at Harvard Medical School (HMS), HMS Ophthalmology Vice Chair of Basic Research, and Senior Scientist and Ankeny Scholar of Retinal Molecular Biology at Schepens. As Director of Research, Dr. D'Amore will serve as the senior leader at Schepens and as a member of the Mass. Eye and Ear research leadership team, reporting to HMS Department of Ophthalmology Chief and Chair at Mass. Eye and Ear, Mass General Hospital and HMS, Joan W. Miller, MD, FARVO and to the Schepens Board of Directors. Dr. Miller will also nominate her for appointment as the Charles L. Schepens Professor of Ophthalmology at HMS. Dr. D'Amore's selection follows a rigorous, eight-month effort by an HMS-appointed search committee to identify a highly accomplished academic and scientific leader who has achieved significant success in advancing the field of vision science.

2. HMS Ophthalmology Centers of Excellence Promote Collaboration Department-Wide

Program initiatives and development within the newly formed HMS Department of Ophthalmology Centers of Excellence (COE) made significant progress in 2012. COEs are designed to drive collaboration across the full, three-tier mission of the department—clinical care, education and research—by bringing together the exceptional expertise, talent and resources of the entire Harvard Medical School community. COEs have been established in several key, subspecialty areas, including age-related macular degeneration, diabetes, cornea, glaucoma, and vision rehabilitation. Two additional discipline-based centers include the Ocular Genomics Institute (OGI), launched in 2011, and the Minda De Gunzburg Institute for Ocular Regeneration. Luk Vandenberghe, PhD, an expert in gene therapy delivery, joined the OGI and the Berman Gund Laboratory for the Study of Retinal Degenerations in April, 2012. He is working closely with OGI director Eric Pierce, MD, PhD and directing a state-of-the-art laboratory at Schepens that includes a Retina Gene Transfer Core.

3. Clinical Trials Growth and Infrastructure Enhancements

Clinical trial growth in the Department of Ophthalmology grew significantly during calendar year 2012 with a 25 percent increase in active clinical research studies. Mass. Eye and Ear Department of Ophthalmology recently opened a clinical research office to provide administrative and study coordination support to its expanding team of clinical investigators. The department has also made infrastructure enhancements. Examples of both are noted below.

- In September, 2012, Mass. Eye and Ear received a $2,345,534 contract to lead an international clinical trial through a competitive process for which the sole vision award funded was awarded to Mass. Eye and Ear. The goal of the project, led by principal investigator Reza Dana, MD MPH, MSc is to test bevacizumab, an anti-VEGF agent, in a randomized, multicenter study for its ability to prevent corneal neovascularization and to promote graft survival in the setting of vascularized high-risk corneal transplantation.
- A recent remodeling project and capital purchases were completed at Schepens Eye Research Institute/Mass. Eye and Ear. The renovations create both animal procedure space and two imaging rooms for epifluorescent intravital and two-photon confocal microscopy, including an Ultima Microscope and two Ti/Sapphire lasers. The new Imaging Core Facility includes an associated Imaris image analysis station and an EMC Isilon X-series computational cluster with 30 Tb storage capacity for image data storage and processing. The new facility is under the direction of Pedram Hamrah MD, Director of the Ocular Surface Imaging Center at Mass. Eye and Ear.

4. Genetic Risk Factors for Glaucoma "Common variants at 9p21 and 8q22 are associated with increased susceptibility to optic nerve degeneration in glaucoma" PLoS Genetics, 2012; 8(4):e1002654

Glaucoma is the second leading cause of blindness worldwide. The condition results in damage to the retinal ganglion cells, which are the retinal neurons that communicate with the brain. High intraocular pressure is a major risk factor, but the cause of the elevated pressure is not known, nor is there an explanation of the fact that some individuals develop the characteristic lesion of glaucoma despite normal intraocular pressure. A team led by Drs. Janey Wiggs and Louis Pasquale has carried out a meta analysis of two existing datasets that identified significant associations between two loci and glaucoma: the CDKN2BAS region on 9p21 (rs2157719 [G], OR?=?0.69 [95%CI 0.63-0.75], p?=?1.86×10?¹8), and the SIX1/SIX6 region on chromosome 14q23 (rs10483727 [A], OR?=?1.32 [95%CI 1.21-1.43], p?=?3.87×10?¹¹). In sub-group analysis, two loci were significantly associated with normal pressure glaucoma: 9p21 containing the CDKN2BAS gene (rs2157719 [G], OR?=?0.58 [95% CI 0.50-0.67], p?=?1.17×10?¹²) and a probable regulatory region on 8q22 (rs284489 [G], OR?=?0.62 [95% CI 0.53-0.72], p?=?8.88×10?¹°). Both NPG loci were also nominally associated with a second type of glaucoma, exfoliation syndrome glaucoma (rs2157719 [G], OR?=?0.59 [95% CI 0.41-0.87], p?=?0.004 and rs284489 [G], OR?=?0.76 [95% CI 0.54-1.06], p?=?0.021), suggesting that these loci might contribute more generally to optic nerve degeneration in glaucoma. Because both loci influence transforming growth factor beta (TGF-beta) signaling, they performed a genomic pathway analysis that showed an association between the TGF-beta pathway and normal pressure glaucoma (permuted p?=?0.009). These results suggest that neuro-protective therapies targeting TGF-beta signaling could be effective for multiple forms of glaucoma.

Oral & Maxillofacial Surgery (OMFS)

Leonard B. Kaban, MD, DMD, Chief

1. Minipig model of Distraction Osteogenesis Hansen GM, Lawler ME, Williams WB, Troulis MJ, Kaban LB. BMP4 Localization and PCNA expression during distraction osteogenesis of the porcine mandible. International J Oral & Maxillofac Surg. 2012 June; 41:867-873. Epub 2012 Jan. Papadaki M, Kaban L, Troulis M. Minipig Model of Maxillary Distraction Osteogenesis; Immunohistochemical and Histomorphometric Anaylsis of the Squence of Osteogenesis. J of Oral Maxillofac Surg, 2012 Nov;70(11):2629-40. Epub 2012 Apr.

Our laboratory has developed a minipig model for midface and mandibular bone lengthening by distraction osteogenesis. These 2 studies, using the minipig models of distraction for the mandible and midface, respectively document the cellular sequence of healing of the mandibular and midface distraction wound. The ultimate goal is to use this information to better understand the biology of distraction osteogenesis in order to manipulate the wound to improve the rate and quality of bone formation.

2. Studies on the clinical behavior of primary mesenchymal jaw bone tumors in children. Abramowicz S, Goldwaser B, Troulis M, Padwa B, Kaban LB. Primary jaw tumors in children. J Oral & Maxillofac Surg. Epub 2012 July. Abramowicz S, Kaban LB, Kozakewich H, Perez-Atayde A, Padwa B. Myofibromas of the Jaws in Children. J Oral & Maxillofac Surg. 2012 Aug; 70 (8):1880-4.

Primary mesenchymal jaw tumors in children are rare and few clinicians have extensive experience with these lesions. Furthermore, there are no good animal models or biomarkers that reliably predict the biological or clinical behavior of the tumors. In these retrospective studies, we document the clinical behavior and response to treatment of primary mesenchymal jaw tumors in children and develop guidelines for diagnosis and management that will be helpful to clinicians.

3. Fagin A, Susarla S, Donoff RB, Kaban LB, Dodson TB. Outcomes following operative management of trigeminal nerve injuries: What factors are associated with functional sensory recovery following lingual nerve repair? J Oral Maxillofac Surg 2012 Dec 70:2907-15.

The Department is a regional referral center for evaluation and management of trigeminal nerve injuries as a result of dentoalveolar surgery or trauma. As part of our program to standardize treatment and improve outcomes for lingual nerve injuries, investigators from the Department's Center for Applied Clinical Investigation designed and implemented a retrospective cohort study and enrolled a sample of patients undergoing lingual nerve repair between 2004 and 2010. Consistent with our previous results, 75% of subjects regained functional sensory return within one year of lingual nerve repair. The most significant factor associated with functional sensory recovery was young age at time of injury.

4. Bouchard C, Magill JC, Nikonovskiy V, Byl M, Murphy BA, Kaban LB, Troulis MJ. Osteomark: A surgical navigation system for Oral and Maxillofacial Surgery. Int J Oral Maxillofac Surg. 2012 Feb; 41: 265-270.

Currently available surgical navigation systems are cumbersome for oral and maxillofacial surgery procedures and the fixation device prevents movement of the head. The purpose of this project was to design, test and validate a novel surgical navigation system (Osteomark) specifically for oral and maxillofacial surgery procedures. The tool consists of a pencil-like wand to mark the bone and fiducial markers which are attached to the teeth. No head frame is required and the head can be turned during the procedure. The system is designed to help execute a surgical treatment plan in a "simple" yet effective way. Osteomark in these studies permitted accurate localization of pre-drilled bone holes and osteotomies with acceptable accuracy (within 2mm). The system is now being validated in live animal studies prior to clinical use. (NIH-SBIR- 2R44DE019322).

Key Achievements/Publication Highlights for 2012

Orthopaedics

Harry E. Rubash, MD, Chief

1.CR Bragdon, M Doerner, HE Rubash, YM Kwon, J Martell, J Clohisy, R White, C Della Valle, D Berry, B Jarrett, PF Lachiewicz, K Bertin, PE Johanson, H Palm, WH Harris, H Malchau. The John Charnley Award: Clinical Multi-center Studies of the Wear Performance of Highly Crosslinked Remelted Polyethylene in THR. 2012 Clinical orthopaedics and related research. 2013;471(2):393-402.

