Beth Israel Deaconess Medical Center

A teaching hospital of Harvard Medical School

Department of Medicine Annual Report 2009

View of the Carl J. Shapiro Clinical Center, on the corners of Brookline and Longwood Avenues

Cover:
Diana C. Gallagher, MD
Pulmonary, Critical Care & Sleep Medicine

Table of Contents

From the Chairman

Dear Colleagues and Friends,

We are delighted to bring you the Department's annual report for academic year 2008-2009. Since then, the Department has undergone its 5 year review, conducted by a distinguished panel of outside experts (Robert Schrier, Kenneth Polonsky, and Sharon Wardlaw). The reviewers were strongly impressed with our performance in all of our missions, and offered several terrific suggestions, which we are implementing. It is fair to say that we are performing in all of our missions at a higher level than at any time in the Department's history:

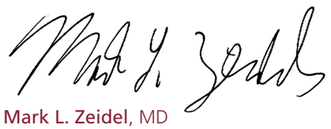
Clinical Care – To thrive in a highly competitive market, we must provide care of superb quality, with outstanding patient experience, and with the highest possible efficiency. Over the past 5 years the Department has experienced strong growth in outpatient and inpatient visit volume, and in GI procedural volume. Clearly, the increases in clinical activity are helping the hospital to achieve its financial goals. Although we had originally intended to focus growth in certain clinical areas, financial analyses revealed that increased ambulatory activity in many areas gave significant downstream effect. We have provided a separate detailed report on quality improvement efforts; this report documents continued rapid progress and national leadership in this arena.

Education – We continue to run robust medical student, residency and fellowship programs. Our faculty members continue to win recognition locally and nationally for outstanding and innovative teaching efforts. Our residency is becoming nationally known for its innovative approaches towards teaching quality improvement, and we find increasing numbers of candidates choosing our program with this strength in mind. We are extending training in quality improvement to our fellowship programs. Important elements of postgraduate education include a medical grand rounds series that features Clinical Crossroads, a series of case vignettes which are published as a feature in *JAMA*.

Research – As detailed in the individual divisional reports, the research mission of the department has never been stronger, in terms of overall funding, dollar density, and the quality and importance of the scientific work we are performing. We focus as strongly as possible on initiatives to develop physician-scientists. Specific programs are in place or are in development to augment the transitions of fellows to independent investigators, new researchers to established investigators, and established people to professorial rank and national recognition.

Administration – This past year we began a formal annual evaluation process for each faculty member. When we can coordinate it with HMS, we will include in this all teaching evaluations. We now include clinical activity and productivity, as well as quality measures, all research, as evaluated by publications and grants, and teaching evaluations. Faculty members complete a self-evaluation and review it in detail with their Division Chief. Division chiefs, in turn, review each faculty member annually with the Chair. These reviews give us the opportunity to identify faculty members who are not progressing adequately, so that we can help them succeed, and assure that we promote people in a timely manner.

On a personal note, it is an enormous privilege to attend to (and hopefully serve effectively) our exceptional faculty. Our gifted, compassionate and tireless clinicians, our inspirational and motivated teachers, and our outstanding and innovative investigators serve as a constant inspiration to me and to our students and trainees. As shown in this report, by continuing to excel in all of our missions during increasingly challenging times, our faculty exemplifies quality, compassion, originality and character.

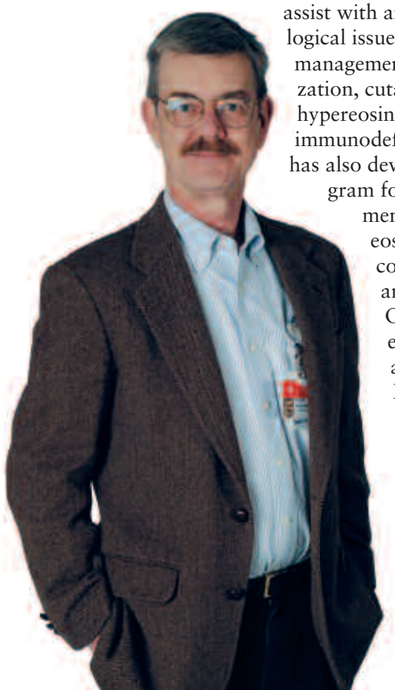


Mark L. Zeidel, MD
Chair, Department of Medicine

Division of Allergy & Inflammation

The Division of Allergy and Inflammation has as its mission to provide excellent patient care, teaching and research pertinent to allergic and related immunologic diseases. Clinical and research faculty are nationally and internationally recognized for their expertise. The staff of the Division includes physicians supported by experienced nurses and a nurse-practitioner. Educational activities are aimed at Harvard Medical School students, medical residents in training at Beth Israel Deaconess Medical Center and others. Research activities, focusing on basic mechanisms of allergies and inflammation, coordinate with international centers and provide research training opportunities for national and international research fellows.

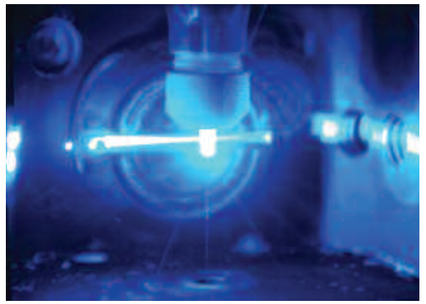
The Division staffs an inpatient consultation service at the main Beth Israel Deaconess Medical Center campus. We are available to assist with any inpatient allergic or immunological issues, including the evaluation and management of drug allergy, drug desensitization, cutaneous eruptions, anaphylaxis, hypereosinophilic disorders and primary immunodeficiency workup. The Division has also developed an interdisciplinary program for the evaluation and management of systemic mast cell and eosinophilic disorders, which is a coordinated effort between Allergy and Inflammation, Hematology-Oncology, Dermatology, Gastroenterology, Clinical Pathology, and the Division of Experimental Pathology.



Peter F. Weller, MD, Chief
Vice Chairman for Research

CLINICAL ACTIVITIES

The Division provides clinical services and expertise related to allergic diseases, asthma and immunodeficiency disorders in both inpatient and outpatient settings. With the needs of patients in mind, the Division emphasizes quick access to care. Services provided include consultative, diagnostic evaluations and primary allergy clinical care. The Division's clinical services are provided in a team approach with three Board certified allergy and immunology physicians, a full time allergy nurse practitioner and other nursing staff working collaboratively. The Division provides outpatient allergy and clinical immunology services at a primary practice site at one Brookline Place, Brookline, at the main Beth Israel Deaconess Medical Center campus, as well as at Lexington and Chelsea satellite facilities. In the past year, the Division had more than 5500 outpatient visits. Our physicians have expertise in the diagnosis and management of allergic and inflammatory diseases, including allergic rhinitis, allergic conjunctivitis, sinusitis, asthma, food allergy, atopic dermatitis, urticaria, angioedema, anaphylaxis, drug hypersensitivity, latex allergy, hypereosinophilic syndromes, mast cell disorders, and immunodeficiency disorders.



A Flow Cytometry Core research facility at BIDMC, overseen by Dr. Peter Weller, provides access for investigators to state-of-the-art flow cytometry-based analyses and cell-sorting.

Jason Zenakis,
Research Assistant

HONORS AND AWARDS

Peter F. Weller, MD was recognized by Best Doctors in America 2008–2010. Javed Sheikh was recognized in 2008–2009 by Best Doctors in Boston – *Boston Magazine* and America's Top Doctors – Castle Connolly Medical Ltd.

Kathy Corley, RN, NP was recognized in 2009 with the Excellence in Advanced Practice Nursing Award

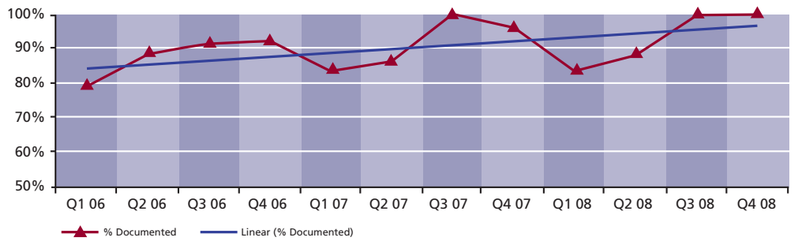
Research staff and trainees Josi Neves, PhD and Haibin Wang, MD, PhD received awards for presentations at the International Eosinophil Society meeting in Belgium.

Drs. Weller, Spencer and Akuthota received highly meritorious reviews on NIH peer-reviewed grant submissions.

FACULTY

Praveen Akuthota, MD
Ionita Ghiran, MD
Zhuang Jin, PhD
Anna Kovalszki, MD
Rosanna Melo, PhD
Anne Nicholson-Weller, MD
Javed Sheikh, MD
Lisa A. Spencer, PhD
Haibin Wang, MD, PhD
Peter F. Weller, MD

Dr. Javed Sheikh, the Clinical Director of the Division and the Clinical Director of the Center for Eosinophilic Disorders, has special interests in urticaria, mast cell disorders, eosinophilic disorders, asthma, and allergic rhinitis. He also has expertise in food-related allergic/immunologic disorders, and is a member of the BIDMC Celiac Center. Dr. Anna Kovalszki has joined the Division as a full-time Allergy physician. The clinical activities of Dr. Peter Weller, Division Chief, fall in both the Division of Infectious Diseases and the Division of Allergy and Inflammation. Dr. Weller has special interests in eosinophil-associated diseases and works closely with Drs. Sheikh and Kovalszki to provide expertise in evaluating and treating patients with eosinophilic disorders. Clinical services are also provided by Kathleen Corley, nurse practitioner, who has expertise in general allergy and asthma evaluation and coordinates patient education services.



Prescription of Epipen / Twinject for patients at risk for anaphylactic reactions

Lisa A. Spencer, PhD

QUALITY IMPROVEMENT

The Division has ongoing quality assurance programs and tracks rates of anaphylactic reactions to desensitization therapy, documents administration of injectable epinephrine to patients with a history of anaphylaxis, monitors rates of asthmatic patients receiving inhaled steroids as well as a number of appointment access measures.

EDUCATIONAL PROGRAMS

The Division plays a major role in the education of BIDMC Internal Medicine housestaff, Harvard Medical School students, and Harvard Allergy/ Immunology clinical fellows. BIDMC medicine residents have the option of a three-week outpatient rotation in allergy and clinical immunology and have also designed basic science or clinical research electives with Division faculty. Third year Harvard Medical School students may rotate through the outpatient allergy practice as part of their Core Medicine rotation.

RESEARCH ACTIVITIES

The research activities of the Division include both clinical research and basic research. Basic research is supported by an NIH grant and is conducted in 3000 square feet of lab space in BIDMC's new Center for Life Sciences building.

The Division maintains a program for industry-sponsored clinical research. In a multinational study of a neutralizing antibody to interleukin-5 for eosinophilic diseases, the Division was the only study center in New England. The Division has also collaborated on clinical projects with other HMS institutions and divisions, and has collaborated on

SELECTED PUBLICATIONS

Neves JS, Peres SAC, Spencer LA, Melo RCN, Reynolds L, Ghiran I, Mahmudi-Azer S, Odemuyiwa S, Dvorak AM, Moqbel RM, Weller PF. Eosinophil granules function extracellularly as receptor-mediated secretory organelles. *Proc Natl Acad Sci USA* 2008; 105:18478-83.

Spencer L, Szela CT, Perez SAC, Kirchhoffer CL, Neves JS, Radke AL, Weller PF. Human eosinophils constitutively express multiple Th1, Th2 and immunoregulatory cytokines that are rapidly and differentially secreted. *J Leukocyte Biol* 2009; 85:117-123.

Karnchanaphanurach P, Mirchev R, Ghiran I, Asara JM, Papahadjopoulos-Sternberg B, Nicholson-Weller A, Golan DE. C3b deposition on human erythrocytes induces the formation of a membrane skeleton-linked protein complex. *J Clin Invest* 2009; 119:788-801.

Ogbogu PU, Bochner BS, Butterfield JH, Gleich GJ, Huss-Marp J, Kahn JE, Leiferman KM, Nutman TB, Pfab F, Ring J, Rothenberg ME, Roufosse F, Sajous MH, Sheikh J, Simon D, Simon HU, Stein ML, Wardlaw A, Weller PF, Klion AD. Hypereosinophilic syndrome: A multicenter, retrospective analysis of clinical characteristics and response to therapy. *J Allergy Clin Immunol* 2009; 124:1319-25.

Sheikh J, Weller PF. Advances in diagnosis and treatment of eosinophilia. *Curr Opin Hematol* 2009; 16:3-8.

Melo RCN, Spencer LA, Dvorak AM, Weller PF. Mechanisms of eosinophil secretion: large vesiculotubular carriers mediate transport and release of granule-derived cytokines and proteins. *J Leukocyte Biol* 2008; 83:229-36.

Melo RCN, Spencer LA, Perez SAC, Neves JS, Bafford S, Morgan ES, Dvorak AM, Weller PF. Vesicle-mediated secretion of human eosinophil granule-derived major basic protein (MBP). *Lab Investi* 2009; 89:769-781.

Akuthota P, Wang H, Spencer LA, Weller PF. Immunoregulatory roles of eosinophils: a new look at a familiar cell. *Clin Exp Immunol* 2008; 38:1254-63.

Ghiran I, Glodek AM, Weaver G, Klickstein LB, Nicholson-Weller A. Ligation of erythrocyte CR1 induces its clustering in complex with scaffolding protein FAP-1. *Blood* 2008; 112:3465-73.

Radke AL, Reynolds LE, Melo RCN, Dvorak AM, Weller PF, Spencer LA. Mature eosinophils express functional Notch ligands mediating eosinophil autocrine regulation. *Blood* 2009; 113:3092-101.

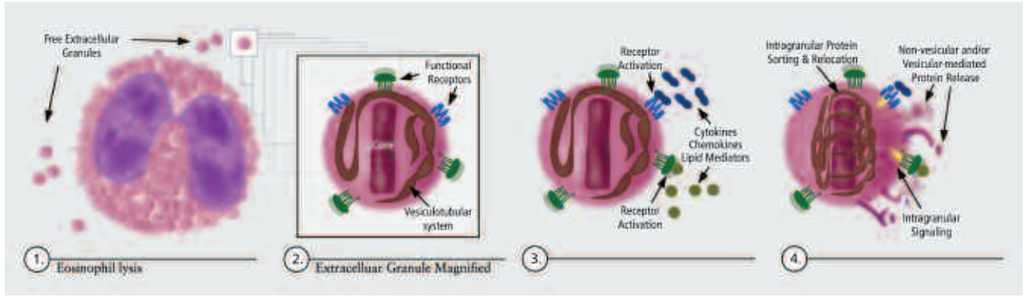


Illustration: Matt Pickett

Intracellular organelles, the cytoplasmic granules of human eosinophils, function as secretion competent structures even when cytolytically released from eosinophils, as occurs in human diseases.

epidemiological research with the Channing Lab and the Harvard School of Public Health.

Cellular and Molecular Bases of Inflammation – Studies by Peter F. Weller, MD, Lisa Spencer, PhD, Praveen Akuthota, MD and colleagues are centered around understanding mechanisms of eosinophil and other leukocyte functioning in forms of inflammation. The two principal areas of investigation are: 1) the immunobiology of eosinophilic leukocytes and 2) the intracellular regulation and compartmentalization at cytoplasmic lipid bodies of inducible mediators of inflammation in neutrophils and other leukocytes. Studies of human eosinophils are aimed at defining mechanisms whereby eosinophils may collaboratively interact with other cellular elements of the immune system. Notable findings include demonstrating that cell-free extracellular eosinophil granules, as found in vivo in asthma and sites of allergic and anthelminthic responses, are ligand receptor-mediated secretion competent organelles.

Studies of the Complement System – Ionita Ghiran, MD and Anne Nicholson-Weller, MD are interested in the normal regulation of the human complement system and how inflammation is modified through complement activation, and specifically the role of CD35 (complement receptor 1, or CR1). The complement system is an integral part of the innate immune system, and as such, complement participates in immune surveillance for pathogens and augments the adaptive immune system.

Haibin Wang, MD, PhD, Instructor

Division of Cardiovascular Medicine

The Cardiovascular Division at BIDMC is devoted to providing the highest level of patient care, committed to the unwavering educational mission of academic medicine, and is dedicated to state-of-the-art research on the clinical, basic and translational forefronts of cardiovascular medicine. The numerous accomplishments of the Division are made possible by the outstanding, nationally and internationally recognized faculty.

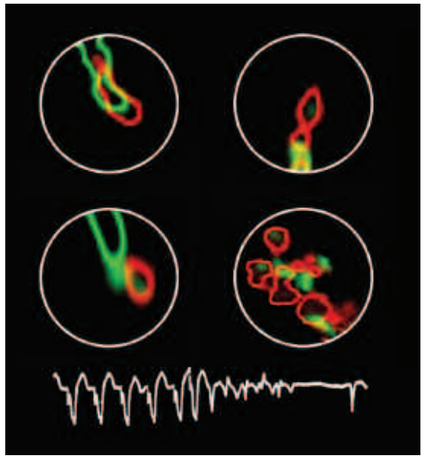
CLINICAL ACTIVITIES

Cardiac Catheterization Laboratory – The Interventional Cardiology section consists of eight full-time faculty who together perform over 4,000 diagnostic and coronary interventional procedures annually. As one of the first centers in the country to offer around-the-clock emergency angioplasty treatment for blocked arteries causing heart attacks, we have had continued success in improving these procedures which has resulted in a door-to-balloon time within 90 minutes of arrival (national benchmark) over the past 6 months.

Structural Heart Center – A new multidisciplinary program has been established to treat non-coronary cardiac diseases. Our physician team utilizes the most innovative and less invasive percutaneous techniques in treating congenital heart defects (e.g. patent foramen ovale atrial septal defect), hypertrophic obstructive cardiomyopathy, arrhythmias, atrial appendage exclusion, and valvular heart disease (e.g. mitral and aortic stenosis).

Mark Josephson, MD, Chief

Cardiac Electrophysiology – The members of the Harvard-Thorndike Electrophysiology Institute and Arrhythmia Service are internationally recognized as pioneers in the understanding of the pathophysiology of arrhythmias and their treatment. The reputation of our EP Program is highlighted by the publication of Dr. Josephson's text *Clinical Cardiac Electrophysiology* (aka the "Bible" of Electrophysiology), and *Practical Clinical Electrophysiology* by Drs. Zimetbaum and Josephson. In addition, the electrophysiology faculty published over forty-five manuscripts, chapters and editorials during the past year. The EP Service provides the entire spectrum of diagnostic and ablative therapies, including those for AF and VT/VF, as well as the latest in implantable devices and pacemakers.



Top panel shows co-localization of Cx43 (red) with ZO-1 (green) in normal myocardium (upper left), and in infarct border zone myocytes following coronary occlusion for 30 min (upper right), 1 hr (lower left) and 3 hrs (lower right). Bottom panel shows an EKG 5 days after infarction during programmed electrical stimulation. Premature stimulated impulse is followed by a run of polymorphic non-sustained ventricular tachycardia caused by gap junction remodeling (Dr. Heather Duffy).

There is an active inpatient and outpatient consultative service, including a dedicated atrial fibrillation clinic directed by Dr. Zimetbaum. A Non-Linear Dynamics Laboratory, directed by Dr. Goldberger, is devoted to signal processing and serves as a national resource. The ECG Laboratory directed by Dr. Markis and an Ambulatory Monitoring Service directed by Dr. Shvilkin processed over 70,000 ECGs and over 2,500 ambulatory monitoring studies respectively over the last year.

Kudakwashe Mutyambizi, MD, examining a patient in the Coronary Care Unit

FACULTY

Evan Appelbaum, MD
Zoltan Arany, MD, PhD
Julian Aroesty, MD
Aparna Bhagavat, MD
James Chang, MD
Donald E. Cutlip, MD
Federica del Monte, MD, PhD
Heather Duffy, PhD
Loryn S. Feinberg, MD
Eli Gelfand, MD
Ernest Vincent Gervino, ScD
C. Michael Gibson, MS, MD
Charles Ismail Haffajee, MD
Yuchi Han, MD
Thomas Henry Hauser, MD
Kalon Ho, MD, MSc
Francis Hubbard, MD
Mark Josephson, MD
Lillian Joventino, MD
Peter Myung-Hoon Kang, MD
Joseph Peter Kannam, MD
Benet Sosnik Kolman, MD
Maria Irene Kontaridis, PhD
Roger Joseph Laham, MD
David Eli Leeman, MD
Stanley Lewis, MD
Jian Li, PhD
William Maisel, MD, MPH
Warren Manning, MD
Takashi Matsui, MD, PhD
Murray A. Mittleman, MD, DrPH
Bruce Nearing, MD
Reza Nezafat, PhD
J. Peter Oettgen, MD
Thomas D. O'Halloran, MD
Panagiotis Papageorgiou, MD, PhD
Dana C. Peters, PhD
Duane Sidney Pinto, MD
Jeffrey Popma, MD
Carl Rasmussen, MD, PhD
Matthew R. Reynolds, MD, MSc
Anthony Rosenzweig, MD
Samuel Shubrooks, MD
Alexei V. Shvilkin, MD
Karen Thomas, MD
Richard L. Verrier, PhD
Francine Welty, MD, PhD
Peter J. Zimetbaum, MD

Advanced Heart Failure Service – Our advanced heart failure service is directed by Dr. Chang and includes an outpatient and inpatient service. We continue to enhance our program with the creation of a dedicated heart failure unit and an ambulatory diuretic infusion clinic. We are developing a program for ventricular assist device therapies and have established a relationship with Tuft's Cardiovascular Center for cardiac transplantation.

Non-Invasive Cardiac Imaging Section – This section is led by Dr. Manning and provides diagnostic services for BIDMC inpatients and outpatients.

Echocardiography Laboratory – Our state-of-the-art laboratories perform 15,000 studies annually, including over 600 transesophageal studies, and nearly 1,700 stress echocardiograms. Evening and weekend outpatient appointments are available, as well as options for scanning offsite at our Lexington and Chelsea offices. All interpreting physicians have passed the advanced competency examination administered by the American Board of Echocardiography. The echocardiography laboratory is certified by the Intersocietal Commission on Echocardiography Laboratories (ICAEL) for all studies.

Cardiovascular Magnetic Resonance – Our Cardiovascular Magnetic Resonance Center (CMR) is the second oldest dedicated CMR Center in the United States. More than 700 studies are performed annually to assess structure and function in valvular and myopathic conditions and congenital heart disease; arrhythmogenic substrate; and as a guide to pulmonary vein isolation proce-

Mark Josephson, MD, Chief, on rounds with fellows

dures. Collaboration with electrophysiologists has lead to multiple seminal publications.

Nuclear Cardiology – Under the supervision of Dr. Hauser, nuclear cardiology is a collaborative effort with the Department of Radiology and provides fellows with the experience necessary to use and interpret a spectrum of cardiac radionuclide exams including PET/CT, SPECT/CT and SPECT. Nearly 3,000 stress nuclear studies are performed annually (treadmill, bicycle, dipyridamole).

Cardiovascular Clinical Physiology Laboratory – These laboratories, under the direction of Dr. Gervino, provide both physiologic (treadmill and bicycle ergometry) as well as pharmacologic stress testing. Non-nuclear stress tests have also been made available on the weekends through collaboration with the Emergency Department. More than 7,000 cases are performed annually, including more than 2,000 non-imaging treadmill stress tests, and nearly 5,000 stress imaging studies.

Cardiovascular Health and Lipid Center – The Center, under the direction of Dr. Oettgen, is a multidisciplinary prevention clinic. The major clinical focus of the clinic is to assess and reduce cardiovascular risk. Many patients have complex lipid disorders or hypertension not easily managed with standard therapies. The Center is also a forum for clinical research. All clinical information and laboratory results are incorporated into a longitudinal database tracking patient responses to dietary and pharmacological strategies.

Ambulatory Cardiology – Under the direction of Dr. Gelfand, the Outpatient Cardiovascular Clinics see approximately 20,000 patient visits annually. The Clinic provides prompt, comprehensive assessment of patients with conditions spanning the whole spectrum of cardiovascular disorders and offers dietary counseling, ECGs, stress testing, echocardiography, pacemaker and defibrillator interrogation services on-site. The introduction of a Cardiology Call Center allows the Clinic to accommodate all outpatient consultation requests within 48 hours. Same-day appointments are also freely available for returning patients with urgent cardiovascular issues.

Russian Cardiovascular Clinic – Founded in 2006 by Dr. Gelfand, the BIDMC Russian Cardiovascular Clinic serves patients who emigrated to the U.S. from Eastern Europe, and provides culturally-sensitive, comprehensive cardiovascular care to this high-risk population. The Clinic has a bilingual appointment line and consultations are conducted in the patient's native language. The Clinic has attracted a wide and growing referral base from all of New England.

QUALITY IMPROVEMENT

Dr. Ho has led the Divisional efforts to track indices of quality and improve our performance. Beth Israel Deaconess Medical Center continues to be cited by the Centers for Medicare and Medicaid Services as having a risk-adjusted 30-day mortality rate for patients with heart failure that is better than the U.S. national rate. Our recent performance on Joint Commission core measures of cardiac care has been excellent, especially for heart attack care, where we have a 100% door-to-balloon time of less than 90 minutes for patients presenting acute ST segment elevation myocardial infarctions.

We have continued our focus on radiation safety. We have developed materials to educate patients and their referring health care providers about the risks of radiation. Other safety initiatives this year have lead to a decrease in vascular complications related to cardiac catheterization. We have also undertaken interventions to reduce the incidence of urinary tract infections following invasive procedures, to ensure appropriate use of high risk anti-coagulant and anti-platelet drugs, and to improve communication between different teams of providers caring for patients undergoing invasive procedures.

Finally, members of the Division remain leaders in state, national and international quality improvement efforts and comparative effectiveness research at the Massachusetts Department of Public Health, the National Cardiovascular Data Registry, the American College of Cardiology, the Food and Drug Administration and the International Guidelines Applied in Practice Door-to-Balloon (D2B) Alliance.

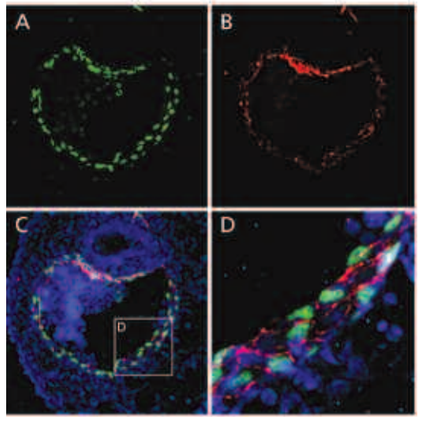
EDUCATIONAL PROGRAMS

Our educational programs have enjoyed significant success this year. Scholarly activity has increased amongst the fellows and they have garnered prestigious national awards and grants such as the American College of Cardiology, Merck, American Heart Association and Johnson & Johnson Cordis Corporation Fellowship awards. The fellows have presented their work at national meetings and published their work in prestigious journals and books. Drs. Gelfand and Pinto have spearheaded initiatives in the general cardiology fellowship aimed at improving didactic teaching, evaluation tools and mentorship. The ACGME gave a full 5-year accreditation to all three fellowship programs (general cardiology, interventional cardiology and electrophysiology) and offered commendation to the general cardiology fellowship. Admission to the fellowships remains highly competitive with more than 700 applicant submissions received yearly. Drs. Maisel and Cutlip have directed the electrophysiology and interventional fellowship programs – both of which are highly competitive.

Additionally, our faculty continues to actively educate the medical community. This year one of Harvard Medical School's top-ranked education programs was "ECGs in Clinical Practice: Pearls and Pitfalls."

HONORS AND AWARDS

Dr. Han won the ACCF/GE Cardiovascular Imaging Career Development Award for 2008-2010. Dr. Josephson was presented with the prestigious American College of Cardiology "Gifted Teacher Award" for his many years as an exemplary role model and outstanding teacher of medical students, residents, fellows, and physicians both nationally and internationally. Drs. Josephson, Manning, and Gibson were also recognized in *Boston Magazine's Boston's Best Doctors* list in 2009 for their clinical efforts in Electrophysiology, General Cardiology, and Interventional Cardiology respectively.



Confocal expression of the endothelial restricted transcription factor ERG in embryonic stem cell derived embryoid body sections. Green: ERG; Red: VE-cadherin; Blue: nuclei. (Dr. Peter Oettgen)

Furthermore, Dr. Josephson and his colleague Dr. Wellens are completing their 28th consecutive year teaching "Understanding Complex Arrhythmias" in the USA and Europe.

RESEARCH ACTIVITIES

Over the past three years, Drs. Josephson and Rosenzweig have strengthened and expanded the already vibrant cardiovascular research program at Beth Israel Deaconess Medical Center. These efforts have included strategic recruitment of five new basic and translational science faculty and development of the cardiovascular laboratories within the Center for Life Sciences (CLS), as well as interactions with and ongoing leadership roles at the university, national and international research levels. Overall, these efforts have culminated in over one hundred basic and translational publications in the last academic year, numerous new and continued extramural research awards, and several national and international program grants.

These include a NIH/NHLBI Specialized Center of Clinically Oriented Research (SCCOR) program in vascular injury, repair and remodeling, which is directed by Dr. Welty, and a Leducq Foundation Transatlantic Network of Research Excellence, for which Dr. Rosenzweig serves as the American Coordinator and which involves eleven international laboratories investigating signaling networks in metabolic syndromes and their relationship to heart failure.

Cardiology faculty members serve as investigators in all major clinical trial areas within Interventional Cardiology and often play leadership roles or serve as national or international Principal Investigators of these studies. Our collaboration with Harvard Clinical Research Institute and international reputation in angiographic core laboratory analyses also supports our involvement in the early evaluation of "cutting edge" technology and bringing these exciting developments to the bedside. In addition to clinical trial research, exciting work in translational research is also an important focus and has led to interesting discoveries in the study of coronary plaque development using CT angiography, stem cells and angiogenesis. Between these and other research areas, the Interventional Cardiology faculty has published over 40 peer-reviewed articles in the past year.

The Harvard-Thorndike Electrophysiology Institute and Arrhythmia Service includes both basic and clinical investigation of arrhythmogenesis. A large animal lab provides support for integrative physiology using epicardial and endocardial mapping through the efforts of Drs. Josephson, Verrier and Duffy.

SELECTED PUBLICATIONS

An X, Jin Y, Guo H, Foo S, Cully BL, Wu J, Zeng H, Rosenzweig A, Li J. Response gene to complement 32, a novel hypoxia-regulated angiogenic inhibitor. *Circulation* 2009; 120:617-627.

Arany Z, Foo SY, Ma Y, Ruas J, Bommi-Reddy A, Girnum G, Cooper M, Laznik D, Rosenzweig A, Spiegelman BM. HIF-independent regulation of VEGF and angiogenesis by the metabolic sensor and transcriptional coactivator PGC-1alpha. *Nature* 2008; 451(7181):1008-1012.

Chinsomboon J, Ruas J, Gupta RK, Thom R, Shoag J, Rowe G, Sawada N, Raghurama S, Arany Z. The transcriptional coactivator PGC-1alpha mediates exercise-induced angiogenesis in skeletal muscle. *Proc Natl Acad Sci USA* 2009; 106(50):21401-6.

Duffy, HS. The ever shrinking world of ion channel remodeling: The role of microRNAs in heart disease. *Heart Rhythm* 2009; 6(12):1810-1811.

Foo SY, Heller ER, Wykrzykowska J, Sullivan CJ, Manning-Tobin JJ, Moore KJ, Gerszten RE, Rosenzweig A. Vascular effects of a low-carbohydrate high-protein diet. *Proc Natl Acad Sci USA* 2009; 106:15418-15423.

Jin Y, An X, Ye Z, Cully B, Wu J and Li J. RGS5, a hypoxia inducible apoptotic stimulator in endothelial cells. *J Biol Chem* 2009; 284 (35): 23436-43.

Morissette MR, Stricker JC, Rosenberg MA, Buranasombati C, Levitan EB, Mittleman MA, Rosenzweig A. Effects of myostatin deletion in aging mice. *Aging Cell* 2009; 8:573-583.

Verrier RL, Josephson ME. Impact of sleep on arrhythmogenesis. *Circ Arrhythmia Electrophysiol* 2009; 2:450-459.

Reynolds MR, Zimetbaum P, Josephson ME, Ellis E, Danilov T, Cohen DJ. Cost effectiveness of radiofrequency catheter ablation compared with antiarrhythmic drug therapy for paroxysmal atrial fibrillation. *Circ Arrhythmia Electrophysiol* 2009; 4:362-9.

Tung R, Zimetbaum P, Josephson ME. A critical appraisal of implantable cardioverter-defibrillator therapy for the prevention of sudden cardiac death. *J Am Coll Cardiol* 2008; 14:1111-21.

Gibson C, Pride Y, Buros J, Lord E, Shui A, Murphy S, Pinto D, Zimetbaum P, Sabatine M, Cannon CP, Josephson M. Association of impaired thrombolysis in myocardial infarction, myocardial perfusion grade with ventricular tachycardia and ventricular fibrillation following fibrinolytic therapy for ST - segment elevation myocardial infarction. *J Am Coll Cardiol* 2008; 51:546-51.

Shvilkin A, Bojovic B, Vajdic B, Gussak I, Zimetbaum P, Josephson ME. Vectorcardiographic determinants of cardiac memory during normal ventricular activation and continuous ventricular pacing. *Heart Rhythm* 2009; 6:943-948.

BOOKS

Atlas of Cardiovascular Magnetic Resonance. Manning WJ, ed. Braunwald E, series editor. Springer-Current Medicine Group, Philadelphia. 2009.

Clinical Cardiac Electrophysiology. Josephson ME, Wolters Kluwer | Lippincott Williams & Wilkins 2008.

Practical Clinical Electrophysiology. Zimetbaum P, Josephson ME, Wolters Kluwer | Lippincott Williams & Wilkins 2009.

Active clinical projects include risk stratification through analysis of T-wave alternans heterogeneity (Dr. Verrier), substrate characterization with correlation of electrophysiology and cardiac MR (Drs. Josephson, Duffy and Peters), as well as clinical trials of devices or other ablative strategies.

The Cardiovascular Epidemiology Research Unit is directed by Dr. Mittleman and applies sophisticated biostatistical methods to the study of cardiovascular disease including investigation into triggers for cardiovascular events, the role of environmental factors such as air pollution, and interactions of these factors with genetic and epigenetic mechanisms. Dr. Mittleman also serves as Chair of the Master of Public Health program at the Harvard School of Public Health, establishing an important cross-institutional link for our faculty and trainees.

Productive interactions with institutional and university-wide programs have also been strengthened. Dr. Rosenzweig was the first cardiovascular program head for the Harvard Stem Cell Institute (HSCI) and continues to serve on the executive board as well as co-directing HSCI-supported efforts in the BIDMC Core Flow Cytometry facility.

Fellow research is often supported through a NIH/NHLBI T32 Cardiovascular Training Grant, which is now entering its 32nd year and recently competed successfully for renewal under the direction of Dr. Rosenzweig and Associate Directors Drs. Mittleman and Oettgen. The grant supports both basic and clinical training in cardiovascular research. Dr. Oettgen, whose work focuses on vascular transcriptional mechanisms, is also the Associate Chief of the Division of Molecular and Vascular Medicine at BIDMC, providing an important programmatic connection and fruitful scientific collaborations.

Cardiology fellows on the Zoll Service

Division of Clinical Informatics

The Division of Clinical Informatics, created almost 40 years ago by Drs. Howard Bleich and Warner V. Slack, was among the first academic divisions in the world to concentrate on the use of computers for patient care, teaching and medical research. The goals of the Division have been to improve the quality and reduce the cost of medical care, to enhance the quality of medical education, to improve the relationship between doctor and patient, and to explore innovative approaches to research through computing.

CLINICAL ACTIVITIES

The Division developed "ReportWriter" a cloud-based electronic health record, customized for the workflows for chronic disease care in the ambulatory setting in the Middle East. Led by Dr. Henry Feldman, Report Writer allows clinicians to represent the flow of problems seamlessly, with plans flowing from one evolution of the problem to the next in a chain. Further, ReportWriter is designed to facilitate communication between the provider and the patient. A handout can be generated for patients so they can see their goals and progress – a crucial factor as studies have shown that patients don't remember all of the physician's instructions.

Charles Safran, MD, Chief

QUALITY IMPROVEMENT

The Division has created real-time dashboards to monitor 84 quality metrics for patients with diabetes. This approach, which monitors not only trends in physiological variables but also physician interventions, is being evaluated in the Joslin Dubai Diabetes Center.

EDUCATIONAL PROGRAMS

Dr. Charles Safran directs the fellowship program that is part of the Harvard/HST Medical Informatics Training Program funded by the National Library of Medicine. We had four post-doctoral fellows this year, three of which graduated in June and the fourth will remain for a second year.

Dr. Warner V. Slack, together with other physicians from BIDMC, teaches a course for Harvard College undergraduates, "The Quality of Health Care in America." Dr. Stephen Locke is the founding course director for HST921, a graduate elective in the Harvard-MIT Division of Health Sciences and Technology (HST) which is taught every spring semester. Dr. Stan N. Finkelstein co-directs the Harvard MD/MBA program. Along with Dr. Safran, he co-directs HMS IN 601 "Medicine & Management."

FACULTY

Howard L. Bleich, MD
James A. Cartreine, PhD
Roger B. Davis, SCD
Meghan M. Dierks, MD
Henry J. Feldman, MD
Stan N. Finkelstein, MD
James Gray, MD
John D. Halamka, MD
Steven E. Locke, MD
Alexa T. McCray, PhD
Larry Nathanson, MD
David M. Rind, MD
Charles Safran, MD
Daniel Z. Sands, MD, MPH
Warner V. Slack, MD

RESEARCH ACTIVITIES

Dr. Alexa McCray is funded from the Boston area Autism Consortium to conduct research leading to methods for the integration and dissemination of the results of autism research through the use of advanced informatics technologies. Dr. Henry Feldman, along with Dr. Thomas Delbanco, is conducting a 2-year multicenter trial of opening primary care notes via a patient portal and examining doctor/patient relationships, provider workload and patient satisfaction. He is directing the technical aspects of the trial which is funded by the Robert Wood Johnson Foundation. He has also applied his research interests in designing a functional prototype of the PatientSite patient portal at BIDMC.

Dr. James Gray's research is focused on advancing the integration of evolving information technologies into the practice and evaluation of newborn care, while Dr. Meghan Dierks' is focused on Systems Engineering/Human Factors Engineering–applied human performance in high-risk settings such as the Intensive Care Unit and Operating Room. Dr. Charles Safran is funded by the Center for Disease Control and Prevention to support the informatics strategy related to disaster preparedness and countermeasure response to address epidemiological problems, such as pandemic influenza. Dr. James A. Cartreine is developing a self-guided interactive media program to deliver treatment of depression to astronauts on the Space Station, the Moon and Mars; and a multimedia, computer-based, self-directed, autonomous, stress and anxiety-management countermeasure to train crewmembers how to recognize, assess, prevent and manage stress and anxiety on extended spaceflights. Dr. Shane Reti leads the Division's international informatics research with evaluation of cultural attitudes towards information technology in health care in the Middle East. He is also conducting a study using cell phone text messaging to improve the management of gestational diabetes in Dubai.

Doctors from Dubai collaborate with Division faculty.

HONORS AND AWARDS

Dr. James Cartreine received the Distinguished Scholar Award at the International Conference on Advances in Management.

Dr. Steven Locke received the Stangler Prize for innovation from the American Association for Technology in Psychiatry; and he was made a Distinguished Life Fellow in the American Psychiatric Association.

SELECTED PUBLICATIONS

Vizenor LT, Bodenreider O, McCray AT. Auditing associative relations across two knowledge sources. *J Biomed Inform* 2009 Jun; 42:426-39.

Talmon J, Safran C, de Marin H, Geissbuhler A, Degoulet P. A look forward to online only publishing. *Int J Med Inform* 2008 Jan; 77:1-3.

McCray AT, Lee K. Exploring semantic locality patterns in the biomedical literature. *Intelligent Data Analysis in Biomedicine and Pharmacology* 2008; 63-68.

Aronsky D, Leong TY, Talmon J, Haux R, Safran C. Writing for publication in biomedical informatics. *AMIA Annu Symp Proc* 2008; 1229-32.

Berkman M, Ufberg J, Nathanson LA, Shapiro NI. Anion gap as a screening tool for elevated lactate in patients with an increased risk of developing sepsis in the Emergency Department. *J Emerg Med* 2009; 36(4):391-4.

McCray AT, Lee K. Exploring semantic locality patterns in the biomedical literature. *Intelligent Data Analysis in Biomedicine and Pharmacology* 2008; 63-68.

Tisminetzky M, Bray B, Miozzo R, Aupont O, Locke S, McLaughlin T. Identifying classes of response to treatment of depression, anxiety and function in patients after an acute coronary syndrome (L13). *Am J Epidemiol* 2009; 169(suppl):S1-S6.

Marin HF, Safran C. Celebrating health informatics–a sampling of MEDINFO 2007. *Int J Med Inform* 2009; 78 Suppl 1:S1-2.

Safran C, Shabot M., Munger S, Holmes JH, Steen EB, Lumpkin JR, Detmer E. Program requirements for fellowship education in the subspecialty of clinical informatics. *J Am Med Inform Assoc* 2009; 16:158-66.

Reti SR, Feldman HJ, Safran C. Governance for personal health records. *J Am Med Inform Assoc* 2009; 16(1):14-7.

Sands DZ. Failed connections: why connecting humans is as important as connecting computers. *Medscape J Med* 2008; 10:262.

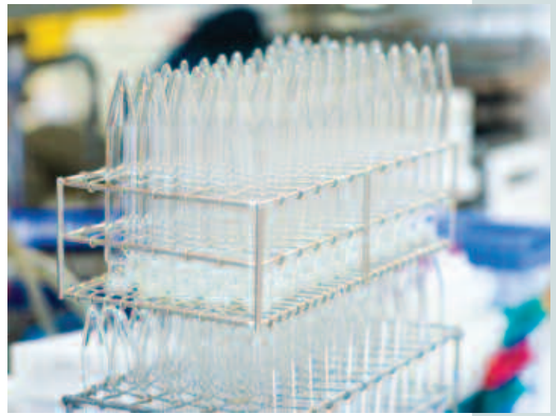
Division of Clinical Nutrition

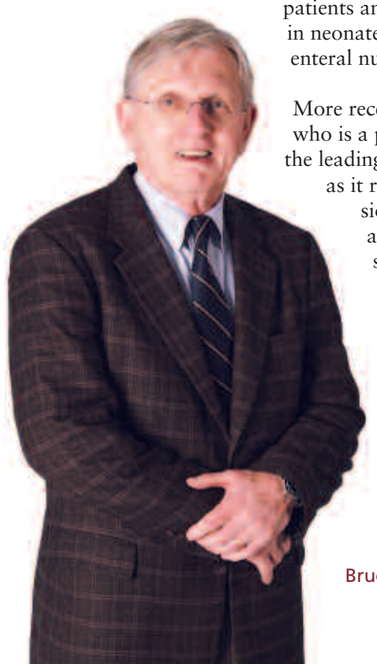
The Division of Clinical Nutrition has become primarily a research division since 2002 when the clinical activities of the Nutrition Support Service at Beth Israel Deaconess Medical Center was discontinued, including the fellowship program which trained more than 100 fellows over a period of 26 years. More than 30 of these trainees have become full Professors of Medicine or Surgery.

RESEARCH ACTIVITIES

The Nutrition/Infection Laboratory directed by Dr. Bistrian has been investigating the pathophysiology of protein calorie malnutrition, the interactions of nutrition and infection, the development of immune-enhancing enteral feeding formulas and novel parenteral fats including medium chain triglycerides, structured lipids and marine oils, and investigations into the medical and surgical treatment of obesity. Pei-Ra Ling, MD is a long-time research collaborator of Dr. Bistrian involved in animal studies of systemic inflammation due to infection, burn injury, or endotoxin exposure. The laboratory has also been involved in collaborative laboratory and clinical research with investigators at Tufts University and Children's Hospital in the role of fish oil supplementation orally to reduce the consequences of HAART in HIV patients and parenterally to treat liver failure in neonates requiring long-term total parenteral nutrition.

More recently with David Driscoll, PhD, who is a pharmacist widely recognized as the leading expert in particle size technology as it relates to the stability of lipid emulsions employed in feeding solutions and as drug vehicles, substantial research has been conducted in small animals demonstrating oxidative injury when some commercially available emulsions are infused. In part as a result of this work, Dr. Driscoll was appointed Vice Chairman of Parenteral Products Committee of the United States Pharmacopeia and co-directed the creation of a Sterile Products (797) chapter that enhances infusion safety. These guidelines are enforceable by the Food and Drug Administration. Dr. Driscoll published the first validated method for establishing the stability and subsequent safety of intravenous lipid emulsion infusions in the US based on this research. This has led to the completion of the Official USP Monograph, Chapter 729, that details the specifications for safe lipid emulsions. This Chapter was accepted in 2007 and will be enforceable by the Food and Drug Administration in January 2008. In partial recognition of this fine work Dr. Driscoll was the first awardee of the Stanley Serlick Award by the American Society for Parenteral and Enteral Nutrition in recognition of his contributions to improving safe practices for parenteral nutrition in 2008, and The Stanley Dudrick Research Scholar Award in 2009 for excellence in nutritional research. Dr. Driscoll left the BIDMC at the end of 2009 to enter private industry.

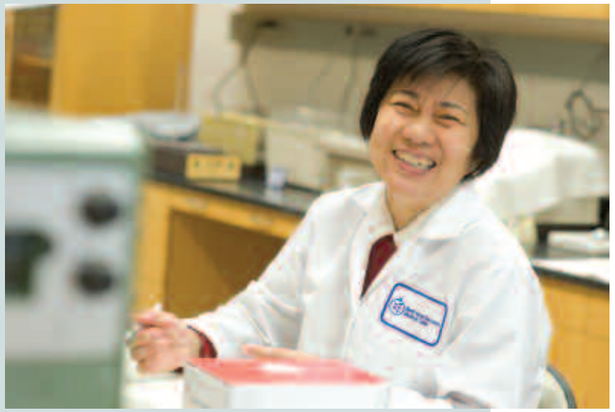




Bruce R. Bistrian, MD, Chief

HONORS AND AWARDS

Dr. Bistrian has been on the editorial board of the *Harvard Health Letter* and the *Woman's Health Watch* for more than 10 years. Dr. Bistrian is also a long-term member of the Editorial Board of *Critical Care Medicine*. He was appointed Vice Chairman of the International Editorial Advisory Board of the *European Journal of Clinical Nutrition* for 2007-2009. Dr. Bistrian also continues to serve on the Institutional Review Board, a role he has performed either at the former New England Deaconess Hospital and now the Beth Israel Deaconess Medical Center for nearly three decades. Dr. Bistrian served on the Board of the Federation of American Societies for Experimental Biology and as its President. He was also reappointed for 2007-2010 to the Committee on Military Nutrition Research of the Institute of Medicine and appointed this year as Chairman of the Nutrition Risk Standing Review Panel of the NASA Human Research Program. In relation to the latter we made our recommendations at a recent 3 day meeting at NASA headquarters in Houston regarding space flight for return trips to the Moon and proposed trips to Mars.



Pei-Ra Ling, MD

FACULTY

Bruce R. Bistrian, MD, PhD
David Driscoll, PhD
Pei-Ra Ling, MD
Karen McCowen, MD

SELECTED PUBLICATIONS

Singh H, Dumas GJ, Silvestri AP, Young S, Martin CR, Bistrian BR, Driscoll DF. Physical compatibility of neonatal total parenteral nutrition admixtures containing organic calcium and inorganic phosphate salts in a simulated infusion at 37 degrees C. *Pediatr Crit Care Med* 2009; 10:213-6.

Driscoll DF, Ling PR, Andersson C, Bistrian BR. Hepatic indicators of oxidative stress and tissue damage accompanied by systemic inflammation in rats following a 24-hour infusion of an unstable lipid emulsion admixture. *J Parenter Enteral Nutr* 2009; 33:327-35.

Woods MN, Wanke CA, Ling PR, Hendricks KM, Tang AM, Andersson CE, Dong KR, Sheehan HM, Bistrian BR. Metabolic syndrome and serum fatty acid patterns in serum phospholipids in hypertriglyceridemic persons with human immunodeficiency virus. *Am J Clin Nutr* 2009; 89:1180-7.

Driscoll DF, Thoma A, Franke R, Klütsch K, Nehne J, Bistrian BR. Lipid globule size in total nutrient admixtures prepared in three-chamber plastic bags. *Am J Health Syst Pharm* 2009; 66:649-56.

Ling PR, Bistrian BR. Comparison of the effects of food versus protein restriction on selected nutritional and inflammatory markers in rats. *Metabolism* 2009; 58:835-42.

Driscoll DF, Ling PR, Bistrian BR. Pharmacopeial compliance of fish oil-containing parenteral lipid emulsion mixtures: Globule size distribution (GSD) and fatty acid analyses. *Int J Pharm* 2009; 379:125-30.

Woods MN, Wanke CA, Ling PR, Hendricks KM, Tang AM, Knox TA, Andersson CE, Dong KR, Skinner SC, Bistrian BR. Effect of a dietary intervention and n-3 fatty acid supplementation on measures of serum lipid and insulin sensitivity in persons with HIV. *Am J Clin Nutr* 2009 Oct; 90(6):1566-78

Joy J, Silvestri AP, Franke R, Bistrian BR, Nehne J, Newton DW, Driscoll DF. Calcium and phosphate compatibility in low-osmolarity parenteral nutrition admixtures intended for peripheral vein administration. *J Parenter Enteral Nutr* 2009; 34(1):46-54

Bistrian B. Nutritional Assessment in Cecil and Loeb Textbook of Medicine. 23rd Edition. Saunders, Philadelphia, 2010.

Bistrian B, Driscoll D. Enteral and Parenteral Nutrition in Harrison's Principles of Internal Medicine, McGraw Hill, 2010.

Division of Endocrinology, Diabetes & Metabolism

The mission of the Endocrinology, Diabetes and Metabolism Division is to provide clinical care, consultation and training, and to perform basic and clinical research in the areas of endocrinology and metabolism.

CLINICAL ACTIVITIES

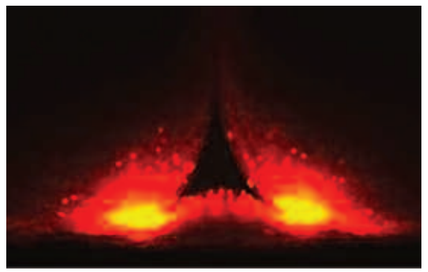
The clinical program is a joint venture with the Joslin Diabetes Center. This collaboration joins the nationally-known BIDMC endocrinology practice with the illustrious and world-renowned diabetes clinical practice at the Joslin. The combined program in Endocrinology, Diabetes and Metabolism ranked 13th in the nation in the 2009 *US News & World Report* list of "Best Hospitals" in the US. Dr. James Hennessey is Director of the Clinical Endocrinology Program and Dr. Martin Abrahamson is the Medical Director of the Joslin Diabetes Center.

The greater size and overall strength of the combined clinical program have allowed for growth. The Division added two new full-time clinical faculty members and continues to develop new programs, including initiatives in obesity, nutrition and polycystic ovary syndrome. A full range of outpatient and inpatient endocrine services is available for problems including diabetes, obesity, thyroid disease, metabolic bone disease (especially osteoporosis), calcium disorders, pituitary disease, adrenal disease, and reproductive and growth disorders. Outpatient consultation services are available in the Shapiro Clinical Center. In the last year, the Division increased outpatient visits by ten percent. The highly successful Thyroid Nodule Clinic offers the coordinated services of radiology, pathology, surgery and endocrinology. This results in a higher level of customer satisfaction, as comprehensive services are available in one visit. The Osteoporosis Prevention and Treatment Center, directed by Dr. Harold Rosen, offers expert consultative services and state-of-the-art dual energy X-ray absorptiometry to diagnose patients with osteopenia and osteoporosis. The Division has expanded its neuroendocrine-pituitary service with a monthly multi-disciplinary conference including neuro-surgery, neurology, endocrinology, neuro-radiology, neuro-opthamology, and radiation oncology.

Barbara B. Kahn, MD, Chief

QUALITY IMPROVEMENT

Among the Quality Improvement activities of the Division are two programs to monitor the adequacy and disposition of thyroid biopsies and to assess antithyroid therapy in patients with Graves' disease. In the thyroid program, the biopsies are tracked and the safety of antithyroid drug therapy is monitored.

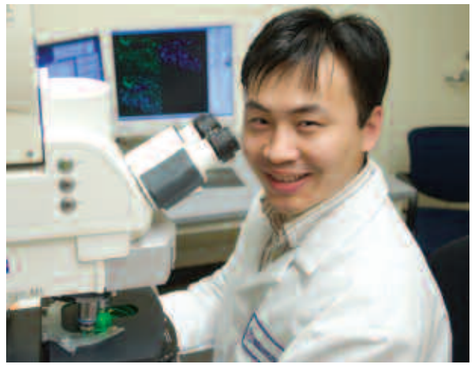


AgRP neurons in the Arcuate hypothalamus, which play key roles in regulating glucose and energy homeostasis, are genetically tagged by the red fluorescent protein - td Tomato. These, and related genetic tools, make it possible to manipulate the activity of these neurons in awake, behaving mice.

EDUCATIONAL PROGRAMS

The Division recruits three new subspecialty fellows yearly into a unified fellowship training program with the Joslin Diabetes Center. The director of the Fellowship Program is Evan Rosen, and the site director for the Joslin is Allison Cohen. Alan Malabanan serves as Associate Director for Clinical Education.

The BIDMC/Joslin fellowship program was recently reviewed by the ACGME and was found to be performing at an excellent level. The clinical year is conducted jointly with Brigham and Women's Hospital, and involves inpatient rotations at BIDMC and Brigham and Women's Hospital, continuity clinics in endocrinology and diabetes at both BIDMC and the Joslin, and sub-specialty clinics in pediatric endocrinology, lipids, reproductive endocrinology, metabolic bone disease and obesity. A major aspect of the fellowship training is an in-depth research experience in one of the outstanding laboratories at BIDMC, Joslin or other Boston area research programs. Many graduates remain in academia. The program is supported by two NIH training grants. In addition to nine clini-



Dong Kong, PhD, Research Fellow in Dr. Lowell's lab

HONORS AND AWARDS

Terry Maratos-Flier, MD who continues to carry out basic research, became the Director of the BIDMC Office for Academic Careers and Faculty Development.

Christos Mantzoros, MD, DSc received the Hygeia Award from the New England Hellenic Medical and Dental Association for Lifetime Contributions to Science and Hellenism.

Tony Hollenberg, MD received a 2008 Honorary Phi Beta Kappa at Harvard University.

Evan Rosen, MD, PhD, received two new NIH R01 awards, including one administered through the Roadmap Program, and was elected to the American Society for Clinical Investigation.

Martin Abrahamson, MD, Medical Director at the Joslin Clinic, has been chosen to receive the inaugural Samuel Eichold II Memorial Award for contributions to diabetes from the American College of Physicians in April 2011.

Barbara Kahn, MD, was the Roger Guillemin Nobel Lecturer at the Salk Institute in La Jolla, CA, and the Inaugural Willard J. and Priscilla F. Visek Lecturer at the University of Illinois, Urbana. She was cited as one of the Top Doctors in Endocrinology reported in *Boston Magazine*. She was also selected to receive the Gerald Aurbach Award for outstanding contributions to research in Endocrinology at the Endocrine Society Annual Meeting in June, 2010.

Johanna Pallotta, MD was chosen to receive the AACE Outstanding Clinical Endocrinologist Award in April 2010 in recognition of her "dedicated and compassionate care provided to patients with Endocrine diseases and exceptional knowledge and expertise in the field of clinical endocrinology."

Jim Hennessey, MD was named the Chair of the Public Health Committee for the American Thyroid Association.

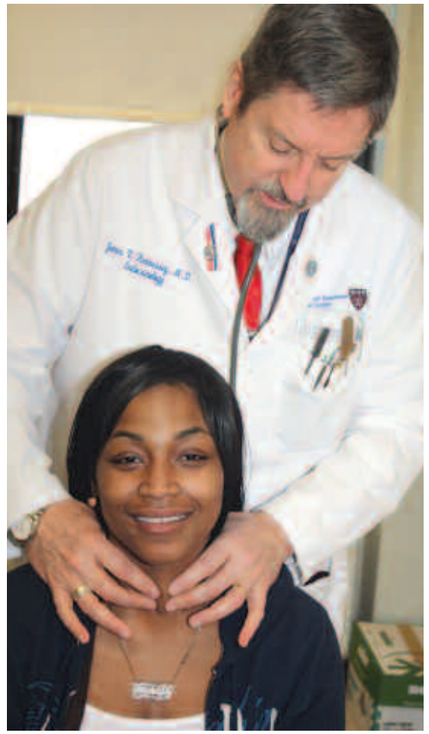
FACULTY

Martin Abrahamson, MD
Christian Bjorbaek, PhD
Allison Cohen, MD
Jody Dushay, MD
Jeffrey Flier, MD
Jeffrey Garber, MD
Alina Gavrila, MD
Pamela Hartzband, MD
James Hennessey, MD
Mark Herman, MD
Anthony Hollenberg, MD
Barbara Kahn, MD
Young-Bum Kim, PhD
Brad Lowell, MD, PhD
Alan Malabanan, MD
Christos Mantzoros, MD, DSc
Eleftheria Maratos-Flier, MD
Johanna Pallotta, MD
Odile Peroni, PhD
Pavlos Pissios, PhD
Arturo Rolla, MD
Evan Rosen, MD, PhD
Harold Rosen, MD
Amin Sabet, MD
Shanti Serdy, MD
Greeshma Shetty, MD
Mala Sivanandy, MD
Richard Spark, MD
Gordon Strewler, MD
Anny Usheva, PhD
Janice Zabolotny, PhD
Laura Zemany, MD

cal fellows there are more than fifty postdoctoral research fellows working within the Endocrine Division research laboratories. Endocrine faculty also participate in the education of medical students and residents.

RESEARCH ACTIVITIES

The Division has a highly successful, cutting-edge research portfolio which includes research initiatives supported by the National Institutes of Health, private foundations and the pharmaceutical industry. Key research areas include in vivo physiology, adipocyte biology, cell signaling, gene transcription, mouse genetics, hormone action and resistance, neuroendocrinology of obesity and glucose homeostasis, insulin secretion, basic investigations of gene structure and function, and clinical studies in the pathophysiology of obesity and type 2 diabetes. The entire research division moved to state-of-the-art laboratory space in the new BIDMC Center for Life Science near the Harvard Medical School quadrangle in August, 2008.
In addition to monthly joint lab meetings, the entire Division has a yearly research retreat at which many of the trainees have an opportunity to present their work.



James Hennessey, MD, Clinical Director of Endocrinology, examines the glands of a thyroid patient.

Division investigators such as Jeff Flier, Barbara Kahn, Brad Lowell, Terry Maratos-Flier, Christian Bjorbaek, Christos Mantzoros and Evan Rosen are well-known for their research in diabetes, obesity, and energy metabolism. A particular strength is the investigation of the pathogenesis of obesity, including leptin biology and signaling, hypothalamic peptides and appetite regulation, neuronal circuitry, reward behavior and regulation of adipogenesis. These investigators also have programs investigating the molecular mechanisms for insulin resistance in diabetes and obesity. Specific studies relate to insulin signaling including the role of protein tyrosine phosphatases and suppressors of cytokine signaling, regulation of glucose transport in insulin resistance and the role of novel adipocyte-secreted molecules in insulin resistance. Studies of insulin secretion focus on the role of uncoupling proteins. Techniques include sophisticated mouse genetics, viral vectors, state-of-the-art in vivo metabolic assessment of rodent models of obesity, electrophysiology and patient-based studies.

The Division has a large NIH-funded Program Project in obesity pathophysiology with a primary focus on the biology of the fat-derived hormone leptin, including the physiologic role of this hormone in the integration of energy balance, signaling pathways mediating the biological effects of leptin, leptin receptor biology, mechanisms of leptin resistance and behavioral aspects of leptin action. Other work using mouse genetics and gene targeting technologies investigates the basic mechanisms regulating energy expenditure and thermogenesis, including the biology of brown adipose tissue, novel uncoupling proteins and beta adrenergic receptors. Studies using neuron-specific knockout and knockin approaches are defining the functional neurocircuitry of body weight control. The Division faculty have other large NIH collaborative grants including one focused on the epigenetics of obesity.

Tony Hollenberg is a leader in the area of thyroid hormone action and nuclear receptor function. His group also studies the role of nuclear co-activator and co-repressor proteins and their involvement in cell signaling. Anny Usheva is exploring basic mechanisms of gene regulation at the transcription level. A specific interest is the effect of nutrition on transcription, and computational analyses are carried out in collaboration with the Theoretical Physics Division at the National Laboratory in Los Alamos.

Clinical and translational research activities of Christos Mantzoros' group focus on leptin physiology, the etiology and treatment of the HIV-associated metabolic syndrome and the role of IGF-1 in the pathogenesis of malignancy.

Christos Mantzoros, MD, DSc

SELECTED PUBLICATIONS

Astapova I, Lee LJ, Morales C, Tauber S, Bilban M, Hollenberg AN. The nuclear corepressor, NCoR, regulates thyroid hormone action in vivo. *Proc Natl Acad Sci* 2008; 105:19543-19548.

Badman MK, Koester A, Flier JS, Kharitonenkov A, Maratos-Flier E. Fibroblast growth factor 21-deficient mice demonstrate impaired adaptation to ketosis. *Endocrinology* 2009 Nov; 150(11):4931-40. Epub 2009 Oct 9.

Fargnoli J, Fung T, Olenczuk D, Chamberland J, Hu FB, Mantzoros CS. Adherence to healthy eating patterns is associated with increased circulating total and high molecular weight adiponectin and decreased resistin concentrations in women from the Nurses' Health Study. *Am J Clin Nutr* 2008; 88(5):1213-24.

Hill JW, Williams KW, Ye C, Luo J, Balthasar N, Coppari R, Cowley MA, Cantley LC*, Lowell BB*, Elmquist JK*. Acute effects of leptin require PI3K signaling in hypothalamic proopiomelanocortin neurons in mice. *J Clin Invest* 2008; 18:1796-805. * Senior co-authors.

Huo L, Gamber K, Greeley S, Silva J, Huntoon N, Leng XH, Bjørbaek C. Leptin-dependent control of glucose balance and locomotor activity by POMC neurons. *Cell Metab* 2009 Jun; 9(6):537-47.

Preitner F, Mody N, Graham TE, Peroni OD, Kahn BB. Long-term fenretinide treatment prevents high fat diet-induced obesity, insulin resistance and hepatic steatosis. *Am J Physiol Endo Metab* 2009; 297:E1420-E1429.

Ramadoss P, Unger-Smith NE, Lam FS, Hollenberg AN. STAT3 targets the regulatory regions of gluconeogenic genes in vivo. *Mol Endocrinol* 2009 June; 23(6):827-37.

Smith LP, Nierstenhoefer M, Yoo SW, Penzias AS, Tobiasch E, Usheva A. The bile acid synthesis pathway is present and functional in the human ovary. *PLoS One* 2009; 4(10):e7333.

Tong Q, Ye C, Jones JE, Elmquist JK, Lowell BB. Synaptic release of GABA by AgRP neurons is required for normal regulation of energy balance. *Nat Neurosci* 2008; 11:998-1000.

Xue B, Pulinikunnil T, Murano I, Bence KK, He H, Minokoshi Y, Asakura K, Lee A, Haj F, Furukawa N, Catalano KJ, Delibegovic M, Balschi JA, Cinti S, Neel BG, Kahn BB. Neuronal protein tyrosine phosphatase 1B deficiency results in inhibition of hypothalamic AMPK and isoform-specific activation of AMPK in peripheral tissues. *Mol Cell Biol* 2009; 29:4563-4573.

Division of Experimental Medicine

The mission of the Division of Experimental Medicine is to perform laboratory research that provides insights into developing clinical therapies for patients with unmet needs. The Division has diversified considerably from its initial focus on HIV and on hematopoiesis, moving into the biology of solid tumors, angiogenesis, organ transplantation, cannabinoids and the brain.

The Division currently numbers 23 scientists and support personnel. Staff are divided into five research teams, each headed by a faculty member. Although each team has its own set of projects, collaborations are frequent and expertise and reagents are shared.

RESEARCH ACTIVITIES

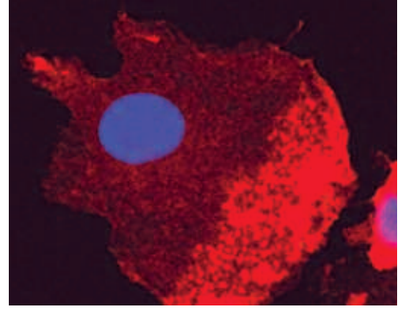
Dr. Jerome Groopman's laboratory is studying novel pathways in the immune response to HIV as well as molecular targets in a variety of cancers that may be susceptible to experimental apoptosis inducers. His work has progressed on cell cycle inhibitors as potential therapeutics in lymphoma, particularly mantle cell lymphoma that has a signature genetic abnormality with over-expression of cyclin D. Clinical trials of the inhibitor ON1910 began at NIH and other centers, enrolling patients with lymphoma and myelodysplasia.

Dr. Hava Avraham, PhD is pursuing several researcher studies: VEGF-VEGFR 1 autocrine survival system and its role in chemotherapy resistance of breast cancer stem cells; BRCA1 and oxidative stress in sporadic and inherited breast cancer and the functional interaction of BRCA1 and Oct 1; the role of Kelch related proteins, such as Mayven, Mrp2 and NRP/B, in cytoskeleton reorganization during invasion and migration of tumor cells; and endocannabinoid regulation of stem cells.

Shalom Avraham, MD, PhD is focusing on the biology of the blood-brain barrier in breast cancer metastasis and in HIV infection. He is also elucidating how the kelch-related proteins NRP/B, Mayven and Mrp2, act in glial cell differentiation and brain tumorigenesis. Finally, he is characterizing the effects of the endocannabinoid system on neural stem cells.

Dr. John Ladias, over the past year, submitted numerous grant applications. His success in securing funding will allow him to pursue structure-based inhibitors of BRCA1 to enhance breast cancer sensitivity to radiation therapy and chemotherapy, as well as the structural basis for the TSC1-TSC2 complex function.

Dr. Ernest Terwilliger's group has two primary complementary areas of interest. One involves gene therapy approaches to regener-



Dendritic cell stained for leukocyte-specific protein-1 redistributed to the plasma membrane during cell migration. LSP-1 may be important in dendritic cell recognition of pathogens like HIV.

FACULTY

Hava Avraham, PhD
Shalom Avraham, MD, PhD
Anil Prasad Bailluguttu, PhD
Gabriel Birrane, PhD
Jerome Groopman, MD
John Ladias, MD
Huchun Li, PhD
Seyha Seng, PhD
Ernest Tewilliger, PhD
Jianfeng Xu, MD, PhD
Xuefeng Zhang, PhD

HONORS AND AWARDS

Dr. Jerome Groopman was again awarded the Knowles Scholar for undergraduate teaching at Harvard College in 2009.

SELECTED PUBLICATIONS

Avraham HK, Lu TS, Seng S, Tachado SD, Koziel H, Makriyannis A, Avraham S. Cannabinoids inhibit HIV-1 Gp120-mediated insults in brain microvascular endothelial cells. *J Immunol* 2008; 181:6406-16.

Birrane G, Soni A, Ladias JAA. Structural basis for DNA recognition by the human PAX3 homeo domain. *Biochemistry* 2009; 48:1148-55.

Seng S, Avraham HK, Birrane G, Jiang S, Li H, Katz G, Bass C, Zagozdzon R, Avraham S. NRP/B mutations impair Nrf2-dependent NQO1 induction in human primary brain tumors. *Oncogene* 2009; 28(3):378-89.

Hinton CV, Avraham S, Avraham HK. Contributions of integrin-linked kinase to breast cancer metastasis and tumorigenesis. *J Cell Mol Med* 2008; 12(5A):1517-26.

Durney MA, Birrane G, Anklin C, Soni A, Ladias JAA. Solution structure of the human Tax-interacting protein-1. *J Biomol NMR* 2009; 45:329-34.

Cournarie F, Wattel A, Kamel S, Terwilliger EF, Brown EM, Brazier M. The calcium-sensing receptor is involved in strontium ranelate-induced osteoclast apoptosis: New insights into the associated signaling pathways. *J Biol Chem* 2009; 284(1):575-84.

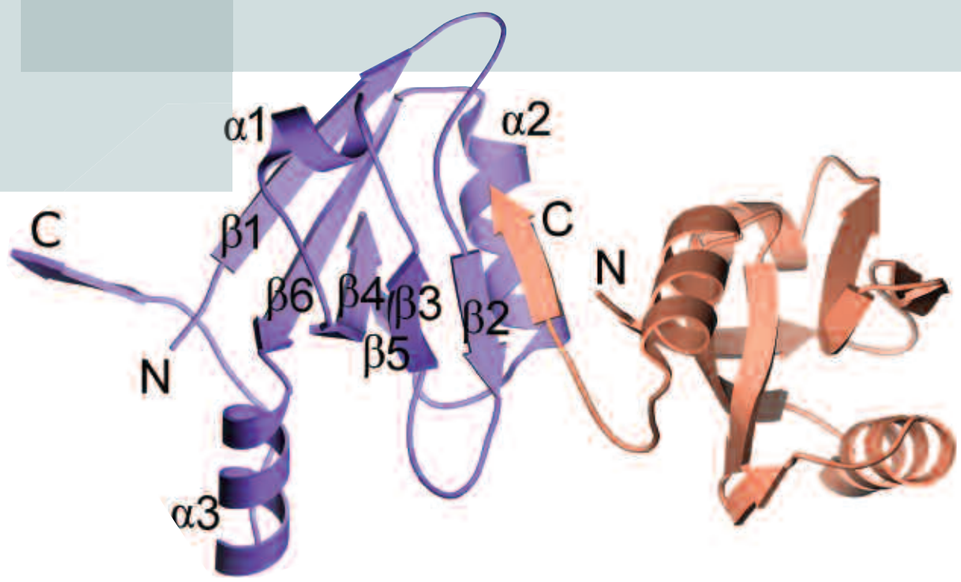
Li H, Sekine M, Seng S, Avraham S, Avraham HK. BRCA1 interacts with Smad3 and regulates Smad3-mediated TGF-beta signaling during oxidative stress responses. *PLOS One* 2009; 4(9)e7091.

Prasad A, Park IW, Allen H, Zhang X, Reddy MVR, Boominathan R, Reddy EP, Groopman JE. Styryl sulfonyl compounds inhibit translation of cyclin D1 in mantle cell lymphoma cell. *Oncogene* 2009; 28(12):1518-28.

Ross HE, Freeman S, Spiegel L, Ren X-H, Terwilliger EF, Young LJ. Variation in oxytocin receptor density in the nucleus accumbens has differential effects on affiliative behaviors in monogamous and polygamous voles. *J Neurosci* 2009; 29(5):1312-18.

Ho KJ, Bass C, Kroemer AHK, Ma C, Terwilliger EF, Karp SJ. Optimized AAV8 produces hepatocyte-specific Cre-mediated recombination without toxicity or affecting liver regeneration. *Am J Physiol Gastrointest Liver Physiol* 2008; 295(2):G412-19.

Jerome E. Groopman, MD, Chief

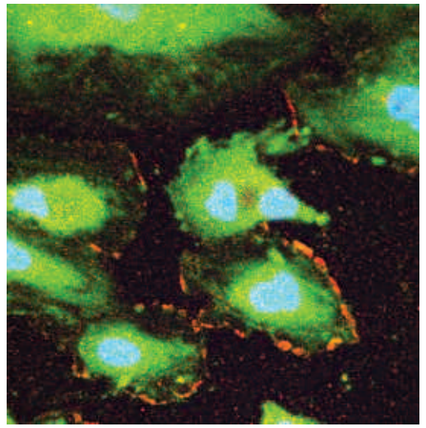


Crystal structure of the first PDZ domain from PDZK1 in complex with the C-terminal tail of the Scavenger receptor class B type-1. The structure was solved in collaboration with Dr. Oliver Kocher, Department of Pathology, BIDMC.

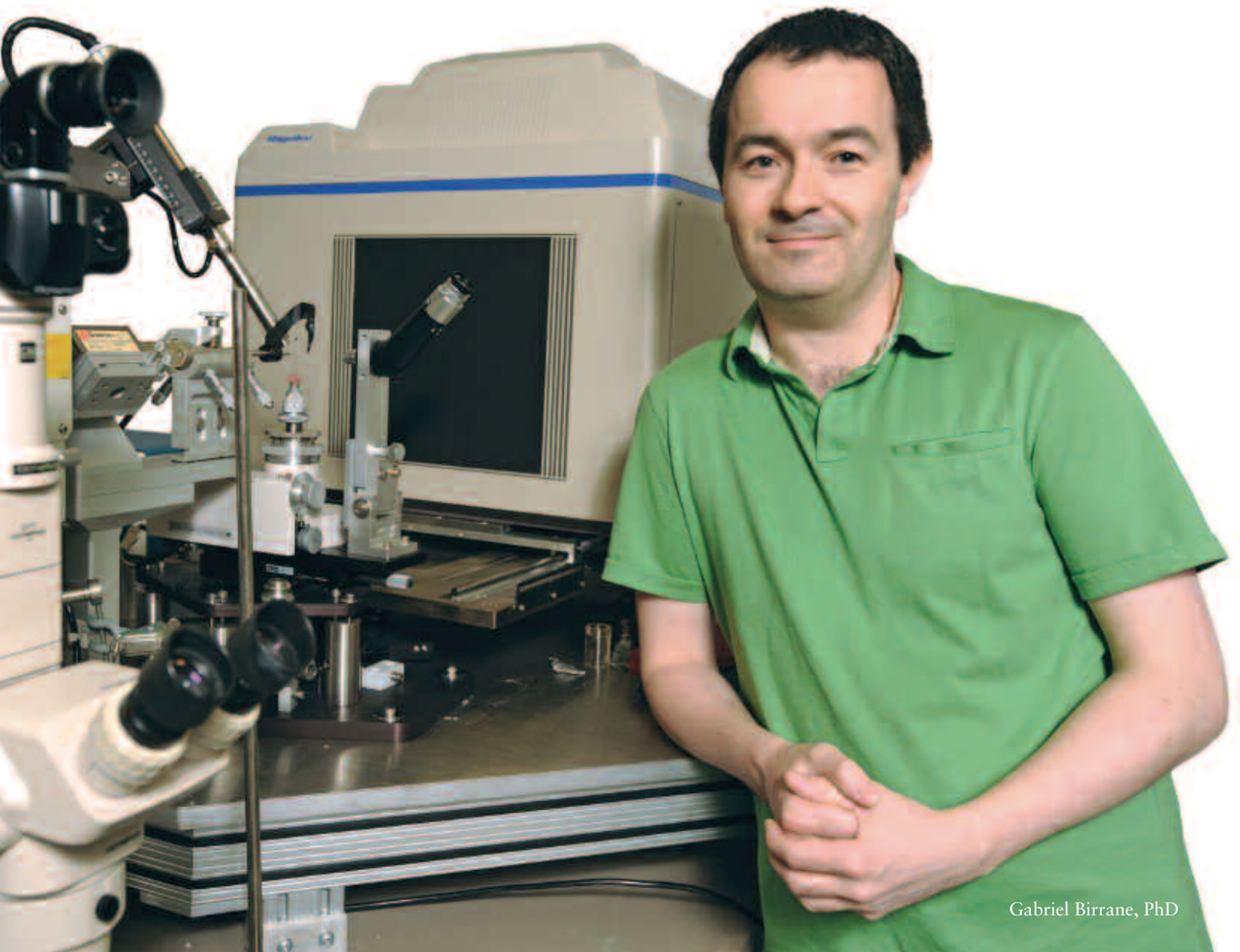
ative medicine. His projects aim to promote neural regeneration following spinal cord injury. Another project focuses on the growth of new bone matrix or articular cartilage after injury or osteoarthritis. He collaborates with investigators in the Division of Transplant Immunology, focusing on liver regeneration, immune tolerance and kidney development.

EDUCATIONAL PROGRAMS

Frequent seminars are open to all members of the Division. Fellows present their ongoing work and learn how to analyze and defend data. On other occasions, they lead a journal club, critically assessing published work relevant to their fields. In addition, there is training of postdoctoral fellows as well as graduate students and undergraduates in laboratory research.



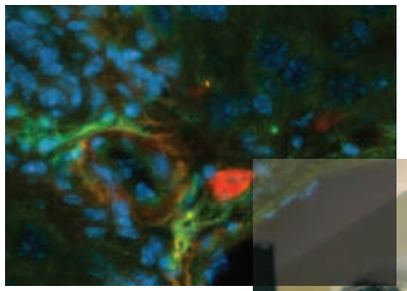
HIV-1 envelope protein gp120 (red) and activated integrin beta-1 (green) are co-localized on the surface of lymphatic endothelial cells (yellow). This may allow for lymphatic permeability and dissemination of HIV in the host.



Gabriel Birrane, PhD

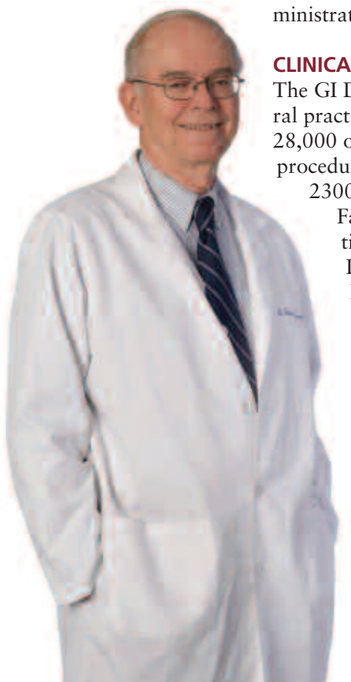
Division of Gastroenterology

The Gastroenterology Division at Beth Israel Deaconess Medical Center is one of the largest academic units in the United States on the basis of clinical volume, number and expertise of faculty, and scope of research activities. The Division employs 37 physicians and 8 research faculty, 18 clinical and research fellows, and 35 research associates.



Mouse liver regeneration shown 24 hours post-70% hepatectomy in wild type mice. Immunofluorescence microscopy showing CD34 progenitor cell marker (green, Alexa fluor 488); CD39L1 ectonucleotidase expression in portal nerves and myofibroblasts (red, Alexa fluor 594) and cell nuclei (Hoechst Blue DNA stain). x400

The goals of the Division are: to provide compassionate, timely and cost-effective patient care; to carry out cutting-edge clinical and basic research; to teach the science and art of our specialty; and to nurture the career development of our faculty. The Division organizes its clinical and academic activities under the leadership of J. Thomas Lamont, Chief of the Division; Myron Falchuk, Director of Clinical Services; Ram Chuttani, Chief of Endoscopy; Nezam Afdhal, Director of the Liver Center; Ciarán Kelly, Director of Fellowship Training; and Eileen Joyce, Administrative Director.



CLINICAL ACTIVITIES

The GI Division has one of the largest referral practices in the United States, seeing 28,000 outpatients and performing 27,000 procedures annually, including more than 2300 advanced procedures. Myron Falchuk is Director of Clinical Operations in GI, and Michael Curry is the Liver Center Clinical Director. The Division is annually listed in the top by *US News and World Report*. A new state-of-the-art Endoscopy Unit, opened in early 2008, provides our patients and physicians with a modern and patient-friendly facility that is one of the busiest in the New England region. Our Endoscopy Unit has one of the highest procedure volumes nationwide, and is well known for its highly skilled and successful treatment of patients referred for advanced endoscopic procedures. Janet Lewis, nurse manager of GI Endoscopy, supervises a professional team of more than 50 nurses, technicians, practice assistants and other staff.

Ram Chuttani, MB, BS and Douglas Pleskow, MD

Multidisciplinary Liver Tumor Group – Hepatocellular carcinoma is currently the fastest growing cause of cancer-related death among men. Favorable outcomes in this rapidly growing tumor can only be achieved with early diagnosis and treatment. The Liver Tumor Group at Beth Israel Deaconess Medical Center provides open access and rapid response to disease management by a multidisciplinary team. The group, under the direction of Gerond Lake-Bakaar, provides a comprehensive multidisciplinary service for both benign and malignant hepatocellular cancer, cholangiocarcinoma, gallbladder cancer, metastatic cancer and rarer forms of cancer.

J. Thomas Lamont, MD, Chief

QUALITY IMPROVEMENT

Under the leadership of Dan Leffler and Mark Aronson, the GI Division developed and tested a system to alert patients that they were due for a follow-up (screening) colonoscopy. Electronic medical records were reviewed to identify patients approaching the date for a surveillance (screening) colonoscopy based on prior findings at initial screening colonoscopy. Patients were randomized to standard of care group or a new intervention group which involved letters to PCPs and patients, and a phone call to all patients who had not scheduled a colonoscopy by their procedure due date. The intervention was very successful in improving adherence to endoscopic follow-up recommendations. Only a quarter of the patients in the standard of care area (no reminder by GI Division) scheduled their surveillance colonoscopy versus more than half in the intervention area. This work provides evidence to support the development of reminder systems to improve patient compliance with medical guidelines.

EDUCATIONAL PROGRAMS

The Gastroenterology Division sponsors one of the most competitive fellowship training programs in the country, under the direction of Ciarán Kelly and Douglas Horst. The Division has twelve ACGME-accredited fellows, four in each of the three years. We offer three training pathways for: basic researchers, clinical or translational researchers, or clinician/teachers. The Division also offers advanced one-year fellowships in liver disease, therapeutic endoscopy, motility and IBD. Seventy-five percent of our graduates enter academic full-time careers at top academic centers across the country and abroad.