Highly cross-linked polyethylene was introduced for use in total hip arthroplasty in order to reduce the debilitating periprosthetic osteolysis associated with wear debris. This long-term multi-center clinical outcome study documented the dramatic decrease in wear and the absence of periprosthetic osteolysis in patients followed as long as 13 years after surgery.

2.Yao Q, Wang S, Shin JH, Li G, Wood KB. Lumbar Facet Joint Motion in Patients with Degenerative Spondylolisthesis. J Spinal Disord Tech. 2012 Nov 16. [Epub ahead of print]

Although the morphologic changes of the facet joints in patients with degenerative lumbar spondylolisthesis (DLS) have been reported in a few studies, no data have been reported on the kinematics of these facet joints. This study investigated the in vivo biomechanical effect of DLS on the motion of the facet joint during various functional weight-bearing activities. The data indicated that the range of rotation decreased at the facet joints at the DLS level (L4-L5) in patients compared with those in healthy subjects and DDD patients. This decrease in range of rotation implies that the DLS disease may cause re-stabilization of the joint. The data may help the selection of conservative treatment or different surgical techniques for the DLS patients.

3.Systematic kinome shRNA screening identifies CDK11 (PITSLRE) kinase expression is critical for osteosarcoma cell growth and proliferation. Duan Z, Zhang J, Choy E, Harmon D, Liu X, Nielsen P, Mankin H, Gray NS, Hornicek FJ.

To identify the potential therapeutic kinase targets in osteosarcoma cells, Duan and colleagues performed a comprehensive kinome-wide screening. Their results show that knocked down CDK11 expression inhibits tumor cell growth and induces apoptosis. High CDK11 expression levels in osteosarcoma patients were associated with significantly shorter survival than were low levels of CDK11 expression in osteosarcoma patients. Systemic in vivo administration of siRNA of CDK11 reduced the tumor growth. These observations demonstrate that CDK11 signaling is essential in osteosarcoma cell growth and survival. CDK11 may be a promising therapeutic target in the management of osteosarcoma.

4.Ootes D, Lambers KT, Ring DC. The epidemiology of upper extremity injuries presenting to the emergency department in the United States. Hand 2012; 7: 18-22.

The National Electronic Injury Surveillance System is a database of emergency department visits based on sampling of selected hospitals. In this paper, the database was used to assemble the most accurate and reliable estimates of the epidemiology of upper extremity injuries that are seen in the emergency rooms of the United States.

Otolaryngology

Joseph B. Nadol, MD, Chief

1. Mizutari K, Fujioka M, Hosoya M, Bramhall N, Okano HJ, Okano H, Edge A. Notch Inhibition Induces Cochlear Hair Cell Regeneration and Recovery of Hearing after Acoustic Trauma. Neuron. 2013 Jan;77(1):58-69.

In the Jan. 10 issue of Neuron, Albert Edge, PhD, demonstrates 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. In collaboration with Seok-Hyun Yun, PhD, from the Wellman Center for Photomedicine at Massachusetts General Hospital, Jeffrey Tao Cheng, PhD, is developing a probe that can be applied to Optical Coherence Tomography (OCT) for a revolutionary noninvasive diagnostic tool for middle ear disease.

3. James W. Rocco, MD, PhD, has begun recruiting participants to his NIH-funded study of biomarkers for predicting outcome in oropharyngeal cancer. With Edmund Mroz, PhD, he has developed a way to use DNA sequencing of tumors to measure differences among cancer cells within individual tumors. Their work indicates that such "intra-tumor heterogeneity" contributes to poor outcomes in head and neck cancer.

4. Konstantina Stankovic, MD, PhD, in collaboration with Anantha P. Chandrakasan, PhD from the Massachusetts Institute of Technology, was the first to have extracted energy from the biologic battery in the inner ear to power electronics without damaging hearing. This sets the stage for future autonomous sensing of key molecules in the inner ear and its vicinity to establish diagnosis and guide therapy.

Key Achievements/Publication Highlights for 2012

Pathology

David N. Louis, MD, Chief

1. ENCODE Project Consortium, Dunham I, Kundaje A, Aldred SF, Collins PJ, Davis CA, Doyle F, Epstein CB, Frietze S, Harrow J, Kaul R, Khatun J, Lajoie BR, Landt SG, Lee BK, Pauli F, Rosenbloom KR, Sabo P, Safi A, Sanyal A, Shoresh N, Simon JM, Song L, Trinklein ND, Altshuler RC, Birney E, Brown JB, Cheng C, Djebali S, Dong X, Dunham I, Ernst J, Furey TS, Gerstein M, Giardine B, Greven M, Hardison RC, Harris RS, Herrero J, Hoffman MM, Iyer S, Kelllis M, Khatun J, Kheradpour P, Kundaje A, Lassman T, Li Q, Lin X, Marinov GK, Merkel A, Mortazavi A, Parker SC, Reddy TE, Rozowsky J, Schlesinger F, Thurman RE, Wang J, Ward LD, Whitfield TW,Wilder SP, Wu W, Xi HS, Yip KY, Zhuang J, Bernstein BE, et al. An integrated encyclopedia of DNA elements in the human genome. Nature. 2012; 489: 57-74.

This paper provides an overview of the Encyclopedia of DNA Elements (ENCODE) project, conducted by a consortium of labs including a major center focused on epigenomics led by Bradley Bernstein of MGH Pathology and the Broad Institute. The results of this large-scale project will provide a genome-wide resource that encompasses functional elements involved in the regulation of gene expression.

2. Lau KS, Cortez-Retamozo V, Philips SR, Pittet MJ, Lauffenburger DA, Haigis KM. Multi-scale in vivo systems analysis reveals the influence of immune cells on TNF-a-induced apoptosis in the intestinal epithelium. PLoS Biol. 2012; 10(9): e1001393.

This report describes the identification of an intercellular communication network in which epithelial cells and immune cells cooperate in the gut to control the response to TNF-a, a pro-inflammatory cytokine. More broadly, this work illustrates that applying computational modeling approaches to mouse models of disease is a powerful way to uncover how cells work together to maintain normal tissue homeostasis.

3. Reyon D, Tsai SQ, Khayter C, Foden JA, Sander JD, Joung JK. FLASH assembly of TALENs for high-throughput genome editing. Nat Biotechnol. 2012; 30:460-5.

In this paper, high-efficiency targeted alteration of 84 human genes important for human cancer and epigenetics was performed using TALENs assembled using a novel high-throughput strategy known as FLASH. This large-scale experiment conclusively demonstrates that TALENs are a highly robust technology that can be used to target ANY desired gene or sequence of interest with high efficiency. The FLASH platform will enable and spur high-throughput, genome-scale functional analysis of sequence variants in human cells and other model organisms, thereby accelerating our discovery and understanding of disease-associated gene mutations.

4. In vivo imaging of tumor-propagating cells, regional tumor heterogeneity, and dynamic cell movements in embryonal rhabdomyosarcoma. Ignatius MS, Chen E, Elpek NM, Fuller AZ, Tenente IM, Clagg R, Liu S, Blackburn JS, Linardic CM, Rosenberg AE, Nielsen PG, Mempel TR, Langenau DM. Cancer Cell. 2012; 21(5):680-93.

This publication highlights the diversity of cellular phenotypes within cancer cells and suggests that relapse-driving cells need not be the metastatic cell type in cancer. Moreover, this work is one of the first to directly visualize tumor cells within the context of the normal microenvironment using fluorescent transgenic approaches to label cells based on differentiation status.

Pediatrics

Ronald E. Kleinman, MD, Chief

1. Whalen, Michael: Determined the previously unknown mechanisms that transduce necrotic cell death downstream of RIPK1 following traumatic brain injury.

Dr. Whalen's group determined the previously unknown mechanisms that transduce necrotic cell death downstream of RIPK1 following traumatic brain injury. They showed that Akt and mTOR inhibition dramatically reduce cell death following TBI opening up novel opportunities to interfere with brain injury following trauma.

2. Stuart, Lynda: Rathinam VA, Vanaja SK, Waggoner L, Sokolovska A, Becker C, Stuart LM, Leong JM, Fitzgerald KA, TRIF Licenses Caspase-11-Dependent NLRP3 Inflammasone Activation by Gram-Negative Bacteria. Cell. 2012; 150 (3); 606-19.

This work, a collaboration with the Fitzgerald Lab at UMass describes a previously unknown and important link between two pathways of immune sensing and established the mechanisms underlying detection and response to enteropathogens. Dr. Stuart's lab contributed critical experiments to understand the role of phagocytes in this process. These pathways provide new opportunities for enhancing defenses against enteropathogen invasion.

3. Misra, Madhusmita: Ackerman, KE, Slusarz K, Guereca G, Pierce L, Slattery M. Mendes, N, Herzog DB, Misra M. Am J Physiolo Endocrinol Metab. 2012 Apr 1:302 (7): E800-6.

This study demonstrates for the first time that nocturnal ghrelin and leptin concentrations determine LH pulsatility patterns in adolescent and young adult female athletes and provides the missing link between energy status and LH pulsatility patterns, thus providing new opportunities for approaches to health issues related to body weight and fertility.

4. Boyce, Joshua A: Giannattasio G, Ohta S, Boyce JR, Xing W, Balestrieri B, Boyce JA. J Immunol. 2011 Aug 1; 187(3): 1486-95. doi: 10.4049/jimmunol.1003669

Dr. Boyce and his group determined that purinergic receptors and prostaglandin E2 play important roles in allergic pathophysiology. These discoveries continue to refine our understanding of the mechanisms by which environmental allergens induce inflammatory reactions and open new pathways for potential therapeutic interventions.