HONORS AND AWARDS

Sanjiv Chopra, MB, BS was elected to Mastership of the American College of Physicians.

Adam Cheifetz, MD was listed in *Boston Magazine* as "Best of Boston" for Gastroenterology.

Xinhua Chen, PhD received the Young Investigator Award for Probiotic Research from the Global Probiotics Council.

Simon Robson, MB, CHB, PhD delivered the thirtieth Bernard Pimstone Lecture at the University of Cape Town Research Day.

Kenneth Falchuk, MD was listed as one of the "Best Doctors" in the US for 2008-2009.

Michelle Lai, MD and Dan Leffler, MD each received an NIH-K23 Mentored Research Award.

Jacqueline Wolf, MD was included in the Massachusetts Medical Law Report "Rx for Excellence."

Yury Popov, MD, PhD was appointed to the editorial board of the *American Journal of Physiology*: GI and Liver.

Douglas Pleskow, MD was named Man of the Year by the National Pancreas Foundation.

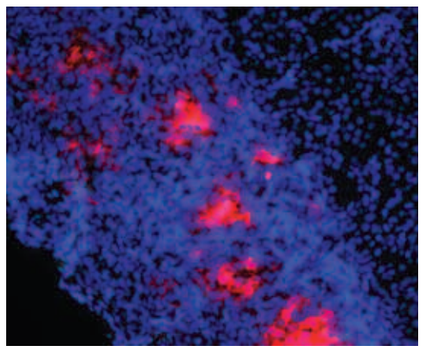
Helen Shields, MD was the Keynote Speaker at the Annual International Society for Pathophysiology Meeting in Shanghai.

Mark Peppercorn, MD was listed in Guide to America's Top Gastroenterologists and also in Best Doctors in America.

Daryl Lau, MD was named Program Director for the Harvard Hepatitis B Consortium, an NIDDK sponsored hepatitis B research network.

Alan Moss, MD received a Poster Award from the American College of Gastroenterology and the Excellence in Tutoring Award from the Academy at Harvard Medical School.

Steven Freedman, MD was the Alpha Omega Alpha Visiting Professor at Morehouse School of Medicine and was appointed as Chairman, Board of Trustees, Harvard Clinical Research Institute.

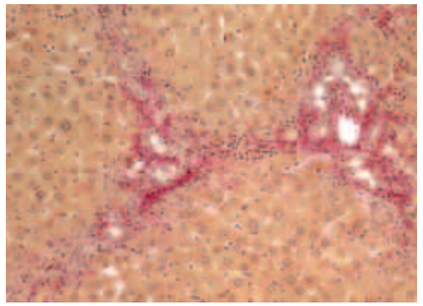


Mouse islets shown post-allotransplantation under renal capsule (DBA, wild type to C57BL/6, wild type at 72 hours). Immunofluorescence microscopy showing occasional caspase 3 (apoptosis-related, cysteine peptidase) expressing cells (green, Alexa fluor 488); high levels of insulin expression in beta cells (red, Alexa fluor 594) and cell nuclei (Hoechst Blue DNA stain). x200

Helen Shields, one of the leading teachers at Harvard Medical School, is course director of the second year medical school course "Gastrointestinal Pathophysiology." This course is annually rated as one of the highest by our medical students. Sanjiv Chopra, a faculty member in the Liver Center, is Faculty Dean for CME at Harvard.

RESEARCH ACTIVITIES

Basic science, translational and clinical research programs in GI are supported by extramural funding of approximately $7 million in 2008. A total of 13 faculty members engaged in basic research are supported by 21 grants from NIH, and additional grant support from disease-related foundations and industry. The GI Division occupies 14,000 square feet of laboratory space and is responsible for research training of 20 post-doctoral fellows.



Development of portal fibrosis in Cd39 null mouse 2 weeks following bile duct ligation. Inflammatory expansion of portal tracks with increased collagen (red on dark yellow) deposition in these and linking areas; tissue stains by Picro-sirius red solution. x200

FACULTY

Nezam Afdhal, MD
Harry Anastopoulos, MD
Michael Apstein, MD
Alphonso Brown, MD
Adam Cheifetz, MD
Xinhua Chen, PhD
Catherine Cheney, MD
Sanjiv Chopra, MB, BS
Ram Chuttani, MB, BS
Michael Curry, MD
Richard Doyle, MD
Keiichi Enjyoji, PhD
Kenneth Falchuk, MD
Myron Falchuk, MD
Steven Freedman, MD, PhD
Douglas Horst, MD
Gail Kaufman, MD
Andrew Keates, PhD
Sarah Keates, PhD
Ciarán Kelly, MD, MB
Susan Kelly, MD
Efi Kokkotou, MD, PhD, SC.D
Gerond Lake-Bakaar, MD
Michelle Lai, MD
J. Thomas Lamont, MD
Daryl Lau, MD
Daniel Leffler, MD
Anthony Lembo, MD
Raza Malik, MD
Diarmuid Manning, MD
Seema Maroo, MD
Alan Moss, MD
Mark Peppercorn, MD
Douglas Pleskow, MD
Yuri Popov, MD, PHD
James Rabb, MD
Simon Robson, MD, PhD
Stanley Rosenberg, MD
Mandeep Sawhney, MB, BS
Detlef Schuppan, MD, PhD
Sunil Sheth, MD, MB, BS
Helen Shields, MD
David Wang, MD, PhD
Jacqueline Wolf, MD
Yan Wu, PhD

Basic science research in GI is led by 14 faculty investigators, all of whom receive extramural research support. Nezam Afdhal's laboratory is exploring the contribution of mucin glycoproteins to cholesterol gallstone nucleation and the biophysics of mucin polymerization and gelation. Steven Freedman studies basic secretory mechanisms of pancreatic ductular secretion and the role of fatty acids and eicosanoids in cystic fibrosis. Ciarán Kelly and Xinhua Chen study intestinal immune responses to *Clostridium difficile* infections and the molecular mechanisms of probiotics. Daryl Lau's laboratory collaborates with investigators in the Infectious Diseases Division on immunopathogenesis of hepatitis B virus. Efi Kokkotou studies how brain-gut neuropeptides interact with adipocyte, neuronal and epithelial receptors during intestinal inflammation. Simon Robson and Keiichi Enjyoji explore basic themes in xenotransplantation and vascular biology, particularly the role of endothelial cell ectonucleotidases in thromboses, inflammation and liver disease. Detlef Schuppan's research group, including Yury Popov, explores the immunopathogenesis of celiac disease and mechanisms of liver injury related to fibrosis and cirrhosis. David Wang studies basic mechanisms of cholesterol gallstone disease including hormonal and genetic contributions to lithogenesis in mice and humans. Sarah Keates studies the molecular pathogenesis of *Helicobacter pylori* infection. The Skip Ackerman Center for Molecular Therapeutics, directed by Chiang Li and Andrew Keates, will initiate in 2010 the first clinical trial of an RNA inhibitor to treat familial intestinal polyposis.

The GI Division also has a well-funded and productive clinical research group of ten faculty investigators. Nezam Afdhal and his faculty co-investigators Michael Curry, Diarmuid Manning and Gerond Lake-Bakaar in the Liver Center conduct clinical trials in viral hepatitis and cirrhosis. The Pancreas Center, under the direction of Steven Freedman, studies genetic profiles in pancreatitis and novel therapies for chronic pancreatitis and cystic fibrosis. Ram Chuttani, Douglas Pleskow and Mandeep Sawhney in the Center for Interventional Endoscopy and the Swallowing Center are conducting trials of state-of-the-art technologies to diagnose and treat reflux esophagitis, GI cancer and pancreatico-biliary diseases. The Celiac Disease Center, staffed by Ciarán Kelly, Detlef Schuppan and Dan Leffler, is one of the largest of its kind in the US and is testing new diagnostic tests and treatment regimens for patients with gluten-sensitive enteropathy. The Motility Center, led by Tony Lembo, is studying new drugs for gastric retention and irritable bowel syndrome (IBS), and is the clinical arm of a large NIH-funded study of the placebo effect in IBS patients. The IBD Center, which includes Adam Cheifetz, Mark Peppercorn, Alan Moss and Ken Falchuk, is exploring new therapies for Crohn's disease and ulcerative colitis. Helen Shields is exploring histopathologic variants of Barrett's esophagus. Mandeep Sawhney studies quality measures in colon cancer screening and other endoscopic tests. Alphonso Brown specializes in pancreatic diseases and is exploring the role of endothelial cell molecules in the pathophysiology of acute pancreatitis and also as an early marker of severe acute pancreatitis.

Seema Maroo, MD and Joshua Hansen, Clinical Research Assistant.

SELECTED PUBLICATIONS

Moss A, Fernandez-Becker N, Jo Kim K, Cury D, Cheifetz AS. The impact of infliximab infusion reactions on long-term outcomes in patients with Crohn's disease. *Aliment Pharmacol Ther* 2008; 28(2):221-7.

Freedman SD, Uppot RN, and Mino-Kenudson M. Case records of the Massachusetts General Hospital: A 32 year old man with cystic fibrosis with abdominal pain and distention. *N Engl J Med* 2009; 361(8):807-16.

Lau DTY, Fish PM, Sinha M, Lemon SM, Gale M Jr. Patterns of IRF-3 activation, hepatic interferon-stimulated gene expression and immune cell infiltration in patients with chronic hepatitis C. *Hepatology* 2008; 47(3):799-809.

Hyett B, Martinez FJ, Gill BM, Mehra S, Lembo A, Kelly CP, Leffler DA. Delayed radionucleotide gastric emptying studies predict morbidity in diabetics with symptoms of gastroparesis. *Gastroenterology* 2009 Aug; 137(2):445-52.

Ornellas LC, Stefanidis G, Chuttani R, Gelrud A, Kelleher TB, Pleskow DK. Covered Wallstents for palliation of malignant biliary obstruction: primary stent placement versus reintervention. *Gastrointest Endosc* 2009; 70(4):676-83.

Popov Y, Patsenker E, Stickel F, Zaks J, Bhaskar KR, Niedobitek G, Kolb A, Friess H, Schuppan D. Integrin alphavbeta6 is a marker of the progression of biliary and portal liver fibrosis and a novel target for antifibrotic therapies. *J Hepatol* 2008; 48(3):453-64.

Shields HM, Recht A, Wang HH. Exposure to both radiation and chemotherapy increases the risk of Barrett's and multilayered epithelium. *Dig Dis Sci* 2009; 54:2143-2149.

Afdhal NH, Lok AS, Di Bisceglie AM. Clinical decisions. Management of incidental hepatitis C virus infection. *N Engl J Med* 2009; 360(18):1902-6.

Friedman DJ, Künzli BM, A-Rahim YI, Sevigny J, Berberat PO, Enjyoji K, Csizmadia E, Friess H, Robson SC. CD39 deletion exacerbates experimental murine colitis and human polymorphisms increase susceptibility to inflammatory bowel disease. *Proc Natl Acad Sci USA* 2009; 106(39):16788-93.

Badizadegan K, Wolf JL. Liver pathology in pregnancy. In: Odze RD, Goldblum JR, editors. Surgical pathology of the GI tract, liver, biliary tract, and pancreas. 2nd edition. Philadelphia: Saunders/Elsevier, Inc. 2009; p.1231-1244.

Kelly, CP, Lamont JT. Clostridium difficile – more difficult than ever. *N Engl J Med.* 2008; 359:1932-1940.

Division of General Medicine & Primary Care

The Division of General Medicine and Primary Care at BIDMC was established in 1972. We are a national leader in providing compassionate, high-quality care for patients from all walks of life; developing innovative medical education; and performing cutting-edge clinical and health services research. Major clinical programs include hospital medicine; Healthcare Associates (HCA) including programs on women's health and caring for patients with HIV; college health; palliative care; and ethics. Our research agenda includes projects designed to improve care for vulnerable populations; develop innovative approaches to clinical conditions and risk reduction; and foster patient-centered care and improved clinical decision making.

Russell S. Phillips, MD, Chief

CLINICAL ACTIVITIES

Healthcare Associates – Healthcare Associates (HCA) is our hospital-based primary care teaching practice. HCA provides care to over 40,000 patients and accounts for more than 100,000 visits annually, and in FY09, we increased our volume by more than 13% as we met the increased demand for primary care services. Louise Mackisack, MA, is the Division and HCA Administrative Director. Drs. James Heffernan and Daniel Sullivan serve as Medical Director and Associate Medical Director of the practice, respectively.

HCA is a leading site for innovation in patient care and teaching, and over the past year we have been increasing our capacity to serve as a patient-centered medical home and have developed a registry for patients with diabetes that will enable population-based management. We developed new guidelines for the management of patients who are prescribed narcotics chronically, and implemented these guidelines across the practice. We opened a post-discharge clinic, led by Dr. Lauren Doctoroff, with the goal of reducing hospital readmissions.

Hospital Medicine (Hospitalist) Program – Dr. Joseph Li directs the program, which continued its remarkable growth during this past year. The program's 33 physicians account for approximately 38,000 annual inpatient visits, a 10% increase from the last year. In 2009, we celebrated our tenth anniversary with Dr. Robert Wachter from University of California/San Francisco as our visiting professor and we hosted a symposium on hospital medicine.

College Health Program – Led by Dr. Kay Petersen, we work with local colleges and universities that seek BIDMC assistance to provide clinical services to their students.

Clinical Ethics Programs – Dr. Lachlan Forrow directs BIDMC's Ethics Programs.

Palliative Care Programs – The Palliative Care Consult Service, headed by Dr. Forrow, provides comprehensive, interdisciplinary consultation for BIDMC inpatients with life-threatening illnesses and their families, support for clinical staff, and bereavement follow-up.

QUALITY IMPROVEMENT

Healthcare Associates – HCA's Quality Improvement Program is led by Drs. Mark Aronson, Gila Kriegel and Hans Kim. Accomplishments from the past year include development of the diabetes registry and the capability of producing reports on important disease parameters; implementation of a flow-sheet for narcotic use in OMR (Online Medical Record); success in optimizing emergency response in HCA; development of specifications for a referral management system that would track high-risk referrals electronically; performance reviews that show that patients on anticoagulation treatment and patients with HIV receive care that meets or exceeds benchmarks; and implementing housestaff recommendations to improve our rate of immunization.

Stephanie Mueller, MD, Hospitalist

FACULTY

Kim Ariyabuddhiphongs, MD
Mark D. Aronson, MD
David August, MD
Nisha Basu, MD
Carol K. Bates, MD
Diane M. Brockmeyer, MD
Catherine Buettner, MD, MPH
Risa B. Burns, MD, MPH
Booker T. Bush, MD
Mary K. Buss, MD, MPH
Rafael Campo, MD
J. Jacques Carter, MD, MPH
Marc L. Cohen, MD
Lisa Conboy, MA, MS, ScD
Roger Davis, ScD
Tom Delbanco, MD
David Eisenberg, MD
Caitlin M. Fawcett, MD
Sara B. Fazio, MD
Leonor Fernandez, MD
Kelly D. Ford, MD
Lachlan Forrow, MD
Angela Fowler-Brown, MD, MPH
Frederic Goldman, MD
Peter H. Gonzalez, MD
Mary E. Hamel, MD, MPH
James J. Heffernan, MD, MPH
Thomas Isaac, MD, MBA
Joyce S. Jen, MD
John F. Jewett, MD
Katherine Johnston, MD
Ted Kaptchuk
Catherine Kerr, PhD
Hans S. Kim, MD
Gila R. Kriegel, MD
Bruce E. Landon, MD, MBA
Suzanne Leveille, PhD, RN
James W. Levenson, MD, MPH
Howard Libman, MD
Fenny Lin, MD
Julia Lindenberg, MD
Timothy S. Loo, MD
Weidong Lu, MB, MPH
Harvey J. Makadon, MD
Edward R. Marcantonio, MD, SM
Ellen P. McCarthy, PhD, MPH
Felipe J. Molina, MD
Kenneth J. Mukamal, MD, MPH
Long Huu Ngo, PhD
Richard A. Parker, MD
Kay M. Petersen, MD
Russell S. Phillips, MD
Jennifer E. Potter, MD
Kristin E. Remus, DO
Eileen E. Reynolds, MD
David Rind, MD
Daniel Z. Sands, MD, MPH
Mara A. Schonberg, MD, MPH
Amy N. Ship, MD
Gerald W. Smetana, MD
C. Christopher Smith, MD
Wendy Stead, MD
Daniel J. Sullivan, MD, MPH
William C. Taylor, MD
Michael Thane, MD
Michael Tierney, MD
Karen E. Victor, MD
Pamela Vohra, MD
Janice Walker, BSN, MBA
Peter Wayne, PhD
Christina Wee, MD, MPH
Saul Weingart, MD, PhD
Amy R. Weinstein, MD, MPH
Gloria Y. Yeh, MD, MPH
Li Zhou, MD, MPH

Hospital Medicine

Anu Elizabeth Abraham, MD
Andrew Ahn, MD, MPH
Suzanne Bertisch, MD, MPH
Alexander R. Carbo, MD
Meghan N. Cooper, MD
Jonathan T. Crocker, MD
Lauren Doctoroff, MD
John Fani Srour, MD
Elizabeth A. Farrell, MD
David B. Feinbloom, MD
Henry Feldman, MD
Chethan R. Gangireddy, MD
Caleb P. Hale, MD
James C. Hart, MD, MBA
Matthew P. Hill, MD
Grace Huang, MD
Bijal Jain, MD
Joseph M. Li, MD
Cindy Lien, MD
Melissa Mattison, MD
Diane N. McNally, MD
Owen Mogabgab, MD
Robert N. Nace, MD
Ank Elisabeth V. Nijhawan, MD
Daniele Olveczky, MD
Kenneth F. Sands, MD
Sarah E. Schellhorn, MD
Anjala V. Tess, MD
Nancy Torres Finnerty, MD
Anita Vanka, MD
Anna M. Varghese, MD
Julius J. Yang, MD, PhD
Roger C. Yu, MD

Hospital Medicine – A major new collaborative program involving hospital medicine, gerontology nursing and pharmacy is GRACE (Global Risk Assessment and Careplan for Elders) which addresses the unique needs of vulnerable older adults admitted to the hospital who are at high risk of functional and cognitive decline, by improving the prevention and detection of adverse events in older patients. Dr. Melissa Mattison leads the hospital medicine component of this program.

Dr. Sara Fazio recently became an Associate Master at HMS. Additional HMS educational leadership positions held by Division members include Dr. Dan Sullivan's direction of Patient-Doctor I; Dr. Amy Ship's co-direction of Patient-Doctor II; Dr. Jennifer Potter's leadership of an HMS course on human sexuality; Dr. Amy Weinstein's co-directorship of the prevention and nutrition course; Dr. Sara Fazio's direction of the Core I Medicine Clerkship as well as the Primary Care Clerkship at BIDMC, and Dr. Alex Carbo's leadership of the Core 2 Medicine Clerkship. At HMS, Drs. Taylor and Fazio serve as Associate Masters in the Castle Society and the Holmes Society, respectively.

At the national level, Division members hold several education leadership positions. Dr. Eileen Reynolds serves as a member of the Residency Review Committee (RRC) in internal medicine, which is part of the Accreditation Council for Graduate Medical Education (ACGME). Dr. Carol Bates is treasurer-elect of the Society of General Internal Medicine (SGIM). Dr. Sara Fazio chaired the Curriculum Committee and now sits on the Council of the Clerkship Directors in Internal Medicine (CDIM). Dr. Joseph Li sits on the board of the Society of Hospital Medicine (SHM); chaired the 2009 annual meeting of SHM; and is treasurer-elect of SHM.

HONORS AND AWARDS

Beth Israel Deaconess Medical Center honored Dr. Booker Bush with the 2009 Robert Moellering Award for Excellence in Teaching; Dr. Alex Carbo with the Herrman Blumgart Faculty Award, Hospital Medicine Teacher of the Year Award and Hospital Medicine Clinician of the Year Award; Drs. Jim Heffernan and Jacques Carter with Preceptor of the Year Awards; Dr. Caitlin Fawcett with Practice Attending of the Year Award; Dr. Amy Ship with the David Calkins Primary Care Advocacy Award; and Dr. Julius Yang with the Hospital Medicine Clinician of the Year Award.

Harvard Medical School bestowed the 2008-09 Clifford A. Barger Award for Excellence in Mentoring on Dr. Ed Marcantonio; the Harold Amos Faculty Diversity Award on Drs. Jenny Potter and Harvey Makadon; and an Excellence in Tutoring Award to Dr. Carbo.

Dr. Rafael Campo was the recipient of the Nicholas Davies Memorial Scholar Award for Outstanding Contributions to Humanism in Medicine, American College of Physicians.

Dr. Sara Fazio received the Society of General Internal Medicine Award for Scholarship in Medical Education.

Drs. Li and Mattison were named Top Ten Hospitalists by the American College of Physicians.

Dr. Eileen Reynolds was awarded the Parker J. Palmer Courage to Teach Award from the ACGME. Dr. Amy Ship was the recipient of the Kenneth Schwartz Compassionate Caregiver of the Year Award.

Drs. Tess, Carbo, Mattison, Feinbloom, Torres-Finnerty, and Li were all named fellows in the Society of Hospital Medicine.

EDUCATIONAL PROGRAMS

The leadership of our Internal Medicine residency program is centered in the Division as all five residency program directors are faculty members. Dr. Carol Bates directs our primary care residency program and is Director of Education for the Division. Drs. Booker Bush and Jim Heffernan serve as firm chiefs and Drs. Leonor Fernandez and Chris Smith serve as associate firm chiefs directing inpatient resident and student education. Dr. Ken Mukamal co-directs our Resident Research Program. Dr. William Taylor directs the primary care residency at Harvard Vanguard, and at Brigham and Women's Hospital. Drs. Julius Yang and Caleb Hale lead simulation exercises to provide team training to medical residents.

RESEARCH ACTIVITIES

Our research mission is to conduct interdisciplinary patient-centered research focused on preventing and treating health conditions to maximize patients' quality of life and functional independence. Areas of research include aging, cardiovascular epidemiology, complementary and alternative medicine (CAM), disability, end-of-life/palliative care, health care disparities, obesity, patient safety and quality of care. Our faculty were awarded nearly $20 million in grants in FY09.

Sara Fazio, MD, General Internal Medicine, with Amanda Powell, MD.

SELECTED PUBLICATIONS

Buettner C, Mukamal KJ, Gardiner P, Davis RB, Phillips RS, Mittleman MA. Herbal supplement use and blood lead levels of United States adults. *J Gen Intern Med* 2009; 24:1175-82.

Schonberg MA, Davis RB, McCarthy EP, Marcantonio ER. An index to predict 5-year mortality of community-dwelling adults aged 65 and older. *J Gen Intern Med* 2009; 24:1115-1122.

Herzig S, Howell M, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA* 2009; 301:2120-8.

Huang GC, Newman LR, Schwartzstein RM, Clardy PF, Feller-Kopman D, Irish JT, Smith CC. Procedural competence in internal medicine residents: validity of a central venous catheter insertion assessment instrument. *Acad Med* 2009; 84:1127-34.

Leveille SG, Jones RN, Kiely DK, Hausdorff JM, Shmerling RH, Guralnik JM, Kiel DP, Lipsitz LA, Bean JF. Chronic musculoskeletal pain and the occurrence of falls in an older population. *JAMA* 2009; 302:2214-21.

Saper RB, Phillips RS, Sehgal A, Khouri N, Davis RB, Paquin J, Thuppil V, Kales SN. Lead, mercury, and arsenic in US- and Indian-manufactured Ayurvedic medicines sold via the Internet. *JAMA* 2008; 300:915-23.

Defer T, Fazio S. Revision of a national internal medicine curriculum: process and outcomes. *Am J Med* 2008; 121:1019-1025.

Smith AK, Fisher J, Schonberg MA, Pallin DJ, Block SD, Forrow L, Phillips RS, McCarthy EP. Am I doing the right thing? Provider perspectives on improving palliative care in the emergency department. *Ann Emerg Med* 2009; 54:86-93.

Tess AV, Smetana GW. Medical evaluation of patients undergoing electroconvulsive therapy. *N Engl J Med* 2009; 360:1437-44.

Wee CC, Girotra S, Weinstein AR, Mittleman MA, Mukamal KJ. The relationship between obesity and atherosclerotic progression and prognosis among patients with coronary artery bypass grafts: the effect of aggressive statin therapy. *J Am Coll Cardiol* 2008; 52:620-5.

Dr. Edward Marcantonio is Director of Research and directs the Program to Improve the Quality of Care and Outcomes of Hospitalized Older Adults. He is principal investigator for four NIH-funded studies in the area of delirium (acute confusion), including two new studies funded over the past year.

Dr. Christina Wee is Co-Director of Research and directs the Health Services and Behavioral Research Program in Obesity. She has two R01s funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDKD) examining the effect of race on health outcomes associated with obesity, and how obese patients value weight loss and make decisions about weight treatments.

Dr. Russell Phillips focuses on clinical trials of CAM modalities for chronic medical conditions, including a study of Tai Chi for the treatment of chronic heart failure. Dr. Phillips also directs the Division Program on Innovations in Primary Care. This program is designed to evaluate the effectiveness of innovative models of primary care delivery and payment on health outcomes and costs.

Dr. Suzanne Bertisch recently joined our research faculty and won an NIH K23 Career Development Award to study the physiology of mind-body therapies with a focus on meditative breathing and autonomic adaptations.

Dr. Catherine Buettner is interested in the use of supplements to prevent or treat cardiovascular disease, in particular the use of Co-enzyme Q10 for the treatment of statin-induced myalgia. She recently won an NIH K23 Career Development Award to pursue these research interests.

Dr. Bruce Landon focuses on quality of care and the relationship between organizational and physician characteristics and the provision of care. He is Principal Investigator on two R01s from the National Institute of Aging (one as part of a Program Project Grant) examining the relationship between physician financial incentives and care patterns for Medicare beneficiaries and informal physician information sharing networks.

Dr. Ellen McCarthy researches health disparities caused by age, race and ethnicity in cancer and end-of-life care. She is currently studying racial and ethnic differences in the use of hospice and palliative care and is

Kim Ariyabuddiphongs, MD, Primary Care Physicaian

developing novel approaches to better target cancer screening modalities. She recently won two large grants from the American Cancer Society. The first will evaluate the end of life care experience and preferences for Asian-Americans with cancer and the second examines the effect of screening for breast cancer in elderly women, taking into account competing risks and the impact of comorbid illness on both the risks and benefits of screening.

Dr. Kenneth Mukamal studies the determinants of cardiovascular disease and its prognosis, particularly behavioral risk factors such as alcohol intake. He is conducting an NIH-funded epidemiological study examining the modulation of alcohol effects by genetic polymorphisms and a pilot randomized trial examining the effects of moderate alcohol intake on cardiovascular risk factors. He recently won two R01 grants. The first will examine novel pathways in the incidence and cardiovascular consequences of diabetes in older adults and the second will examine endothelial dysfunction, oxidative stress, and risk of peripheral arterial disease.

Training and Mentorship – The centerpiece of our research training program is the HMS General Medicine Fellowship Program. This is a two-year, NIH-funded research fellowship designed to train academic generalist researchers. BIDMC is the home of the Harvard-wide program, which includes 6 sites in all, with Dr. Phillips serving as director along with Dr. John Ayanian at Brigham and Women's Hospital.

Complementary and Alternative Medicine – The Division has strong ties to the HMS Osher Research Center (formerly the Osher Institute) and Division for Research and Education in Complementary and Integrative Medical Therapies, directed by Dr. David Eisenberg. Osher Research Center faculty members with appointments in our Division include Associate Professor Ted Kaptchuk and Drs. Andrew Ahn, Lisa Conboy, Catherine Kerr, Weidong Lu, Peter Wayne, and Gloria Yeh. Professor Kaptchuk leads a major research effort that focuses on the placebo effect. Dr. Ahn studies the mechanism of action of acupuncture. Dr. Conboy examines multi-level models of healing. Dr. Kerr's primary interest is in meditation and integrating qualitative research with mechanistic research concerning brain plasticity and mediation (including the use of fMRI). Dr. Lu received the first OsherFoundation/ NIH research career development award to a CAM practitioner; he is studying acupuncture for patients with head and neck cancer. Dr. Peter Wayne is studying tai chi and other mind-body therapies. Dr. Yeh studies tai chi for patients with chronic illness. Dr. Phillips is the director of fellowship training and Dr. Roger Davis serves as senior biostatistician.

Fred Goldman, MD,
Primary Care Physician

Division of Genetics

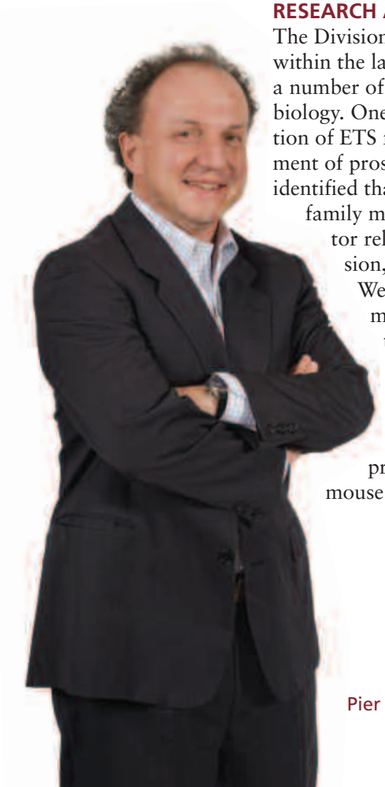
Since its creation in 2007, the Division of Genetics has firmly established itself within the Department of Medicine. The Division aims to understand the impact of genes on signaling pathways, transcriptional networks and pathogenesis of cancer and other diseases. A direct genetic approach in engineered mouse models, mouse primary cells derived from these mutants and the characterization of human samples are utilized as tools for mechanistic discovery. Additionally, faithful mouse models of diseases provide an ideal system for pre-clinical testing and development of novel therapeutics. Our approach has enabled us to make several important contributions to the understanding of the pathogenesis of human cancer, in addition to establishing a framework for a Co-Clinical Trial approach to promote the rapid development of novel cancer therapies.

FACULTY

Pier Paolo Pandolfi, MD, PhD
Keisuke Ito, MD, PhD
Letizia Longo, PhD

RESEARCH ACTIVITIES

The Division has had a productive period within the last twelve months and has made a number of important findings for cancer biology. One such finding concerns contribution of ETS family members to the development of prostate cancer. Our work has identified that aberrant expression of the ETS family member ERG is an important factor relating to prostate cancer progression, rather than cancer initiation. We developed a transgenic mouse model to activate expression of the ERG protein specifically in prostate tissues. Studies on this model allowed us to establish that the aberrant expression of this gene was unable to initiate prostate cancer development in the mouse by itself. However, the aberrant expression of this gene promotes a marked acceleration and progression to prostate adenocarcinoma in a genetic background displaying Pten deficiency, a model that we have already shown is prone to developing high grade intraepithelial neoplasia (HGPIN), a precursor to malignant cancer. This is supported by the fact that we identified genes under the control of ERG that promote cell migration and tumor progression without altering cell proliferation per se.



Pier Paolo Pandolfi, MD, PhD, Chief

Alice Berger, PhD candidate in Dr. Pandolfi's lab

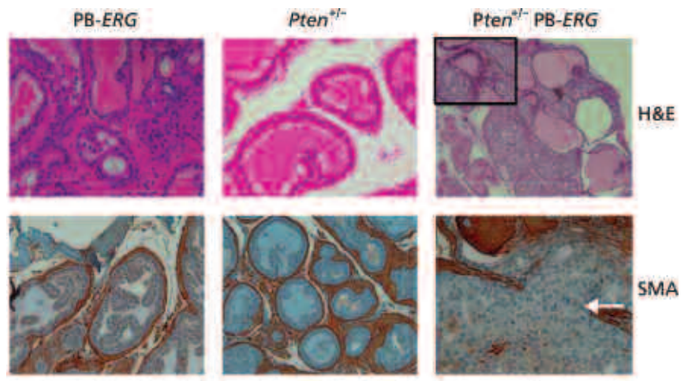
In addition we recently published the first in vivo model expressing a mutation of the gene nucleophosmin (NPM1). This gene encodes for a nucleolar protein with several important cellular functions and is the most frequently mutated gene in acute myeloid leukemias (AML). The mutations identified result in a delocalization of the protein to the cytoplasm of the cell, resulting in its designation as NPMc+, and an ability also to relocalize the remaining endogenous and wild-type nucleophosmin, causing a severe deficiency within the nucleus. Our model utilized the myeloid specific MRP promoter to drive expression of the mutant protein specifically in committed myeloid progenitor and mature myeloid cell types. Interestingly these mice developed myeloproliferation in bone marrow and spleen while non-transgenic mice remain disease free, providing the first in vivo evidence indicating that the NPMc+ state confers a proliferative advantage in the myeloid lineage. We are further refining our model and elaborating our studies to understand how exactly this mutation contributes to leukemia development and how we can target it for therapeutic gain.

The Division has also been very excited to set a framework for the development of a new platform we termed the "Co-Clinical Trial Project." Our goal is to develop a proof of principle foundation and appropriate methodology towards a "Co-Clinical" approach whereby preclinical trials in genetically engineered mouse models (GEMs) of human cancer are run in parallel with human clinical trials. The data obtained and integrated will lead to stratification of patients on the basis of genetics and molecular criteria, accelerated drug approval and optimized combinatorial targeted therapies.

HONORS AND AWARDS

Pier Paolo Pandolfi, MD, PhD was awarded the international prizes Premio Roberto Cortese 2008-Napoli per la Ricerca from the Guido and Roberto Cortese Foundation, as well as the Ischia 2009 International Award for contribution to Medical Research. He was also awarded the Prostate Cancer Foundation Creativity Award in 2009.

Keisuke Ito, MD, PhD, was awarded the Shibasaburo Kitazato Award (Best Scientist of the Year) from Keio University in 2008, and the Best Young Investigator Award (Uera Award) from the Japan Leukemia Research Fund also in 2008.



High-power (x200) histological images of prostatic adenocarcinoma in Pten +/-; PB-ERG mice compared to controls in mice 6 months of age. Immunohistochemistry for smooth muscle actin shows invasion.

Dr. Pandolfi consults with Dr. Lewis Cantley, Division of Signal Transduction

Jennifer Giuseffi, MD

SELECTED PUBLICATIONS

Ito K, Bernardi R, Morotti A, Matsuoka S, Saglio G, Ikeda Y, Rosenblatt J, Avigan DE, Teruya-Feldstein J, Pandolfi PP. PML targeting eradicates quiescent leukemia initiating cells. *Nature* 2008; 453:1072-8.

Song MS, Salmena L, Carracedo-Perez A, Egia A, Lo Coco F, Teruya-Feldstein J, Pandolfi PP. The deubiquitinylation and localization of PTEN are regulated by a HAUSP-PML network. *Nature* 2008; 455:813-7.

Cheng K, Sportoletti P, Ito K, Clohessy J, Teruya-Feldstein J, Kutok J, Pandolfi PP. The cytoplasmic NPM mutant induces myeloproliferation in a transgenic mouse model. *Blood* 2009; 11S(16):3341-5.

Nardella C, Carracedo-Perez A, Alimonti A, Hobbs R, Clohessy JG, Chen Z, Egia A, Fornari A, Fiorentino M, Loda M, Kozma S, Thomas G, Cordon-Cardo C, Pandolfi PP. Differential requirement of mTOR in post-mitotic tissues and tumorigenesis. *Sci Signal* 2009; 457(7231):E1; discussion E2-3.

Carver BS, Tran J, Chen Z, Carracedo-Perez A, Alimonti A, Nardella C, Gopalan A, Scardino PT, Cordon-Cardo C, Gerald W, Pandolfi PP. ETS genetic rearrangements are progression events in prostate tumorigenesis. *Nature* 2009; 457:E1; discussion E2-3.

Lin H-K, Wang G, Chen Z, Teruya-Feldstein J, Nakayama KI, Erdjument-Bromage H, Tempst P, Pandolfi PP. Phosphorylation-dependent regulation of Skp2 cytosolic localization and oncogenic function by Akt/PKB. *Nat Cell Biol* 2009; 11:420-432.

Carver BS, Tran J, Gopalan A, Chen Z, Carracedo A, Alimonti A, Nardella C, Varmeh S, Scardino PT, Cordon-Cardo C, Gerald W, Pandolfi PP. Aberrant ERG expression cooperates with loss of PTEN to promote cancer progression in the prostate. *Nat Genet* 2009; 41:619-24.

Chen Z, Carracedo A, Lin HK, Koutcher JA, Behrendt N, Egia A, Alimonti A, Carver BS, Gerald W, Teruya-Feldstein J, Loda M, Pandolfi PP. In vivo differential outcome of p19Arf-loss in prostate cancer uncoupled from p53. *Sci Signal* 2009; 2:ra44.

Maeda T, Ito K, Merghoub T, Poliseno L, Hobbs RM, Wang G, Dong L, Maeda M, Dore LC, Zelent A, Luzzatto L, Teruya-Feldstein L, Weiss MJ, Pandolfi PP. LRF is an essential downstream target of GATA1 in erythroid development and regulates BIM-dependent apoptosis. *Dev Cell* 2009; 17:527-40.

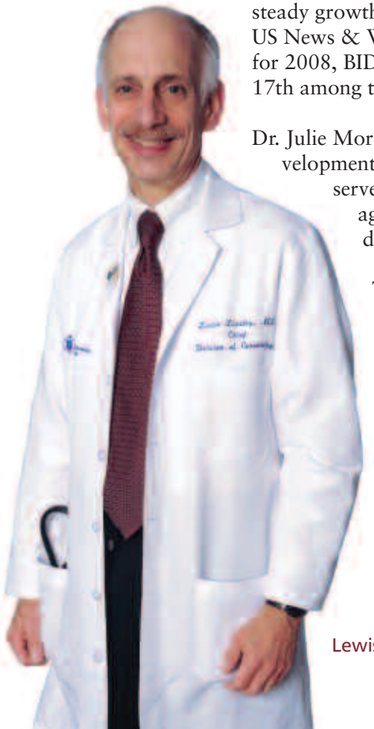
Carracedo A, Ma L, Teruya-Feldstein J, Rojo F, Salmena L, Alimonti A, Egia A, Sasaki AT, Thomas G, Kozma SC, Papa A, Nardella C, Cantley LC, Baselga J, Pandolfi PP. Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer. *J Clin Invest* 2008; 118:3065-74.

Division of Gerontology

The Division of Gerontology was established in 1976 to support a core faculty of geriatricians and gerontologists committed to the advancement of knowledge about aging and to the improvement of health care for the older population. It includes clinical and research faculty from Hebrew SeniorLife, one of the nation's leading clinical research centers in gerontology, providing multilevel long-term care and rehabilitation services for seniors.

This 162 acre campus in Dedham, MA serves a community of seniors ranging from the most independent and fit to the most dependent and chronically ill. It also supports a day school for children, who interact with the seniors. The Department of Medicine provides outpatient geriatric care and a new model of patient-centered long-term care that focuses on the maintenance of independence, functional ability and choice.

Suzanne Salamon, MD, Associate Chief for Clincal Programs



Lewis A. Lipsitz, MD, Chief

CLINICAL ACTIVITIES

Dr. Suzanne Salamon leads the clinical activities which includes ambulatory care, inpatient and outpatient consultation, acute inpatient care, a dedicated inpatient unit, long-term care, geropsychiatry, and rehabilitation services.

Senior Health @ BIDMC – The ambulatory geriatrics practice at BIDMC increased patient volume by 6.4% this year, showing steady growth over the past five years. In the US News & World Report "Best Hospitals" for 2008, BIDMC Geriatrics Division ranked 17th among the nation's 5,462 hospitals.

Dr. Julie Moran founded the Aging and Developmental Disabilities Clinic, which serves the increasing population of aging adults with developmental disabilities.

The Hebrew SeniorLife Department of Medicine supports many of the Division's faculty who provide rehabilitative, long-term, and acute care for nearly 5,000 elderly people. This year marked the completion of New Bridge on the Charles, one of the largest and most innovative continuing care retirement communities in the nation.

Making the Hospital Safe for Geriatric Patients – The Division has begun a strategic initiative called the "GeroSafe" Program, which includes: geriatric co-management of elderly surgical patients, care of patients over age 80 on a dedicated 15-bed inpatient acute geriatric unit, improving transitions of care to postacute care facilities or patient homes, and the GRACE (Global Risk Assessment and Careplan for Elders) Project, a geriatric order set and checklist of interventions to prevent delirium and other complications.

QUALITY IMPROVEMENT

This year we successfully reduced the use of benzodiazepines for our patients while assuring that those who remain on them are appropriately assessed for cognitive changes and fall risk. We continue to assess our attention to bone health, pneumococcal vaccination and urinary incontinence in our ambulatory patients. Currently we are 100% compliant in addressing bone health, 83% successful in giving pneumococcal vaccine, 80% compliant on addressing fall risk, and 77% compliant on addressing urinary incontinence.

FACULTY

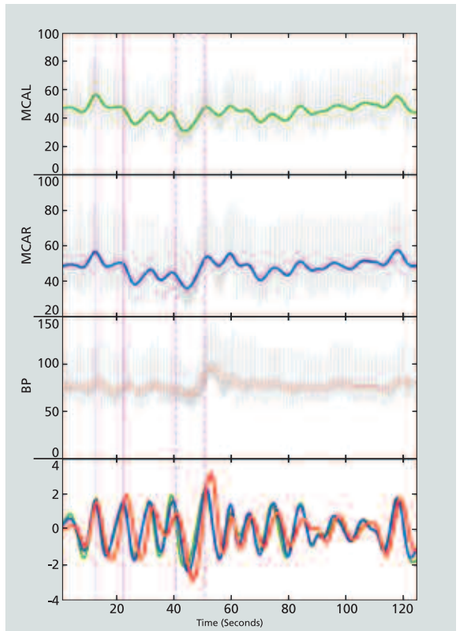
Alan Abrams, MD
Randi Berkowitz, MD
Sarah Berry, MD
Tamara Bloch, NP
Angela Botts, MD
Jennifer Brinckerhoff, MD
Virginia Cummings, MD
Katalin Danji, MD
Tamara Fong, MD
Anupama Gangavati, MD
Jane Givens, MD
Ihab Hajjar, MD
Marian Hannan, DSc
Yi-Hsiang Hsu, ScD
Sharon Inouye, MD
Richard Jones, ScD
Susan Kalish, MD
Ruth Kandel, MD
David Karasik, PhD
Konstantin Khrapko, PhD
Douglas Kiel, MD, MPH
Lewis Lipsitz, MD
Katherine Lyman, NP
Edward Marcantonio, MD
Robert McLean, DSc
Eran Metzger, MD
Susan Mitchell, MD
Julie Moran, DO
Medha Munshi, MD
Howard Nachamie, MD
Vera Novak, PhD
Erin O'Fallon, MD
Jennifer Rhodes-Kropf, MD
Shivani Sahni, PhD
Suzanne Salamon, MD
Elizabeth Samelson, PhD
Robert Schreiber, MD
Jason Strauss, MD
David Tsai, MD
San Wang, MD
Frances Yang, PhD

EDUCATIONAL PROGRAMS

The Donald W. Reynolds funded Program for the Advancement of Geriatrics Education at Harvard Medical School and Beth Israel Deaconess Medical Center has entered its 4th year. This program has produced:

- A day-long experience at Hebrew SeniorLife for all second year Harvard Medical Students to teach the physical examination of elderly patients and organization of long term care.
- Seven web-based, interactive, case-based educational modules about dementia, delirium, pain management, wound care, blood pressure management, osteoporosis and ethical issues in the elderly.
- Electronic medical record enhancements that automatically guide and track resident performance in the care of elderly patients.
- Geriatrics scholarships for hospitalists that teach them to practice and teach geriatric medicine.

The HMS Geriatric Medicine Fellowship program has trained 205 new specialists in geriatric medicine since 1980. With the support of a Geriatric Training Grant from the Health Resources and Services Administration, the program developed an interdisciplinary curriculum for the training of Geriatric Medicine, Psychiatry and Dental Fellows. This past year, the program was cited by AHRQ as a "best practice" for the clinical care provided to homeless elders.



Dr. Vera Novak, Director of the Syncope and Falls in the Elderly Laboratory and Dr. Kun Hu, in collaboration with Dr. C.K. Peng and his team, developed a new measure of cerebral autoregulation that relates oscillations in systemic blood pressure (red lines) to brain blood flow (blue and green lines). Lo et al. *J Appl Signal Processing 2008*.

HONORS AND AWARDS

Dr. Shivani Sahni, a postdoctoral fellow, and Yi-Hsiang Hsu, Instructor in Medicine, received the ASBMR Young Investigator award, American Society for Bone and Mineral Research.

Dr. Marian T. Hannan was asked to join the Board of Directors for the US Bone & Joint Decade, an organization under the W.H.O. umbrella that provides a worldwide focus on musculoskeletal health across the world and prevention of disability.

Dr. Julie Moran was awarded the 2008 Provider of the Year award from Growthways Inc., a community agency serving the aging patient with developmental disabilities.

Dr. Randi Berkowitz was awarded a "Practice Change" fellowship from Atlantic Philanthropies to reduce re-hospitalizations from post-acute care units.

RESEARCH ACTIVITIES

The Division of Gerontology research program spans BIDMC and Hebrew SeniorLife's Institute for Aging Research, where projects range from basic studies of mitochondrial mutations to genetic epidemiology and health policy.

Dr. Konstantin Khrapko is studying mitochondrial mutations in aging and has developed a novel approach for the simultaneous high throughput sequencing of hundreds of mitochondrial genomes using an Illumina sequencing platform with barcoding of individual mitochondrial genomes.

Dr. Susan L. Mitchell, Director of the Palliative Care Research Program at Hebrew SeniorLife, reported the high utilization of antibiotics in nursing home residents with advanced dementia at the end of life, which may lead to colonization with multiple drug resistant organisms.

Dr. Douglas P. Kiel, along with a former post-doctoral trainee in the Division, Dr. Heike Bischoff, published a meta-analysis showing that nonvertebral fracture prevention with vitamin D is dose dependent, and a higher dose should reduce fractures by at least 20% for individuals aged 65 years or older.

SELECTED PUBLICATIONS

Sorond FA, Schnyer DM, Serrador JM, Milberg WP, Lipsitz LA. Cerebral blood flow regulation during cognitive tasks: effects of healthy aging. *Cortex* 2008; 44:179-184.

Lipsitz LA. Dynamic models for the study of frailty. *Mech Ageing Dev* 2008; 129:675-676.

Fong TG, Jones RN, Shi P, Marcantonio ER, Yap L, Rudolph JL, Yang FM, Kiely DK, Inouye SK. Delirium accelerates cognitive decline in Alzheimer's disease. *Neurology* 2009; 72:1570-1575.

O'Fallon E, Pop-Vicas A, D'Agata EMC. The emerging threat of multidrug resistant gram negative organisms in a long-term care facility. *Gerontol A: Med Sci* 2009; 64(1):138-4

Berry SD, Samelson EJ, Ngo L, Bordes M, Broe KE, Kiel DP. Subsequent fracture in nursing home residents with hip fracture: a competing risks approach. *J Amer Ger Soc* 2008; 56:1887-1892.

Munshi M, Hayes M, Sternthal A, Ayers D. Use of serum c-peptide level to simplify diabetes treatment regimens in older adults. *Am J Med* 2009; 122(4):395-7.

Hajjar I, Yang F, Sorond F, Jones RN, Milberg W, Cupples LA, Lipsitz LA. A novel aging phenotype of slow gait, impaired executive function, and depressive symptoms: Relationship to blood pressure and other cardiovascular risks. *J Gerontol A Biol Sci Med Sci* 2009; 64(9):994-1001.

Sahni S, Hannan MT, Gagnon D, Blumberg J, Cupples LA, Kiel DP, Tucker KL. High vitamin C intake is associated with lower 4-year bone loss in elderly men. *J Nutr* 2008; 138:1931-8.

Hu K, Peng CK, Huang NE, Wu Z, Lipsitz LA, Cavallerano J, Novak J. Altered phase interactions between spontaneous blood pressure and flow fluctuations in type 2 diabetes mellitus: nonlinear assessment of cerebral autoregulation. *Physica A* 2008; 387(10):2279-2292.

Leveille SG, Kiel DP, Jones RN, Roman A, Hannon MT, Sorond FA, Kang HG, Samelson EJ, Gagnon M, Freeman M, Lipsitz L. The MOBILIZE Boston Study: Design and methods of a prospective cohort study of novel risk factors for falls in an older population. *BMC Geriatrics* 2008; 8:16.

Medha Munshi, MD

Division of Hematology & Oncology

The mission of the Division of Hematology/Oncology is to provide the highest caliber of technologically expert and humane clinical care for men and women with cancer and benign hematological disorders through the combined efforts of superior clinicians, leading-edge scientists and training programs of unsurpassed excellence. The Division has 65 faculty members with diverse clinical, educational and scientific interests. In addition to the Division Chief Dr. Lowell E. Schnipper, Dr. Michael Atkins serves as Deputy Director for the Division, Dr. Daniel Tenen is Associate Director and Head of the Cancer Biology Program, Dr. Steven Come serves as Medical Director of the Hem/Onc ambulatory unit, Dr. James Levine serves as the Medical Director for the Heme Malignancy/BMT ambulatory unit and the Medical Director of both the General Oncology inpatient unit and the Heme Malignancy/BMT inpatient unit. Dr. Reed Drews is Director of the Hematology/Oncology fellowship program. Dr. Marc Garnick is the Director of Network Operations. The administrative Directors are Ellen Volpe and Kerry Brown.

Lowell E. Schnipper, MD, Chief

CLINICAL ACTIVITIES

The clinical programs span the breadth of the specialties and emphasize clinical genetics, prevention/risk reduction, diagnosis, management and longitudinal follow-up of patients with diverse hematological disorders and neoplastic diseases. Many of the clinical programs are key components of multidisciplinary disease site programs within the Beth Israel Deaconess Cancer Center.

Within the past several years two new contiguous inpatient hematology-oncology units have opened.

The organization of the inpatient service is built around the model of an attending physician-led service, and the teaching program directed at the housestaff has been strengthened by naming Dr. Stephen Cannistra as the physician-teacher in charge. The ambulatory programs continue to serve as a major resource for clinical education of housestaff and fellows.

Kun Ping Lu, MD, PhD

Specialized clinical programs form the basis of a number of our tertiary care activities. These include translational research in prostate, ovarian, breast, lung and kidney cancers, personalized cancer vaccine trials for patients with multiple myeloma, renal, ovarian and breast neoplasms, and chemoembolization of primary and secondary hepatic cancers.

QUALITY IMPROVEMENT

In the past year the Hem/Onc Division in collaboration with the pharmacy, nursing and IT departments have completed and implemented the online computerized inpatient chemotherapy ordering system. Records of all chemotherapy ordering and administered dosing are now available as part of the patients' online medical record. The new system has a menu of over 260 chemotherapy regimens and supportive care therapies available for use by ordering physicians. New regimens can be added to the regimen dictionary after approval by the appropriate disease group leadership. The Division of Hem/Onc is justifiably proud of this significant accomplishment which will result in improved patient safety and cost-effective care.

EDUCATIONAL PROGRAMS

Six outstanding 1st-year fellows joined the BIDMC Hematology-Oncology program in July 2008, having completed internal medicine residency training programs at BIDMC (Erin DeRose, Kelly Bodio), Tufts Medical Center (Greg Britt, Rodney Jamil), Case Western (Ayad Hamdan), and St. Elizabeth's Hospital (Katarina Luptakova). Senior fellows pursuing various research projects received the following awards: American

HONORS AND AWARDS

In 2008, Michael Atkins, MD received the Kenneth B. Schwartz Compassionate Caregiver Award.

Daniel Costa, MD was awarded the 2009 ASCO Cancer Foundation Career Development Award.

John Fragioni, MD, PhD was the recipient of the Edward M. Kennedy Award for Healthcare Innovation, Center for Integration of Medicine and Innovative Technology, Cambridge, MA (2008).

The Stephen H. Robinson Memorial Teaching Award for Excellence in Teaching in Hematology/Oncology at BIDMC (2008 – 2009) was awarded to Robin Joyce, MD.

Rebecca Miksad, MD was awarded an NIH Mentored Patient-Oriented Research Career Development Award (K23).

Daniel Cho, MD received an NIH Mentored Patient-Oriented Research Career Development Award (K23).

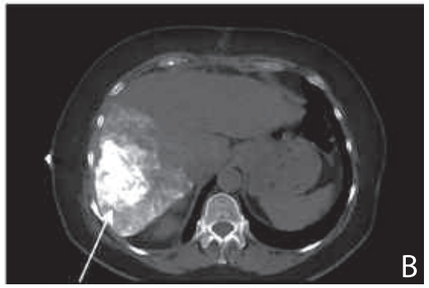
Panos Konstantinopoulos, MD, PhD received a career development award from the Department of Defense program on ovarian cancer.

FACULTY

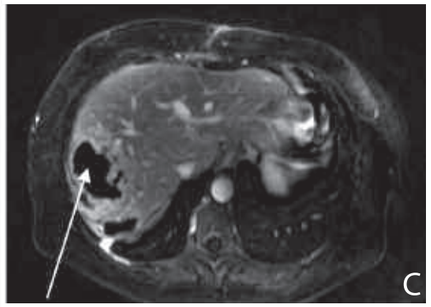
Michael B. Atkins, MD
David Avigan, MD
Steven Balk, MD, PhD
Rupal Bhatt, MD, PhD
Stuart Bless, MD
Vassiliki Boussiotis, MD, PhD
Glenn Bubley, MD
Mary Buss, MD
Stephen A. Cannistra, MD
Lisa Cavacini, PhD
Daniel Cho, MD
Hak Soo Choi, PhD
Amy Comander, MD
Steven Come, MD
Daniel Costa, MD
Bruce Dezube, MD
Reed Drews, MD
Alexander Ebralidze, PhD
Mark Exley, PhD
Laurie Feldman, PhD
Paula Fraenkel, MD
John V. Frangioni, MD, PhD
Marc Garnick, MD
Michael Goldstein, MD
Christina Herold, MD
Mark Huberman, MD
Robin Joyce, MD
Susumu Kobayashi, MD, PhD
Panos Konstantinopoulos, MD, PhD
Stephen Landaw, MD
Roger Lange, MD
Tae Ho Lee, PhD
Elana Levantini, PhD
James D. Levine, MD
Lequn Li, MD, PhD
Bing Lim, MD, PhD
Fangbing Liu, PhD
Kun Ping Lu, MD, PhD
David F. McDermott, MD
James Mier, MD
Rebecca Miksad, MD
Susan Pandya, MD
David Panka, PhD
Lucia Pastorino, PhD
Akash Patnaik, MD
Hanna Radomska, PhD
Jacalyn Rosenblatt, MD
Diane Savarese, MD
Lowell Schnipper, MD
Ralph Scully, MBBS, PhD
Dimitrios Spentzos, MD
Ryan Sullivan, MD
Arthur Sytkowski, MD
Daniel Tenen, MD
Sheila Thomas, PhD
Nadine Tung, MD
Dimitrios Tzachanis, MD
Gerburg Wulf, MD
Anyong Xie, PhD
Min Ye, PhD
Xiaocong Yu, PhD
Xin Yuan, MD, PhD
Pu Zhang, MD
Xiao Zhou, MD
Jeff Zwicker, MD

Hepatocellular cancer (HCC) before (A), immediately after (B), and one month after transarterial chemoembolization (TACE) (C).

Viable HCC tumor



Bright area = HCC tumor treated with TACE



Black area = necrotic (non-viable) HCC tumor

Society of Hematology and European Hematology Association Translational Research Training in Hematology Award (Brett Glotzbecker); American Society of Clinical Oncology Genitourinary Symposium Fellow Merit Award (Jessica Clement); Amgen Hematology & Oncology Fellowship Award (Brett Glotzbecker, Akash Patnaik); Clinical Investigator Training Program Award (Akash Patnaik); NIH Loan Repayment Award (Erin Hofstatter); Paul S. Carbone Award (Ryan Sullivan).

Mentor/Mentee Program – The Division of Hematology/Oncology at BIDMC is committed to providing an academic and work environment that fosters professional growth and personal satisfaction. Although faculty at every level of academic achievement are important to our mission, we recognize that staff at the Instructor and Assistant Professor level are at a critical stage in their academic development. This group of staff members often struggles to balance the need for clinical productivity against the need for protected time for research, as well as the need for time to devote to family and personal well-being.

Recognizing the needs of our junior faculty, Dr. Stephen Cannistra has spearheaded an effort to develop a mentorship program that pairs selected senior faculty with mentees at the Instructor or Assistant Professor level. The mentor is specifically selected to be outside of the mentee's disease program, to provide objectivity and enable the mentee to feel comfortable in sharing concerns that may be program related. The mentor's role is designed to be supportive as opposed to directly evaluative. At least two official Mentor-Mentee meetings are scheduled per year, followed by a Mentors-Chief meeting and a final meeting with the Division Chief.

RESEARCH ACTIVITIES

Research programs in the Division range from basic biology and translational research, to investigational imaging and numerous clinical trials (over 400 open trials) involving novel therapies, risk reduction and chemoprevention of cancer.

Kidney Cancer Program – BIDMC continues to be the lead site for the Dana Farber Harvard Cancer Center (DFHCC) Kidney Cancer Program. In 2009 its Specialized Program of Research Excellence (SPORE) competitive renewal grant was renewed. The goal of the SPORE remains the translation of laboratory and technological advances into clinical benefit for patients with kidney cancer. As the only NCI funded SPORE focused on kidney cancer the renewal application included investigators from all the Harvard affiliated hospitals and featured five major projects. These projects included: clinical correlations of WTX inactivation in Wilms tumor, led by Drs. Dan Haber and Miguel Rivera from MGH; targeting of HIF2a with SiRNA, led by Drs. Bill Kaelin and Toni Choueiri from DFCI and Sabina Signoretti from BWH; acquired resistance to VEGF receptor blockade: underlying mechanism and therapeutic options, led by Drs. Nahum Goldberg, James Mier and Michael Atkins from BIDMC; targeting the PI3-kinase/Akt pathway in RCC led by Drs. James Mier and David McDermott from BIDMC; adoptive immunotherapy for renal carcinoma using dendritic cell/tumor fusions, led by Drs. David Avigan from BIDMC and Don Kufe from DFCI.

Prostate Cancer Research Program – The prostate cancer research program has large basic and translational components. The basic research is led by Dr. Steven Balk, whose lab has the overall goal of improving understanding of Androgen Receptor (AR) biology in prostate cancer (PCa). The standard systemic treatment for PCa is to suppress AR activity by androgen deprivation therapy (surgical or medical castration), but patients invariably relapse with aggressive tumors that have been termed castration resistant prostate cancer (CRPC). The Balk lab has shown that AR is reactivated in CRPC despite castrate systemic androgen levels, and has identified mechanisms including AR mutations and enhanced intratumoral androgen synthesis that mediate this reactivation. Dr. Balk and clinical collaborators including Dr. Glenn Bubley are developing and conducting clinical trials of combination therapies targeting the AR in CRPC. Moreover, research in the lab is uncovering basic mechanisms that regulate AR synthesis, stability, nuclear trafficking, and transcriptional activity and developing novel AR antagonists.

Thoracic Oncology Program – The Thoracic Oncology clinical and basic research programs (Drs. Tenen, Costa, Huberman, Goldstein and Kobayashi) continue to unravel the basis of resistance to gefitinib and erlotinib (oral EGFR inhibitors) in lung cancer patients with somatic EGFR mutations. The program also has made key clinical observations in cancers with a novel somatic translocation (EML4-ALK) found in never smokers with non-small-cell lung cancer and helped develop a novel ALK inhibitor specific for this population. The program is involved in clinical trials of novel target therapies for lung cancer and is a key member of the DFHCC Lung SPORE's efforts to identify factors involved in the pathogenesis of lung cancer.

Breast cancer SNL mapping. Sentinel lymp node mapping for breast cancer using the FLARE™ imaging system. (**A**) Color video, (B) Near-infrared fluorescence, (**C**) Color-NIR merge

SELECTED PUBLICATIONS

Tzachanis D, Boussiotis VA. Tob, a member of the APRO family, regulates immunological quiescence and tumor suppression. *Cell Cycle* 2009 Apr 1; 8(7):1019-25.

Frangioni JV. New technologies for human cancer imaging. *J Clin Oncol* 2008; 26:4012-4021.

Lee T H, Lim J, Tun-Kyi A, Finn G, Shi R, Balastik M, Pastorino L, Wulf, Zhou X Z and Lu KP. Essential role of Pin1 in the regulation of TRF1 stability and telomere maintenance. *Nat Cell Biol* 2009; 11:97-105.

Rosenblatt J, Wu Z, Vasir B, Zarwan C, Stone R, Mills H, Friedman T, Konstantinopoulos P, Spentzos D, Ghebremichael M, Stevenson K, Neuberg D, Levine J, Joyce RM, Tzachanis D, Boussiotis VA, Kufe D, Avigan D. Generation of tumor-specific T lymphocytes using dendritic cell/tumor fusions and anti CD3/CD28. *J Immunol* 2010; 33:155-66.

Konstantinopoulos PA, Spentzos D, Cannistra SA. Gene expression profiling in epithelial ovarian cancer. *Nat Clin Pract Oncol* 2008 Oct; 5(10):577-87.

Chen S, Kesler CT, Paschal BM, and Balk SP. Androgen receptor phosphorylation and activity are regulated by an association with protein phosphatase 1. *J Biol Chem* 2009; 284:25576-25584.

Fraenkel PG, Gibert Y, Holzheimer JL, Lattanzi VJ, Burnett SF, Dooley KA, Wingert RA, Zon LI. Transferrin-a modulates hepcidin expression in zebrafish embryos. *Blood* 2009; 113:2843-50.

Atkins MB, Hsu J, Lee S, Cohen GI, Flaherty LE, Sosman JA, Sondak VK, Kirkwood JM. Eastern Cooperative Oncology Group. *J Clin Oncol* 2008 Dec 10; 26(35):5748-54.

Division of Hemostasis & Thrombosis

The Division of Hemostasis and Thrombosis was formed in 2000, incorporating the Center for Hemostasis and Thrombosis Research and the Hemophilia and Thrombosis Clinical Center. This Division is focused on basic and clinical research related to blood coagulation and vascular biology, as well as clinical activities related to bleeding and thrombotic disorders.

CLINICAL ACTIVITIES

The Division maintains an outpatient specialty clinic, the Hemophilia and Thrombosis Clinical Center. Patients are seen weekly with fellows by Drs. Furie, Roth, Bauer and Flaumenhaft. This clinic represents a referral center for patients with bleeding or thrombotic disorders. Several clinical trials involved in understanding the relationship of cancer-associated thrombosis are closely integrated into this clinical program.

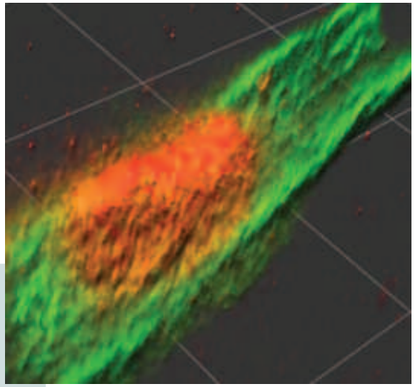
Bruce Furie, MD
Barbara Furie, PhD
Division Co-Chiefs

EDUCATIONAL PROGRAMS

Drs. Bruce Furie and Barbara C. Furie were Presidents of the 22nd Congress of the International Society on Thrombosis and Haemostasis that met in Boston in July 2009. Drs. Bruce Furie and Barbara C. Furie also served as Presidents of the International Society on Thrombosis and Haemostasis from 2007 to 2009. Dr. Kenneth Bauer was the Vice President of this congress and Dr. Robert Flaumenhaft was the editor of its state-of-the-art book. Approximately 8,000 delegates from 99 countries attended this medical/scientific meeting.

The fifth edition of the leading textbook in hematology, Hematology: Basic Principles and Practice, was published in 2009. Dr. Bruce Furie is a co-editor of this text, and Dr. Barbara C. Furie, Dr. Bruce Furie and Dr. Kenneth Bauer are chapter contributors.

Dr. Bruce Furie delivered plenary lectures at the 52nd GTH Congress in Wiesbaden, Germany in 2008, the European Hematology Association meeting in Copenhagen, Denmark in 2008 and the XX Congress of the Latin American Group for Hemostasis and Thrombosis in Buenos Aires, Argentina in 2008. He also gave the Reneman Lecture at the Cardiovascular Research Institute, Maastricht The Netherlands, a plenary lecture at the 10th Annual Conference on Atherosclerosis, Thrombosis and Vascular Biology of the American Heart Association in 2009, and the Keynote Lecture at the 5th European Meeting on Vascular Biology and Medicine in Marseille, France. He was the Ralph Nachman Distinguished Visiting Professor at Weill Cornell Medical College in 2009. Both Drs. Bruce and Barbara Furie gave plenary lectures at the Japanese Society of Hematology meeting in Kyoto, Japan in October 2008.



Thrombus formation in the living mouse. Furie & Furie, NEJM, 2008.

HONORS AND AWARDS

During the Fall of 2009, Drs. Bruce and Barbara Furie were invited visiting professors at the University of Cambridge and the Wellcome Trust Sanger Institute in Cambridge, England. This one month visit engaged them in a series of genomics projects related to platelets and cardiovascular disease.

Dr. Bruce Furie was elected Executive Director of the International Society on Thrombosis and Haemostasis. He serves for five years in a volunteer capacity.

During this period, Dr. Bruce Furie was awarded a new NIH Program Project Grant. Drs. Bruce Furie and Barbara C. Furie were each awarded new NIH Research Grants and Dr. Bruce Furie received renewal of a large NIH postdoctoral training grant.

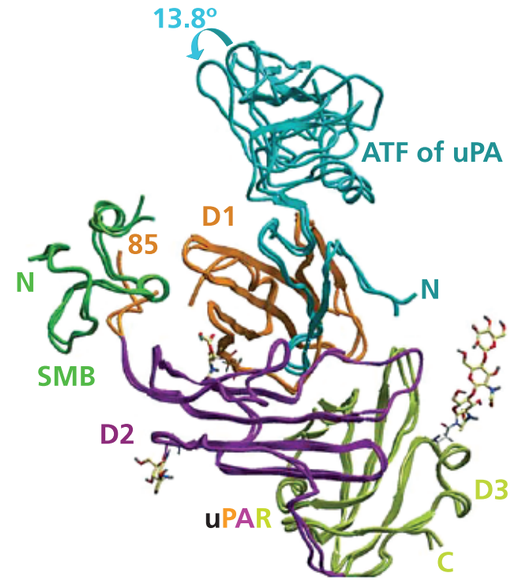
Dr. Robert Flaumenhaft was awarded an Established Investigatorship from the American Heart Association.

FACULTY

Kenneth Bauer, MD
Natalia Beglova, PhD
Robert Flaumenhaft, MD, PhD
Barbara C. Furie, PhD
Bruce Furie, MD
Mingdong Huang, PhD
David Roth, MD

RESEARCH ACTIVITIES

Major activities in the laboratory include the study of thrombus formation in vivo using novel instrumentation developed by this group for real time in vivo confocal and widefield imaging in the microcirculation of a living mouse. High resolution X-ray crystallographic structural studies have focused on the urokinase-urokinase receptor complex, Factor VIII and conformers of tissue factor. In addition, the molecular basis of granule secretion in platelets is under study.



Recognition of both the urokinase N-terminal fragment (ATF) and the vitronectin SMB domain by the urokinase receptor, uPAR. Superimposed crystal structures of the uPAR–ATF–SMB complex and the uPAR–ATF–SMB-antibody complex are shown. The carbohydrate moieties of uPAR are shown in sticks. The three domains of uPAR are colored differently.

SELECTED PUBLICATIONS

Cho J, Furie BC, Coughlin S, Furie B. A critical role for extracellular protein disulfide isomerase during thrombus formation in vivo. *J Clin Invest* 2008; 118:1123-1131.

Ngo J, Huang M, Roth DA, Furie BC, Furie B. Crystal structure of human factor VIII: Implications for the formation of the factor IXa-factor VIIIa complex. *Structure* 2008; 16:597-606.

Furie B, Furie BC. Mechanisms of thrombus formation. *N Engl J Med* 2008; 359:938-949.

Huai Q, Zhou A, Lin L, Mazar AP, Parry GC, Callahan J, Shaw DE, Furie B, Furie BC, Huang M. Crystal structures of two human vitronectin, urokinase and urokinase receptor complexes. *Nat Struct Mol Biol* 2008; 15:422-423.

Graham GJ, Ren Q, Dilks JR, Blair P, Whiteheart SW, Flaumenhaft R. Endobrevin/VAMP-8-dependent dense granule release mediates thrombus formation in vivo. *Blood* 2009; 114:1083-90.

Flaumenhaft R, Dilks JR, Richardson J, Alden E, Patel-Hett SR, Battinelli E, Klement GL, Sola-Visner M, Italiano JE Jr. Megakaryocyte-derived microparticles: direct visualization and distinction from platelet-derived microparticles. *Blood* 2009; 113:1112-21.

Hoffman R, Benz EJ, Shattil SJ, Furie B, Silberstein L, McGlave P, Heslop H. Hematology: Basic principles and practice. Elsevier/Churchill-Livingstone, Philadelphia PA, Fifth edition, 2009.

Dowal L, Flaumenhaft R. Targeting platelet G-protein coupled receptors (GPCRs): Looking beyond conventional GPCR antagonism. *Curr Vasc Pharmaco* 2010; 8(2):140-54.

Zwicker JI, Liebman HA, Neuberg D, Lacroix R, Bauer KA, Furie BC, Furie B. Tumor-derived tissue factor-bearing microparticles are associated with venous thromboembolic events in malignancy. *Clin Cancer Res* 2009; 15:6830-6840.

Beglov D, Lee CJ, De Biasio A, Kozakov D, Brenke R, Vajda S, Beglova N. Structural insights into recognition of beta2-glycoprotein I by the lipoprotein receptors. *Proteins* 2009; 77:940-949.

Martina Nowak, MD,
Instructor in Anesthesia and
a member of Dr. Robson's
research team

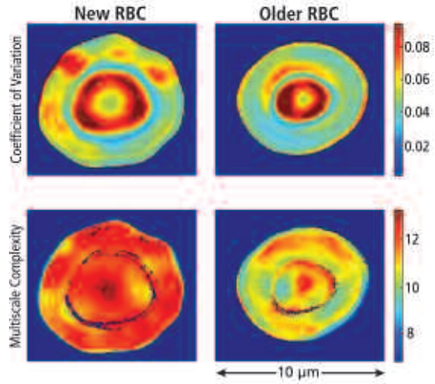
Division of IMBIO

The Division of Interdisciplinary Medicine and Biotechnology (IMBIO) is a relatively new division. IMBIO is organized under the leadership of Dr. Sukhatme, as Division Director, and Dr. A. Goldberger, as the Associate Director. Its faculty have significant ties with the Harvard Catalyst (the NIH award to Harvard Medical School for fostering clinical and translational research at HMS and its affiliated hospitals) and the Wyss Institute. It anticipates many interfaces with other institutions both locally and nationally.

IMBIO believes that we are at a unique time in medical history. The deciphering of the human genome affords an unprecedented platform for basic science discoveries in biology. This "genomics revolution" coupled to the information technology revolution and technological advances, such as robotic methods for high-throughput screening, developments in mass spectrometry, novel imaging modalities, etc, will make medicine an information rich discipline in which health and disease will be increasingly assessed by multi-parameter data that will be easy to gather, transmit and mine.

Such information – if properly extracted and analyzed – will inexorably shift healthcare from a "one size fits all" paradigm to "individualized care." Additionally, there will be more emphasis on preventative and predictive care and less on "symptomatic" care. In turn, biomarkers will streamline the drug development process and a subset of them will be linked to the pathophysiology of a disease process, thus providing novel therapeutic targets. Finally, the ability to view disease as a "systems problem" will lead to new insights with diagnostic and therapeutic implications. Thus the "hardware" to elicit and detect "signals" from biological systems including humans ("translational technologies") both in vivo and ex vivo and the analysis with sophisticated computational methods of the data obtained will lead to novel insights into disease pathophysiology – the central goal in IMBIO.

IMBIO's other mission is to initiate and facilitate linkage from BIDMC to university departments in engineering, computational sciences, physics and chemistry. Insights from public health law and business will also be welcome. IMBIO will also facilitate interactions within the Department of Medicine by helping identify clinical or scientific problems that may benefit from such interactions or from methodologies that cross divisional lines.



Quantitative analysis of the membrane fluctuations of a newly formed (left panels) and an older (right panels) red blood cell (RBC) from the same subject. Top plots show the coefficient of variation maps. Bottom plots show the multiscale complexity maps calculated using the multiscale entropy method.

FACULTY

Manoj Bhasin, PhD
Barden Chan, PhD
Madalena D. Costa, PhD
Ary L. Goldberger, MD
Xuesong Gu, PhD
Junichi Hanai, MD, PhD
Zaheed Husain, PhD
Towia A. Libermann, PhD
Mohini Lutchman, PhD
Chung-Kang Peng, PhD
Pankaj Seth, PhD
Vikas P. Sukhatme, MD, PhD
Griffin Weber, MD, PhD

Ary L. Goldberger, MD, Co-Chief
Vikas P. Sukhatme, MD, PhD, Chief

HARVARD CATALYST PROFILES

Profiles is a research networking and expertise discovery website developed by Griffin Weber, MD, PhD, for the Harvard Catalyst, which contains profiles for 22,000 HMS and HSPH faculty, with plans to extend to other Harvard schools. In addition to presenting investigators' names, titles, degrees, awards, narratives and publications, Profiles uses automated data mining techniques based on natural language processing and artificial intelligence to connect researchers into networks based on characteristics such as being co-authors on articles, having similar interests, or having offices that are physically close. Computational analysis and visualization of these networks reveal how people collaborate in various disciplines, identify foci where new ideas are emerging, and discover connections between different academic fields. These tools can suggest novel approaches and recommend the best faculty for solving challenging research problems. Visit Profiles at http://connects.catalyst.harvard.edu/profiles

HONORS AND AWARDS

CK Peng, PhD was the 2009 Keynote Speaker at the Complexity and CAM Research Conference, Minneapolis, MN and the 2009 Landmark Lecture, IX World Congress of International Society for Adaptive Medicine, Taipei, Taiwan.

Junichi Hanai, MD, PhD, was an invited speaker at the Center for Regenerative Medicine, Brigham and Women's Hospital, 2009.

Towia Libermann, PhD received a Prostate Cancer Foundation Research Award.

RESEARCH ACTIVITIES AND EDUCATIONAL PROGRAMS

Dr. Sukhatme's group (Hanai and Husain) is interested in tumor metabolism and tumor immunology and the interface of the two, with projects that extend from laboratory research to clinical trials. They collaborate on these studies with Dr. Seth in IMBIO and others in radiology and immunology. Dr. Chan is investigating the role of an angiogenic protein Tie-1 in atherosclerosis and cancer.

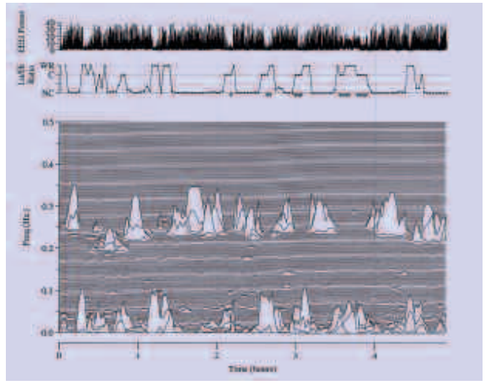
Drs. Goldberger, Peng and Costa focus on understanding nonlinear dynamics and fundamental mechanisms of complex systems. They have developed quantitative algorithms to probe some of the generic features of these systems and applied them to such diverse

Madalena Costa, PhD

areas as heart rhythms in health and disease, forecasting drug toxicity, complexity analysis of coding and noncoding human DNA sequences and gait stability. Dr. Goldberger is a founding member of the Wyss Institute.

Dr. Libermann (as director) and Drs. Gu, Zerbini and Bhasin run the BIDMC Genomics Center and Cancer Proteomics Core at the Dana Farber Cancer Institute. Their research has a major focus in renal, prostate and ovarian cancer. Additionally, they have collaborated with a wide range of scientists both locally and nationally.

Dr. G. Weber is a medical bioinformatician whose research focuses on ways in which biomedical informatics can improve medical education, research and patient care. He has established a Biomedical Research Informatics Core (BRIC), to provide informatics services to BIDMC researchers and is a major investigator in the Harvard Catalyst.



The EKG-derived sleep spectrogram technology was developed by Dr. Goldberger in concert with physicist Dr. Peng, bioengineer Joseph Mietus, and sleep/pulmonary researcher Dr. Robert J. Thomas. This patented method allows investigators and clinicians to analyze sleep using only a continuous, single-lead EKG, in place of much more expensive and cumbersome polysomnographic studies.

SELECTED PUBLICATIONS

Cao P, Hanai J, Taksale P, Imamura S, Sukhatme VP, Lecker SH. Statin-induced muscle damage atrogin-1 induction is the result of a geranylgeranylation defect. *FASEB J* 2009; 23(9):2844-54.

Chan B, Sukhatme VP. Suppression of Tie-1 in endothelial cells in vitro induces a change in the genome-wide expression profile reflecting an inflammatory function. *FEBS Lett* 2009; 583:1023-8.

Weber GM, Churchill S, MacFadden D, McMurry J, Murphy SN, Nigrin DJ, Kohane IS. The Shared Health Research Information Network (SHRINE): A prototype federated query tool for clinical and translational data repositories. *J Am Med Inform Assoc* 2009; 5:624-30.

Costa M, Ghiran I, Peng C-K, Nicholson-Weller A, Goldberger AL. Complex dynamics of human red blood cell flickering: Alterations with in vivo aging. *Phys Rev E* (Rapid Comm) 2008; 78:020901.

Elinoff J, Talmor D, Subramaniam B, Karmpaliotis D, Goldberger AL, Malhotra A. Effects of mechanical ventilation on the electrocardiogram in adults. *Lung* 2008; 186:219-23.

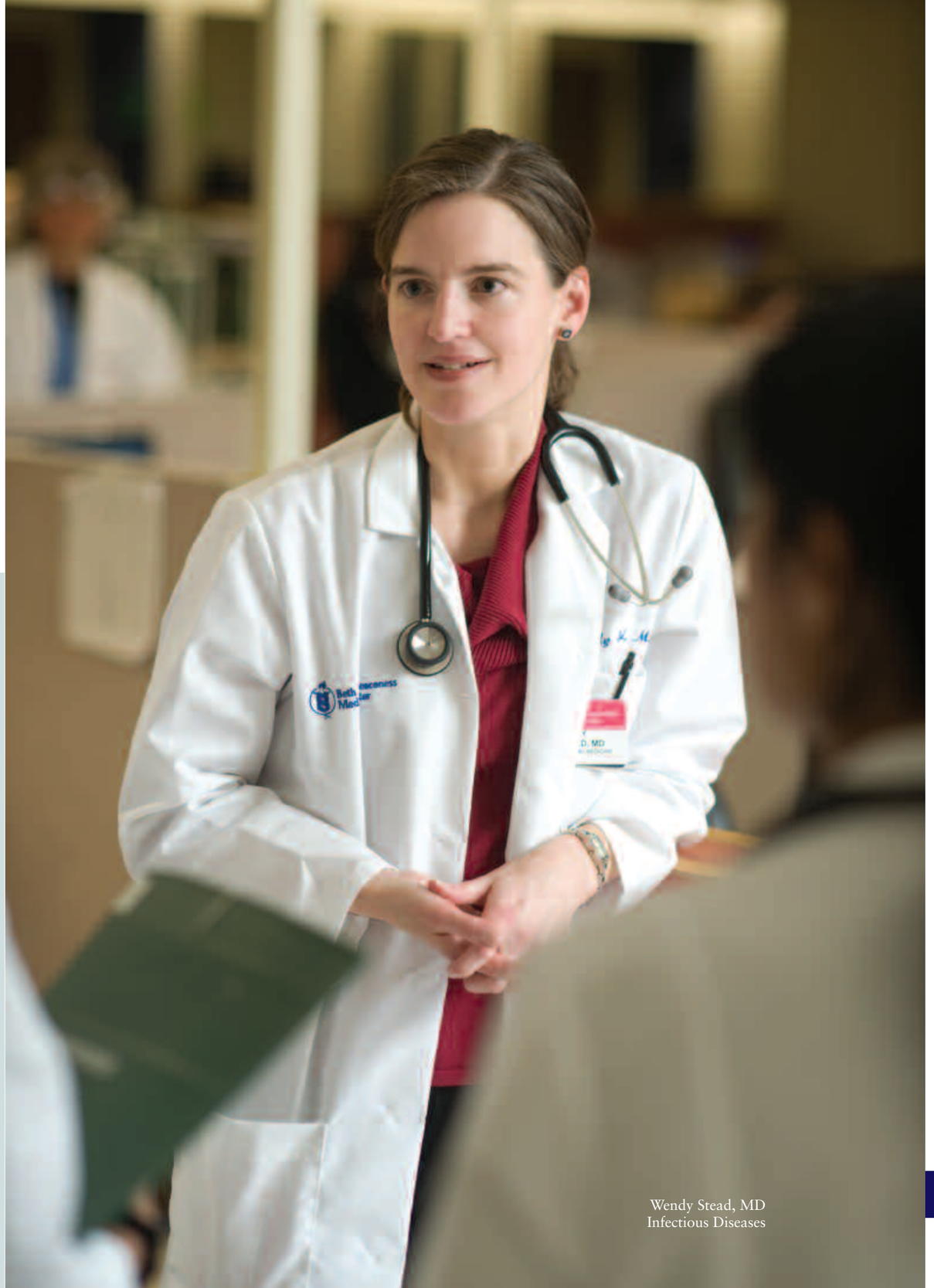
Peng C-K, Costa M, Goldberger AL. Adaptive data analysis of complex fluctuations in physiologic time series. *Adv Adapt Data Anal* 2009; 1:61-70.