Key Achievements/Publication Highlights for 2012

Psychiatry

Jerrold F. Rosenbaum, MD, Chief

1. Castro VM, Gallagher PJ, Clements CC, Murphy SN, Gainer VS, Fava M, Weilburg JB, Churchill SE, Kohane IS, Iosifescu DV, Smoller JW, Perlis RH. Incident user cohort study of risk for gastrointestinal bleed and stroke in individuals with major depressive disorder treated with antidepressants. BMJ Open. 2012 Mar 30;2(2):e000544.

Antidepressants are among the most widely used medications in the United States.The authors applied informatic data mining techniques to electronic health records (EHRs) in the Partners HealthCare system to address the question of whether antidepressants raise the risk for hemorrhagic and vascular adverse events. In a cohort of more than 36,000 patients with depression treated with antidepressants, they found a significant increase in the risk of GI bleeding and stroke that was associated with affinity of the antidepressant drugs for the serotonin transporter. These results provide important information for clinical decision making and the risk-benefit ratio of different classes of antidepressants and demonstrate the utility of large-scale EHR-based analyses for pharmacovigilance research.

2. Holmes AJ*, Lee PH*, Hollinshead M, Bakst L, Roffman JL, Smoller JW, Buckner RL. Individual differences in amygdala-medial prefrontal anatomy link negative affect, impaired social functioning, and polygenic depression risk. Journal of Neuroscience (in press). *Co-first authors.

Investigators in the MGH Department of Psychiatry, led by Randy Buckner (Director of Psychiatric Neuroimaging) and Jordan W. Smoller (Director of Psychiatric Genetics) have launched the MGH Brain Genomics Superstruct Project (GSP). Over a 4 year period, the GSP has collected the largest single resource (>3500 individuals) with structural and functional MRI data, quantitative measures of neurocognitive and affective traits, DNA and genomewide genotyping. This paper represents the first publication from the GSP combining neuroimaging and genetic methods to examine the biological basis of mood and anxiety-related phenotypes.

3. Holt DJ, Coombs G, Zeidan MA, Goff DC, Milad MR. Failure of neural responses to safety cues in schizophrenia. Arch Gen Psych 2012; 69: 893-903. PMID: 22945619

This paper describes the first demonstration of changes in brain function during fear extinction memory, or “safety signaling”, in schizophrenia. Earlier (Holt et al, 2009) we showed that fear extinction memory is impaired in schizophrenia for the first time; the current study replicates that result and identifies the neural basis of this abnormality—dysfunction of the ventromedial prefrontal cortex. Generally, this study provides some of the first quantitative evidence for impaired emotional function in schizophrenia, linked to the presence of active delusions. This type of objective biomarker will be useful in future clinical studies, for following treatment responses and detecting psychosis early or before the onset of the full syndrome

4. Jensen KB, Kaptchuk TJ, Kirsch I, Raicek J, Lindstrom KM, Berna C, Gollub RL, Ingvar M, Kong. Nonconscious activation of placebo and nocebo pain responses. J.Proc Natl Acad Sci U S A. 2012 Sep 25;109(39):15959-64. PMID:23019380

Both placebo and nocebo effects are important research issues with broad clinical implications for human self-healing and self-harming. In this study, we found that the mechanisms responsible for placebo and nocebo effects can operate without conscious awareness of the triggering cues. The results provide a unique experimental verification of the influence of nonconscious conditioned stimuli on placebo/nocebo effects and it challenges the exclusive role of awareness and conscious cognitions in placebo and nocebo responses.

Radiation Oncology

Jay S. Loeffler, MD, Chief

1. Stylianopoulos T, Martin JD, Chauhan VP, Jain SR, Diop-Frimpong B, Bardeesy N, Smith BL, Ferrone CR, Hornicek FJ, Boucher Y, Munn LL, Jain RK. Causes, consequences, and remedies for growth-induced solid stress in murine and human tumors. Proceedings of the National Academy of Science U S A. 2012, Sep 18;109(38):15101-8.

This study identified components responsible for therapy-blocking solid stress and suggested therapeutic strategies. Abnormal blood and lymphatic vessels cause fluids to accumulate, and the uncontrolled proliferation of cancer cells within limited space leads to the buildup of what is called solid stress. Both types of pressure can interfere with the effectiveness of anticancer drugs, but while strategies have been developed that reduce fluid pressures, little has been known about the impact of solid stress or potential ways to alleviate it. Our research team has identified factors that contribute to solid stress within tumors, suggesting possible ways to alleviate it, and has developed a simple way to measure such pressures.

2. Science of Oncology Award to Dr. Rakesh Jain

Created in 2005, the Science of Oncology Award and Lecture is presented annually by the American Society of Clinical Oncology in recognition of a recipient's outstanding contributions to basic or translational research in cancer. Dr. Rakesh Jain is the 2012 recipient in recognition of his lifetime's dedication and substantial contributions to cancer biology and translational oncologic research.

3. Chauhan VP, Stylianopoulos T, Martin JD, Popovic Z, Chen O, Kamoun WS, Bawendi MG, Fukumura D, Jain RK. Normalization of tumour blood vessels improves the delivery of nanomedicines in a size-dependent manner. Nature Nanotechnology. 2012, Apr 8;7(6):383-8.

Combining two strategies designed to improve the results of cancer treatment—antiangiogenesis drugs and nanomedicines—may only be successful if the smallest nanomedicines are used. This report in Nature Nanotechnology showed that normalizing blood vessels within tumors, which improved the delivery of standard chemotherapy drugs, can block the delivery of larger nanotherapy molecules.

4. Kodack DP, Chung E, Yamashita H, Incio J, Duyverman AM, Song Y, Farrar CT, Huang Y, Ager E, Kamoun W, Goel S, Snuderl M, Lussiez A, Hiddingh L, Mahmood S, Tannous BA, Eichler AF, Fukumura D, Engelman JA, Jain RK. Combined targeting of HER2 and VEGFR2 for effective treatment of HER2-amplified breast cancer brain metastases. Proceedings of the National Academy of Science U S A. 2012, Oct 15 [Epub ahead of print].

Adding an angiogenesis inhibitor to treatment with a HER2-inhibiting drug could improve outcomes for patients with HER2-positive breast cancer who develop brain metastases. In this paper published online in PNAS Plus, we report the first preclinical study combining antiangiogenic and anti-HER2 drugs in an animal model of brain metastatic breast cancer. This has led to the initiation of a clinical trial combining lapatinib, trastuzumab and bevacizumab in breast cancer patients with brain metastases at MGH.

Ragon Institute of MGH, MIT & Harvard

Bruce D. Walker, MD, Director

1. Chen H, Ndhlovu ZM, Liu D, Porter LC, Fang JW, Darko S, Brockman MA, Miura T, Brumme ZL, Schneidewind A, Piechocka-Trocha A, Cesa KT, Sela J, Cung TD, Toth I, Pereyra F, Yu XG, Douek DC, Kaufmann DE, Allen TM, Walker BD. TCR clonotypes modulate the protective effect of HLA class I molecules in HIV-1 infection. Nat Immunol. 2012 Jun 10; 13(7):691-700. doi: 10.1038/ni.2342. PubMed PMID: 22683743.

Some remarkable persons maintain durable control of HIV without the need for medications. In previous studies (Pereyra et al, Science 2010) we showed that 20% of the variability in viral load is due to host genetics, namely a surface molecule called HLA class I that allows the immune system to recognize infected cells. Here we show that viral load is strongly influenced by the nature of the T cell receptors on killer cells from infected persons. These receptors recognize the infected cells by seeing viral peptides in the HLA binding groove. The actual T cell clonotypes in controllers include a population that is highly efficient not only at recognizing HIV, but also variations in the virus that may occur in vivo. These results build on a previously funded Gates Foundation grant to study so-called "elite controllers" and have led to a newly acquired $12M grant from the Gates Foundation to support this work both in Boston and at our site in South Africa.

2. Dudek TE, No DC, Seung E, Vrbanac VD, Fadda L, Bhoumik P, Boutwell CL, Power KA, Gladden AD, Battis L, Mellors EF, Tivey TR, Gao X, Altfeld M, Luster AD, Tager AM, Allen TM. Rapid evolution of HIV-1 to functional CD8? T cell responses in humanized BLT mice. SciTransl Med. 2012 Jul 18;4(143):143ra98. PubMed PMID: 22814851.

While the development of mouse/human chimeras holds great promise to facilitate the study of human immunity to pathogens, little data exist regarding how well immune responses in these mice accurately reflect those seen in humans. Humanized BLT (bone marrow, liver, thymus) mice infected with HIV demonstrated HIV-specific CD8+ T cell responses that closely resemble those in humans in terms of their specificity, kinetics, immunodominance, and ability to drive viral escape. Mice expressing the protective HLA-B*57 allele also exhibited enhanced control of viral replication through immune targeting of the same conserved regions of HIV Gag that are critical to its control of HIV in humans, revealing their ability to accurately re-capitulate human pathogen–specific immunity and the fundamental immunological mechanisms required to control a model human pathogen. This work led to the successful application by a team of researchers led by Dr. Todd Allen of the Ragon Institute for a 5-year, $12.4 million HIV Vaccine Research and Design (HIVRAD) award from the National Institutes of Health (NIH).