Cho JY, Lee M, Ahn JM, Park ES, Cho JH, Kim BG, Heo SH, Park HJ, Zerbini L, Hwang D, Libermann T. Proteomic analysis of a PDEF Ets transcription factor-interacting protein complex. *J Proteome Res* 2009; 8:1327-37.

Arredouani MS, Lu B, Bhasin M, Eljanne M, Yue W, Mosquera JM, Li V, Rubin MA, Libermann TA, Sanda MG. Identification of the transcription factor simple-minded homologue 2 as a potential biomarker and immunotherapy target in prostate cancer. *Clin Cancer Res* 2009; 15:5794-802.

Xie H, Valera VA, Merino MJ, Amato AM, Signoretti S, Linehan WM, Sukhatme VP, Seth P. LDH-A inhibition, a therapeutic strategy for treatment of hereditary leiomyomatosis and renal cell cancer. *Mol Cancer Ther* 2009; 8:626-35.

Boguski MS, Mandl KD, Sukhatme VP. Drug discovery. Repurposing with a difference. *Science* 2009; 324:1394-5.



Wendy Stead, MD
Infectious Diseases

Division of Immunology

The Immunology Division at Beth Israel Deaconess Medical Center conducts basic research of innate and adaptive immune responses using knockout and knock-in approaches. The goals of the Division are to carry out cutting-edge basic research of innate and adaptive immune responses; to teach graduate students and Research Fellows; and to provide a nurturing environment for the career development of research fellows and faculty. The Division employs 2 research faculty, 12 research fellows and 3 graduate students.

Active collaborations exist with investigators in the Divisions of Gastroenterology, Allergy and Inflammation and Rheumatology at BIDMC. Cox Terhorst and George Tsokos, Chief of the Division of Rheumatology, co-direct a T32 training program on systemic autoimmunity. Through this program fellows in rheumatology, nephrology, dermatology and other subspecialties, as well as in basic sciences, will be mentored to become independent investigators in the field of systemic autoimmune diseases.

Cox Terhorst, PhD, Chief

Cox Terhorst serves as Associate Director of the Harvard Center for the Study of Inflammatory Bowel Diseases and as Associate Director the Harvard Center for Primary Immuno Deficiencies. He is also Course Director of Immunology 219 (HMS 726) "The Primary Immunodeficiencies," which is attended by graduate students of the Harvard Immunology Program and by undergraduates from Harvard College.

RESEARCH ACTIVITIES

The SLAM Gene Family controls innate and adaptive immunity – The SLAM family of nine cell surface receptors is emerging as a crucial set of regulatory genes for both adaptive and innate immunity. SLAM (Signaling Lymphocyte Activation Molecule or SLAMF1) is a self-ligand receptor at the interface between T cells and professional antigen presenting cells. But, SLAMF1 is also the primary receptor for measles virus, which causes a severe immune suppression. We find that SLAM f1-, f2-, f4-, f6- and f8-deficient mice have abnormal responses to both bacteria and parasites. This is the result of a defect in the final stage of CD4+ T cell differentiation and/or of defective killing of bacteria by SLAM-deficient macrophages, tissue dendritic cells and neutrophils. Thus, SLAM family members serve as regulators of the innate and adaptive immune response to bacterial and viral infections. Indeed, mutations in several mouse SLAM genes regulate bacterial killing by phagocytes and consequently affect the development of murine IBD.

FACULTY

Cox Terhorst, PhD
Ninghai Wang, MD

Pathogenesis of experimental Inflammatory Bowel Disease – Studies with genetically well-defined mouse models of Inflammatory Bowel Diseases, i.e. experimental colitis, led to an understanding that perturbations of the finely tuned balance between the immune system and the vast antigenic load of the colon can result in disease. Aggressor CD4+ T helper 1 (Th1) cells accumulate in the lamina propria followed by inflammation of the intestinal mucosa. Bacterial antigens are presented to these T cells by professional Antigen Presenting Cells (APC). In healthy mice the aggressor Th1 cells are prevented from expanding and thus initiating colitis by regulatory T cells (Treg). However, we do not understand the interactions of these cell types in the regulation of normal and abnormal immune responses to colonic bacteria.

Our current studies are designed to examine the homeostatic balance between colitis-inducing Th1, Th2, Th17 and Treg cells. The fundamental strategy is to examine the contribution of key dendritic cells, macrophages and T cell surface receptor / ligand pairs, i.e. SLAMF receptors and MIF/MIF receptors, in the education of the pathogenic T cells and Treg cells in IBD. The results of these studies have suggested therapeutic strategies that can be applied to IBD patients for we have successfully used a series of antibody reagents to ameliorate experimental colitis in the mouse.

SLE – Surprisingly, polymorphisms in SLAMF6 are implicated in a propensity to develop murine lupus. Together with the Tsokos lab we have just begun to evaluate whether distinct polymorphisms in the human SLAM genes can be correlated with the disease manifestations of SLE patients.

X-linked lymphoproliferative disease – Childhood primary immunodeficiency disorders can be viewed as "experiments of nature" in which a discrete genetic defect affects the expression and/or the structure/function of essential lymphocyte proteins and results in immune dysfunctions. X-linked lymphoproliferative (XLP) disease is a primary immunodeficiency caused by a defect in the SH2D1A gene with three major disease manifestations: fatal infectious mononucleosis, B cell lymphomas and dysgammaglobulinemia.

Drs. Gong Liao, Scott Berger and Katie Holmes discussing recent findings in the lab.

SELECTED PUBLICATIONS

Sintes J, Romero X, Marin P, Terhorst C, Engel P. Differential expression of CD150 (SLAM) family receptors by human hematopoietic stem and progenitor cells. *Exp Hematol* 2008; 36:1199-204.

Maganto-Garcia E, Punzon C, Terhorst C, Fresno M. Rab5 activation by Toll-like receptor 2 is required for Trypanosoma cruzi internalization and replication in macrophages. *Traffic* 2008; 9:1299-315.

Freitag T, Junker Y, Popov Y, Rietdijk S, Bhan AK, Terhorst C, Kelly CP, Schuppan D. Gliadin-primed CD4+CD45RBlowCD25- effector/memory T cells drive gluten-dependent small intestinal damage after adoptive transfer into lymphopenic mice. *Gut* 2009; 58:1597-1605.

Cooper M, Nayak S, Hoffman BE, Terhorst C, Cao O, Herzog RW. Improved induction of immune tolerance to Factor IX by hepatic AAV-8 gene transfer. *Hum Gene Therap* 2009; 20(7):767-76.

Martino AT, Nayak S, Hoffman BE, Cooper M, Liao G, Markusic DM, Byrne BJ, Terhorst C, Herzog RW. Tolerance Induction to Cytoplasmic β-galactosidase by hepatic AAV gene transfer – Implications for antigen presentation and immunotxicity. *PLoS One* 2009; 4(8):e6376.

Manocha M, Rietdijk S, Laouar A, Liao G, Bhan A, Borst J, Terhorst C, Swamy M. Blocking CD27-CD70 costimulatory pathway suppresses experimental colitis. *J Immunol* 2009; 183:270-276.

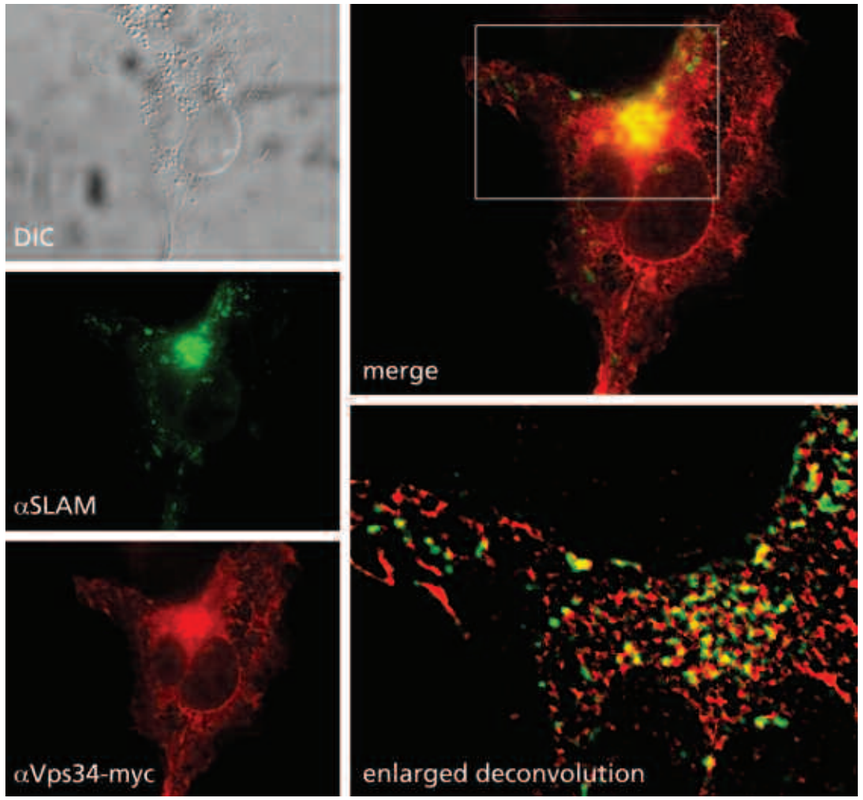
Liao G, Regueiro J, Berger SB, Romero X, Terhorst C. GITR engagement preferentially enhances the proliferation of CD4+CD25+FoxP3+ regulatory T cells. *Int Immunol* 2010; 22(4):259-70.

Sintes J, Romero X, de Salort J, Terhorst C, Engel P. Mouse CD84 is a pan-leukocyte cell surface molecule that modulates LPS-induced cytokine secretion by macrophages. *J Leukocyte Biol* 2010; In press.

Lanyi A, Barth M, Peterfi Z, Orient A, Bogel G, Orient A, Simon T, Petrovszki E, Kis-Toth K, Sirokmany G, Rajnavolgyi E, Terhorst C, Buday L, Geiszt M. The novel adaptor HOFI, a homolog of FISH regulates Lamellipodia formation and cell spreading. *J Biol Chem* 2010; In press.

Rucci F, Notarangelo LD, Fazeli A, Patrizi L, Hickernell T, Paganini T, Coakley K, Cheng H-L, Feldman L, Wang J, Balter B, Zha S, Detre C, Walter JE, Keszei M, Poliani PL, Giliana S, Terhorst C, Alt FW, Yan C. Homozygous DNA Ligase IV R278H mutation in mice leads to leaky SCID and represents a model for human LIG4 syndrome. *Proc Natl Acad Sci USA* 2010; 107(7):3024-9.

Detre C, Keszei M, Romero X, Tsokos G, Terhorst C. SLAM Family Receptors and the SLAM Associated Protein (SAP) modulate T cell functions. *Semin Immunopathol* 2010; 32(2):157-71.



Co-localization of SLAM and VPS34 in COS cells

SH2D1A encodes SAP (SLAM Associated Protein), which is a single free SH2-domain protein that controls signal transduction in T lymphocytes, NKT cells, NK cells and a B cell subset. Physicochemical and biochemical studies emphasize the unique interactions of SAP with the cytoplasmic tails of six of the SLAM-family of receptors. Through a second set of unique interactions, SAP recruits tyrosine phosphokinases to the SLAM receptors. We thus have the systems in place to clarify how the absence of SAP causes XLP.

Hemophilia B gene therapy – Both natural regulatory T cells and activated effector CD4+ T cells express high levels of Glucocorticoid-Induced TNF Receptor (GITR). Using a high affinity soluble Fc-GITR-Ligand dimer, we specifically enhanced in vitro and in vivo proliferation of functionally competent regulatory T cells, while minimally affecting effector T cells. In order to test the efficacy of this treatment in a therapeutic setting, we employed a C3H/HeJ Hemophilia B mouse model. Whereas liver-targeted hF.IX gene therapy in this model induces liver toxicity and the subsequent failure of hF.IX expression, injection of Fc-GITR-L increased the expression of F.IX and reduced the anti-coagulation factors. This novel therapeutic approach will be tested in other mouse models of immune dysfunction.

Anita Vanka, MD
Hospital Medicine

Division of Infectious Diseases

The Division of Infectious Diseases is recognized worldwide for excellence in clinical care, teaching and a broad research agenda.

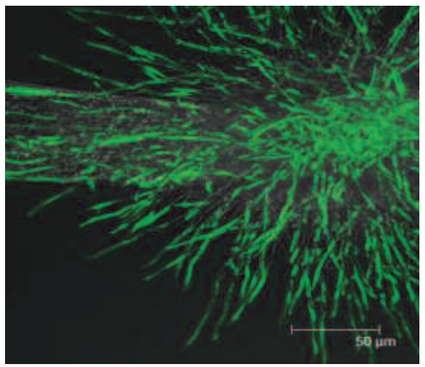
CLINICAL ACTIVITIES

The Division annually provides consultative services to approximately 1,800 patients hospitalized at BIDMC and to outpatients in the Infectious Disease Clinic. This clinic, with approximately 7,000 visits annually, also provides primary care for approximately 500 human immunodeficiency virus (HIV)-infected patients. The Clinic also provides Zostavax, a live virus vaccine to prevent shingles, to eligible adults, approximately 900 individuals annually. Within the Clinic is the multi-disciplinary Anal Screening Clinic, which is focused on prevention and treatment of anal papilloma and cancer in at-risk males. The Travel Clinic annually provides preventive care to 3,000 patients who plan international travel. Infectious disease consultative services at the Manchester New Hampshire Veterans Administration Hospital and at the Hebrew Senior Life Center are provided by Drs. Howard Gold and Erika D'Agata, respectively. Drs. Wendy Stead, Elisa Choi and two infectious disease fellows assist in the staffing of the HIV Evaluation and Consultation Clinic in Healthcare Associates bringing subspecialty expertise to the 500 HIV-infected patients who receive care in the General Medicine Clinic. Drs. Christopher Rowley and Rachel Baden staff a highly regarded weekly HIV Clinic at Outer Cape Health Services in Provincetown, MA. Dr. Lori Panther provides Anal Screening Clinic services on site at Outer Cape Health and the Fenway Community Health Center. Dr. Michael Wong continues to provide HIV care at Dimock Community Health Center.

Peter F. Weller, MD, Chief
Vice Chairman for Research

QUALITY IMPROVEMENT

Dr. Sigall Bell directs the Division's Quality Assurance initiative. Dr. Bell, working with the Information Systems team, developed a comprehensive, continuously-updated data base with information drawn from the BIDMC electronic medical record. This ongoing system allows analysis of aggregate institutional and provider specific care for HIV patients and compliance with guidelines for the care of HIV-infected patients. Monitored measures include appropriate timing of initiation of antiretroviral therapy, appropriate prophylaxis of opportunistic infections, baseline serologic surveillance and immunizations, monitoring of immune function and HIV suppression, and screening and treatment of co-morbid conditions (diabetes, lipid abnormalities). Notably, rates for prophylaxis for specific opportunistic infections, where indicated, ranged from 91 to 96% and the initiation rate of appropriate antiretroviral therapy was 97%. Areas identified for improvement include cholesterol and glucose surveillance.



Overwhelming infection with *Candida albicans* in *C. elegans* showing filaments penetrating the worm body. Green fluorescence highlights the *C. albicans* filaments.

Dr. Howard Gold, in collaboration with the Pharmacy Department, directs the hospital-wide antibiotic stewardship program which seeks to ensure appropriate usage of antimicrobials throughout the hospital. The Infectious Diseases Division also actively monitors all reports of significant positive blood cultures and provides consultative services to bacteremic and fungemic patients.

HONORS AND AWARDS

George Eliopoulos, MD and Robert Moellering, MD are co-editors of the *Sanford Guide to Antimicrobial Therapy*.

Robert Moellering, MD is Editor-in-Chief (consulting editor) of *Infectious Disease Clinics of North America* and received the Alexander Fleming Award for Lifetime Achievement from the Infectious Diseases Society of America and the Yen Memorial Award from the International Society for Chemotherapy.

Michael Wong, MD serves on the Massachusetts Public Health Council.

Peter Weller, MD co-edits a major textbook entitled *Tropical Infectious Diseases – Principles, Pathogens, and Practice* and is an Associate Editor for the *Journal of Infectious Diseases*.

Adolf Karchmer, MD, a prior President of the International Society of Cardiovascular Infectious Diseases, is an Associate Editor of Clinical Infectious Diseases.

Additionally, Drs. Eliopoulos, Karchmer, Moellering and Weller were selected as "Best Doctors in America."

EDUCATIONAL PROGRAMS

The educational activities of the Division are focused on Harvard Medical School students, medical residents, fellows and practicing physicians. Drs. George Eliopoulos (Tullis Firm), John Doweiko (Kurland Firm) and Elisa Choi (Robinson Firm) continue in leadership roles in the housestaff Firm System. Dr. Clyde Crumpacker directs the Harvard-MIT Health Science and Technology "Mechanisms of Microbial Pathogenesis" course (HST 040) for second year students. Drs. Peter Weller, Rachel Baden and Lori Panther direct a highly rated annual postgraduate course, HIV Update, through the HMS Department of Continuing Education and Dr. Adolf Karchmer co-directs the long-standing Winter Course in Infectious Diseases with faculty from non-Harvard institutions. Electives for medical residents and HMS students built around the clinical consulting services and the Infectious Disease and Travel Clinics are offered.

The outstanding Infectious Disease Fellowship, under the leadership of Drs. Jennifer Mitty, Wendy Stead and Rachel Baden, admits five fellows annually, each of whom typically spends a minimum three years in clinical and research training. The program offers three tracks: clinician-teacher, clinical investigation and laboratory investigation. The clinical investigation pathway offers participation in the Clinical Effectiveness summer curriculum of the Harvard School of Public Health. Laboratory research training is offered by laboratories in the Division and in the laboratories of the Division of Viral Pathogenesis and Vaccinology. The Division participates in three NIH-funded T32 Harvard-wide infectious diseases training grants.

RESEARCH ACTIVITIES

The research programs of the Division cover a broad range of important epidemiologic, clinical, translational and basic science areas.

Clinical research efforts are focused on HIV/AIDS, the epidemiology of antibiotic-resistant bacteria, nosocomial infections, studies of new anti-infective agents, and travel medicine. Dr. Mary Albrecht leads the BIDMC site of the NIH-funded Harvard AIDS Clinical Trials Group (ACTG). Dr. Lori Panther studies the role of human papilloma virus (HPV) in anal infection and its treatment. Dr. Sigall Bell studies immunologic events of primary HIV infection as related to disease expression.

Drs. Adolf Karchmer and Michael Wong conduct studies of epidemiology and treatment of invasive fungal infections as well as treatment trials with experimental antifungal agents and new antibacterial agents. Dr. Wong participates in studies of solid organ transplantation in HIV infected persons. Drs. Erika D'Agata and Sharon Wright pursue studies directed at the epidemiology of nosocomial infection and the spread of resistant organisms in the hospital environment, in long term care facilities, in hemodialysis units and in ambulatory HIV infected persons. Dr. Karchmer also directs Centers for Disease Control-funded studies in travel medicine.

Dr. Roger Shapiro conducts NIH-funded research efforts in Botswana on the prevention of maternal to infant transmission of HIV and the impact of breast feeding on infants born to HIV positive women.

Dr. Nira Pollock is investigating techniques to diagnose *Mycobacterium tuberculosis* infection including the development of a test to detect *M. tuberculosis* antigen in urine. Dr. Christopher Rowley investigates antiretroviral resistance in HIV isolated from women in Botswana who have received antiretroviral therapy to prevent HIV transmission to their newborn. Dr. Elisa Choi investigates immune responses to HIV infection and HIV vaccine development through the Division of Viral Pathogenesis. Dr. Jose Trevejo investigates the use of volatile bacterial products as targets for the diagnosis of infection, especially tuberculosis. Dr. Chen (Sabrina) Tan continues her studies of viral infections of the central nervous system, focused on JC virus, in the laboratory of Dr. Igor Koralnik in the Division of Viral Pathogenesis.

The laboratories directed by Dr. Peter Weller and Dr. Anne Nicholson-Weller are described under the Allergy Division.

FACULTY

Mary A. Albrecht, MD
Rachel P. Baden, MD
Sigall K. Bell, MD
Barbra Blair, MD
Elisa I. Choi, MD
Clyde S. Crumpacker, MD
Erika M.C. D'Agata, MD, MPH
John P. Doweiko, MD
George M. Eliopoulos, MD
Joyce D. Fingeroth, MD
Howard S. Gold, MD
Camilla Graham, MD
Adolf W. Karchmer, MD
Margaret Koziel, MD
Jennifer A. Mitty, MD
Robert C. Moellering, Jr. MD
Anne Nicholson-Weller, MD
Lori A. Panther, MD, MPH
Satish K. Pillai, MD
Nira Pollack, MD, PhD
Christopher F. Rowley, MD
Roger L. Shapiro, MD
Wendy Stead, MD
Chen Sabrina Tan, MD
Jose Trevejo, MD, PhD
Peter F. Weller, MD
Michael T. Wong, MD
Sharon B. Wright, MD
Dori Zaleznik, MD
Jie Lin Zhang, MD

Laboratory research conducted by Division faculty and their associates is focused on antibiotic resistance, herpes viruses, human immunodeficiency virus, hepatitis C virus, and inflammation. Drs. Robert Moellering, George Eliopoulos, Satish Pillai, Howard Gold and Claudie Thauvin-Eliopoulos in the laboratory of Antibiotic Resistance study the mechanism of action and resistance of antimicrobials with particular emphasis on resistance in enterococci and the genetic events in methicillin-resistant *S. aureus* (MRSA) that are responsible for the increasingly recognized ability of MRSA to evade vancomycin therapy.

Dr. Joyce Fingeroth studies viruses that are causally associated with human cancer at the basic and translational levels, including characterization of cell surface receptors for the Epstein-Barr virus (EBV) and the Kaposi sarcoma virus (KSHV, also called human herpes virus 8). Translational studies focus on characterizing targets for antiviral therapy of EBV and KSHV.

Michael T. Wong, MD

SELECTED PUBLICATIONS

D'Agata E, Mitchell S. Antimicrobial utilization patterns among nursing home residents with advanced dementia. *Arch Int Med* 2008; 168:357-62.

D'Agata EMC, Webb GF, Horn MA, Moellering RC, Ruan S. Modeling the invasion of community-acquired methicillin-resistant Staphylococcus aureus into the hospital setting. *Clin Infect Dis* 2009; 48:274-284.

Johnson LE, D'Agata EMC, Paterson DL, Clarke L, Potoski BA, Peleg AY. Pseudomonas aeruginosa bacteremia over a 10-year period: Multidrug resistance and outcomes in transplant recipients. *Transplant Infect Dis* 2009; 11:227-34.

Melia M, O'Neill S, Calderon S, Hewitt S, Bithell-Taylor K, Affeln D, Wright SB. Development of a flexible, computerized database to prioritize, record, and report influenza vaccination rates for health care personnel. *Infect Control Hosp Epidemiol* 2009; 30:361-9.

Murdoch DR, Corey GR, Hoen B, Miro JM, Fowler VG Jr, Bayer AS, Karchmer AW, Olaison L, Pappas PA, Moreillon P, Chambers ST, Chu VH, Falco V, Holland DJ, Jones P, Klein JL, Raymond NJ, Read KM, Tripodi MF, Utili R, Wang A, Woods CW, Cabell CH for the International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators: Clinical presentation, etiology, and outcome of infective endocarditis in the 21st Century. The International Collaboration on Endocarditis-Prospective Cohort Study. *Arch Intern Med* 2009; 169:463-473.

Peleg AY, Tampakakis E, Burgwyn Fuchs B, Eliopoulos GM, Moellering RC Jr, Mylonakis E. Prokaryote-eukaryote interactions identified by using Caenorhabditis elegans. *Proc Nat Acad Sci USA* 2008; 105:14585-14590.

Pillai SK, Wennersten C, Venkataraman L, Eliopoulos GM, Moellering RC Jr, Karchmer AW. Development of reduced vancomycin susceptibility in methicillin-susceptible Staphylococcus aureus. *Clin Infect Dis* 2009; 49:1169-1174.

Pollock NR, Campos-Neto A, Kashino S, Napolitano D, Behar SM, Shin D, Sloutsky A, Joshi S, Guillet J, Wong M, Nardell E. Discordant QuantiFERON-TB gold test results among US healthcare workers with increased risk of latent tuberculosis infection: A problem or solution? *Infect Control Hosp Epidemiol* 2008; 29:878-86.

Schille S, Farnon E, Kuehnert M, Wong M, Arya M, Gautam A, Sulis C, Tormey P, Barry A, LCMV Investigation Team. Transplant-associated LCMV transmission – Massachusetts, 2008. *MMWR* 2008; 57:799-801.

Szumowski JD, Wener KM, Gold HS, Wong M, Venkataraman L, Runde CA, Cohen DE, Mayer KH, Wright SB. Methicillin-resistant Staphylococcus aureus colonization, behavioral risk factors, and skin and soft-tissue infection at an ambulatory clinic serving a large population of HIV-infected men who have sex with men. *Clin Infect Dis* 2009; 49:118-21.

Division of Matrix Biology

The Division of Matrix Biology is located on the 11th floor of the Center for Life Sciences and the 4th and 7th floors of the DANA/Research East building. The Division consists of 7 investigators with primary appointments. They are Drs. Raghu Kalluri, Michael Zeisberg, Warren Hill, Elizabeth Zeisberg, Damian Medici, Keizo Kanasaki and Hikaru Sugimoto, and 2 affiliated investigators, Drs. Rajan Dewar and Yuchi Han. The goal of the Division is to create the translational research program in the broad area of extracellular matrix biology and medicine. The Division currently trains 23 physician-scientists, 8 graduate and medical students including a Doris Duke Research Fellow, and 9 basic scientists. The Division brings together physician-scientists from diverse fields of nephrology, oncology, gastroenterology, pulmonary medicine, endocrinology, pathology and general medicine. The central mission of the Division is research, education and training of our next generation of physician-scientists and basic scientists in the area of matrix biology.

EDUCATIONAL PROGRAMS

Dr. Kalluri is the founding course director of the HMS cell biology minicourse on basement membranes and cell-matrix interactions. Dr. Kalluri teaches courses in the Harvard-MIT Division of Health Sciences and Technology on tumor pathophysiology and renal pathophysiology. Dr. Kalluri serves as a tutor for the HMS Medical Course on the Chemistry and Biology of the Cell. Dr. Dewar serves as tutor for HMS Medical Course on Pathology and Dr. Sugimoto lectures on Mouse Pathology in the HMS-sponsored nano-course. The Division also sponsors a monthly seminar series in the broad areas of Cell and Matrix Biology that attracts over 150 scientists. Since the formation of the Division of Matrix Biology in 2006, our faculty delivered over 162 invited lectures, including 42 plenary/keynote lectures and published around 100 articles. The faculty organized 5 different international meetings and also served on 22 program committees for international conferences.

Raghu Kalluri, MD, PhD, Chief

MENTORSHIP AND TRAINING

In total, 27 post-doctoral fellows completed their training since the formation of the Division and 18 of them have started new independent faculty positions in various academic institution of the world. Five students completed their thesis work at the HMS or Harvard-MIT programs during this period. Several high school, undergraduate and medical students performed research in the Division as part of the Harvard-SHURP program, DFCI-CURE program, Doris Duke Clinical Research Fellowship, American Society for Clinical Pathology Fellowship, American Heart Association Fellowship, American Society of Nephrology Fellowship, American Brain Research Society Fellowship and others. Currently, 22 out of 26 research fellows are funded by individual or institutional training grants. Development of junior faculty is of paramount interest to the Division and this is constantly encouraged via on-the-floor teaching, monthly progress assessments, grant writing workshops and importantly, fostering constant collaborations between all Division members on a daily basis.

HONORS AND AWARDS

Dr. Raghu Kalluri received the 2009 Champalimaud Foundation Metastasis Investigator Award and became a member of the American Society for Clinical Investigation, 2009.

FACULTY

Rajan Dewar, MD, PhD
Yuchi Han, MD
Warren Hill, PhD
Raghu Kalluri, MD, PhD
Keizo Kanasaki, MD, PhD
Damian Medici, PhD
Hikaru Sugimoto, MD, PhD
Elizabeth Zeisberg, MD
Michael Zeisberg, MD

HIGHLIGHTS

The Division of Matrix Biology has evolved into an interdisciplinary organization performing research in the areas of extracellular matrix biochemistry, cell-matrix interaction, vascular biology, tumor microenvironment, cancer metastasis, organ fibrosis, cell plasticity and tissue engineering. The Kalluri laboratory is currently training 19 physician-scientists, 8 graduate and medical students and 5 basic scientists. Physician-scientist trainees include fellows and attending physicians in the areas of nephrology, oncology, gastroenterology, pulmonary medicine, endocrinology, pathology and general medicine.

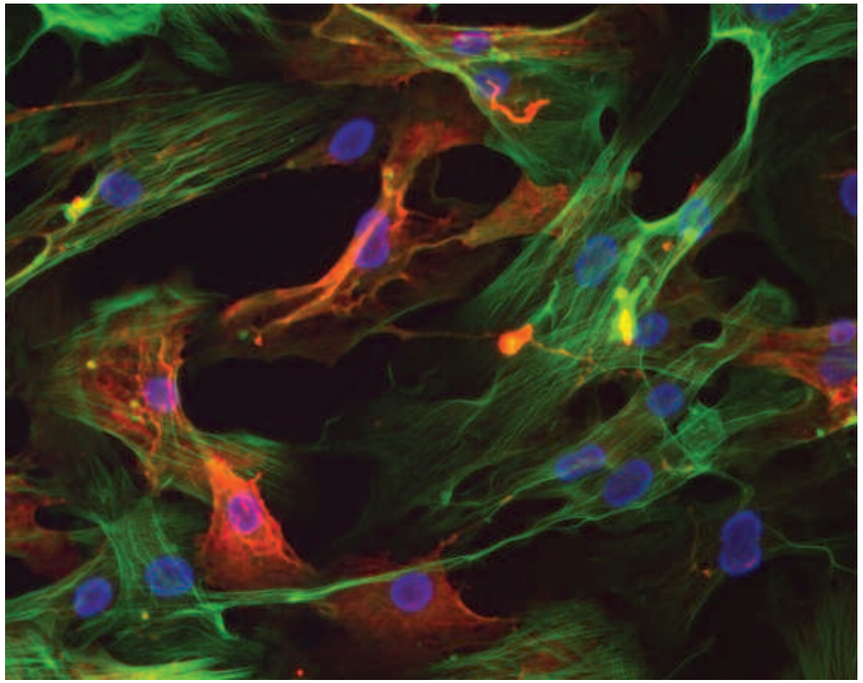
Michael Duncan, PhD, Postdoctoral fellow

RESEARCH ACTIVITIES

The Division has developed a multi-disciplinary research program in basic, clinical and translational science in the areas of extracellular matrix biochemistry, cell-matrix interaction, vascular biology, tumor microenvironment, cancer metastasis, organ fibrosis, stem cell biology and tissue engineering. The Division of Matrix Biology was created in 2006. In the past 3.5 years, the Division has recruited 6 faculty members in addition to Dr. Kalluri. The Division currently occupies 6,000 square feet of laboratory space, and consists of around 40 postdoctoral fellows, students and research scientists.

Dr. Hill is a physiologist who studies the role of integrins in bladder development and function. Dr. Kalluri studies the biology of basement membranes and extracellular matrix with a specific focus on organ fibrosis, cancer progression and epithelial-to-mesenchymal transition. Dr. Kanasaki is interested in evaluating vascular and matrix defects associated with the placenta and the urogenital system. Dr. Medici has a specific interest in evaluating the impact of extracellular matrix and growth factors on stem cells, phenotypes of vascular endothelial cells and its relation to vascular diseases such as hemangiomas. Dr. Sugimoto is interested in the molecular mechanisms behind the glomerular basement membrane, mesangial matrix expansion and interstitial fibrosis associated with diabetic nephropathy. Dr Michael Zeisberg's lab studies epigenetic changes associated with organ fibrosis and in identifying molecular targets to inhibit organ fibrosis. Dr. Elisabeth Zeisberg studies matrix-regulated cellular transitions in organ fibrosis and cancer progression with specific focus on endothelial to mesenchymal transition. The major emphasis of Dr. Dewar is the study of molecular mechanisms associated with myelofibrosis. Dr. Han has a specific interest in cardiac hypertrophy.

The Division encompasses a wide expertise in the area of matrix biology with specific emphasis on structure, cell/molecular biology and biochemistry. The Division exploits mouse models to unravel mechanism behind human diseases and strives to apply this knowledge towards translational research to help our patients.



Tumor associated pericytes are important regulators of cancer progression and metastasis.

SELECTED PUBLICATIONS

LeBleu V, Sugimoto H, Mundel TM, Gerami-Naini B, Finan E, Miller CA, Gattone VH 2nd, Lu L, Shield CF 3rd, Folkman J, Kalluri R. Stem cell therapies benefit Alport syndrome. *J Am Soc Nephrol* 2009; 20(11):2359-70.

Bechtel W, Zeisberg M. Twist: a new link from hypoxia to fibrosis. *Kidney Int* 2009; 75(12):1255-6.

Zeisberg M, Neilson EG. Biomarkers for epithelial-mesenchymal transitions. *J Clin Invest* 2009; 119(6):1429-37.

Chang SH, Kanasaki K, Gocheva V, Blum G, Harper J, Moses MA, Shih SH, Nagy JA, Joyce J, Bogyo M, Kalluri R, Dvorak HL. VEGF-A induces angiogenesis by perturbing the cathepsin-cysteine protease inhibitor balance in venules, causing basement membrane degradation and mother vessel formation. *Canc Res* 2009; 69(10):4537-44.

Lee SB, Kanasaki K, Kalluri R. Circulating TGF-beta 1 as a reliable biomarker for chronic kidney disease progression in the African-American population. *Kidney Int* 2009 Jul; 76(1):10-2.

Schweitzer MH, Zheng W, Organ CL, Avci R, Suo Z, Freimark LM, Lebleu VS, Duncan MB, Vander Heiden MG, Neveu JM, Lane WS, Cottrell JS, Horner JR, Cantley LC, Kalluri R, Asara JM. Biomolecular characterization and protein sequences of the Campanian hadrosaur B. canadensis. *Science* 2009; 324(5927):626-31.

Kalluri R, Weinberg RA. The basics of epithelial-mesenchymal transition. *J Clin Invest* 2009; 119(6):1420-8.

Kalluri R, Weinberg RA. EMT: when epithelial cells decide to become mesenchymal-like cells. *J Clin Invest* 2009; 119(6):1417-9.

Zeisberg EM, Potenta SE, Sugimoto H, Zeisberg M, Kalluri R. Fibroblasts in kidney fibrosis emerge via endothelial-to-mesenchymal transition. *J Am Soc Nephrol* 2008; 19(12):2282-7.

Potenta S, Zeisberg E, Kalluri R. The role of endothelial-to-mesenchymal transition in cancer progression. *Br J Cancer* 2008 Nov 4; 99(9):1375-9.

Leanne Lee, MD,
Joseph M. Smith
Community Health Center

Division of Molecular & Vascular Medicine

The Division of Molecular and Vascular Medicine is located on the second and third floors of Research North. The goal of the Division is to create the first-of-its-kind bench-to-bedside program in vascular/endothelial biomedicine. The Division consists of 7 investigators with primary appointments (Drs. Ruhul Abid, William Aird, Christopher Carman, Marianne Grant, Erzsébet Ravasz Regan, Alan Rigby, and Huiyan Zeng) and 4 investigators with secondary appointments to the Division (Drs. Ananth Karumanchi, Peter Oettgen, Kiichiro Yano and Nathaniel Shapiro). Division members are also members of the Center for Vascular Biology Research. The Center, which consists of 27 core investigators occupying contiguous space in Research North, brings together scientists and clinicians from diverse fields with the goal of formulating and applying interdisciplinary methods to the study of vascular biology.

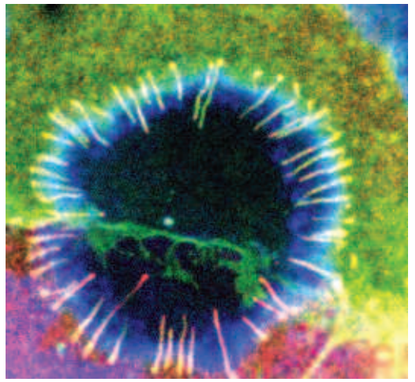
EDUCATIONAL PROGRAMS

Dr. Aird is founding Co-Director of an annual one-week course in Comparative Physiology for BIDMC medical residents at Mount Desert Island, Maine. Dr. Aird directs the Hematology Module of that course, and Drs. Rigby and Grant participate as faculty members. Dr. Carman lectures in the Harvard Medical School Immunology 202 (Imm202) and Human Physiology and Pathophysiology (DMS220) courses.

William C. Aird, MD, Chief
J. Peter Oettgen, MD, Associate Chief

RESEARCH ACTIVITIES

The Division occupies 12,000 square feet of laboratory space, and consists of some 50 postdoctoral fellows, students and research assistants. Faculty members cover a wide breadth of basic research. Dr. Abid studies the role of redox signaling in vascular biology and has an interest in the role of forkhead transcription factors in the endothelium. Dr. Aird's laboratory studies the spatial and temporal dynamics of the endothelium. Specifically, they study the mechanisms of cell signaling in vitro and in vivo, transcriptional networks in the endothelium, and the role of the endothelium in pathophysiological states such as sepsis and tumors. Dr. Carman employs intravital microscopy and other cutting-edge imaging technologies to dissect mechanisms of leukocyte-endothelial cell interactions.

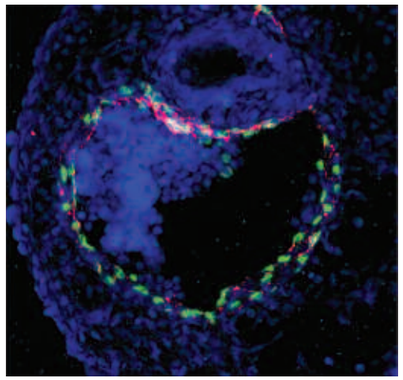


Monocyte Adhesion to Endothelium (Carman)
Red = Endothelium/VCAM-1; Blue = Monocyte/LFA1; Green = ICAM-1/Endothelium

HONORS AND AWARDS

Christopher Carman, PhD received an American Heart Association Scientist Development Award and a Roche Transplantation Research Foundation Award.

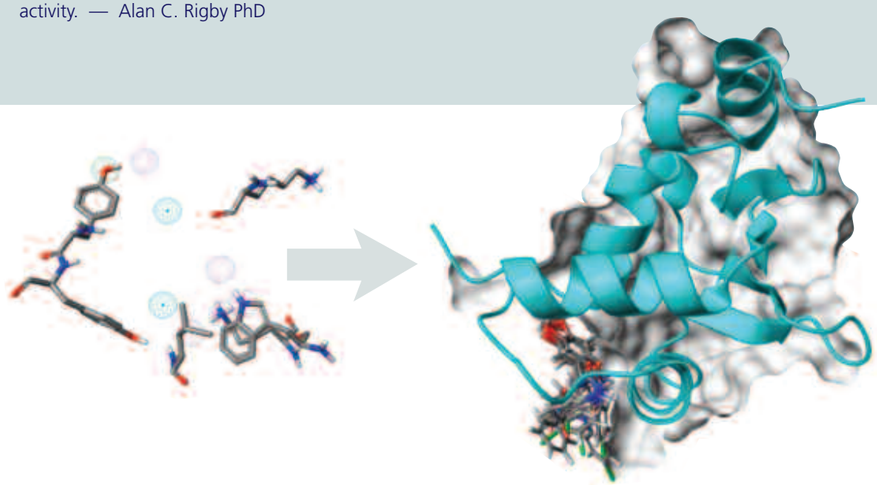
Alan Rigby, PhD was the recipient of a Harvard Clinical and Translational Catalyst Award and a Prostate Cancer Foundation Creativity Award.



Embryoid bodies (Oettgen & Carman)
Red = VE-cadherin; Blue = Nuclei; Green = ERG

COMPUTER-AIDED DRUG DISCOVERY: TRANSLATIONAL INNOVATION AT THE INTERFACE

Macromolecular complex assemblies comprised of protein-protein and/or protein-DNA interactions are the functional cornerstones of signal transduction, immune response and other essential cellular processes that are dependent upon specific protein-DNA interactions. The concept of selectively targeting and inhibiting the interaction interfaces of protein-protein and/or protein-DNA complexes represents a paradigm shift in therapeutic strategies aimed at reprogramming specific pathways or programs of gene expression that are deregulated in cancer, inflammation and other complex disease states where there is still considerable unmet therapeutic need. One approach that has been used to interrogate this novel interaction interface that is within the expanded "druggable genome" is computer-aided drug discovery (CADD). Our CADD platform, which was developed in the Division of Molecular and Vascular Medicine operates on computer grids/cluster that is capable of screening virtual libraries comprised of increasingly large numbers of unique small molecules (~5M) using target or ligand pharmacophores (illustrated). This platform has enabled us to accelerate hit identification, lead validation and hit-through-lead optimization for numerous targets including: transcription factors (TFs), key metabolic enzymes, ligand-dependent nuclear receptor TFs as well as several kinases. Illustrated is a member of the ETS family of transcription factors with small molecules that have been validated *in vitro*, *in cellulo* and *in vivo* for Ets-1 inhibitory activity. — Alan C. Rigby PhD



Target-specific computer aided drug discovery (CADD) initiatives that are carried out in the Division of Molecular and Vascular Medicine use critical structural descriptors of the target being screened. These structure-function features are extracted from the target protein and projected in three-dimensional space together with ligand-based pharmacophores. This CADD platform enables hit-through-lead small molecule discovery screens to be carried out in any target space including the transcription factor-DNA interaction interface as illustrated here.

Dr. Grant employs multidimensional NMR spectroscopy to study the structural biology of proteins with regulatory and signaling function, with the goal of using protein structure to gain mechanistic insight into protein function. Dr. Regan is interested in investigating biological systems from a complex networks perspective, with special emphasis on transcriptional regulatory networks and the logic of biological regulation. Dr. Rigby's laboratory is focused on using structural biology to better understand anticoagulation, apoptosis, gene expression and receptor ligand interactions, with a particular interest in structure-based in silico drug discovery. Dr. Zeng studies the molecular mechanisms underlying physiological and pathological angiogenesis. The major focus of Dr. Karumanchi's group is the role of angiogenic factors in the pathogenesis of pre-eclampsia. Dr. Oettgen's laboratory studies the role of selected transcription factors in the regulation of vascular inflammation, angiogenesis, vascular development and endothelial differentiation. Drs. Shapiro and Yano focus on basic and translational studies of sepsis.

FACULTY

Ruhul Abid, MD
William Aird, MD
Christopher Carman, PhD
Marianne Grant, PhD
Erzsébet Ravasz Regan, PhD
Alan Rigby, PhD
Huiyan Zeng, PhD
Ananth Karumanchi, MD
Peter Oettgen, MD
Kiichiro Yano, PhD
Nathaniel Shapiro, MD, MPH

SELECTED PUBLICATIONS

Abid MR, Nadeau RJ, Spokes KC, Minami T, Li D, Shih SC, Aird WC. Hepatocyte growth factor inhibits VEGF-forkhead-dependent gene expression in endothelial cells. *Arterioscler Thromb Vasc Biol* 2008; 28:2042-8.

Carman CV. Mechanisms for trans cellular diapedesis: probing and pathfinding by 'invadosome-like protrusions'. *J Cell Sci* 2009; 122:3025-35.

Grant MA. A protein structure prediction method in structure-based ligand design and virtual screening. *Comb Chem High Throughput Screen* 2009; 12:940-60.

Grant MA, Baron RM, Macias AA, Layne MD, Perrella MA, Rigby AC. Netropsin improves survival from endotoxaemia by disrupting HMGA1 binding to the NOS2 promoter. *Biochem J* 2009; 418:103-12.

Jin E, Liu J, Suehiro J, Yuan L, Okada Y, Nikolova-Krstevski V, Yano K, Janes L, Beeler D, Spokes KC, Li D, Regan E, Shih SC, Oettgen P, Minami T, Aird WC. Differential roles for ETS, CREB and EGR binding sites in mediating VEGFR1 expression in vivo. *Blood* 2009; 114(27):5557-66.

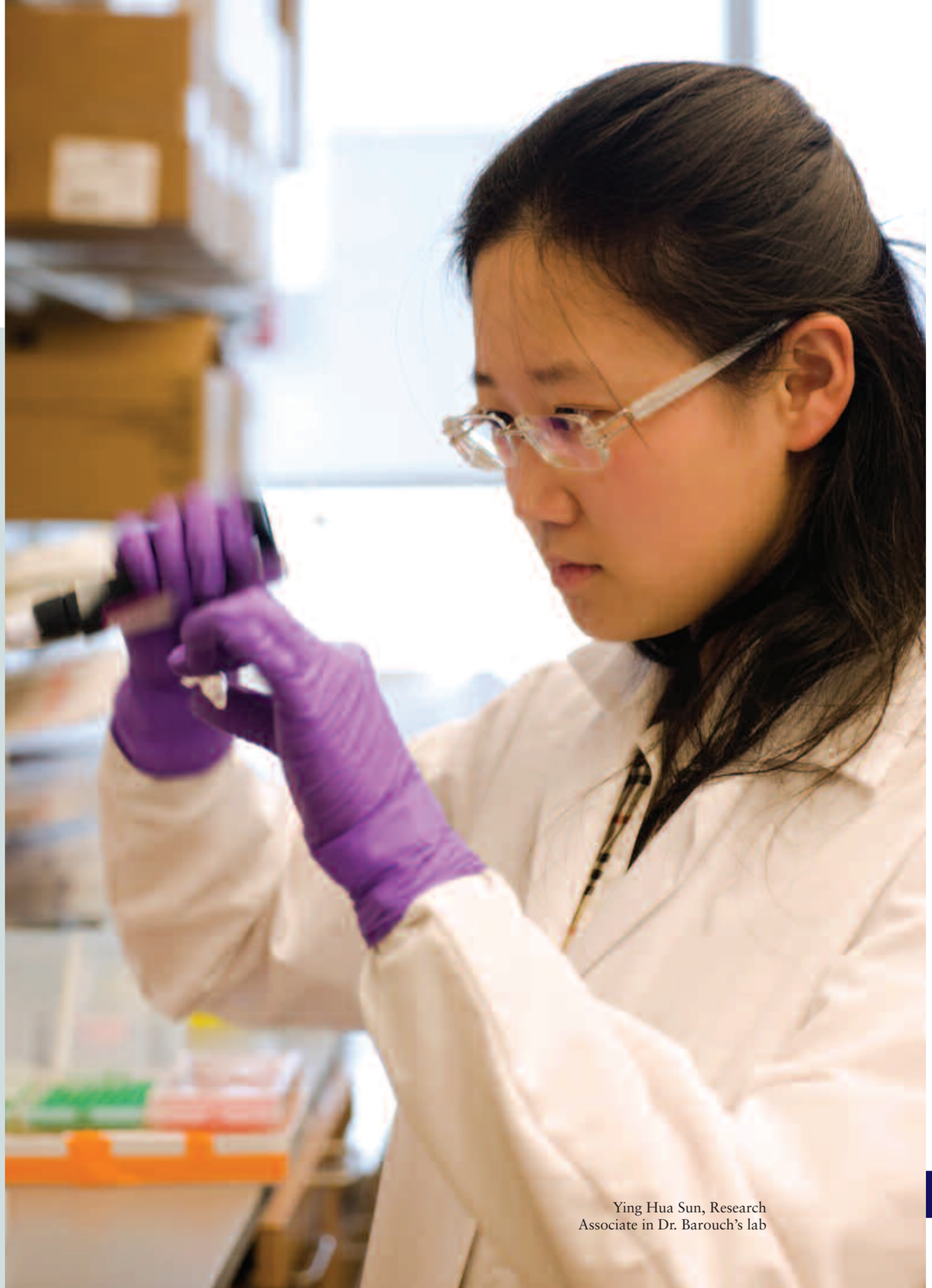
Liu X, Zhao D, Qin L, Li J, Zeng H. Transcription enhancer factor 3 (TEF3) mediates the expression of Down syndrome candidate region 1 isoform 1 (DSCR1-1L) in endothelial cells. *J Biol Chem* 2008; 283:34159-67.

Peer D, Park EJ, Morishita Y, Carman CV, Shimaoka M. Systemic leukocyte-directed siRNA delivery reveals cyclin D1 as an anti-inflammatory target. *Science* 2008; 319:627-30.

Rigby AC. Computer-aided drug discovery: Targeting complex interfaces using an expanding chemical hay stack. *Future Medicinal Chemistry* 2009; 1(4):577-81.

Sharma AK, Zhou GP, Kupferman J, Surks HK, Christensen EN, Chou JJ, Mendelsohn ME, Rigby AC. Probing the interaction between the coiled coil leucine zipper of cGMP-dependent protein kinase Ialpha and the C terminus of the myosin binding subunit of the myosin light chain phosphatase. *J Biol Chem* 2008; 283:32860-9.

Yuan L, Nikolova-Krstevski V, Zhan Y, Kondo M, Bhasin M, Varghese L, Yano K, Carman CV, Aird WC, Oettgen P. Antiinflammatory effects of the ETS factor ERG in endothelial cells are mediated through transcriptional repression of the interleukin-8 gene. *Circ Res* 2009; 104:1049-57.



Ying Hua Sun, Research Associate in Dr. Barouch's lab

Division of Nephrology

The Division provides expert care for patients with all varieties of renal disease, provides highly effective teaching and training in renal physiology, pathophysiology and the clinical care of patients for medical students, residents and fellows, and performs highly significant and cutting-edge research in a broad spectrum of renal diseases. These activities are organized under the interim leadership of Dr. Zeidel, as Division Chief, and Dr. Brown, as the Clinical Chief. Drs. Brown and Williams serve as dialysis Co-directors and Dr. Pavlakis is Director of renal transplantation.

Following an extensive national search, Martin R. Pollak, MD has signed on as our new Division Chief in Nephrology, on February 1, 2010. A nationally-renowned leader and rising star in nephrology, Dr. Pollak's research focuses on the genetics of glomerular diseases, and his work is developing novel insights into the control of glomerular filtration and the pathways by which glomeruli are damaged.

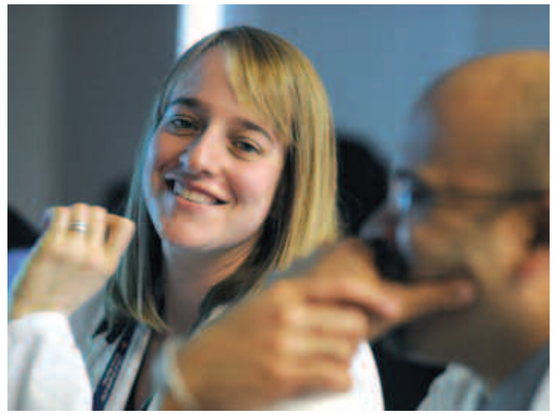
We are also delighted to welcome Laurence Turka, MD, the current editor of the *Journal of Clinical Investigation* and former Chief of the Renal and Electrolyte Division at Penn. Larry, who is an extremely prominent investigator in the area of transplant immunology, will co-lead the transplant immunology effort with Dr. Terry Strom.

We note with great sadness the passing of Dr. Franklin Epstein, a giant in nephrology who led this Division and department with great distinction. Frank made important contributions to our understanding of fluid and electrolyte metabolism and the mechanisms of renal damage in preeclampsia, hypertension and acute renal failure. He was an inspirational clinician, who helped define for a generation of Beth Israel trainees what it means to provide the kind of care to patients that we would want for our family members.

Martin R. Pollak, MD, Chief

CLINICAL ACTIVITIES

Our clinic practices have shown extraordinary growth in the past two years, in part attributed to providing new patient referral access in less than two days – an effort spearheaded by Dr. Zeidel. Dr. Kaldany has developed a number of ESRD programs abroad, especially in the Middle East. In addition he has a new Vascular Graft Device – US Patent No: 7,351,257, issued in April 2008, in development. Dr. Pavlakis, the Medical Director of kidney and pancreas transplantation, together with Drs. Mandelbrot and Goldfarb, evaluate and follow patients in transplant clinics in the Transplant Institute. Along with the Department of Surgery and the Transplant Institute, the Division has opened a new dialysis access center in Brighton. Our ESRD patients now benefit from prompt outpatient opening of clotted accesses, and services which prevent clotting and failure of accesses.



Nephrology Fellows Suzanne Martin, MD, and Ranil DeSilva, MD

QUALITY IMPROVEMENT

Dr. Mutter has led a Division-wide CQI project on provision of adequate hemodialysis and CVVHD treatment to patients hospitalized with acute renal failure. Phase 1 results will be presented at the 2009 National Forum on Quality Improvement in Health Care of the Institute for Healthcare Improvement.

A Distinguished Visiting Professor program has been initiated by Dr. Steinman. This has brought in international speakers to the Division and the Boston community as several of these speakers participate in inter-hospital Renal Rounds. In addition, a broad array of didactic activities have been organized. These include a weekly conference with Dr. Rose, the founder of UpToDate; pathology sessions with Dr. Stillman; a Monday series of conferences that include journal clubs, basic science and research forums; a clinical conference every Friday; weekly rounds with Dr. Zeidel, Lecker or Brown; and joint laboratory research conferences twice each month.

FACULTY

Seth L. Alper, MD, PhD
Robert S. Brown, MD
Robert A. Cohen, MD
John Danziger MD
John D'Elia, MD
David Friedman, MD
Alexander Goldfarb, MD, PhD
Junichi Hanai, MD PhD
Warren Hill, PhD
Melanie Hoenig, MD
Antoine Kaldany, MD
S. Ananth Karumanchi, MD
Stewart H. Lecker, MD, PhD
Didier Mandelbrot, MD
C. John Mathai, PhD
Bryce MacIver, PhD
Walter Mutter, MD
Samir M. Parikh, MD
Martha Pavlakis, MD
Martin R. Pollak, MD
Burton Rose, MD
Bijan Roshan, MD
Terry B. Strom, MD
Robert C. Stanton, MD
Theodore I. Steinman, MD
Isaac Stillman, MD
Vikas P. Sukhatme, MD, PhD
Laurence Turka, MD
Mark E. Williams, MD
Hai-Tao Yuan, PhD, MD
Mark L. Zeidel, MD

We completed a Quality assurance study, "QI Evaluations of Renal Biopsies," for evaluation of the satisfactory performance of kidney biopsies by nephrology fellows in training with attainment of 100% satisfactory results (as compared with "needs improvement"). With the active participation of all nephrologists managing ESRD patients, we have reviewed in detail the access used to dialyze our patients, and have minimized wherever possible the use of catheters. We continue to push hard to reduce catheter usage during initiation of dialysis. We also review regularly our compliance with DOQI guidelines, and plan to focus on the outpatient peritoneal dialysis program over the upcoming year.

Robert S. Brown, MD, reviews the Nephrology Clinic process and procedures to incoming Nephrology Fellows.

EDUCATIONAL PROGRAMS

After many years leading the nephrology fellowship program, Dr. Robert Brown has stepped down as the Program Director, and Dr. Stewart Lecker has become the new Program Director. The Division plays an active role in training fellows, residents and students. It has an enviable record in fellowship training. Since 1973, its 99 fellow graduates now include 70 academic physicians, of whom 17 are full professors, 15 associate professors, 22 assistant professors, 10 nephrology division chiefs, 2 vice-chairs, and 3 associate deans. Dr. Hoenig is the course director for renal pathophysiology at Harvard Medical School and a large number of faculty contribute to the course. Second year fellows have an opportunity to participate as well.

RESEARCH ACTIVITIES

The Division and faculty members who are related closely to it perform ground-breaking research in a wide variety of areas related to renal physiology and kidney disease. For clarity, we have listed the research by category and investigator:

Ion and water transport – The laboratories of Drs. Alper, Zeidel, Hill, Mathai and MacIver are active in this area, with studies on: the

molecular physiology of bicarbonate transport in cell pH and volume regulation; potassium homeostasis in red cell hemoglobinopathies and in secretory epithelia; how water, protons and small non-electrolytes cross biological membranes; how intracellular signaling pathways modulate the secretion of chloride by rectal glands of elasmobranchs and many elements of the cell biology of mammalian bladder epithelium.

role for the orphan endothelial specific receptor Tie-1 in atherosclerosis has been elucidated (Chan and Sukhatme), as have downstream signaling pathways (Yuan, Karumanchi, Chan and Sukhatme). Dr. Friedman's research focuses on the role of purinergic signaling (ectonucleotidases and purinergic receptors) in vascular disease. Using mouse models, he is investigating microvascular injury in diabetic nephropathy

HONORS AND AWARDS

Samir Parikh, MD, received multiple awards and honors: the Klarman family scholarship, an Amgen Medical Institute Junior Investigator Award, a Clinical LRP scholar from NIH, Carl Gottschalk Award from the American Society of Nephrology, is a Principal Investigator-R01-NIH/NHLBI and received a Harvard Medical School teaching award.

Martha Pavlakis, MD was promoted to Associate Professor of Medicine, 2008.

Mark E. Williams, MD was appointed to ASN Council on Geriatric Nephrology.

Burton Rose, MD was the recipient of the 2009 Robert Narins award from the American Society of Nephrology.

David Friedman, MD was a Nominee, Harvard Medical School Humanism in Medicine Award, 2008.

S. Ananth Karumanchi, MD was awarded a 2008 Young Investigator Award, American Society of Nephrology and was named a 2008 Howard Hughes Investigator.

Vascular biology – Dr. Parikh is studying the role of the angiopoietin family of ligands in vascular leak syndromes in man. A translational focus has been on clinical trials of

and large vessel disease in studies of arteriovenous fistula maturation and stenosis.

Walter Mutter, MD and
Alexander Goldfarb, MD, PhD

novel anti-angiogenesis drug combinations for cancer therapy (Sukhatme). Dr. Karumanchi's research aims at understanding the pathophysiology of preeclampsia. A novel

Proteinuria – Drs. Karumanchi and Mutter have generated microarray data from podocytes grown in high and normal glucose in studies aimed at deciphering novel targets and pathways. Transcriptional profiles of podocytes lacking nephrin (mutated in congenital Finnish nephrotic syndrome) and LMX-1b (mutated in nail-patella syndrome) are in progress. Urine proteomics data from diabetic patients with and without nephropathy are being analyzed in order to identify novel urine markers that predict worse renal outcomes. Dr. Mutter is investigating soluble mediators of proteinuria in Minimal Change Disease.

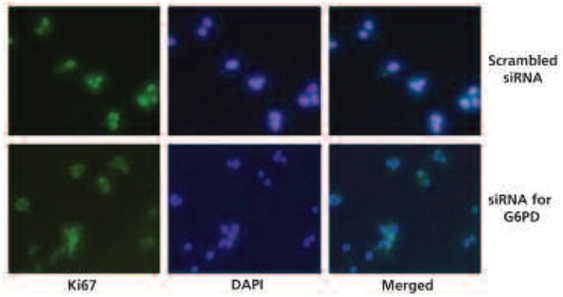
States of muscle atrophy – Dr. Lecker's research explores the molecular mechanisms behind the muscle wasting which occurs in uremia and other chronic illnesses such as cancer, sepsis and diabetes. Dr. Lecker's studies have identified a group of about 100 genes (termed "atrogenes") that are coordinately regulated during wasting. A recent collaboration with Drs. Hanai and Sukhatme has shed new light into the mechanisms of statin induced myopathy, which they have discovered is mediated by atrogin-1.

Cellular metabolism – Dr. Stanton's laboratory has focused on elucidating the regulation of glucose 6-phosphate dehydrogenase (G6PD), the main source of NADPH, the principal reductant in the cell. A key role of aldosterone in impairing vascular reactivity through diminishing G6PD has been recently elucidated.

Polycystic Kidney Disease – The Alper laboratory is studying the deficient shear/flow signaling phenotype of human PKD cyst cells of defined mutant genotype. Dr. Steinman is examining the role of ACE inhibitors/ARBs in effecting cyst growth and glomerular filtration rate in ADPKD patients. A second study in ADPKD examines the role of a V2 receptor antagonist in slowing progression of disease.

Renal cancer – Drs. Seth and Sukhatme have defined novel targets for renal cancer via a whole genome RNAi screen. The metabolism of cancer cells is also a focus of new studies.

Renal function – One of Dr. Mandelbrot's research efforts is on novel technologies for measuring renal function. He has described the use of neutron activation to measure glomerular filtration rate and future studies will use this method to measure renal blood flow.



Inhibition of the protein glucose 6-phosphate dehydrogenase by siRNA causes decreased cell proliferation in cell cultures of mouse pancreatic beta cells. Ki67 is a marker of cell proliferation. DAPI is a marker of the nucleus. In control cells (upper panel), Ki67 protein is in the nucleus, consistent with proliferating cells. Inhibition of G6PD (lower panel) leads to no clear nuclear localization, consistent with impaired proliferation.

Public Policy and Research Initiative to Improve the Care of ESRD Patients – In April of 2009, under the overall leadership of Ted Steinman, a highly successful international conference and call to action entitled, "International Conference on ESRD: State of the Art and Charting the Challenges for the Future" was held in Boston. This effort has catalyzed an international movement to examine and change the quality of care delivered to the patient with ESRD.

SELECTED PUBLICATIONS

Yuan HT, Khankin EV, Karumanchi SA, Parikh SM. Angiopoietin-2 is a partial agonist and antagonist of the Tie-2 receptor. *Mol Cell Biol* 2009; 29(8):2011-22.

Mathai JC, Missner A, Kügler P, Saparov SM, Zeidel ML, Lee JK, Pohl P. No facilitator required for membrane transport of hydrogen sulfide. *Proc Natl Acad Sci USA* 2009; 106(39):16633-8.

Xu Y, Zhang Z, Hu J, Stillman IE, Leopold JA, Handy DE, Loscalzo J, Stanton RC. Glucose-6-phosphate dehydrogenase-deficient mice have increased renal oxidative stress and increased albuminuria. *FASEB J* 2010; 24(2):609-16.

Stewart AK, Kurschat CE, Vaughan-Jones RD, Alper, SL. Putative re-entrant loop 1 of AE2 transmembrane domain has a major role in acute regulation of anion exchange by pH. *J Biol Chem* 2009; 284:6126-29.

Egbuna O, Davis R, Chudzinski R, Pavlakis M, Rogers C, Molakatalla P, Johnson S, Karp S, Monaco A, Tang H, Hanto D, Mandelbrot D. Outcomes with conversion from calcineurin inhibitors to sirolimus after renal transplantation in the context of steroid withdrawal or steroid continuation. *Transplantation* 2009; 88:684-92.

Mandelbrot DA, Pavlakis M, Johnson S, Karp S, Hanto D, Rodrigue JR. Long-term follow-up of living kidney donors: a survey of U.S. transplant center practices. *Transplantation* 2009; 88:855-860.

Friedman DJ, Talbert ME, Bowden DW, Freedman BI, Mukanya Y, Enjyoji K, Robson SC. Functional ENTPD1 polymorphisms in African Americans with diabetes and end-stage renal disease. *Diabetes* 2009; 58(4):999-1006.

Friedman DJ, Künzli BM, A-Rahim YI, Sevigny J, Berberat PO, Enjyoji K, Csizmadia E, Friess H, Robson SC. From the Cover: CD39 deletion exacerbates experimental murine colitis and human polymorphisms increase susceptibility to inflammatory bowel disease. *Proc Natl Acad Sci* USA 2009; 106(39):16788-93.

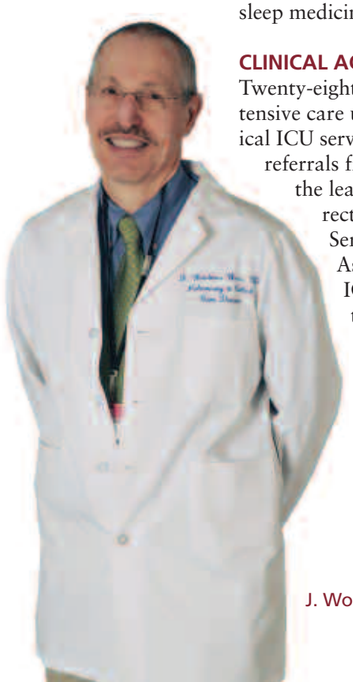
Steinman, TI. Reducing morbidity and mortality in incident hemodialysis patients with an early intervention program. *Nat Clin Pract Nephrol* 2008; 4:248-249.

Brown RS, Karumanchi SA, Sukhatme VP, Zeidel ML. Franklin H. Epstein – Researcher, teacher, clinician, and humanist. *Clin J Am Soc Nephrol* 2009; 4:1285-1289.

Division of Pulmonary, Critical Care & Sleep Medicine

The Division of Pulmonary, Critical Care & Sleep Medicine has a range of inpatient and outpatient clinical activities. In addition to running the Medical Intensive Care Service and overseeing the care of all critically ill patients on the Medical Service, the Division provides pulmonary medicine and sleep medicine consultations for both ambulatory patients and inpatients. While providing these services Division members also play an active role in undergraduate and graduate medical education and sustain an active research portfolio.

The leadership of the Division includes: J. Woodrow Weiss, Division Chief, and Richard Schwartzstein, Associate Chief, who simultaneously serves as Vice President for Education at Beth Israel Deaconess Medical Center. Clinical pulmonary activities are directed by David Roberts, Clinical Director of the Division; by Peter LaCamera, Director of the Pulmonary Consultation Service; by Peter Clardy, Director of the Medical Intensive Care Service with Michael Howell, Associate Director; and by Geoffrey Gilmartin coordinator of the program in sleep medicine and the sleep laboratory.

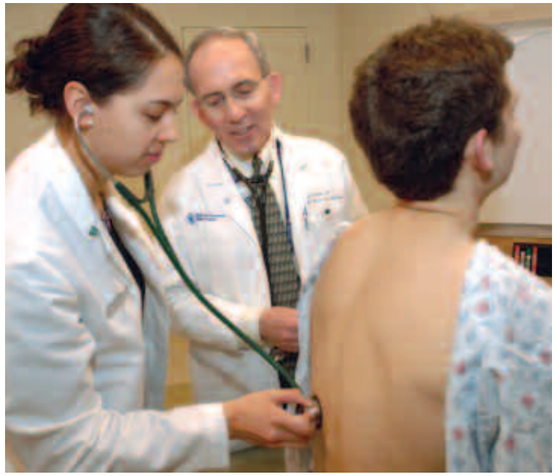


J. Woodrow Weiss, MD, Chief

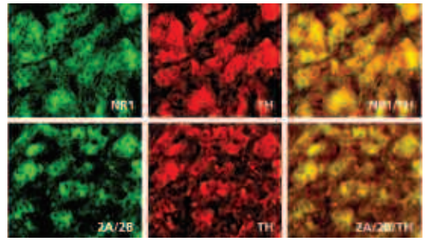
CLINICAL ACTIVITIES

Twenty-eight medical ICU beds in three intensive care units constitute the largest medical ICU service in the region and support referrals from all of New England. Under the leadership of Peter Clardy, the Director of the Medical Intensive Care Service and Michael Howell, the Associate Director, the Medical ICU (MICU) service has been at the forefront of national efforts to improve the quality of care in critical care. Over the last three years, central line infections have almost been eliminated and ventilator-associated pneumonias have been dramatically reduced. In addition, initiatives to enhance patient-centered care in the ICU have won national attention (see Quality Improvement).

Outpatient consultations in Pulmonary and Sleep Medicine are provided in the Shapiro Clinical Center and at the Lexington site. Numerous specialty programs target care of patients with specific problems. For example, the Center for Interstitial Fibrosis brings together basic and clinical scientists with an interdisciplinary group of radiologists, surgeons and pathologists to provide sophisticated diagnostic evaluations of patients with interstitial lung disease. The Center is among the most active in the country at enrolling patients in novel treatment trials, and has received tremendous regional participation in its creative patient education (See Program Highlights). Another specialty program is the Sleep Disorders Center, which is nationally known for its innovative therapeutic and diagnostic approaches to patients with sleep-disordered breathing. Six senior clinicians, all with specialty training in sleep medicine, as well as pulmonary and critical care, staff the Center which is among the busiest sleep programs in the Northeast. In addition to these active and growing activities, the Division provides unique services through the Interventional Pulmonary-Complex Airway Disease Center. Run in collaboration with Thoracic Surgery, this program represents the most active Interventional Pulmonology service in the U.S. The Interventional Pulmonology Center performs novel procedures with the collaboration of the outstanding Chest Radiology section of the Department of Radiology and with the Division of Thoracic Surgery in the Department of Surgery.



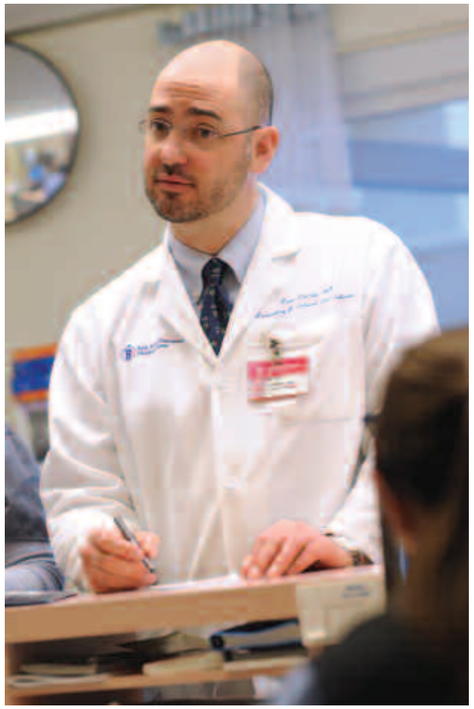
Medical student Daphne Ponce and Ronald Silvestri, MD



Glomus cells from rat carotid bodies double stained for the neurotransmitter tyrosine and for either the glutamate NMDA receptor NR1 or the glutamate NMDA receptor NR2A/2B.

PROGRAM HIGHLIGHTS

The Interstitial Lung Disease Center, under the direction of Drs. Joseph Zibrak and Peter LaCamera, was created in 2007 in an attempt to consolidate and promote the Division's research and clinical efforts for this class of diseases. Through outreach to pulmonary physicians in Massachusetts and surrounding states, the Center has benefited from an increasing number of referrals. It has participated in more clinical trials investigating therapies for idiopathic pulmonary fibrosis (IPF) than other area hospitals and has had great success recruiting patients into these trials. In September, Drs. Zibrak and LaCamera hosted the second annual Symposium for Those Living with Idiopathic Pulmonary Fibrosis which consisted of a day-long program of talks, question and answer and small group sessions covering a broad range of topics relevant to those diagnosed with IPF. There were over 130 responses to the invitation and similar to the previous year, the program was remarkably well received by the attendees.



Peter Clardy, MD

QUALITY IMPROVEMENT

Michael Howell, Associate Director of the MICU and Director of Critical Care Quality for the Medical Center, led a multidisciplinary effort this year to improve person-centered care in the ICU. This effort led to the creation of the novel ICU Patient and Family Advisory Council as well as implementation of the FS-ICU Family Satisfaction Survey Instrument in the critical care areas. Both efforts were designed to elicit the best possible guidance from families about their experiences and the experiences of their loved ones in the ICUs. These communication efforts have led to a novel training program using simulation to train residents and fellows to conduct family meetings; efforts to include

families on multidisciplinary work rounds; improved availability of spiritual care to patients and families; revitalization of the waiting room serving MICU 7; and many other initiatives.

EDUCATIONAL PROGRAMS

The Division is a core member of the Harvard Combined Fellowship in Pulmonary & Critical Care Medicine for which the Division provides important rotations in consultative pulmonary medicine as well as medical critical care. Pulmonary and critical care fellows rotate, as well, through the longitudinal pulmonary clinic. Fellowship training in pulmonary and critical care medicine is coordinated by Patricia Kritek, the Associate Director of the Harvard Combined Fellowship in Pulmonary & Critical Care. Robert Thomas directs one of the first ACGME accredited multi-disciplinary fellowships in sleep medicine. Adnan Majid coordinates the highly sought after fellowship program in interventional pulmonology. These fellowships reflect the remarkable educational success of the Division in the last 5 years. The Combined Harvard Fellowship is among the most sought after and largest training programs in pulmonary and critical care in the United States. The fellowship in sleep medicine is among the most prestigious training programs in the United States, and the interventional fellowship is the most selective in the country with intense competition for the few training positions.

In addition to the Pulmonary & Critical Care and Sleep Fellowships, members of the Division play active roles in post-graduate and medical student teaching. Richard Schwartzstein serves as Vice President for Education at the Medical Center and oversees medical student and resident educational programs at the institution. Dr. Schwartzstein also serves as overall coordinator of the Harvard Medical School Human Systems block, a major component of the 1st year experience for medical students. David Roberts has recently assumed the title of Assistant Director of the Shapiro Institute and is Director, Undergraduate Education within the Institute. Dr. Roberts is also Co-Director of the of pulmonary pathophysiology block taught to 2nd year Harvard medical students. Other courses run by Division faculty include: clinical clerkships in the medical intensive care unit coordinated by Dr. Clardy; an integrated Harvard-wide clerkship in pulmonary medicine coordinated by Dr. Silvestri; an elective in consultative pulmonary medicine coordinated by Dr. Silvestri; and an elective in sleep disorders medicine coordinated by Drs. Thomas and Pogach.

HONORS AND AWARDS

Dr. Praveen Akuthota received an Assembly on Allergy, Immunology, and Inflammation Travel Award for Outstanding Research Abstract from the American Thoracic Society (2008), was an invited participant to the University of North Carolina, Respiratory Diseases Young Investigators' Forum and the Clinical Immunology Society, Hypersensitivity School (2008).

Dr. Peter Clardy was the recipient of the 2009 S. Robert Stone Award for Excellence in Teaching from Harvard Medical School and the 2008 Robert M. Meltzer Leadership Award.

Dr. Sean Gilman received an Excellence in Tutoring Award from the Harvard Medical School's Academy Center for Teaching and Learning (2009).

Dr. Michael Howell was awarded the 2008 RX for Excellence Award (from the Massachusetts Medical Law Report). He was one of 40 providers, attorneys, health plan leaders and lawmakers selected statewide for this award, which honors Best Practices in Medicine in the Commonwealth. He was also the recipient of the 2008 Robert M. Meltzer Leadership Award.

Dr. Melanie Pogach attended the 2008 Leadership Course for Junior Faculty: Preparing for a Leadership Career in Academic Medicine, Center for Faculty Development, Harvard Medical School.

Dr. David Roberts was a nominee for the 2008 Faculty Prize for Excellence in Teaching (Years 1 & 2), Harvard Medical School.

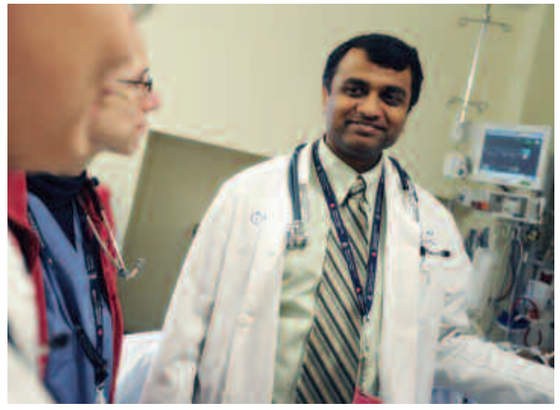
Dr. Laura Rock received an Excellence in Tutorial Facilitation award (2009) from Harvard Medical School.

Dr. Richard Schwartzstein holds the Ellen and Melvin Gordon for Medical Education and was named Director of The Harvard Medical School Academy. In 2009, he was a visiting professor at The Haile T. Debas Academy of Medical Educators, University of California, San Francisco Medical School, San Francisco, CA and was the Interactive Physiology Grand Rounds Section Editor, *Chest*.

Dr. Joseph Zibrak won a teaching award for Respiratory Pathophysiology (2008).

Dr. Ronald Silvestri received an Excellence in Ambulatory Student Teaching in Subspecialty Medicine award, Beth Israel Deaconess Medical Center and was nominated for the Harvard Medical School Prize for Excellence in Teaching (Years I & II).

Dr. Mourad Toporsian received a 2008 Young Investigator Award from the Klarman Family Foundation.



Naimish Patel, MD

The success of the Division's teaching efforts is attested to by the numerous teaching awards won by faculty. These awards are voted on annually by medical students, residents and pulmonary fellows and the Division's harvest each year is impressive testimony to the efforts made by Division faculty.

RESEARCH ACTIVITIES

The Division of Pulmonary, Critical Care & Sleep Medicine conducts basic, translational and clinical research programs supported by grants from the National Institutes of Health, foundations and industry. Basic laboratories focus on vascular biology pulmonary macrophage biology, and mechanisms of ventilatory control. Since the last report, two new faculty have joined the Division: Mourad Toporsian is based in the Center for Vascular Biology and is examining fundamental mechanisms of pulmonary hypertension; and Souvenir Tachado has joined collab- orators interested in innate immunity of the lung after receiving investigator-initiated research support from the National Institutes of Health.

Translational laboratories focus on the consequences of obstructive sleep apnea and on respiratory sensations. Among the investigators interested in sleep-disordered breathing, Robert Thomas has several NIH funded clinical trials. Robert Banzett, working with Richard Schwartzstein, continues his efforts to better understand how shortness of breath is experienced as a symptom by patients with different diseases of the lung, using these data to explore novel symptomatic therapies. A number of clinical research projects are conducted by the Division. Armin Ernst has performed a series of investigations to better define the role of bronchoscopy and thoracoscopy in the management of complex airway and pleural disease. Joe Zibrak and Peter LaCamera are active participants in clinical trials for interstitial lung disease, working with investigators from around the country.

As an extension of his clinical and administrative duties in Critical Care, Michael Howell has created a nationally-recognized research group to test measures undertaken to promote quality in care of the critically ill. His efforts have been recognized with a research award from the Robert Wood Johnson Foundation.

FACULTY

Praveen Akuthota, MD
Amit Anand, MD
Robert Banzett, PhD
Jacqueline Chang, MD
Peter Clardy, MD
David Delaney, MD
Michael Donnino, MD
Armin Ernst, MD
Diana Gallagher, MD
Norma Gerard, PhD
Geoffrey Gilmartin, MD
Sean Gilman, MD
Henry Koziel, MD
Peter LaCamera, MD
Adnan Majid, MD
Gaetane Michaud, MD
Souvenir Tachado, MD
Naimish Patel, MD
Melanie Pogach, MD
David Roberts, MD
Laura Rock, MD
Richard Schwartzstein, MD
Ronald Silvestri, MD
Robert Thomas, MD
Mourad Toporsian, PhD
J. Woodrow Weiss, MD
Joseph Zibrak, MD

SELECTED PUBLICATIONS

Belik J, Jerkic M, McIntyre BA, Pan J, Leen J, Yu LX, Henkelman RM, Toporsian M, Letarte M. Age-dependent endothelial nitric oxide synthase uncoupling in pulmonary arteries of endoglin heterozygous mice. *Am J Physiol Lung Cell Mol Physiol* 2009 Dec; 297(6):L1170-8.

Binks AP, Cunningham VJ, Adams L, Banzett RB. Gray matter blood flow change is unevenly distributed during moderate isocapnic hypoxia in humans. *J Appl Physiol* 2008; 104(1):212-7.

Day CS, Yu YY, Yeh A, Newman L, Arky R, Roberts DH. Musculoskeletal pre-clinical medical school education: meeting an underserved need. *J Bone Joint Surgery Am* 2009; 91(3):733-9.

Gilmartin GS, Tamisier R, Curley MJ, Weiss JW. Ventilatory, hemodynamic, sympathetic nervous system, and vascular reactivity changes after recurrent nocturnal sustained hypoxia in humans. *Am J Physiol Heart Circ Physiol* 2008; 295(2):H778-85.

Herzig SJ, Howell MD, Ngo LH, Marcantonio ER. Acid-suppressive medication use and the risk for hospital-acquired pneumonia. *JAMA* 2009; 301(20):2120-8.

Huang GC, Newman LR, Schwartzstein RM, Clardy PF, Feller-Kopman D, Irish JT, Smith CC. Procedural competence in internal medicine residents: validity of a central venous catheter insertion assessment instrument. *Acad Med* 2009; 84(8):1127-34.

Hunt BE, Tamisier R, Gilmartin GS, Curley M, Anand AN, Weiss JW. Baroreflex responsiveness during ventilatory acclimatization in humans. *Am J Physiol Heart Circ Physiol* 2008; 295(4):H1794-801.

Liu Y, Ji ES, Xian S, Tamisier R, Tong J, Huang J, Weiss JW. Exposure to cyclic intermittent hypoxia increases expression of functional NMDA receptors in the rat carotid body. *J Appl Physiol* 2009; 106:259-67.

Tachado SD, Li X, Swan K, Patel N, Koziel H. Constitutive activation of phosphatidylinositol 3-kinase signaling pathway down-regulates TLR4-mediated tumor necrosis factor-alpha release in alveolar macrophages from asymptomatic HIV-positive persons in vitro. *J Biol Chem* 2008; 283(48):33191-8.

Tachado SD, Samrakandi MM, Cirillo JD. Non-opsonic phagocytosis of Legionella pneumophila by macrophages is mediated by phosphatidylinositol 3-kinase. *PLoS One* 2008; e3324.

Ernst, A (ed). *Introduction to Bronchoscopy*. *Cambridge University Press* - 2009.