3. Lindqvist M, van Lunzen J, Soghoian DZ, Kuhl BD, Ranasinghe S, Kranias G, Flanders MD, Cutler S, Yudanin N, Muller MI, Davis I, Farber D, Hartjen P, Haag F, Alter G, Schulze zurWiesch J, Streeck H. Expansion of HIV-specific T follicular helper cells in chronic HIV infection. J Clin.Invest. 2012 Sep 4;122(9):3271-80. doi: 10.1172/JCI64314. Epub 2012 Aug 27. PubMed PMID: 22922259; PubMed Central PMCID: PMC3428098.

HIV targets CD4 T cells, which are required for the induction of protective antibody responses and the formation of long-lived B cell memory. The depletion of HIV-specific CD4 T cells during HIV infection is therefore believed to impede the development of protective B cell immunity. Although several different HIV-related B cell dysfunctions have been described, the role of CD4 T follicular helper (TFH) cells that largely reside in lymph nodes has been unknown. Here, we assessed HIV-specific TFH responses in the lymph nodes of treatment-naive and antiretroviral-treated HIV-infected individuals. Strikingly, both the bulk TFH and HIV-specific TFH cell populations were significantly expanded in chronic HIV infection and were highly associated with viremia. In particular, our study suggests that high levels of HIV viremia drive the expansion of TFH cells, which in turn leads to perturbations of B cell differentiation, resulting in dysregulated antibody production. This work contributed to our receiving a seven year NIH grant for HIV vaccine discovery that began in July 2012.

4. Certificate of Occupancy for Ragon Institute Building

The Ragon Institute was established to foster cross-disciplinary interactions among clinicians, immunologists, vaccinologists, engineers, physical scientists and computational biologists. In May construction began on a new facility to house the Ragon Institute, located adjacent to the MIT campus in Tech Square. This 70,000 square foot facility includes a state of the art BL3 containment facility for working on TB and HIV, imaging facilities to track immune responses in vivo, a large specimen processing laboratory for preservation of human samples, ample laboratory space at BL2 containment for working on HIV, and a large auditorium. On December 14, 2012 we received the occupancy certificate, and we will move the entire Institute to these new facilities in January 2013.

Key Achievements/Publication Highlights for 2012

Surgery

Keith Lillemoe, MD, Chief

BURNS

RONALD TOMPKINS, MD, DIVISION CHIEF

1. Inflammation and the Host Response to Injury: Large-Scale Collaborative Research Program

Our "Glue Grant" research program in injury investigates the innate inflammatory response to improve our systems level understanding of the key regulatory elements, and their relative roles and importance that drive the host's response to serious injury and its accompanying severe systemic inflammation. The collaborative research program utilizes high throughput genomic/proteomic and bioinformatics approaches to determine the total cellular proteome and genome-wide expression profiles of the innate inflammatory response to injury to illuminate further the mechanisms orchestrating the post-injury clinical course of trauma and burn patients. Findings from our program have broad application to virtually all surgical patients, as the innate immune system is central to the field of transplantation and for the pathogenesis of post-operative sepsis and infections in all surgical populations. Accumulated data from our large-scale collaborative research program allowed us for the first time to compare the leukocyte transcriptome in murine models of trauma, burn, and endotoxin challenge with the human diseases they are designed to mimic. We showed in a rigorous systematic evaluation that, in humans, different severe inflammatory stresses produce similar genomic responses. Importantly, these genomic responses are not reproduced in mouse disease models. To further support this conclusion, we analyzed multiple datasets of other acute inflammatory diseases, and found the same lack of correlation between human and mouse responses. Taken together, this article demonstrates fundamental differences between the human and mouse in the response to acute inflammation, and supports a shift of focus to newer methods of studying complex human conditions like inflammatory disease, rather than relying on mouse models. Seok J, Warren HS, Cuenca AG, Mindrinos MN, Baker HV, Xu W, Richards DR, McDonald-Smith GP, Gao H, Hennessy L, Finnerty CC, López MC, 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, Storey JD, Cobb JP, Rahme LG, Lowry SF, Maier RV, Moldawer LL, Herndon DN, Davis RW, Xiao W, Tompkins RG, and the 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. USA. Forthcoming 2012.

2. Center for Medical Innovations at the MGH

We have established a new Center within MGH to provide a multi-disciplinary environment within which multiple departments can interact to create important, new innovations relevant to clinical medicine. These innovations are intended to improve the quality and content of information upon which clinicians make diagnostic and therapeutic decisions. It is highly likely that these innovations will also improve the efficiency and/or cost-effectiveness of hospital functions and activities. When fully developed, it is intended that such projects might touch most all departments within the MGH, including Surgery, Psychiatry, Nuclear Medicine, Pathology, Internal Medicine, Urology, Neurology, Dermatology, and Pediatrics. In one of the innovation center projects enabled by two very powerful intellectual property innovations by our group, we have developed and initially validated a point-of-care device that uses 500 microliters of whole blood to perform a simultaneous, multiplexed panel of hematology and microchemistry tests and selected immunological tests. Very recently, the project team has finalized the designs for the micro-flow cytometry and photometry modules. These modules demonstrate performance metrics relative to large-scale laboratory equipment with the analytical results showing equivalence to that of full-scale systems. The team is completing the integration of

the two modules to combine them into a single, full-automated unit capable of performing a complete blood count with a 5-part differential, 15 microchemistries, and selected immunological tests, with the results available in the Electronic Medical Record within 15 minutes. Two project milestones for further validation are underway. The first is a clinical validation study to compare the accuracy of our results with those of the MGH Central Laboratory using split samples from 300 patients. The second is a clinical impact study to test our assay panel in a MGH clinical setting with prior point-of-care systems experience such as the Emergency Department or one of the oncology units.

3. P50 Burns Research Center

Very recently, the Burns Research Center has been competitively renewed through 2017 to study the effects of systemic inflammation upon the metabolic response of the host to burn injury. Within the Center, we take advantage of very new genomic data and its analyses, and computational biology methods from the NIGMS-funded Glue Grant Program, "Inflammation and the Host Response to Injury" to study the innate inflammatory response postburn injury and its influence upon metabolism. To date, investigators, including our own, have focused on single molecules or individual pathways with excellent, but limited, impact upon hypermetabolism, hyperglycemia, catabolism, a shift from carbohydrate to fatty acid oxidation, and muscle wasting. Many of the research methods and interventions studied, including stable isotope steady-state kinetics, nutrient supplementation, and anabolic agent administration yielded important, but limited improvements. The Center takes into account, in addition to its primarily traditional approaches, new systematic genome-wide technologies to understand the global impact of burn injury on metabolism. Rather than looking at single molecules or pathways, with the successful completion of our projects, new mechanistic-based therapies to enhance skeletal muscle insulin sensitivity might promote an anabolic state, restoring nutrient flux to a level compatible with an optimal and uncomplicated recovery from burn injury. We will develop or employ several novel methodologies, tools, and technologies to explore the inflammatory-induced changes in skeletal muscle metabolism after burn injury.

- A library of antibodies directed against specific phosphoserine sites of Irs1/2
- Unique knockin/knockout technologies to create transgenic murine models
- Availability of a uniquely designed murine transcriptome microarray with exon level expression, alternative splicing, and single nucleotide polymorphisms
- Development of a systems biology-based genomic modeling approach to postburn metabolism
- Specific SIRT1 and GSK-3beta inhibitors not previously used in burns
- The tetra peptide SS31 (D-Arg-Dmt-Lys-Phe-NH2) that scavenges ROS, reduces mitochondrial reactive oxygen species production, inhibits mitochondrial permeability transition, and enhances insulin sensitivity
- Availability of human skeletal muscle tissues after burn injury for future studies
- Availability of a human genome-wide transcriptome database of skeletal muscle after burn injury
- Development of morpholinos (PMO), molecules in a particular structural family used to modify gene expression by an antisense technology (small (~25 base) regions of the base-pairing surfaces of RNA) that has been approved for human use
- Development of a web-based portal for data and knowledgebase as central community resource.

4. Center for Engineering in Medicine

The mission of the Center for Engineering in Medicine is twofold: first, to train MDs, PhDs, and predoctoral students in the fundamentals of biomedical engineering; and second, to bring the principles

and tools of biomedical engineering to the forefront of biomedical research and patient care. The focus at the CEM is neither on a single disease nor on a single group of technologies. Instead, vitality springs from creating novel applications using the tools of disparate disciplines ranging from molecular biology and biochemistry to engineering design and analysis. These technologies are being applied to "thrust areas" in applied immunology, artificial organ development, biopreservation, cancer diagnosis, metabolic engineering, stem cell bioengineering, genomics and proteomics, microfabrication and nanotechnology, drug delivery, and tissue repair. Drug-induced hepatotoxicity is the most common cause of death due to acute liver failure and is a significant public health problem (~10% of all adverse drug reactions, >50% of all cases of acute liver failure, and ~1% of all general medical admissions in the U.S. annually), as well as a major barrier to drug development (~40% of drug candidate failures). Unfortunately, treatments remains limited to withdrawal from the offending drug, supportive care, and transplantation. Our recent publication offers a new way to significantly reduce drug toxicity incidents. By uncovering a previously unappreciated mechanism involved with liver toxicity, the authors use their insights to propose new methods for prevention, treatment, and rescue of hepatotoxicity. Specifically, the authors describe a pharmacological strategy that targets gap junction communication thereby preventing hepatotoxicity related morbidity and mortality. This strategy of inhibition of toxicity could transform current limitations in drug dosing, especially for applications involving cancer chemotherapy and the many drugs used in the ICU. In addition, the gap junction propagation mechanism detailed in this paper may help explain the progression of chronic inflammation and nonalcoholic steatohepatitis in the liver into cirrhosis and hepatocellular carcinoma. The article was carried by numerous news sources throughout the world, and has been recommended as a "must read" by the Faculty of 1000. Patel SJ, Milwid JM, King KR, Stefan Bohr S, Iracheta-Velle A, Matthew Li M, Vitalo A, Parekkadan B, Jindal R, Yarmush ML. Gap junction inhibition prevents drug-induced liver toxicity and fulminant hepatic failure. Nat. Biotechnol. 2012; 30: 179–183.

CARDIAC SURGERY

THORALF M. SUNDT, MD, DIVISION CHIEF

1. First successful protocol to induce tolerance in nonhuman primate recipients of heart allografts

Tolerance has been achieved in nonhuman primates (NHPs) and human recipients of kidney allografts, but it has never been achieved in NHP (or human) recipients of heart allografts…until now. By co-transplanting both organs, we have exploited the tolerogenic potential intrinsic to kidney allografts and achieved long term, rejection-free survival of heart allografts in NHPs recipients for the first time. We now plan to identify the renal element responsible for conferring tolerance to co-transplanted heart allografts in order to develop protocols aimed at inducing tolerance in recipients of solitary heart allografts and other tolerance-resistant organs including lung, islets, and vascularized composite allografts.

2. Liu w, Xiao X, Demirci G, Madsen JC, Li XC. The innate NK cells and macrophages recognize and reject allogeneic non-self in vivo via different mechanisms. Journal of Immunology 2012;188:2703-11.

We show that alloantigen-primed and CD4(+) T cell-helped macrophages (licensed macrophages) exhibit potent regulatory function in vivo in an acute graft-versus-host disease model. Together, our data uncover an important role for macrophages in the alloimmune response and may have important clinical implications.

3. Yamada Y, Boskovic S, Putheti P, Murakami T, Aoyama A, Smith RN, Ochiai T, Nadazdin O, Boenisch O, NajafianN, Bhasin MK, Colvin RB, Madsen JC, StromTB, Sachs DH, BenichouG, Cosimi AB, Tatsuo K. Overcoming memory T cell responses for induction of delayed tolerance in nonhuman primates. American Journal of Transplantation 2012;12:330-40.

Here, we show that such "delayed tolerance" can be induced in nonhuman primates through the mixed chimerism approach, if specific modifications to overcome/avoid donor-specific memory T-cell responses are provided. This expands the utility of this strategy to recipients of deceased donor

4. HirohashiT, Chase CM,Della Pelle P,Sebastian D, Alessandrini A, Madsen JC, Russell PS,Colvin RB. A novel pathway of chronic allograft rejection mediated by NK cells and alloantibody.American Journal of Transplantation 2012;12:313-21.

We show that antibody mediates CAV through NK cells, by an Fc dependent manner. This new pathway adds to the possible mechanisms of chronic rejection and may relate to the recently described C4d-negative chronic antibody-mediated rejection in humans.

CENTER OF LARYNGEAL SURGERY AND VOICE REHABILITATION

STEVEN M. ZEITELS, MD, DIRECTOR
ROBERT E. HILLMAN, PhD, CO-DIRECTOR/RESEARCH DIRECTOR

1. Zeitels, S.M., Wain, J.C., Barbu, A.M., Bryson, P.C., Burns J.A. Aortic Homograft Reconstruction of Partial Laryngectomy Defects: A New Technique. Annals Of Otology, Rhinology And Laryngology. Annals of Otology, Rhinology, and Laryngology 2012; 121(5): 301-306.

Wide-field transcervical partial-laryngectomy (TPL) often precludes tracheotomy decannulation and is done infrequently today. This is primarily due to the popularity of chemotherapy-radiotherapy treatment regimens and limited enthusiasm for TPL after failed radiotherapy. We developed a new reconstructive technique that would provide an alternative to total laryngectomy in a majority of patients. Cryopreserved aortic homograft soft tissue provides the laryngeal cancer surgeon with a new, reliable, and versatile single-stage reconstructive option for performing wide-field partial laryngectomy, while allowing for preservation of voice, an adequate airway caliber, and aerodigestive function. Healing and incorporation of the aortic homograft have been excellent, even if placed in irradiated soft tissues. Apart from excellent functional patient outcomes, technical advantages of this approach include: 1. the mechanical properties of the soft-tissue graft substrate as a scaffold for the airway, 2. the lack of graft immunogenicity, 3. the practical incorporation of the aortic homograft into local soft tissues, and 4. the ease of surgical handling of the graft. We are optimistic that a wide variety of surgical uses for cryopreserved arterial homografts as an organic soft-tissue substrate will likely evolve given the evidence herein.

2. D. D. Mehta, M. Zañartu, S. W. Feng, H. A. Cheyne II, R. E. Hillman. (2012). 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 first-ever use of a smartphone as the data collection and control platform for ambulatory monitoring of voice use. The monitoring aspect of this approach is conceptually similar to other types of wearable diagnostic devices (e.g., Holter/cardiac, pH probe, etc.) that are used to identify abnormalities in body function that may occur as patients go about their normal daily routine, but which might not be detectable during a brief clinical examination. This work is primarily motivated by how difficult it is in a clinical setting to accurately assess/characterize the faulty and/or abusive daily patterns of vocal behavior that are associated with many common voice disorders. The work described here is a logical extension of our group's development of the first commercially-available clinical voice ambulatory monitor approximately 10 years ago.

Key Achievements/Publication Highlights for 2012

CODMAN CENTER FOR CLINICAL EFFECTIVENESS

MICHAEL HUTTER, MD, DIRECTOR
DAVID SHAHIAN, MD, ASSOCIATE DIRECTOR

1. Development of a unified, national Bariatric Data Collection Program: The MBSAQIP (Metabolic and Bariatric Surgery Accreditation and Quality Improvement Program.)

Dr. Hutter is the architect of a Bariatric Data Collection Program for the American College of Surgeons. Over the past year, he and his colleagues have worked to create a unified national Bariatric Accreditation Program—the MBSAQIP. Now all accredited centers (over 700 hospitals) across the country are using this bariatric specific, risk-adjusted, prospective data collection system which tracks outcomes following bariatric surgical procedures over time, including complications and effectiveness.

2. Shahian DM, Nordberg P, Meyer GS, Blanchfield BB, Mort EA, Torchiana DF, Normand SL. Contemporary Performance of U.S. Teaching and Nonteaching Hospitals. Acad Med. 2012 Jun;87(6):701-8

This study analyzed aggregate, publicly reported data on a variety of process, structure, and outcomes metrics, stratified by teaching intensity. Major academic centers had significantly better performance for many outcomes and safety measures, but had generally higher readmission rates and lower scores on individual patient satisfaction indicators. In an era when the incremental value of academic medical centers is often challenged, particularly in view of their increased costs, their generally superior clinical and safety performance is an important finding.

3. Shahian DM, He X, Jacobs JP, Rankin JS, Welke KF, Filardo G, Shewan CM, O'Brien SM.The Society of Thoracic Surgeons Isolated Aortic Valve Replacement (AVR) Composite Score: A Report of the STS Quality Measurement Task Force. Ann Thorac Surg. 2012 Dec;94(6):2166-71

This is the second of a planned series of composite performance measures for cardiac surgery, with the expectation that one new measure will be publicly reported on a voluntary basis each year. Composite measures are increasingly preferred as performance metrics, as they provide multidimensional quality assessment in an easy-to-understand format for consumers. STS has several years experience with a peer-reviewed, NQF-endorsed composite scoring system for CABG. The AVR composite measure is similar in principle and consists of two outcomes domains: risk-standardized operative mortality and the any-or-none occurrence of any of five major complications of heart surgery--stroke, reoperation, sternal infection/mediastinitis, renal failure, or prolonged ventilation

4. Shahian DM, Normand S-LT. Autonomy, beneficence, justice, and the limits of provider profiling. J Am Coll Cardiol. 2012 Jun 19;59(25):2383-6

This editorial responds to an article advocating the position that cardiologists have an ethical obligation to refer patients only to the surgeon with the lowest risk-adjusted mortality rates. We demonstrate the methodological limitations inherent in identifying the "lowest mortality surgeon", and the problems with using mortality alone as the sole criterion for provider selection. These arguments are discussed in an ethical framework of patient autonomy, beneficence, and justice.

GENERAL SURGERY

DAVID RATTNER, MD, DIVISION CHIEF

1. A Pilot Study of Laparoscopy-Assisted Transanal Endoscopic Rectosigmoid Resection for Rectal cancer (Protocol DFCI 10-409, clinicaltrials.gov identifier # NCT01340755).

Over the last 5 years, our MGH research group has standardized a technique of transanal endoscopic rectosigmoid resection with TME, and transitioned from swine to human cadavers to the first clinical case performed for rectal cancer using laparoscopic assistance. In May 2012, we completed accrual for a DFCI IRB-approved pilot study of transanal endoscopic rectosigmoid resection with laparoscopic assistance in 5 subjects with stage I and IIA rectal cancer. The preliminary oncologic safety of this approach for both node negative and node positive resectable rectal cancer was demonstrated. The results were submitted for publication and will serve as the basis for a larger Phase II multicenter Phase II study.

2. Successful competitive renewal of NIH/NCI P01 CA117969, 'Genetics and Biology of Pancreatic Duct Adenocarcinoma, through 2015.