David Roberts, MD
Pulmonary, Critical Care
and Sleep Medicine

Division of Rheumatology

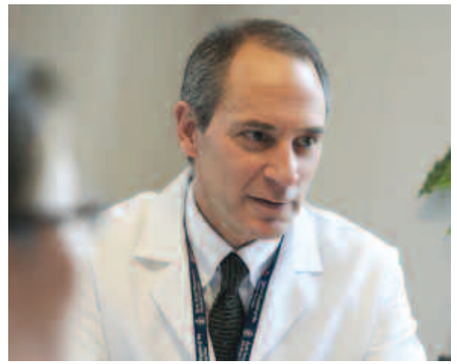
The Division of Rheumatology at Beth Israel Deaconess Medical Center includes strong clinical, educational and research programs. The goals of the Division are to provide outstanding care to patients suffering from rheumatic diseases, exceptional teaching to medical students, medical residents and interns and trainees enrolled in the rheumatology and systemic autoimmunity fellowship programs, and to conduct cutting-edge clinical, translational and basic research.

CLINICAL ACTIVITIES

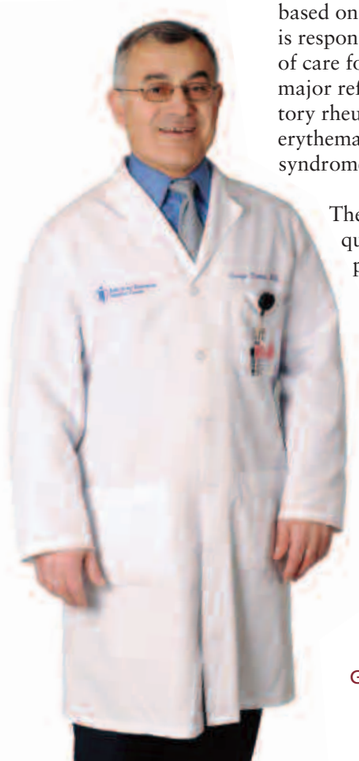
The Rheumatology Division maintains an active outpatient clinical practice and an inpatient consultation service for patients with rheumatic diseases and other musculoskeletal problems. The outpatient practice evaluates and treats more than 2100 new and more than 10,000 established patients each year. This is a unique integrated practice environment that also includes a rheumatology nurse specialist who provides patients with medication teaching and monitoring. All of the full-time members of the Division provide care based on a model in which each physician is responsible for personalized continuity of care for their patients. The division is a major referral center for patients with refractory rheumatoid arthritis, systemic lupus erythematosus (SLE), autoinflammatory syndromes, scleroderma and polychondritis.

The Lupus Center provides high-quality, comprehensive healthcare for patients with SLE by rheumatologists with particular expertise in the treatment of this disease. Collaboration and coordinated care with colleagues in other specialties, including the Nephrology Division, encourages optimal and efficient care.

Under the leadership of Dr. Fadi Badlisi in the Musculoskeletal Medicine Unit, the Division maintains close collaboration with the Department of Orthopedics. This unit provides care for patients with sports injuries, acute and subacute regional pain syndromes and non-operative orthopedic disorders.



Robert H. Shmerling, MD



George C. Tsokos, MD, Chief

QUALITY IMPROVEMENT

Under the leadership of Dr. Shmerling, a number of quality improvement projects are monitored in the division, including documentation of procedures, regular ophthalmologic examinations among patients taking antimalarial medications, appropriate laboratory monitoring of patients taking methotrexate, screening for tuberculosis prior to anti-TNF therapy, improving patient access for appointments, and improved documentation of reproductive counseling prior to the initiation of methotrexate or cyclophosphamide therapy.

EDUCATIONAL PROGRAMS

The Division participates in the Harvard Medical School fellowship program with the Brigham and Women's Hospital. The program provides a three year fellowship, the first year of which is devoted to clinical training and the last two years of which are devoted to research. During the first year, fellows provide coverage for an active inpatient consultation service. Formal teaching rounds are conducted at least twice a week with attending physicians from the Division. In addition, fellows are responsible for daily work rounds on all patients on the service.

Throughout the three-year training period, fellows participate in a continuity outpatient rheumatology practice. Multiple clinical sites are used for this experience.

Under the leadership of Drs. Fitzgerald and Avalos, the Division's weekly Rheumatology Grand Rounds presents local and national experts to discuss updates on clinical and research topics of interest, including a monthly Lupus Lecture Series.

The Division also participates in a monthly Radiology conference coordinated by Drs. Jim Wu and Mary Hochman in Radiology and Dr. Shmerling.

The Division sponsors a Monthly Lupus Lecture Series and an annual one-day Lupus Symposium. Distinguished speakers from around the country and the world are invited to present their findings at these events. Basic and clinical researchers, students and fellows from various Boston institutions attend these events. Dr. Tsokos is the Chair of an Annual School on Systemic Autoimmune Diseases under the aegis of the Clinical Immunology Society.

Dr. Tsokos serves as the director of the FOCIS (Federation of Clinical Immunology Societies) Center of Excellence. The goal of the center is to promote educational and collaborative activities among 20 clinical/basic immunologists at BIDMC.

AUTOIMMUNE INVESTIGATOR TRAINING

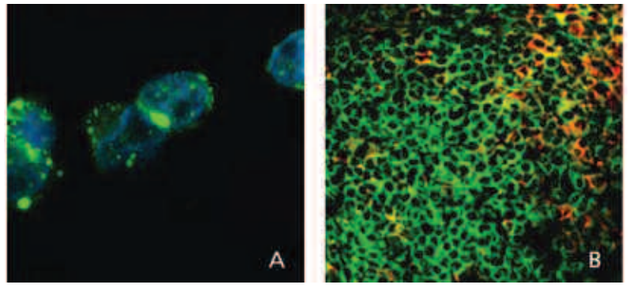
Dr. Tsokos and Dr. Terhorst, the Chief of the Division of Immunology, direct a T32 Training Program on Systemic Autoimmunity. Through this program fellows in rheumatology, nephrology, dermatology and other subspecialties, as well as in basic sciences, will be mentored to become independent investigators in the field of lupus or other systemic autoimmune diseases.

HONORS AND AWARDS

George Tsokos, MD is the Chair of the Hypersensitivity, Autoimmunity and Immune-Mediated Study Section, National Institutes of Health; the Chair of the Alliance for Lupus Research Study Sections; and was elected Master of the American College of Physicians. He was also selected as *Boston Magazine* and Castle Connolly Top Doctor.

Robert Shmerling, MD was selected as a Castle Connolly Top Doctor.

Gwen Kane-Wanger, MD serves as Secretary-treasurer, New England Rheumatism Society.



(A) T cells from SLE patients produce increased amounts of proinflammatory cytokines such as IL-17. The figure shows Tcells from a patient with SLE, stimulated with anti-CD3 and anti-CD28, and stained with anti-IL-17 (green) and a nuclear dye (DAPI; blue) after permeabilization. (B) CD3+ CD4 CD8 (double-negative) T cells are expanded in patients with SLE and infiltrate affected kidneys. The figure shows a dense T cell infiltrate from a renal biopsy of a patient with SLE stained with anti-CD3 (green) and anti-CD4 and CD8 (red). Green cells are double-negative T cells and yellow cells are CD4 and CD8 T cells.

RESEARCH ACTIVITIES

The Division has an active and expansive basic, translational and clinical research program in the field of rheumatic diseases with special emphasis on the study of SLE. The laboratory is located at the Center for Life Sciences building.

FACULTY

Ingrid Avalos, MD
Fadi Badlisi, MD
Jose C. Crispin, MD
Guomin Deng, MD, PhD
Arturo Diaz, MD
Sukran Ergin, MD
Lisa Fitzgerald, MD
Yuang-Taung Juang, MD, PhD
Gwen Kane-Wanger, MD
Vasileios Kyttaris, MD
Peter Lapchack, PhD
Paul Romain, MD
Robert H. Shmerling, MD
Francine Ton-Nghiem, MD, MMSc
David Trentham, MD
George Tsokos, MD

Division investigators are interested in studies of immune cell signaling and gene transcription in SLE, as well as in mechanisms of tissue injury. Peripheral blood, kidney and skin tissues and genetically engineered animals are used to identify novel therapeutic targets and biomarkers for the diagnosis of the disease.

Ingrid Avalos, MD

Ongoing Studies

- Characterization of aberrant immune cell signaling processes in SLE T cells.
- Understanding the transcription events that lead to abnormal expression of genes involved in the pathogenesis of SLE including CD3zeta, FcRgamma, PP2Ac, IL-2, Syk and IL-17.
- Studies to understand the events that lead to increased expression of CD40L in SLE T cells.
- Studies to decipher the role of CaMKIV and CREMalpha in the development of lupus nephritis.
- Studies to unravel the events that lead to expansion of $CD3^{+}CD4^{-}CD8^{-}$ T cells in patients with lupus.
- The development of an SLE Super Array to further classify patients with SLE and follow disease activity.
- The identification of antigens expressed by injured tissues which allow the binding of natural antibodies and the activation of complement.
- Studies to define the role of platelets in tissue injury.

SELECTED PUBLICATIONS

Deng GM, Tsokos GC. The role of lipid rafts in the pathogenesis of lupus. *J Immunol* 2008; 181:4019-4026.

Crispin JC, Oukka M, Bayliss G, Cohen RA, Van Beek CA, Stillman IE, Kyttaris VC, Juang YT, Tsokos GC. Expanded double negative T cells in patients with systemic lupus erythematosus produce IL-17 and infiltrate the kidneys. *J Immunol* 2008; 181: 8761-8766.

Sunahori K, Juang YT, Tsokos GC. CREB binds to demethylated CRE-elements on the PP2Acα promoter and induces its expression. *J Immunol* 2009; 182:1500-1508.

Kulik L, Fleming SD, Moratz C, Reuter JW, Novikov A, Chen K, Andrews KT, Markayan A, Quigg RJ, Silverman GJ, Tsokos GC, Holers VM. Pathogenic natural antibodies recognizing Annexin IV are required to develop intestinal ischemia-reperfusion injury. *J Immunol* 2009; 182:5363-5373.

Zhang Z, Kyttaris VC, Tsokos GC. The role of IL-23/IL-17 axis in lupus nephritis. *J Immunol* 2009; 183:3160-3169.

Crispin JC, Tsokos GC. Human TCR-ab+ CD4-CD8- T cells derive from CD8+ T cells and display an inflammatory effector phenotype. *J Immunol* 2009; 183:4675-81.

Deng GM, Liu L, Kyttaris VC, Tsokos GC. Lupus serum immunoglobulin G induces skin inflammation through TNFR1 signaling pathway. *J Immunol* In press.

Mayadas TN, Tsokos GC, Tsuboi N. Mechanisms of immune complex mediated neutrophil recruitment and tissue injury. *Circulation* 2009; 120:2012-2024.

Neeman N, Aronson MD, Schulze JE, Shmerling RH. Improving pregnancy counseling for women with rheumatoid arthritis taking methotrexate. *Am J Med* 2009; 122:998-1000.

Leveille SG, Jones, RN, Kiely DK, Hausdorff JM, Shmerling RH, Guralnik JM, Kiel DP, Lipsitz LA, Bean JF. Chronic musculoskeletal pain and the occurrence of falls in an older population. *JAMA* 2009; 302:2214-21.

Melissa Mattison, MD
Hospital Medicine

Division of Signal Transduction

The Division of Signal Transduction is a non-clinical Division with a focus on determining the molecular mechanisms of cellular responses to growth factors, hormones and other regulators of cell function. The major goal of this Division is to elucidate biochemical mechanisms that control cell growth, cell survival, cell migration and cell cycle entry and to identify defects in these pathways that lead to human diseases such as cancer, insulin resistance, diabetes, obesity, immune defects and cardiac hypertrophy. Importantly, there is a major interest in validating targets, such as protein kinases and lipid kinases, for pharmaceutical intervention in these diseases. Lewis C. Cantley, PhD, Professor of Medicine and Professor of Systems Biology, is Chief of the Division; Stephen P. Soltoff, PhD is an Assistant Professor of Medicine in the Division. John Asara, PhD is an Assistant Professor in Medicine and Director of the Mass Spectrometry/Proteomics Core located in the Division.

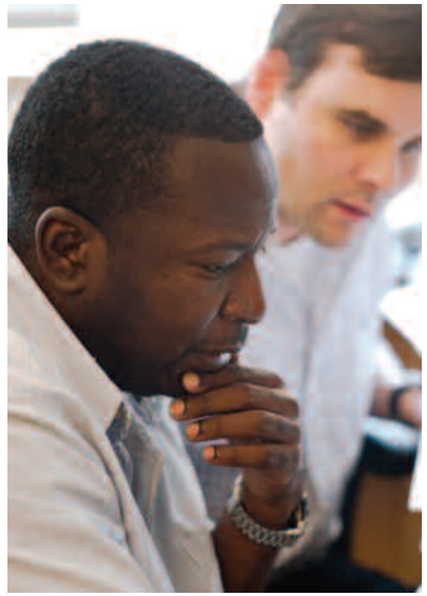
Lewis C. Cantley, PhD, Chief

EDUCATIONAL PROGRAMS

The Division of Signal Transduction plays a major role in training graduate students, medical students and postdoctoral fellows in basic research related to human diseases. Currently, 18 fellows (including MD, PhD and MD/PhD fellows) and 4 graduate students are in training in the Division. These trainees are supported by NIH training grants as well as by private foundations, including the Burroughs Welcome Trust, the Charles A. King Trust, the Leukemia and Lymphoma Society and Damon Runyon. In addition, members of the Division give lectures in first year medical school courses, and in graduate school courses.

RESEARCH ACTIVITIES

The major activity of the Division of Signal Transduction is to conduct basic and translational biomedical research. The research activities are supported by more than $9 million annually from government and non-government grants.



Gary Bellinger, front, Senior Technician and Kevin Courtney, MD, PhD

The research in Dr. Lewis Cantley's laboratory focuses on identifying new targets for intervention in cancer. Dr. Cantley is the leader of a $15 million dollar inter-institutional grant funded by Stand Up To Cancer. This team of scientists and clinicians from the BIDMC, DFCI, Memorial Sloan Kettering, MD Anderson, Vanderbilt, Columbia and Val D'Hebron, Barcelona will target the phosphoinositide 3-kinase (PI3K) pathway in women's cancers. Dr. Cantley is also Principal Investigator on an NIH P01 grant to investigate the molecular basis for prostate cancer. This disease, like breast cancer, frequently results from dysregulation of the phosphoinositide 3-kinase (PI3K) pathway, a pathway discovered in Dr. Cantley's laboratory. By generating mice in which components of this pathway are disrupted, potential targets for pharmaceutical intervention in this disease are being evaluated. Recent studies indicate that the PI3K pathway also plays a critical role in colorectal cancers, in glioblastomas and in lung cancers. Drugs that inhibit PI3K are now in phase 1 clinical trials. Dr. Cantley and Dr. Pandolfi in the Division of Cancer Genetics have initiated a novel Co-Clinical Trial Program in which mice that are engineered to develop cancers (or other diseases) by introducing genetic variations that mimic the genetic events in human disease are then treated with drugs in studies that parallel human clinical trials with the same drugs. The goal of these studies is to identify mutational backgrounds and other biomarkers that predict drug response or drug resistance mechanisms. Finally, research in Dr. Cantley's laboratory has revealed how cancer cells alter their metabolism in order to grow and survive at inappropriate locations. These studies have revealed that certain metabolic enzymes could be targets for pharmaceutical intervention in cancers.

Akash Patnaik, MD, PhD

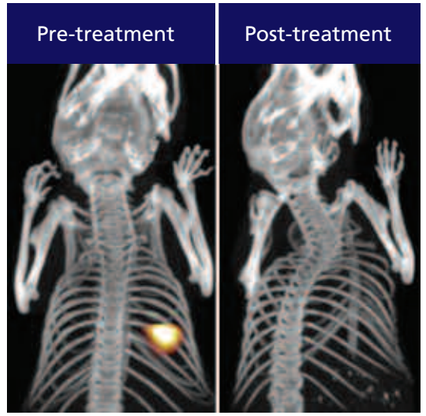
HONORS AND AWARDS

Lewis Cantley, PhD became the leader of a $15,000,000 inter-institutional grant funded by Stand Up To Cancer – Targeting PI3-K in women's cancers. He was also awarded the Rolf Luft Award for Diabetes and Endocrinology Research from the Karolinska Institute, Stockholm, Sweden.

FACULTY

John Asara, PhD
Lewis C. Cantley, PhD
Stephen P. Soltoff, PhD

Dr. Stephen Soltoff's laboratory is studying cell signaling in various cell systems, including the interrelationship between signal transduction proteins and specific ion transport systems in salivary gland epithelial cells.



FDG-PET reveals high glucose uptake in PIK3CA mutant lung tumors that is blocked by a PI3K inhibitor. Engelman et al., 2008 *Nature Medicine* 14,1352.

Other studies done in collaboration with Dr. Cantley's group made the unexpected finding that the C2 domain of PKCdelta, once thought to bind lipids, contains a phosphotyrosine binding domain that enables PKCdelta to bind to proteins phosphorylated on tyrosine having a particular motif, which was identified using peptide library screens. PKCdelta plays a critical role in activation of lymphocytes by antigen-presenting cells. Current studies are exploring the biochemical mechanism by which the C2 domain of PKCdelta regulates its specific functions in immune cells.

Dr. John Asara directs the Mass Spectroscopy Core for BIDMC and also has an independent research program into the development of new Mass Spectroscopy applications for biology. He is developing new techniques for quantifying proteins from cells, tissues or serum. In addition, he is developing a new approach for de novo sequencing of proteins from sources where genomic information is not available. This research has led to the first successful sequencing of proteins from extremely ancient extinct species, including dinosaurs (published in *Science*). In addition, Dr. Asara has recently developed a Mass Spectroscopy Metabolomics Core that allows quantitative assessment of metabolic intermediates from biological samples.

SELECTED PUBLICATIONS

Soltoff SP, Hedden L. Regulation of ERK1/2 by Ouabain and Na,K-ATPase-dependent energy utilization / AMPK activation in parotid acinar cells. *Am J Physiol Cell Physiol* 2008; 295(3):C590-9.

Yuan TL, Choi HS, Matsui A, Benes C, Lifshits E, Luo J, Frangioni JV, Cantley LC. Class 1A PI3K regulates vessel integrity during development and tumorigenesis. *Proc Natl Acad Sci USA* 2008; 105(28):9739-44.

Engelman JA, Chen L, Tan X, Crosby K, Guimaraes AR, Upadhyay R, Maira M, McNamara K, Perera SA, Song Y, Chirieac LR, Kaur R, Lightbown A, Simendinger J, Li T, Padera RF, García-Echeverría C, Weissleder R, Mahmood U, Cantley LC, Wong KK. Effective use of PI3K and MEK inhibitors to treat mutant Kras G12D and PIK3CA H1047R murine lung cancers. *Nat Med* 2008; 14(12):1351-6.

Zheng B, Jeong JH, Asara JM, Yuan YY, Granter SR, Chin L, Cantley LC. Oncogenic B-RAF negatively regulates the tumor suppressor LKB1 to promote melanoma cell proliferation. *Mol Cell* 2009; 33(2):237-47.

Carracedo A, Ma L, Teruya-Feldstein J, Rojo F, Salmena L, Alimonti A, Egia A, Sasaki AT, Thomas G, Kozma SC, Papa A, Nardella C, Cantley LC, Baselga J, Pandolfi PP. Inhibition of mTORC1 leads to MAPK pathway activation through a PI3K-dependent feedback loop in human cancer. *J Clin Invest* 2008; 118(9):3065-74.

Nicklin P, Bergman P, Zhang B, Triantafellow E, Wang H, Nyfeler B, Yang H, Hild M, Kung C, Wilson C, Myer VE, MacKeigan JP, Porter JA, Wang YK, Cantley LC, Finan PM, Murphy LO. Bidirectional transport of amino acids regulates mTOR and autophagy. *Cell* 2009; 136(3):521-34.

Ogino S, Nosho K, Kirkner GJ, Shima K, Irahara N, Kure S, Chan AT, Engelman JA, Kraft P, Cantley LC, Giovannucci EL, Fuchs CS. PIK3CA mutation is associated with poor prognosis among patients with curatively resected colon cancer. *J Clin Oncol* 2009; 27(9):1477-84.

Schweitzer MH, Zheng W, Organ CL, Avci R, Suo Z, Freimark LM, Lebleu VS, Duncan MB, Vander Heiden MG, Neveu JM, Lane WS, Cottrell JS, Horner JR, Cantley LC, Kalluri R, Asara JM. Biomolecular characterization and protein sequences of the Campanian hadrosaur B. canadensis. *Science* 2009; 324(5927):626-31.

Smith A, Blois J, Yuan H, Aikawa E, Ellson C, Figueiredo JL, Weissleder R, Kohler R, Yaffe MB, Cantley LC, Josephson L. The antiproliferative cytostatic effects of a self-activating viridin prodrug. *Mol Cancer Ther* 2009; 8(6):1666-75.

Hutti JE, Shen RR, Abbott DW, Zhou AY, Sprott KM, Asara JM, Hahn WC, Cantley LC. Phosphorylation of the tumor suppressor CYLD by the breast cancer oncogene IKKepsilon promotes cell transformation. *Mol Cell* 2009; 34(4):461-72.

Suzanne E. Gleysteen, MD
APG, Beth Israel Deaconess Health Care
Washington Square Group

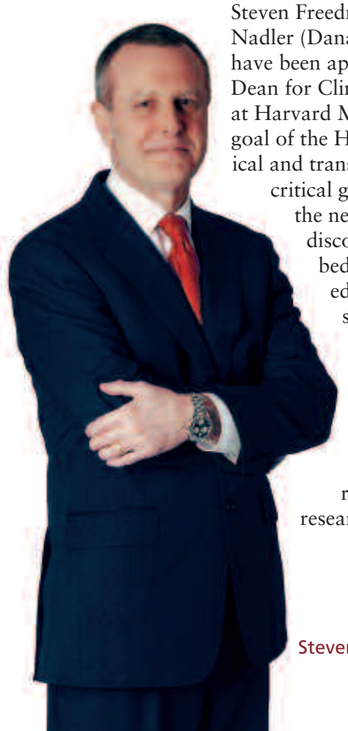
Division of Translational Research

The Division of Translational Research provides a unique "home" for faculty who play a major role in the infrastructure for clinical/translational investigation. The Division is integrated with the Harvard-Thorndike General Clinical Research Center (GCRC) of Beth Israel Deaconess Medical Cen-

Recently, the GCRC was incorporated into the Harvard Clinical Translational Science Center (CTSC) funded through the NIH Clinical and Translational Science Award.

This five-year $200 million grant from the National Institutes of Health, which includes institutional support from Harvard University, Harvard Medical School, and the affiliated Academic Health Care Centers brings together the 11 Harvard schools and 18 Harvard teaching hospitals in an unprecedented collaboration to advance therapeutic discovery and patient care.

The Harvard CTSC is co-directed by Dr. Steven Freedman (BIDMC) and Dr. Lee Nadler (Dana Farber Cancer Institute), who have been appointed as Associate Dean and Dean for Clinical and Translational Research at Harvard Medical School, respectively. The goal of the Harvard CTSC is to enhance clinical and translational research by addressing critical gaps and barriers and providing the needed connections to facilitate discoveries from the bench to the bedside. This includes 10 programs: education and training, regulatory support, biostatistics, biomedical informatics, novel clinical and translational methodologies, translational technologies, participant clinical interactive resources (replaces the GCRCs), diversity and health disparities research, community outreach research and pilot grant funding.



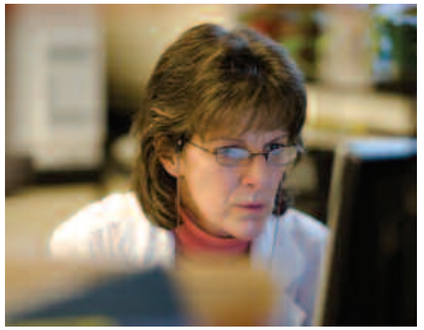
Steven D. Freedman MD, PhD, Chief

EDUCATIONAL PROGRAMS

The Division of Translational Research leads two educational initiatives. The first is Harvard Catalyst-sponsored Career Mentoring Program for fellows and junior faculty at BIDMC focused on a career in clinical/translational research. A second initiative is through the two Harvard Medical School Masters in Clinical Research programs (K30 and Clinical Investigator Training Program (CITP)). Dr. Freedman is the Associate Director of CITP and a member of the Committee on Mentoring and the Advisory Board for the K30 Scholars in Clinical Science Program. With regard to Biostatistics and Epidemiology, Dr. Gautam is a senior tutor in Harvard Medical School's month long Clinical Epidemiological course for first year medical students. Dr. Gautam is also engaged in teaching/training of medical students, residents, fellows and new investigators in the area of research design and critical biostatistical aspects of research.

Anna Johansson, PhD, reviews a training simulation exercise.

IRB Navigation – Dr. Johansson brings her experience as an IRB Vice Chair to a new role in which she provides consultation and guidance to junior faculty and fellows in clinical/translational research in the Department of Medicine as they develop their human research proposals and prepare submissions to the IRB. This is an innovative initiative undertaken by the Department of Medicine in conjunction with the Harvard Catalyst Career Mentoring Program. The specific emphasis is on IRB guidance with respect to navigating the scientific review and IRB review processes. The mentoring targets those investigators receiving training and career development grants, and Catalyst Pilot grants who are new to human subject research.



Joanne Brown, researcher in Dr. Freedman's lab

HONORS AND AWARDS

Steven Freedman, MD, PhD was recently appointed Professor of Medicine, elected to be the Chairman of the Board of Trustees of the Harvard Clinical Research Institute and was the Alpha Omega Alpha Visiting Professor, Morehouse School of Medicine, February 2009.

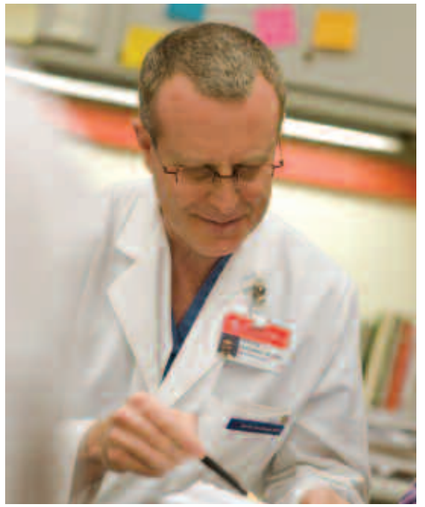
FACULTY

Steven D. Freedman, MD, PhD
Shiva Gautam, PhD
Anna Johansson, PhD

RESEARCH ACTIVITIES

Research activities can be divided into two arenas and represent a broad range of science. The first focuses on providing the infrastructure and tools necessary for clinical/translational investigation. This includes biostatistical support and study design assistance to investigators as provided by Shiva Gautam, PhD. Dr. Gautam also serves as the biostatistical consultant to the medical center's IRB, and works with investigators to address IRB requirements for modifications to study design and statistical analysis. The second area focuses on providing strategic vision and initiatives both at a local BIDMC level and Harvard-wide. This is driven through Dr. Freedman's leadership role as Director of Clinical Research Affairs at BIDMC and Harvard-wide through the CTSC.

Anna Johansson, PhD focuses on social psychology, complex organizations and social science research methods. She brings her expertise to bear on a range of programs in the areas of medical education, simulation training, and team-based patient safety initiatives. Dr. Johansson works with both the Shapiro Institute for Education and Research, and Critical Care Quality to advance research in the areas of team training, critical thinking, and provider-patient communication. Focusing on teams in the medical ICU and simulation, her research involves translating tools from the sociology laboratory to create and test explanatory models of team function, and develop reproducible measurements of team performance.



Steven Freedman, MD, PhD

SELECTED PUBLICATIONS

Andersson C, Al-Turkmani MR, Savaille JE, Alturkmani R, Katrangi W, Cluette-Brown JE, Zaman MM, Laposata M, Freedman SD. Cell culture models demonstrate that CFTR dysfunction leads to defective fatty acid composition and metabolism. *J Lipid Res* 2008; 49(8):1692-1700.

Freedman SD, Uppot RN, Mino-Kenudson M. CPC: 32 year old cystic fibrosis patient with new onset abdominal pain. *N Engl J Med* 2009; 361(8):807-16.

Pall H, Zielenski J, Jonas MM, Dasilva DA, Potvin KM, Yuan X-Y, Huang Q, Freedman SD. Primary sclerosing cholangitis in childhood is associated with abnormalities in cystic fibrosis-mediated chloride channel function. *J Pediat* 2007; 151:255-9.

Fregni F, Freedman SD, Pascual-Leone A. Recent advances in the treatment of chronic pain with noninvasive brain stimulation techniques. *Lancet Neurol* 2007; 6:188-191.

Andersson C, Al-Turkmani MR, Savaille JE, Alturkmani R, Katrangi W, Cluette-Brown JE, Zaman MM, Laposata M, Freedman SD. Cell culture models demonstrate that CFTR dysfunction leads to defective fatty acid composition and metabolism. *J Lipid Res* 2008; 49(8):1692-700.

Zhou P, Gautam S, Recht A. Factors affecting outcome for young women with early stage invasive breast cancer treated with breast-conserving therapy. *Breast Cancer Res Treat* 2007; 101(1):51-5.

Rooks DS, Gautam S, Romeling M, Cross ML, Stratigakis D, Evans B, Goldenberg DL, Iversen MD, Katz JN. Group exercise, education, and combination self-management in women with fibromyalgia. A randomized trial. *Ann Intern Med* 2007; 167(20):2192-200.

Gallagher DC, Parikh SM, Balanov K, Miller A, Gautam S, Talmor D, Sukhatme VP. Circulating Angiopoietin 2 correlates with mortality in a surgical population with ALI/ARDS. *Shock* 2008; 29(6):656-661.

Asimaki A, Tandri H, Huang H, Halushka MK, Gautam S, Basso C, Thiene G, Tsatsopoulou A, Nikos Protonotarios N, McKenna WJ, Calkins H, Saffitz JE. A new diagnostic test for arrhythmogenic right ventricular cardiomyopathy. *N Engl J Med* 2009; 360:1075-84.

O'Fallon E, Gautam S, D'Agata E. Colonization with multidrug-resistant gram-negative bacteria: prolonged duration and frequent co-colonization. *Clin Infect Dis* 2009; 48:1375-81.

Prabhakar Putheti, PhD

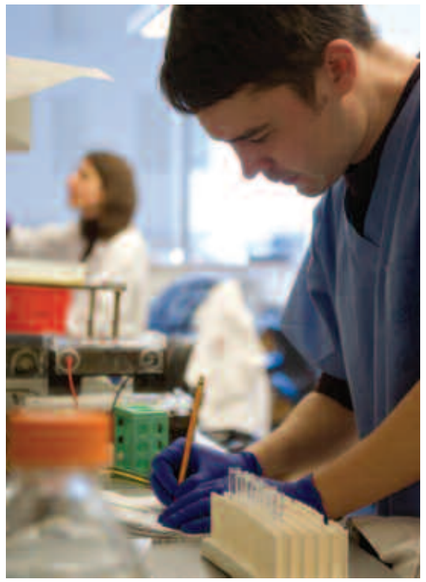
Division of Transplant Immunology

The Division of Transplant Immunology is both an independent entity and a major component of Beth Israel Deaconess Medical Center's Transplant Institute. The Division employs 5 research faculty members, 28 research fellows and 3 research technicians. The Division serves a research, not clinical, function.

Laurence A. Turka, MD joins the Division as the Co-Scientific Director with Terry B. Strom, MD. Dr. Turka is a nephrologist and research investigator and currently the C. Mahlon Kline Professor of Medicine and Surgery, Pediatrics and Pathology and Laboratory Medicine at the University of Pennsylvania. Dr. Turka is an internationally known and respected immunologist who has made seminal contributions to our understanding of the immunobiology of T cells and transplantation. He is currently the Editor-in-Chief of the *Journal of Clinical Investigation*, one of the most prestigious research journals, as well as a member of the Executive Committee of the Immune Tolerance Network.

Laurence A. Turka, MD, Co-Chief
Terry B. Strom, MD, Co-Chief

He has been Chief of the Division of Nephrology at UPenn, President of the American Society of Transplantation and has held numerous other leadership positions in transplantation and immunology in the United States and abroad. He will be bringing and recruiting new faculty and post-doctoral fellows who will strengthen and expand the scope of research being done in the Division.



Andreas P. Hedblom, PhD candidate

EDUCATIONAL PROGRAMS

Many former trainees of the faculty are now prominent academicians or hold senior positions in industry. The Division holds weekly laboratory meetings, participates with other labs in a weekly journal club and holds a monthly science seminar. Drs. Strom and Turka are faculty members of Harvard's graduate program in Immunology. The Harvard Medical School Program in Immunology holds weekly seminars. Drs. Strom and Diane Mathis (Joslin, HMS) direct interlocking Juvenile Diabetes Research Foundation Centers. These Centers hold monthly seminars and a yearly retreat.

HONORS AND AWARDS

Each of the Principal Investigators and several of their colleagues have been awarded new funding and each PI has delivered plenary session lectures at international meetings.

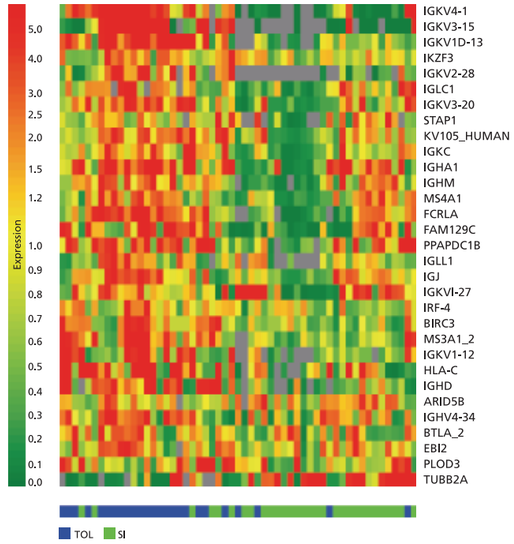
FACULTY

Wenda Gao, PhD
Xian C. Li, MD, PhD
Simon C. Robson, MB, ChB, PhD
Terry B. Strom, MD
Laurence A. Turka, MD

RESEARCH ACTIVITIES

The focus of the highly interactive Strom, Turka, Robson, Li and Gao laboratories is immune tolerance. Using state-of-the-art molecular immunology as a tool, the long-term goal is to enable the development of new approaches and strategies for the induction of tolerance in transplantation and autoimmune diseases, thereby enabling patients to dispense with the need for long-term immunosuppressive drugs and their attendant complications. The approach we have taken is to utilize mouse models, often genetically manipulated mice developed by Dr. Gao, of these disorders to identify potential barriers to tolerance and explore ways to overcome them by creating, often times in Dr. Strom's lab, novel therapies. Through collaboration with Dr. Koulmanda, an adjunct member of the Division, interesting therapeutic ideas are tested in primate transplant models. We define the precise nature of immune tolerance and of immunoregulatory T cells at the molecular and cellular levels. Dr. Li has identified novel T cell costimulatory pathways crucial to tolerance and rejection.

Transplant tolerance is obtained when the functional supremacy of donor reactive immunoregulatory T cells is obtained and remains dominant following the cessation of immunosuppression. Even before Dr. Turka's arrival, collaboration between the Turka, Strom and Li labs created the paradigm that transplant tolerance generally requires the wide-scale depletion of alloaggressive T cells. In the absence of such depletion the cadre of graft protective immunoregulatory T cells can not curtail rejection. Recently Dr. Turka noted that unbiased deletion of all T cells actually can be a barrier to tolerance. These concepts have guided the development of new clinical-trials world wide. A distinctive cell surface phenotype for mouse and human immunoregulatory T cells has been discerned in mice and present, in a variant form, in human regulatory T cells as a direct result of Dr. Robson's interests. The molecular signature consists of two ectoenzymes that catalyze the formation of adenosine, a potent immunoregulatory substance.



Multiplex RT-PCR of peripheral blood identified 31 genes with significant differences of mRNA copies between tolerant kidney transplant recipients (TOL) and patients requiring immunosuppression (SI). The transcript relative expression levels are shown on the heat map.

SELECTED PUBLICATIONS

Zhou Q, Yan J, Putheti P, Wu Y, Kassam N, Enjyoji K, Robson SC, Strom TB, Gao W. Isolated CD39 expression on CD4+ T cells denotes both regulatory and memory populations. *Am J Transplant* 2009; 9:2303-11.

Gao W, Thompson L, Zhou Q, Putheti P, Fahmy TM, Strom TB, Metcalfe SM. Treg versus Th17 lymphocyte lineages are cross-regulated by LIF versus IL-6. *Cell Cycle* 2009; 8:1444-50.

Mariat C, Degauque N, Balasubramanian S, Kenny J, DeKruyff RH, Umetsu DT, Kuchroo V, Zheng XX, Strom TB. Tim-1 signaling substitutes for conventional signal 1 and requires costimulation to induce T cell proliferation. *J Immunol* 2009; 182(3):1379-85.

Porrett PM, Yuan X, LaRosa DF, Walsh PT, Yang J, Gao W, Li P, Zhang J, Ansari JM, Hancock WW, Sayegh MH, Koulmanda M, Strom TB, Turka LA. Mechanisms underlying blockade of allograft acceptance by TLR ligands. *J Immunol* 2008; 181:1692-1699.

Beldi G, Wu Y, Sun X, Imai M, Enjyoji K, Csizmadia E, Candinas D, Erb L, Robson SC. Regulated catalysis of extracellular nucleotides by vascular CD39/ENTPD1 is required for liver regeneration. *Gastroenterology* 2008; 135(5):1751-60.

Allenspach AJ, Lemos MP, Porrett PM, Turka LA, Laufer TM. Migratory and lymphoid-resident dendritic cells cooperate to efficiently prime naive CD4 T cells. *Immunity* 2008; 29:795-806.

Kroemer A, Xiao X, Degauque N, Edtinger K, Demirci G, Li XC. The innate NK cells, allograft rejection, and a key role for IL-15. *J Immunol* 2008; 180:7818-7826.

Xiao X, Kroemer A, Gao W, Ishii N, Demirci G, Li XC. OX40/OX40L costimulation affects induction of Foxp3+ Tregs in part by expanding memory T cells in vivo. *J Immunol* 2008; 181:3193-3201.

Degauque N, Mariat C, Kenny J, Zhang D, Gao W, Vu MD, Alexopoulos S, Oukka M, Umetsu DT, DeKruyff RH, Kuchroo V, Zheng XX, Strom TB. Immunostimulatory Tim-1-specific antibody deprograms Tregs and prevents transplant tolerance in mice. *J Clin Invest* 2008; 118:735-41.

Knosalla C, Yazawa K, Behdad A, Bodyak N, Shang H, Bühler L, Houser S, Gollackner B, Griesemer A, Schmitt-Knosalla I, Schuurman HJ, Awwad M, Sachs DH, Cooper DK, Yamada K, Usheva A, Robson SC. Renal and cardiac endothelial heterogeneity impact acute vascular rejection in pig-to-baboon xenotransplantation. *Am J Transplant* 2009; 9(5):1006-16.

Naved Munir, MSc, Research Associate

Eric Kerns, MD, Resident

Division of Vaccine Research

The new Division of Vaccine Research aims to promote research and education activities related to vaccine-related sciences, including basic, translational and clinical vaccine research. The Division consists of primary and affiliate faculty and focuses on the development of vaccines against infectious, oncologic, degenerative and other diseases.

EDUCATIONAL PROGRAMS

A Division seminar is held every other week to highlight research advances of Division faculty as well as guest speakers. The Division also holds weekly laboratory meetings and weekly meetings and journal clubs for postdoctoral fellows, clinical fellows, and graduate students. The Division has close affiliations with the Divisions of Hematology/Oncology, Infectious Diseases and Viral Pathogenesis as well as with the graduate program in Virology at Harvard Medical School.

RESEARCH ACTIVITIES

Dan Barouch's laboratory focuses on the immunology and virology of HIV-1 infection and the development of novel vaccine strategies. His group has developed a series of novel vaccine vectors based on rare serotypes of adenovirus that are being evaluated in preclinical studies and clinical trials as part of two NIH/NIAID U19 Integrated Preclinical/Clinical AIDS Vaccine Development (IPCAVD) programs. Ray Dolin, Lindsey Baden, and Michael Seaman lead a clinical vaccine trials unit, a specimen processing laboratory, and a neutralizing antibody laboratory to evaluate and to develop vaccines against HIV-1, poxviruses, and other pathogens. David Kaufman is investigating the molecular and cellular mechanisms associated with T lymphocyte trafficking and mucosal immunity.

David Avigan leads a cancer immunology and tumor vaccine program. His laboratory focuses on examining the nature of immune function in patients with malignancy and how this impacts response to cancer vaccines. His group has developed a tumor vaccine model in which patient derived tumor cells are chemically fused with dendritic cells (DC). In this way, a broad array of tumor antigens are presented in the context of dendritic cell derived co-stimulatory molecules, stimulating both helper and cytotoxic T cell responses. Jacalyn Rosenblatt has identified approaches to circumvent tumor mediated immune suppression to further augment vaccine response. David Avigan and Jacalyn Rosenblatt are conducting a series of clinical trials to examine the safety, immunogenicity, and clinical efficacy of the DC/tumor fusion vaccine in patients with multiple myeloma, renal, breast and ovarian cancer.