This project focuses on the mechanisms governing the genesis, progression, and maintenance of pancreatic ductal adenocarcinoma; its central goal is to understand the genetics and biology of this malignancy in sufficient depth to inform the development of effective targeted therapies. Valsangkar NP, Ingkakul T, Correa-Gallego C, Mino-Kenudson M, Lillemoe KD, Fernández-del Castillo C, Warshaw AL, Liss AS, Thayer SP. Survival in ampullary cancer: potential role of different KRAS mutations. Surgery, in press. This paper identifies a subset of ampullary cancers that behave like pancreatic adenocarcinoma. It establishes that a particular mutation, KRASG12D, may identify patients destined to have poor prognoses, and that not all KRAS mutations have an effect on ampullary tumor biology.

3. Intestinal Alkaline Phosphatase Prevents Antibiotic-Induced Susceptibility to Enteric Pathogens

Sayeda Nasrin Alam, MD, Halim Yammine, MD, Omeed Moaven, MD, Rizwan Ahmed, MD, Angela K. Moss, MD, Brishti Biswas, BS, Nur Muhammad, MD, Rakesh Biswas, BS, Atri Raychowdhury, Kanakaraju Kaliannan, MD, Sathi Ghosh, MD, Madhury Ray, MD, Sulaiman Hamarneh, MD, Soumik Barua, Nondita S. Malo, Atul K. Bhan, Madhu S. Malo, MD, and Richard A. Hodin, MD Our major discovery (manuscript submitted and the work was presented at the 2012 American College of Surgeons meeting) is that oral IAP therapy in antibiotic treated mice can prevent c difficile colitis.

4. Nehs MA, Nucera C, Nagarkatti SS, Sadow PM, Morales-Garcia D , Hodin RA, and Parangi S. : Late intervention with anti BRAFV600E therapy induces regression in an orthotopic mouse model of human anaplastic thyroid cancer. Endocrinology. 2012 Feb;153(2):985-94. Epub 2011 Dec 27.PMID: 22202162

Most patients with anaplastic thyroid cancer present late and die within 6 months. Our lab over the last 4 years has made important strides in basic insights into mechanisms by which BRAF mutation leads to thyroid cancer invasion and aggressive behavior. This past year we showed that late intervention with the novel drug PLX4720 targeting the BRAF mutation leads to dramatic tumor shrinkage even when given very late. Based on our results patients with advanced thyroid cancer are having their tumors tested for mutant BRAF and two clinical trials have opened here at MGH and nationwide to treat patients with life threatening aggressive thyroid cancers recurrences with BRAF mutations with these new BRAF inhibitors.

LABORATORY FOR TISSUE ENGINEERING AND ORGAN FABRICATION

JOSEPH P. VACANTI, MD, DIRECTOR
CATHRYN SUNDBACK, SCD, ASSOCIATE DIRECTOR

1. Development of a permanent engineered ear implant

Work continues to address several challenges that prevent advancement of current experimental technologies for auricular cartilage engineering into clinical practice. Previously we have demonstrated the efficacy of a permanent metal framework embedded in a fibrous collagen scaffold in preserving

auricular shape during neocartilage maturation in a small nude animal model. In the past year, the studies were focused on assessing long-term stability of engineered ear-shaped cartilage in a large immunocompetent animal model. Stable neocartilage was demonstrated in sheep; neocartilage quality improved with increased implantation time. High-resolution imaging analysis was performed to understand the behavior of the wire framework within the engineered ear during the formation of new cartilage in the collagen matrix. New rapid prototyping fabrication processes were also investigated to promote tissue integration and achieve greater flexibility. To obtain a sufficient cell population for engineering an adult human ear sized construct, research continues to prevent primary auricular chondrocyte dedifferentiation during in vitro expansion. Promising results were demonstrated in immunocompromised and immunocompetent animal models.

2. Replacement Vascularized Skeletal Muscle for Craniomaxillofacial Reconstruction

Patients without functioning orbicularis oculi cannot close their eyelids and risk potential blindness. Engineered autologous skeletal muscle will eliminate the risks associated with allogeneic sources but must be highly vascularized and innervated to be functional. Previously, we demonstrated that vascular networks engineered in vitro within self-assembled 3D muscles readily anastomosed with the host vasculature in less than 24 hrs post-implantation. During the subsequent 14 days implantation, the engineered vasculature remodeled and matured to a leak-tight physiologic microvasculature. In the past year, the studies focused on demonstrating the impact of innervation on the engineered muscle. Neurite outgrowth from embryonic spinal cords successfully innervated the muscle constructs, inducing myofiber hypertrophy throughout the 3D muscle. An electrical stimulating bioreactor, designed to deliver neural-like electrical signals, was fabricated and fully tested. The average specific force generated by muscle constructs stimulated for 48 hrs was similar to the specific force generated by human orbicularis oculi muscles and was more than 100% greater than that of unstimulated muscle constructs.

PEDIATRIC SURGERY

JOSEPH P. VACANTI, DIVISION CHIEF
PATRICIA DONAHOE, MD, RESEARCH LAB DIRECTOR
DAVID T. MCLAUGHLIN, PhD, ASSISTANT RESEARCH LAB DIRECTOR

1. Lage K, Greenway SC, Rosenfeld JA, Wakimoto H, Gorham JM, Segrè AV, Roberts AE, Smoot LB, Pu WT, Pereira AC, Mesquita SM, Tommerup N, Brunak S, Ballif BC, Shaffer LG, Donahoe PK, Daly MJ, Seidman JG, Seidman CE, Larsen LA. Genetic and environmental risk factors in congenital heart disease functionally converge in protein networks driving heart development. PNAS 2012; 109 (35): 14035-40

Dr. Lage, in a close collaboration with the Seidman laboratory at Brigham and Woman's, integrated very large data bases from two separate patient cohorts on genetic and environmental risk factors present during 19 sequential phases of embryonic heart development, with protein networks known to drive heart developmental processes. His important analysis shows that a complex pattern of functional interactions between genomic variation and environmental exposures can modulate critical biological systems during heart development to induce congenital heart defects. These significant findings make it likely that similar interactions exist between risk factors responsible for or contributing to other complex birth defects that can now be studied using his unique methodologies.

2. Coron E, Auksorius E, Pieretti A, Mahe MM, Liu L, Steiger C, Bromberg Y, Bouma B, Teraney G, Neunlist M, Goldstein AM. Full-field optical coherence microscopy is a novel technique for imaging enteric ganglia in the gastrointestinal tract. Neurogastroenterol Motil. 2012 (12):e611-e621.

Neurointestinal diseases cause significant gastrointestinal morbidity, but the diagnosis of these conditions is limited by the need for intestinal biopsies, which are invasive and prone to sampling error. Moreover, standard histopathology is time-consuming and results can vary depending on conditions. Allan Goldstein and his collaborators designed this study as a first step toward developing optical microscopic imaging as a novel clinical tool for noninvasive imaging of the enteric nervous system. Full-field optical coherence microscopy (FFOCM) captures a thin optical section with very high lateral and transverse resolutions. Their group showed that FFOCM is able to image the myenteric plexus of the stomach, small intestine, and colon in mice. As a proof of principle, they used FFOCM to image the colorectum of a mouse model of Hirschsprung's disease and were able to identify consistently the aganglionic segment of distal colon as well as the hypoganglionic transition zone. Their findings demonstrate the potential for FFOCM to provide reliable noninvasive morphologic and quantitative assessment of the enteric nervous system in vivo.

3. Russell MK, Longoni M, Wells J, Maalouf FI, Tracy AA, Loscertales M, Ackerman KG, Pober BR, Lage K, Bult CJ, Donahoe PK. Congenital diaphragmatic hernia candidate genes derived from embryonic transcriptomes. PNAS 2012 Feb 21;109(8):2978-83.

Congenital diaphragmatic hernia (CDH), a common major congenital malformation, results in significant morbidity and mortality, for which the discovery of a CDH loci using standard genetic approaches has been hindered by its genetic heterogeneity. We hypothesized that gene expression profiling of developing embryonic diaphragms would identify genes likely to be associated with clinically relevant diaphragm defects. We generated a time series of whole-transcriptome expression profiles from laser captured embryonic mouse diaphragms during early and late diaphragm development. An integrative filtering strategy identified 27 possible gene candidates for CDH. Gene sets defining molecular pathways and temporal expression trends were intersected by bioinformatic algorithms, then compared with a manually curated list of genes previously shown to cause diaphragm defects in humans and in mouse models, knockout of one, Pbx1, which displayed a range of previously undetected diaphragmatic defects in a mouse knockout for one of these genes. Thus, genetic characterization of normal development can be used to prioritize genes responsible for CDH. This approach can be extended to other developmental anomalies, which fill 1/3 of beds in pediatric hospitals in the U.S..

4. Meirelles K, Benedict LA, Dombkowski D, Pepin D, Preffer FI, Teixeira J, Tanwar PS, Young RH, MacLaughlin DT, Donahoe PK, Wei X. Human ovarian cancer stem/progenitor cells are stimulated by doxorubicin but inhibited by Mullerian inhibiting substance. PNAS 2012 Feb 14;109(7):2358-63.

Women with late-stage ovarian cancer usually develop chemotherapeutic-resistant recurrence; it has been theorized that a rare cancer stem/progenitor cell is responsible. We have isolated from multiple ovarian cancer cell lines an ovarian cancer stem cell-enriched population marked by CD44, CD24, and Epcam (3+) and by negative selection for Ecadherin (Ecad-) that comprises less than 1% of cancer cells and has increased colony formation and shorter tumor-free intervals in vivo after limiting dilution. These cells are not only resistant to chemotherapeutics such as doxorubicin, but also are stimulated by it, as evidenced by the significantly increased number of colonies in treated 3+Ecad- cells. Similarly, proliferation of 3+Ecad- cells in monolayer increased with treatment by doxorubicin, compared with the unseparated or cancer stem cell-depleted 3-Ecad+ cells. However, these cells are sensitive to Mullerian inhibiting substance (MIS), which decreased colony formation. These results suggest that since chemotherapeutics may be stimulative to cancer stem cells, selective inhibition of these cells by treating with MIS or a recently deiscovered small molecule MIS mimetic should be considered in the development of therapeutics.

PLASTIC SURGERY

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

1. Bélanger E, Henry FP, Vallée R, Randolph MA, Kochevar IE, Winograd JM, Lin CP, Côté D. In vivo evaluation of demyelination and remyelination in a nerve crush injury model. Biomed Opt Express. 2011 Sep 1;2(9):2698-708. Epub 2011 Aug 24.

Nerves of the peripheral nervous system have, to some extent, the ability to regenerate after injury, particularly in instances of crush or contusion injuries. After a controlled crush injury of the rat sciatic nerve, demyelination and remyelination are followed with functional assessments and imaged both ex vivo and in vivo over the course of 4 weeks with video-rate coherent anti-Stokes Raman scattering (CARS) microscopy. A new procedure compatible with live animal imaging is developed for performing histomorphometry of myelinated axons. This allows quantification of demyelination proximal and remyelination distal to the crush site ex vivo and in vivo respectively.

2. 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. 2012 Nov 15. [Epub ahead of print]

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 birth defects. Detailed analysis of zebrafish palatogenesis revealed distinct mechanisms of palatal morphogenesis: extension, proliferation and integration. We show 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.

3. Leto Barone AA, Zhou ZY, Hughes MW, Park R, Schulman RM, Lee S, Vidar EN, Shiba TL, Weber EL, Cetrulo CL Jr. Lentiviral transduction of face and limb flaps: implications for immunomodulation of vascularized composite allografts. Plast Reconstr Surg. 2012 Feb;129(2):391-400.

Ex vivo introduction of an immunomodulatory transgene into a face or hand allograft may improve the risk-to-benefit ratio of vascularized composite allografts. Abrogation of the immunogenicity of the skin component of a face or hand allograft may decrease alloreactivity and permit the induction of immunologic tolerance. In this study, intradermal delivery of the transgenes proved superior to intravascular perfusion. Optimization of this gene-delivery approach may allow long-term, constitutive expression of immunomodulatory proteins in face and hand allografts. Future goals include replacement of the luciferase and eGFP reporter genes with key immunomodulatory proteins.

4. Lee JH, Kirkham JC, Nicholls A, McCormack MC, Randolph MA, Austen WG Jr. The Effect of Pressure and Shear on Fat Grafting, In press Plastic and Reconstructive Surgery

Fat grafting has become routine in Plastic surgery due to low donor site morbidity, 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. Higher aspiration pressures up to -0.83 atm did not affect fat grafts viability in vivo; however, the efficiency of graft harvest was improved. Positive pressure up to 6 atmospheres over time (up to 3 minutes) 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 shear stress is a more important variable regarding fat graft viability than pressure.

SURGICAL ONCOLOGY

KENNETH K. TANABE, MD, DIVISION CHIEF

1. Completed construction of a database that includes all 173,301 MGH cancer patients that have been entered in the Partners Tumor Registry between 1900 and 2010.

James Michaelson PhD completed construction of a database that includes all 173,301 MGH cancer patients that have been entered in the Partners Tumor Registry between 1900 and 2010. As far as we are aware, in terms of the total mass of data, this is the largest source of information on cancer treatment and outcome in the world. The databases contains 559,921 pathology reports, 575,204 discharge reports, 10,938,444 encounter notes, 304,211 operative reports, 22,009,527 procedure notes, 9,159,232 radiology reports. The database contains all-cause survival information from the Social Security Administration Death Master File (which provides information on all deaths of persons who were issued social security numbers since the inception of this system in 1937), and cause-of-death information from the Massachusetts Death Certificate Database (which contains international classification of disease cause of death information on 1,984,790 people who died in the state of Massachusetts between 1970 and 2008. The database contains TSI billing data for MGH patients from 2005 onward. This database is now being used by the sarcoma, urology, gynecological, head & neck, and breast cancer groups, as well as providing medical usage and cost data to the hospital administration. It is being analyzed by three MIT PhD students, in a collaborative project with the MIT CSAIL group. The data in this and other cancer databases managed by our group underlie the calculations provided by a series of 11 CancerMath.net web calculators, which are used by a very considerable fraction of patients in this country who have breast cancer, colon cancer, renal cell carcinoma, sarcoma, and melanoma. (Calculators for Prostate, Lung, and gynecological cancer are under envelopment.)

2. Mroz EA, Rocco JW. MATH, a novel measure of intratumor genetic heterogeneity, is high in poor-outcome classes of head and neck squamous cell carcinoma. Oral Oncol. 2012 Oct 15. doi:pii: S1368-8375(12)00297-7.10.1016/j.oraloncology.2012.09.007. [Epub ahead of print] PubMed PMID: 23079694.

James Rocco MD, PhD and his group tested a long-standing hypothesis about responses of tumors to treatment: patients with highly heterogeneous tumors, containing many cancer-cell populations, have worse outcomes than those having less heterogeneous tumors. A malignant tumor typically contains several different cancer-cell populations. For over 40 years researchers and clinicians have thought that having more cancer-cell populations gives a tumor more ways to evade therapy. This hypothesis has been difficult to test, because practical methods to measure this “intra-tumor heterogeneity” from biopsy specimens have only recently become available. The Rocco Lab developed a way to use Next Generation DNA sequence results to provide a quantitative measure of intra-tumor heterogeneity. This approach takes advantage of differences in mutation frequencies among the different genes within these tumors. Application of this method to a publicly available Next Generation sequence data from a diverse panel of 74 head and neck squamous cell carcinomas, revealed that 3 poor-outcome classes of head and neck cancer have high intra-tumor heterogeneity, supporting a relation of higher heterogeneity to worse outcome.

Key Achievements/Publication Highlights for 2012

THORACIC SURGERY

DOUGLAS J. MATHISEN, MD, DIVISION CHIEF

1. Our laboratory has reported the first successful induction of long-term transplantation tolerance in a non-human primate transplanted with a fully mismatched, functioning orthotopic lung allograft.

Our laboratory has reported the first successful induction of long-term transplantation tolerance in a non-human primate transplanted with a fully mismatched, functioning orthotopic lung allograft. This experimental animal is now over one year off of immunosuppression without any signs of graft rejection. Achieving transplantation tolerance in the clinical setting would be transformative in management and long-term success of solid organ transplantation.

2. Upscaling of decellularization to human heart (n=11) and lung (n=3), process development, validation and upscaling of human cardiomyocyte differentiation from human derived iPS cells and regeneration of functional human myocardium.

3. Lanuti M, Sharma A, Willers H, Digumarthy SR, Mathisen DJ, Shepard JA. Radiofrequency ablation for stage I non-small cell lung cancer: management of locoregional recurrence. Ann Thorac Surg. 2012 Mar;93(3):921-7; discussion 927-88.

This study characterizes the management of locoregional recurrence in patients with high-risk stage I non-small cell lung cancer (NSCLC) treated with lung radiofrequency ablation (RFA). This is the first study of its kind that investigated the use of SBRT after failed RFA.

4. Meltzer AJ, Veillette GR, Aoyama A, Kim KM, Cochrane ME, Wain JC, Madsen JC, Sachs DH, Rosengard BR†, Allan JS†. Donor brain death inhibits tolerance induction in miniature swine recipients of fully MHC-disparate pulmonary allografts. Am J Transplant, 2012;12:1290-5. Epub 2012 Feb 2.

This paper demonstrates that the inflammatory state of a graft influences its tolerogenicity. The development of clinical protocols that permit tolerance induction of such grafts is of critical importance, given that most harvested organs are obtained under less than ideal laboratory conditions.

TRANSPLANT SURGERY

JAMES F. MARKMANN, MD, PhD, DIVISION CHIEF

1. Yamada Y, Boskovic S, Aoyama A, Murakami T, Putheti P, Smith RN, Ochiai T, Nadazdin O, Koyama I, Boenisch O, Najafian N, Bhasin MK, Colvin RB, Madsen JC, Madsen JC, Strom TB, Sachs DH, Benichou G, Cosimi AB, Kawai T: Overcoming memory T-cell responses for induction of "delayed tolerance" in nonhuman primates. Amer J Transplant. 2012; 330-340. Yamada Y, Aoyama A, Tocco G, Boskovic O, Alessandrini A, Madsen JC, Cosimi AB, Benichoi G, Kawai T: Differential effects of denileukin diftitox IL-2 immunotoxic on NK and regulatory T cells in nonhuman primates. J Immunol 2012; 188 (12): 6063-70.

These publications present for the first time a summary of our observations using our novel "delayed tolerance" protocol. This approach promises to greatly extend the possibility of tolerance induction to more transplant patients, including recipients of all deceased donor organs or tissues.

2. Lee KM, Kim JI, Stott R, O'Connor MR, Yeh H, Zhao G, Eliades P, Soohoo J, Fox C, Cheng N, Deng S, Markmann JF. Anti-CD45RB/anti-TIM-1-induced tolerance requires regulatory B cells. Am J Transplant. 2012 Aug;12(8):2072-8.; Epub ahead of print. PMID: 22494812.

We report one of the first demonstrations of transplant tolerance dependent on B-lymphocytes. Transfer of B cells alone from tolerant hosts to naïve hosts can transfer tolerance. In addition we find that tolerance upon Breg transfer is dependent on Tregs, indicating interplay between these pathways of adaptive immunity. Understanding the nature of this interaction is the focus of ongoing work.

3. Tolerance to heart allografts can be achieved via mixed chimerism induction in NHP when a kidney from the same donor is co-transplanted. Long-term survival of heart/kidney allografts is associated with a lack of alloreactive response by host's inflammatory T cells and concomitant activation/expansion of regulatory T cells. Finally, our results show that the presence of the kidney allograft is necessary for both induction and maintenance of tolerance. Work is in progress to elucidate the mechanisms by which kidney allografts mediate their tolerogenic effects in this model (manuscript in preparation).

TRANSPLANTATION BIOLOGY RESEARCH CENTER

DAVID H. SACHS, MD, DIRECTOR

1. Meltzer AJ, Veillette GR, Aoyama A, Kim KM, Cochrane ME, Wain JC, Madsen JC, Sachs DH, Rosengard BR†, Allan JS†. Donor brain death inhibits tolerance induction in miniature swine recipients of fully MHC-disparate pulmonary allografts. Am J Transplant, 2012;12:1290-5. Epub 2012 Feb 2.

This paper reports studies demonstrating that the inflammatory state of a transplanted lung influences its tolerogenicity. The development of clinical protocols that permit tolerance induction of such transplanted tissues and organs is of critical importance, given that most of these transplants are harvested from deceased donors and are therefore obtained under less than ideal laboratory conditions.

2. Weiner J, Scalea J, Ishikawa Y, Okumi M, Griesemer A, Hirakata A, Etter J, Gillon B, Moran S, Shimizu A, Yamada K, Sachs DH, Tolerogenicity of Donor Major Histocompatibility Complex-Matched Skin Grafts in Previously Tolerant Massachusetts General Hospital Miniature Swine. Transplantation, in Press (2012)

This paper presents the surprising finding that under certain conditions, skin grafts can reinforce tolerance and provides evidence for a mechanism involving the induction of regulatory T cells.

3. Studies in our Plastic Surgery laboratory (C. Cetrulo) have demonstrated equivalent survival of GalT-KO porcine skin and allografts for temporary coverage of full thickness wounds, with no evidence of cross-sensitization. This study suggests that GalT-KO porcine skin and allografts may be used sequentially to provide extended temporary coverage of severe burn wounds (Alex Albritton et al., manuscript in preparation).

4. Previous studies from the Yamada laboratory have demonstrated the importance of a juvenile thymus for tolerance induction as well as demonstrating that factors extrinsic to the thymus are involved in thymic involution (Proc Natl Acad Sci U S A. 2006 Dec 12;103(50):19081-6). Using a protocol involving vascularized thymic transplantation and bone marrow transplantation, studies during the past year have revealed a role for bone marrow as one of the extrinsic factors capable of causing thymic rejuvenation. This result could be of importance in the induction of transplant tolerance in adults, utilizing tolerance-inducing strategies previously only successful in young recipients, due to thymic involution (Vincenzo Villani et al., manuscript in preparation).

Key Achievements/Publication Highlights for 2012

TRAUMA, EMERGENCY SERVICE AND SURGICAL CRITICAL CARE

GEORGE VELMAHOS, MD, DIVISION CHIEF

1. The confirmation that histone-deacetylase inhibitors work in a wide range of inflammatory and septic processes and not only in trauma.

Kochanek AR, Fukudome EY, Li Y, Smith EJ, Liu B, Velmahos GC, deMoya M, King D, Alam HB. Histone deacetylase inhibitor treatment attenuates MAP kinase pathway activation and pulmonary inflammation following hemorrhagic shock in a rodent model. J Surg Res. 2012; 176: 185-194. This article showed that hemorrhagic shock activates pro-inflammatory MAPK signaling pathways and promotes pulmonary neutrophil infiltration, affects that are significantly attenuated by VPA treatment. This may represent a key mechanism through which HDACIs decrease organ damage and promote survival in hemorrhagic shock. Chong W, Li Y*, Liu B, Liu Z, Zhao T, Wonsey DR, Chen C, Velmahs GC, deMoya MA, King DR, Kung AL, Alam HB. Anti-inflammatory properties of histone deacetylase inhibitors: a mechanistic study. J Trauma. 2012; 72(2): 347-354. * As an author to design the study. This study found that treatment with

SAHA attenuates hypoxia-HIF-1a-inflammatory pathway in macrophages and suppresses hypoxia-induced release of proinflammatory NO and TNF-a. SAHA also causes an early increase in cellular PHD2, which provides, at least in part, a new explanation for the decrease in the HIF-1a protein levels.

2. The analysis of our 24/7 attending coverage schedule in the ICU and conclusion that the outcomes benefits are modest to small.

van der Wilden GM, Schmidt U, Chang Yuchiao, Bittner EA, Cobb JP, Velmahos GC, Alam HB, deMoya MA, King DR. Implementation of 24/7 Intensivist Presence in the SICU: Effect of Process of Care. J Trauma Acute Care Surg. In Press. This publication is a true multidiciplinary endeavor between surgery and anesthesia. We were able to demonstrate that adding 247/ ICU coverage to the MGH did not change patient outcome.

3. The ongoing work leading the Research Consortium of New England Centers for Trauma (ReCONECT) with a multicenter study on an annual basis (severe liver injuries for 2012).

van der Wilden GM, Velmahos GC, Emhoff T, Brancato S, Adams C, Georgakis G, Jacobs L, Gross R, Agarwal S, Burke P, Maung AA, Johnson DC, Winchell R, Gates J, Cholewczynski W, Rosenblatt M, Chang Y. Successful nonoperative management of the most severe blunt liver injuries: a multicenter study of the Research Consortium Of New England Centers For Trauma (ReCONECT). Arch Surg 2102;147:423-9.

4. The continuation of the work on diagnosing and treating traumatic pneumothorax, this year by using radar impulse technology.

Using micropower impulse radar technology to screen for pneumothorax: An international bi-institutional study. Van der Wilden G, Albers C, Haefeli P, Zimmerman H, Exadaktylos A, Levy P, Birkham O, Michailidou M, Sideris A, Velmahos G, Alam H, King D, Fagenholz P, Yeh D, de Moya MA. J Trauma Acute Care Surg. 2012 Dec;73(6):1416-9. This is the first study using RADAR technology to diagnosis pneumothoraces in the trauma bay and was a collaborative effort between MGH and University of Berne

VASCULAR AND ENDOVASCULAR SURGERY

RICHARD P. CAMBRIA, MD, DIVISION CHIEF

1. Albadawi H, Haurani MJ, Oklu R, Trubiano J, Laub P, Yoo HJ , Watkins MT. Differential Effect of Zoledronic Acid on Quiescent vs. Proliferating Human Vascular Smooth Muscle Cells, J. Surg. Res. Nov 8. doi:pii: S0022-4804(12)00956-0. 10.1016/j.jss.2012.10.033. [Epub]

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. Kang J, Patel VI, Mukhopadhyay S, Garg A, Cambria M, Conrad MF, LaMuraglia GM, Cambria RP. Long-term clinical and anatomic outcomes following carotid endarterectomy. Journal of Vascular Surgery—in press.

This manuscript was presented by Dr Kang at the spring meeting of the Peripheral Vascular Surgery Society. It details the long-term results of over 3000 carotid endarterectomies performed over a 16 year period. We showed that our 30 day stroke rate remains low at 1.2% and the 10 year survival after CEA is 87%. This paper also detailed the evolution of our operative strategy including the use of patch angioplasty instead of primary closure and the use of statins post-operatively.

3. Conrad MF, Boulom V, Mukhopadhyay S, Garg A, Patel VI, Cambria RP. Progression of Asymptomatic Carotid Stenosis Despite Optimal Medical Therapy. Journal of Vascular Surgery—in press

This manuscript was presented at the New England Society of Vascular Surgery in October. It looks at the ability of medical management (aspirin/statin therapy) to prevent disease progress or symptom development in patients with moderate (50-69%) carotid artery stenosis. It showed that statin therapy decreases symptomatic development in this cohort but failed to halt the progression of disease to severe or very severe (>70%). This is an important first step in determining if medical therapy will effectively prevent stroke in patients with severe asymptomatic carotid stenosis.

4. 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. Journal of Vascular Surgery—in press.

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.

Key Achievements/Publication Highlights for 2012

Urology

Michael Blute, MD, Chief

1. Dr. Michael Blute Kidney Cancer Association Andrew C. Novick Research Award—2012

Awarded to the individual with significant contributions in the field of kidney cancer.

2. Dr. Adam Feldman American Urological Association Foundation Research Forum—New England Section Nominee

Dr. Feldman represented the New England region at the national American Urological Association for his reserach and academic accomplishemnts. The nominee is selected amongst individuals who are within eight years of completing residency training.

3. Dr. Dicken Ko President, Urologic Society for Transplantation and Renal Surgery

As a dedicated urologic transplant surgeon, Dr. Ko has been selected as the president of the Urologic Society for Transplantation and Renal Surgery.

4. Inhibition of TNF-a improves the bladder dysfunction that is associated with type 2 diabetes. Authors: Wang Z, Cheng Z, Cristofaro V, Li J, Xiao X, Gomez P, Ge R, Gong E, Strle K, Sullivan MP, Adam RM, White MF, Olumi AF. Diabetes. 2012 Aug;61(8):2134-45.

Bladder dysfunction is a common secondary complication of type 2 diabetes. This publication defines a genetically defined animal model with type 2 diabetes, and describes the molecular alterations associated with bladder dysfunciton in type 2 diabetes. Targeted molecular therapy reveres the bladder dysfunction associated with type 2 diabetes.

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