Ciaran Kelly leads a basic and translational research program to develop vaccines against gastrointestinal bacteria such as *Clostridium difficile*.

The Division of Vaccine Research is a key part of the Bill & Melinda Gates Foundation Collaboration for AIDS Vaccine Discovery (CAVD), the NIH Center for HIV/AIDS Vaccine Immunology (CHAVI), and the Ragon Institute of MGH, MIT and Harvard.

Dan Barouch, MD, PhD, Chief

Rebecca Dilan, Research Assistant

FACULTY

David Avigan, MD
Lindsey Baden, MD
Dan Barouch, MD, PhD
Raphael Dolin, MD
David Kaufman, MD, PhD
Ciaran Kelly, MD
Jacalyn Rosenblatt, MD
Michael Seaman, PhD

HONORS AND AWARDS

Dan Barouch, MD, PhD was elected to the American Society for Clinical Investigation (ASCI) in 2009. He was also elected as a Fellow of the American College of Physicians and a Fellow of the Infectious Diseases Society of America in 2009.

David Kaufman, MD, PhD received an NIAID Early Career Investigator Award in 2009.

SELECTED PUBLICATIONS

Barouch DH. Challenges in the development of an HIV-1 vaccine. *Nature* 2008; 455:613-619.

Waddington SN, McVey JH, Bhella D, Parker AL, Barker K, Atoda H, Pink R, Buckley SM, Greig JA, Denby L, Custers J, Morita T, Francischetti IM, Monteiro RQ, Barouch DH, van Rooijen N, Napoli C, Havenga MJ, Nicklin SA, Baker AH. Adenovirus serotype 5 hexon mediates liver gene transfer. *Cell* 2008; 132:397-409.

Kaufman DR, Liu J, Carville A, Mansfield KG, Havenga MJE, Goudsmit J, Barouch DH. Trafficking of antigen-specific CD8+ T-lymphocytes to mucosal surfaces following intramuscular vaccination. *J Immunol* 2008; 181:4188-4198.

Liu J, O'Brien KL, Lynch DM, Simmons NL, La Porte A, Riggs AM, Abbink P, Coffey RT, Grandpre LE, Seaman MS, Landucci G, Forthal DN, Montefiori DC, Carville A, Mansfield KG, Havenga MJ, Pau MG, Goudsmit J, Barouch DH. Immune control of an SIV challenge by a T-cell-based vaccine in rhesus monkeys. *Nature* 2009; 457:87-91.

Grandpre LE, Duke-Cohan JS, Ewald BA, Devoy C, Barouch DH, Letvin NL, Reinherz EL, Baden LR, Dolin R, Seaman MS. Immunogenicity of recombinant modified vaccinia Ankara following a single or multi-dose vaccine regimen in rhesus monkeys. *Vaccine* 2009; 27:1549-1556.

O'Brien KL, Liu J, King SL, Sun YH, Schmitz JE, Lifton MA, Hutnick NA, Betts MR, Dubey SA, Goudsmit J, Shiver JW, Robertson MN, Casimiro DR, Barouch DH. Adenovirus-specific immunity after immunization with an Ad5 HIV-1 vaccine candidate in humans. *Nat Med* 2009; 15:873-875.

Barouch DH, Liu J, Lynch DM, O'Brien KL, La Porte A, Simmons NL, Riggs AM, Clark S, Abbink P, Montefiori DC, Landucci G, Forthal DN, Self SG, Carville A, Mansfield K, Goudsmit J. Protective efficacy of a single immunization of a chimeric adenovirus vector-based vaccine against simian immunodeficiency virus challenge in rhesus monkeys. *J Virol* 2009; 83:9584-9590.

Rosenblatt J, Wu Z, Vasir B, Zarwan C, Stone R, Mills H, Friedman T, Konstantinopoulos PA, Spentzos D, Ghebremichael M, Stevenson K, Neuberg D, Levine JD, Joyce R, Tzachanis D, Boussiotis V, Kufe D, Avigan D. Generation of tumor-specific T lymphocytes using dendritic cell/tumor fusions and anti CD3/CD28. *J Immunother* 2010; 33(2):155-66.

Barouch DH, Korber B. HIV-1 vaccine development after STEP. *Annu Rev Med* 2010; 61:153-67.

Seaman MS, Wilck MB, Baden LR, Walsh SR, Grandpre LE, Devoy C, Giri A, Kleinjan JA, Noble LC, Stevenson KE, Kim HT, Dolin R. Effect of immunization with modified vaccinia ankara (ACAM3000) on subsequent challenge with Dryvax. *J Infect Dis* 2010; 201(9):1353-60.

Division of Viral Pathogenesis

The Division of Viral Pathogenesis is a research-based division that explores the immune control of human immunodeficiency virus, related nonhuman primate immunodeficiency viruses and other viruses that affect immunosuppressed individuals. The Division is particularly interested in developing a vaccine against the human immunodeficiency virus.

FACULTY

Dan Barouch, MD, PhD
Raphael Dolin, MD
Igor Koralnik, MD
Norman Letvin, MD
Keith Reimann, DVM
Sampa Santra, PhD
Joern Schmitz, MD, PhD
Michael Seaman, PhD
Xinzhen Yang, PhD

Norman Letvin, MD, Chief

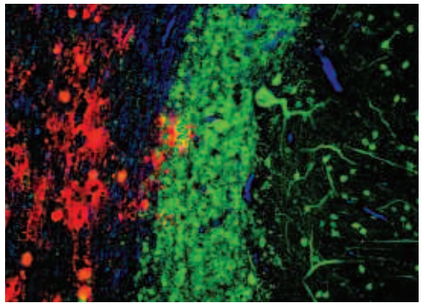
RESEARCH ACTIVITIES

Dr. Dolin's and Dr. Seaman's laboratory provides support for phase I/II human clinical vaccine studies as a Site Affiliated Laboratory (SAL) for the Harvard HIV-1 Vaccine Trial Unit of the HIV-1 Vaccine Trials Network (HVTN) as well as for NIAID/DMID-sponsored clinical trials studying the use of Modified Vaccinia Ankara (MVA) as a novel vaccine against smallpox. The laboratory also performs analyses of antibody immunity elicited by these candidate vaccines. Finally, the laboratory is a pre-clinical neutralizing antibody core laboratory and acute infection specimen acquisition laboratory for the Global HIV/AIDS Vaccine Enterprise (GHAVE) funded by the Bill and Melinda Gates Foundation.

Dr. Koralnik leads the HIV/Neurology Center and his work focuses on the pathogenesis of JC virus in Progressive Multifocal Leukoencephalopathy (PML), a demyelinating disease of the brain occurring in immunosuppressed individuals with AIDS, leukemias, in organ transplant recipients, and patients with multiple sclerosis treated with immunomodulatory medications. The laboratory has characterized a JC virus variant with a novel tropism to granule cell neurons, and is developing immunotherapies for PML. Dr. Letvin's laboratory uses nonhuman primate models to study the role of cellular immunity in controlling HIV spread.

Dr. Reimann's laboratory engineers recombinant antibodies and fusion proteins for use as therapeutics and as research reagents in a wide variety of nonhuman primate disease models.

Dr. Santra is involved in evaluating the efficacy of candidate HIV vaccines in nonhuman primates. The candidate vaccines that are



Infection of the cerebellum white matter by the polyoma virus JC (red) causes progressive multifocal leukoencephalopathy in an immunosuppressed individual. The nearby neurons are stained in green.

being studied in nonhuman primates include unique immunogens to address the problem of the extensive genetic diversity of HIV-1.

Dr. Schmitz's laboratory studies the immunopathogenesis of AIDS in nonhuman primates. His group studies AIDS virus replication and pathogenesis in the African green monkey (AGM), a species that is naturally infected with an AIDS virus but does not develop disease. He and his colleagues are evaluating the role of B lymphocytes in containing infection with HIV. Finally his group is evaluating novel gene-therapy treatments for AIDS in nonhuman primate models.

Dr. Yang's laboratory studies the role of HIV-1 envelope glycoproteins in viral entry. In particular, his laboratory is interested in how antibodies block viral infection and what kind of neutralizing antibody responses are produced in vivo during the course of HIV-1 infections, issues of central importance in the development of an effective HIV vaccine.

Dr. Letvin's laboratory uses nonhuman primate models to study the role of cellular immunity in controlling HIV spread. Much of this work focuses on the generation of cellular immune responses through vaccination and the extent of protection conferred by vaccination. His laboratory is part of the NIH-funded Center for HIV/AIDS Vaccine Immunology (CHAVI), the NIH Vaccine Research Center, and the Gates Foundation-funded Collaboration for AIDS Vaccine Development.

SELECTED PUBLICATIONS

Chen Y, Bord E, Tompkins T, Miller J, Tan CS, Kinkel RP, Stein MC, Viscidi R, Ngo LH, Koralnik IJ. Asymptomatic reactivation of JC virus in patients treated with natalizumab. *N Engl J Med* 2009; 361:1067-74.

Marzocchetti A, Tompkins T, Clifford DB, Gandhi RT, Kesari S, Berger JR, Simpson DM, De Luca A, Koralnik IJ. Determinants of survival in Progressive Multifocal Leukoencephalopathy. *Neurology* 2009; 73:1551-8.

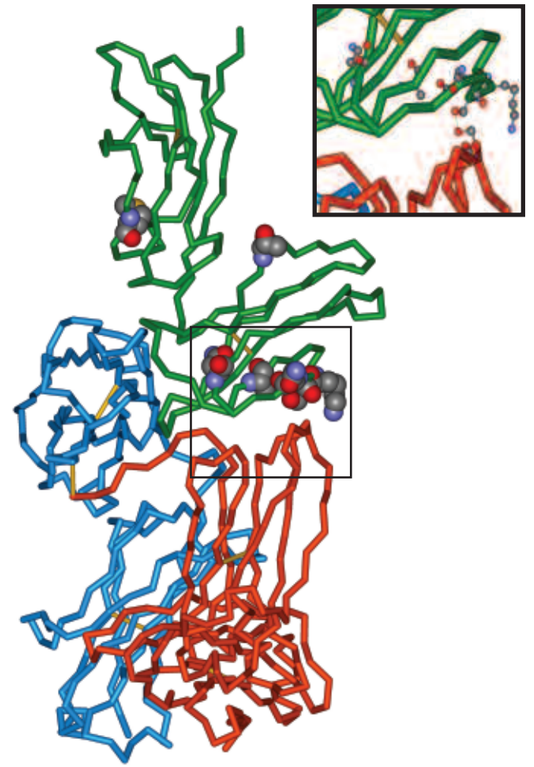
Veazey RS, Acierno PM, McEvers KJ, Baumeister SHC, Foster GJ, Rett MD, Newberg MH, Kuroda MJ, Williams K, Kim E-Y, Wolinsky SM, Rieber EP, Piatak M, Lifson JD, Montefiori DC, Brown CR, Hirsch VH, Schmitz JE. Increased loss of CCR5+ CD45RA-CD4+ T cells in CD8+ lymphocyte-depleted Simian immunodeficiency virus-infected rhesus monkeys. *J Virol* 2008; 82:5618-5630.

Santra S, Korber BT, Muldoon M, Barouch DH, Nabel GJ, Gao F, Hahn BH, Haynes BF, Letvin NL. A centralized gene-based HIV-1 vaccine elicits broad cross-clade cellular immune responses in rhesus monkeys. *Proc Natl Acad Sci* USA 2008; 105:10489-94.

Kim E-Y, Veazey RS, Zahn R, McEvers KJ, Baumeister SHC, Foster GJ, Rett MD, Newberg MH, Kuroda MJ, Rieber EP, Piatak M, Lifson JD, Letvin NL, Wolinsky SM, Schmitz JE. Contribution of CD8+ T cells to containment of viral replication and emergence of mutations in Mamu-A*01-restricted epitopes in Simian immunodeficiency virus-infected rhesus monkeys. *J Virol* 2008; 82:5631-5635.

Whitney JB, Leudemann C, Hraber P, Rao SS, Mascola JR, Nabel GJ, Letvin NL. T-cell vaccination reduces Simian immunodeficiency virus levels in semen. *J Virol* 2009 Oct; 83(20):10840-3.

Zahn R, Hermann FG, Kim E-Y, Wolinsky S, Rett M, Johnson RP, Villinger F, von Laer D, Schmitz JE. Efficient entry inhibition of human and nonhuman primate immunodeficiency virus entry is efficiently inhibited by cell surface-expressed gp41-derived peptides. *Hum Gene Ther* 2008; 15:1210-1222.



Computer modeling of immunoglobulin Fc receptors helps to explain how genetic differences in these cell surface proteins can result in enhanced immune responses in individuals.

Affiliated Physicians Group

The mission of Beth Israel Deaconess HealthCare (BIDHC) is to provide cohesive, high quality health care throughout the life-span of our patients. BIDHC is a network of 157 primary care physicians affiliated with Beth Israel Deaconess Medical Center (BIDMC) in Boston and Beth Israel Deaconess Hospital-Needham. The group of BIDHC physician includes internists or family medicine practitioners at our 31 practice sites, hospitalists who take care of inpatients at four area hospitals, and sub-acute care practitioners who work at 34 assisted living and long-term care facilities.

Megan Mistry, DO

Beth Israel Deaconess HealthCare is a vital source of patient admissions both at BIDMC and Beth Israel Deaconess Hospital-Needham. On average, BIDHC physicians admit 550 patients per month into both hospitals totaling 6,597 patient admissions this year.

CLINICAL ACTIVITIES

Primary Care Medicine – Beth Israel Deaconess HealthCare has continued to respond to the much publicized shortage of primary care physicians in Massachusetts by consistently opening new practices and adding physicians to current practices throughout the year. In total, BIDHC physicians completed 468,172 office visits this year alone.

From July 2008 through June 2009, 18 primary care physicians and 35 nurse practitioners were added along with four new practice sites including the former Urban Medical Group in Jamaica Plain. Urban Medical partnered with Beth Israel Deaconess Medical Center for 33 years before joining Beth Israel Deaconess HealthCare in June. As part of BIDHC, the practice has continued and strengthened its mission to service the elderly and chronically ill in Jamaica Plain and surrounding communities.

Sub-Acute Care Program – The Beth Israel Deaconess HealthCare Sub-Acute Care Program has recently experienced tremendous growth. The June 2009 acquisition of Urban Medical Group added to the 26 long-term care, assisted living and medical home facilities pre-existing in the Sub-Acute Care Program at Beth Israel Deaconess HealthCare. To accommodate the current volume of 1,165 patients BIDHC cares for at these facilities, 27 physicians and nurse practitioners are dedicated full-time to this program.

Hospital Medicine – The mission of the Beth Israel Deaconess HealthCare Hospital Medicine Program is to provide superior inpatient care and seamless communication with primary care providers and specialists. A major benefit of the hospital medicine program is that it allows BIDHC primary care physicians and other subscribers to arrange for direct admission of their patients to particular hospitals when appropriate. These patients are sent to Beth Israel Deaconess Medical Center in Boston when tertiary care is necessary.

In July 2008, a fourth Beth Israel Deaconess HealthCare Hospitalist Medicine Program site was introduced at Good Samaritan Medical Center in Brockton, Massachusetts. The Good Samaritan site is the busiest of all the BIDHC hospital medicine locations with 19 providers and an average volume of 3,380 patients per month.

FACULTY

Jose Abrego, MD
Nancy Adams, MD
Brian Bakofen, DO
Elisabeth Bassler, MD
Brian Blanchette, MD
Stuart Bless, MD
Jonathan Blumberg, MD
Scott Bortman, MD
Kim Bowman, MD
Heather Boxerman, MD
Frank Breslin, MD
Stephen Bresnahan, MD
Gary Brissette, MD
Maria Kane, MD
Barbara Krause, MD
Ellen Kwan, MD
Danru Lee, MD, PhD
Cindy Levine, MD
Thomas Lichauco, MD, MPH
John Looney, MD
Michael Lowney, DO
David H. Lu, MD
Richard Lubens, MD
Charles Maker, MD
Sandra Marwill, MD, MPH
Huma Masood, MD
Yuko McColgan, MD
Hannah Vu, DO
Susan Wainger, MD
Richard Weiner, MD
Joseph Weinstein, MD
Ed Weiss, MD
Martha Wu, MD
Earl Yunes, MD, MPH
Peter Zuromskis, MD, MPH

HOSPITALISTS

Subasit Acharji, MD
Abhishek Agarwal, MD
Gloria Alexander, MD
Mizra Baig, MD

HONORS AND AWARDS

Philip Triffletti, MD was named Beth Israel Deaconess HealthCare 2009 Teacher of the Year. Winners of this award are nominated by colleagues involved with teaching medical students.

The Community Newspaper Company Readers' Choice award winner was Dr. Kim Bowman, MD. She received a First Choice Award, the publication's highest honor. David Buckle, MD, Glenn Kehlman, MD and Earl Yunes, MD, MPH received honorable mentions. Winners are selected by the community members they serve based on the outstanding service and value these individuals bring to their lives.

Several Beth Israel Deaconess HealthCare physicians were selected as Top Rated Primary Care Physicians by *Boston Consumers' Checkbook*. Stephen Bresnahan, MD, John Looney, MD, Dominic Pennachio, MD, Michael Rees, MD, Fern Starr, MD, and Earl Yunes, MD, MPH were all winners. The Top Rated Primary Care Physician award winners are selected by *Boston Consumer Checkbook* and *Boston Consumer Reports* subscribers and are based on a variety of physician care metrics.

David Buckle, MD
Jane Butlin, MD
Matthew Butka, MD
Jayson Carr, MD
Branimir Catipovic, MD
Yoon Choi, MD
Amy Comander, MD
Dino Constantinou, MD
Michele Coviello, MD
David Cunningham, MD
Brian Dalton, MD
Winfred del Mundo, MD
George Despines, MD
Kelly Flynn, MD
Jane Fogg, MD, MPH
Erica Frank, MD, MPH
Susan Frankl, MD
Laura Garelick, MD
Lisa Gilbert, MD
Cindy Gleit, MD
Suzanne Gleysteen, MD
John Guttell, MD
Rachel Haims, MD
Christine Harrington, MD
Perry Hearn, MD
Agostino Iarrobino, DO
David Ives, MD
Renee Jacobs, MD, PhD
Joseph Kagan, MD
Noor Kassamali, MD
Ronald Katz, MD
Harry Katz-Pollack, MD
Glenn Kehlmann, MD
Roger Kligler, MD
Irina Kogan, MD
Xue-June Kong, MD
Risa Korn, MD
William McDonald, DO
Laura McLaughlin, MD
Emily McPhillips, MD
Daniel Melville, MD
Nikolaos Michalacos, MD
Paul J. Mikus, MD
Malina Milan, MD
David Mudd, MD
Arun Mukherjee, MD
Elisa Mulcahy, MD
Maryann Murphy, MD
Peter Ostrow, MD
Bruce Pastor, MD
Patiksha Patel, MD
Dominic Pennachio, MD
Grace Perez-Lirio, MD
Mayra Cruz Polanco, MD
Joseph Raduazzo, MD
Michael Rees, MD
Bruce Ring, MD
Matthew Rosen, MD
David Savitz, MD
Diane Schweitzer, MD
Maura Shaughnessy, MD
Khayam Shaukat, MD
Jonathan Smith, MD
Min Keun Song, MD
Fern Starr, MD
Meredith Talbot, MD
Alla Tandetnik, MD
Cathy Tong, MD
Nicole Touchet, MD
Philip Triffletti, MD
Nicholas Tsanotelis, MD
Polina Tsyvin, MD
Steven Van Dam, MD
Eugene Vaninov, MD
Jennifer Baldwin, MD
Vivek Bansal, MD
Nathalie Celestin, MD
Shobha Chacko, MD
Damien Crawford, MD
Katherine Dallow, MD, MPH
Narayan Dharel, MD
Satya Dondapati, MD
Ghania El Akiki, MD
David Fessler, MD
Vojin Gajic, MD
Faisal Hamada, MD
Christos Katavolos, MD
Kwan Kew Lai, MD
Tariq Khan, MD
Johanna Klein, MD
Mark Krivopal, MD
Chris Maiona, MD
Dan McQuillen, MD
Muhammed Mumtaz, MD
Anagha Paranjape, MD
Roberta Parks, MD
Mamatha Prabhakara, MD
Renu Prakash, MD
Jayalakshmi Punuri, MD
Pablo Quintero, MD
Michelle Roche, MD
Michael Rosenberg, MD
Leorah Ross, MD
Wei Shen, MD
Nitya Shivraman, MD
Meesun Rachel Sim, MD
Chi Chang Daniel Siao, MD
Paul Spiegel, MD
Aswani Suthrave, MD
Jean Yeung, MD

Community Connections

Heart and Soul

The pioneering founders of both the Beth Israel and the New England Deaconess Hospitals shared a common purpose and vision of providing care to the most vulnerable of our society. That cherished legacy continues today with Beth Israel Deaconess Medical Center's deeply ingrained commitment, evidenced in the organization's mission statement: "We have a covenant to care for the underserved and to work to change disparities in access to care." Embraced by all staff as a core BIDMC value, service to the community is not the stand-alone effort of one person or department but rather, woven into the fabric of every provider and staff person's work.

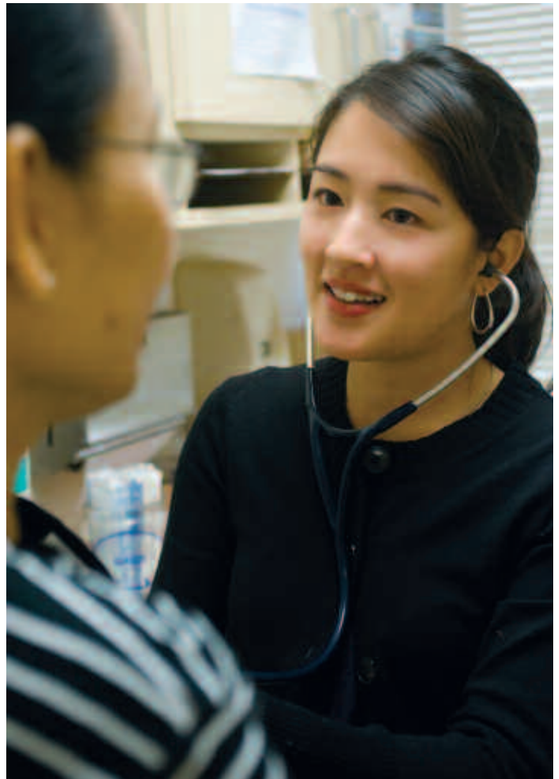
WORKING SIDE BY SIDE WITH COMMUNITY HEALTH CENTERS

Leanne Lee, MD, Joseph M. Smith Community Health Center

The medical center nurtures and builds on the community legacy of its founders by forging partnerships with community-based organizations and in particular, with our seven affiliated community health centers—Bowdoin Street, Dimock, Fenway, Joseph M. Smith, Outer Cape, Sidney Borum Jr., and South Cove. Each year, BIDMC provides millions of dollars in support to the health centers to maximize the scale and scope of community-based primary care, health education and social services. But financial sponsorship is just one piece of our partnership.

The centers help us understand the community's perspective and together, we can identify the specific needs of their diverse populations. In turn, community providers are afforded unique clincial and educational opportunities through staff appointments at BIDMC and Harvard Medical School. By sharing these resources and expertise, we are able to create effective, culturally responsive programs and initiatives to foster healthy communities.

In FY 09, the community health centers (CHC) provided care to more than 87,000 individuals in 426,000 outpatient visits in 12 sites throughout Boston, Waltham, Quincy and Cape Cod. Seventy seven percent of CHC patients are from diverse racial and ethnic backgrounds, many of whom are new arrivals to this country and have never benefited from preventive care. Approximately 20% of patients are without any insurance—



the working poor who exceed the financial guidelines for Medicaid and have no employer-sponsored health care coverage. CHCs are outstanding environments for trainees to focus on the care of sick, underserved populations. BIDMC internal medicine residents train in several of these health centers, including fourteen who worked in weekly primary care practice at Dimock and Fenway Health Centers. Still other residents have maintained ongoing practices at Sidney Borum Jr., Joseph M. Smith and Bowdoin Street Health Centers; while some have elected briefer but intense immersion exposure to CHCs and may work at Outer Cape Health Services in rural Cape Cod.

Joseph Ingelfinger, MD, Bowdoin Street Health Center

COMMUNITY HEALTH CENTERS AFFILIATED WITH BIDMC

1. Bowdoin Street Health Center
2. The Dimock Center
3. Fenway Health
4. Joseph M. Smith Community Health Center (Allston/Brighton and Waltham)
5. Outer Cape Health Services (Provincetown and Wellfleet)
6. Sidney Borum Jr. Health Center
7. South Cove Community Health Center (Boston and Quincy)

In addition to providing primary care for adults, children and teens, the health centers also offer a range of specialty care programs including infectious disease, podiatry, pulmonary, psychiatry and surgical consultations. Housestaff on ambulatory infectious disease electives work with CHC staff providing care for patients with co-morbid HIV/Hep C disease as well as anonymous HIV testing and counseling services. Residents in women's health elective may work with the Fenway program in artificial insemination while those on a complementary medicine elective work with acupuncturists and chiropractors at Fenway.

Working in concert with BIDMC specialists, the health centers' chronic disease management programs in diabetes and cardiovascular disease provide effective medical management and lifestyle interventions that result in improved health status and quality of life. By tailoring these interventions for specific ethnic and cultural groups, we can dramatically improve adherence with therapeutic protocols, thereby decreasing hospitalizations, emergency room utilization, workplace absenteeism and a host of other economic and social issues associated with poor health.

COMMUNITY CARE ALLIANCE

Each of BIDMC's affiliated health centers is unique in terms of size, populations served and services provided. To support their efforts to provide the highest quality, most cost-effective services possible, in 1997, they formed a network called Community Care Alliance (CCA) to collaborate on clinical and administrative issues. As equal members of CCA, the centers collectively contract for services and funds, as well as share resources and expertise to address public health concerns. Through this partnership, each center can provide optimal benefits to its patients and communities, and maintain its organizational independence.

Fenway Health

In March 2009, Fenway Health opened the doors of our new 100,000 square-foot Ansin Building home at 1340 Boylston Street in Boston's West Fens neighborhood. Fenway's new facility is the largest ever constructed by an organization with a specific mission to serve the lesbian, gay, bisexual and transgender (LGBT) community. Our new home has enabled us to expand our services to include dental and eye care and to grow our capacity to serve medical, behavioral health and pharmacy patients.

During 2009, Fenway provided medical and behavioral health care to 13,000 people who made 70,000 patient visits. We provided services to more than 1,400 people living with HIV, making us New England's largest outpatient provider of HIV care. Our Behavioral Health Department had more than 1,600 patient visits for individual therapy, 175 for group therapy and 320 for psychopharmacology visits each month. We also began seeing our first pediatric patients through our dental and eye care practices.

South End Associates of Fenway Health, located at 142 Berkeley Street in Boston's South End neighborhood, continues to offer medical and behavioral health care in a private practice setting. In 2009, South End Associates added several women's health specialists to its staff and continued to grow its patient base.

The Fenway Pharmacy opened a new, street-level storefront at 1340 Boylston Street and continues to operate at South End Associates. Together, both pharmacies fill an average of 300 prescriptions per day. We also participate in several discount programs, accommodating the needs of all Fenway patients, and provide more than $500,000 of free medication per year to patients who might otherwise go without. We also offer free delivery service for homebound patients and others who need it.

We have also been able to increase our ability to conduct LGBT health and HIV/AIDS research, education and advocacy. During 2009, The Fenway Institute was activated as part of a national six city study designed to address high rates of HIV infection among Black men who have sex with men (MSM), who currently have the highest rates of HIV acquisition among any ethnic and racial group of MSM in the U.S. Project S.O.S. (Saving OurSelves) is a collaboration between The Fenway Institute and the Multicultural AIDS Coalition and will evaluate the effectiveness of a variety of prevention interventions among four hundred Black MSM from the greater Boston area.

The Fenway Institute published over 50 peer-reviewed articles, textbook chapters and abstracts for national and international conferences based on our research work. We worked closely with other members of the National Coalition for LGBT Health to lobby the federal government to include LGBT people in Healthy People 2020, the federal government's blueprint for public health policy and spending for 2010 through 2020. Staff from Fenway's Center for Population Research in LGBT Health conducted surveys and created a set of briefs outlining health disparities that affect the LGBT community. Representatives from Fenway and the Coalition also testified at Healthy People 2020 regional meetings and met with members of congress and staff from the Healthy People 2020 office to ensure LGBT inclusion.

Ask the Experts about LGBT Health, an online question and answer service, will allow us to disseminate important medical and public health information to providers and consumers across the country and even around the world. And if you live or work in our neighborhood, are a member of the LGBT community or a person living with HIV/AIDS, Fenway Health remains a great place to get your care.

The newly opened Ansin Building at 1340 Boylston Street

Sneha Parik, DMD. Fenway Health added dental services in 2009.

Fenway Health optician Debra Quinn talks about new eye glasses with a patient

FACULTY

James A. Bonnano, MD
Stephen L. Boswell, MD
Judith B. Bradford, PhD
Patricia Case, MPH, ScD
José Caro, MD
Rich Druyetis, MD
Federico Erebia, MD
Jason Faulhaber, MD
Gregory Fenton, MD
Alex Gonzalez, MPH, MD
Padmini Harigopal, MD
Scott Harris, MD
Melinda Hooton, MD
Julia Ireland, DO
Kevin Kapila, MD
Elizabeth Kass, MD
Harvey J. Makadon, MD
Kenneth H. Mayer, MD
Matthew Mimiaga, MPH, ScD
Conall O'Cleirigh, PhD
Lori A. Panther, MPH, MD
Patricia Raney, MD
Steven Safren, PhD
Scout, PhD

SELECTED PUBLICATIONS

Mimiaga, MJ, et al. Street workers and internet escorts: contextual and psychosocial factors surrounding HIV risk behavior among men who engage in sex work with other men. *Urban Health* 2009; 86(1):54-66.

Safren SA, O'Cleirigh C, Tan J, Raminani S, Reilly LC, Otto MW, Mayer KH. A Randomized Controlled trial of cognitive behavioral therapy for adherence and depression (CBT-AD) in HIV-infected individuals. *Health Psychol* 2009 28(1):1-10.

Lazzarini Z, Case P, Thomas CJ. A walk in the park: a case study in research ethics. *Law Med Ethics* 2009; 37(1):93-103.

Carballo-Diéguez A, Dolezal C, Bauermeister J, Ventuneac A, O'Brien W, Mayer K. Preference for gel over suppository as delivery vehicle for a rectal microbicide: Results of a randomized, crossover acceptability trial among men who have sex with men. *Sex Trans Infect* 2008; 84(6):483-487.

Raja S, Teti M, Knauz R, Echenique M, Capistrant B, Rubinstein S, Allgood K, Gold M. Mayer KH, Illa L, Lloyd L, Glick N. Implementing peer-based interventions in clinic-based settings: Lessons from a multisite HIV prevention with positives initiative. *HIV/AIDS Soc Serv* 2008; 7(1):7-26.

Johnson CV, Mimiaga MJ, Bradford J. Health care issues among lesbian, gay, bisexual, transgender and intersex (LGBTI) populations in the United States:Introduction. *J Homosex* 2008; 54(3):213-24.

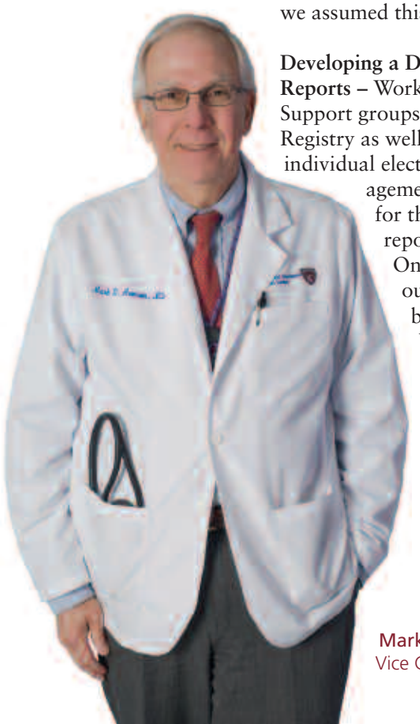
Mayer KH, Bradford J, Makadon H, et al. Sexual and gender minority health: what we know and what needs to be done. *Am J of Public Health* 2008; 98(6):989-995.

Mimiaga M, Fair A, et al. Acceptability of an internet-based partner notification system for sexually transmitted infection exposure among men who have sex with men. *Am J Public Health* 2008; 98(6):1009-1011.

Reisner SL, et al. A review of HIV antiretroviral adherence and intervention studies among HIV-infected youth. *Top HIV Med* 2009; 17(1):14-25.

Quality Improvement

The Department of Medicine Quality Improvement and Patient Safety (QI/PS) program is a comprehensive effort that addresses the Institution of Medicine's dimensions of quality, including safety, effectiveness, efficiency, patient-centered, equitable and timely care. This program includes five major functions: a peer review process; a medical patient care committee which sets the clinical priorities of the QI/PS program; multidisciplinary working groups which work to enhance the quality of patient care; Division-based dashboards and performance improvement projects; and the education of house officers, medical students and faculty in modern QI/PS strategies.



Mark D. Aronson, MD, MACP,
Vice Chairman for Quality

In FY09, we significantly expanded our QI/PS program and undertook many new initiatives to improve patient care. Below are some examples of new QI/PS initiatives we assumed this year:

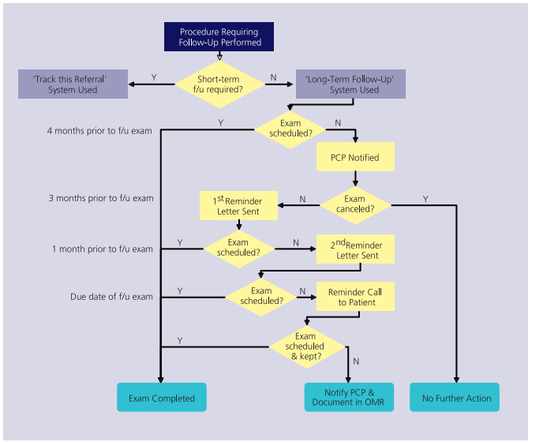
Developing a Diabetes Registry and QI Reports – Working with the IS and Decision Support groups, we have built a Diabetes Registry as well as designed and programmed individual electronic QI reports for the management of diabetic patients. Data for the Diabetes Registry and QI reports were abstracted from our On-line Medical Record system, our scheduling lab, and our billing repository (Casemix). We also obtained some of the data from the Joslin databases.

Improving Adherence to Heart Failure (HF) Treatment Guidelines – In order to improve adherence to HF treatment guidelines, we are working to implement the following interventions: development of a HF Sheet in web OMR which outlines the patient's heart failure profile including etiology of heart failure, comorbidities, medications, procedures and providers; development of a set of "HF Vital Signs" and "HF Parameters" that can be tracked over time and are recorded on the heart failure sheet; and delineation of criteria that will trigger electronic "alerts" if the patient's treatment does not comply with recommended HF guidelines.

The Referral Management System – We have designed and are now in the process of programming a computerized web-based referral management system integrated with the online medical record, which will allow for complete and timely follow up on high-risk referrals, including colonoscopies. This system will alert the specialist electronically when a request for referral is made, verify timing and completion of consultations and colonoscopies, document that the referring clinician both sees the consultative report and follows through on required action items, as well as verify that the recommendations of the specialists are incorporated or at least addressed by the primary care referring clinician.

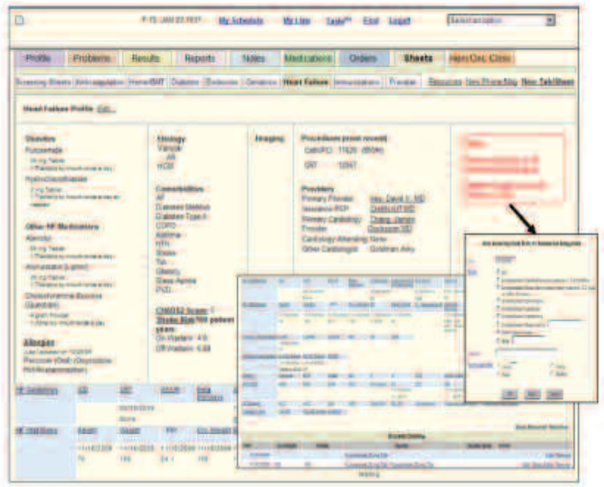
Long Term Follow-up on Endoscopic Procedures – The goal of this initiative is to design a computerized system for ensuring that patients are reminded to schedule follow-up endoscopic tests and that this communication is documented in the online medical record. Follow-up of gastrointestinal endoscopic procedures is the initial study environment, however, concepts are expected to be broadly applicable. By the end of 2009 we have completed writing the specifications for the programmers, and we hope to program the pilot system in 2010.

The TRUST Program – The goal of this program is to create a partnership between physicians and their patients that facilitates bi-directional communication and empowers patients to become equal and informed partners in the management of their care. We have developed a mechanism for improving the process of care for outpatient diagnostic cases by structuring the patient-physician interaction and making the patient an informed partner in their care. This is done by utilizing a physician-patient communication tool incorporated into the Electronic Medical Record (EMR) that prompts detailing of the differential diagnosis and justification of tests. Initial results from a pilot study suggest that patients' and physicians were both highly satisfied with this program and that this program to some extent contributed to improving patients' confiendce about communicating with physicians.



Proposed workflow for long-term follow up on endoscopic procedures

Preventive Medicine – Primary care patients who have recently had a 50th birthday now receive a letter with a list of recommended screening tests that they should discuss with their Primary Care Provider.



A "smart" heart failure sheet in OMR

Education

The BIDMC Department of Medicine leads Harvard Medical School in medical student education, both in the number of leadership positions and in overall faculty participation. We teach in nearly every course.

Key faculty involved in HMS teaching include: Helen Shields, Associate Master, Holmes Society; William Taylor, Associate Master, Castle Society; Robert Stanton, Co-Course Director, Human Systems; Melanie Hoenig, Director, Renal Block, Human Systems; Clyde Crumpacker, Director, Mechanisms of HST Microbial Pathogenesis; and Gordon Strewler, Master, Cannon Society.

In 2009 Sara Fazio succeeded Joyce Sackey as Associate Master of the Holmes Society, when Joyce accepted an offer to join Tufts University School of Medicine as Dean for Multicultural Affairs and Global Health, a tribute to her leadership and mentorship while at BIDMC and HMS.

Richard Schwartzstein, Vice President for Education of the Beth Israel Deaconess Medical Center and Faculty Associate Dean for Education at BIDMC, is also Course Director for the Integrated Human Physiology Course. In 2009 he was named Director of the HMS Academy and Ellen and Melvin Gordon Chair for Medical Education.

Patient-Doctor – Daniel Sullivan replaced Joyce Sackey as the site coordinator at BIDMC for Patient-Doctor I. For Patient-Doctor II, Ronald Silvestri is the overall HMS-wide Course Director, having replaced William Taylor, who had held that position for years. The BIDMC site is the second largest in the course, teaching 38 students under the able direction of Amy Ship and Ronald Silvestri. More than 150 faculty participated in Patient-Doctor II this year.

Principal Clinical Experience – For the past two years, all students have spent their entire third year at one of four Harvard teaching hospitals in the Principal Clinical Experience (PCE). Approximately one-third of Harvard Medical Students complete their third-year Medicine Clerkship at Beth Israel Deaconess Medical Center. Students in the PCE have a number of longitudinal teaching activities, including student-led patient clinics, simulation training, and a number of longitudinal electives. They also enjoy longitudinal mentorship. The PCE Director at BIDMC is David Roberts, a member of the Division of Pulmonary and Critical Care.

Alicia Clark, MD

Eileen E. Reynolds, MD
Director, Internal Medicine Residency Program

Gordon J. Strewler, MD
Vice Chairman for Education

Internal Medicine Clerkships – Sara Fazio is Clerkship Director and directs the ambulatory part of the Clerkship. Reed Drews stepped down as Clerkship Co-Director in 2008, after 15 years of dedication to medical student education; he was replaced by John Danziger, who now directs the inpatient portion of the clerkship and serves as Associate Clerkship Director.

Core II Medicine, the subinternship in Internal Medicine at BIDMC, is co-directed by Pamela Hartzband and Alexander Carbo. Alex replaced Wendy Stead this year. This month-long inpatient experience for fourth-year students prepares them for internship. The Subinternship was redesigned in 2007-2008 with the creation of the Subintern-Resident Service (SIRS), which pairs a resident with one or two subinterns on a service with no intern, a dedicated hospitalist attending and also a dedicated teaching attending. SIRS students are also given sessions in the Simulation Center on dealing with urgent inpatient situations by Caleb Hale and Laura Rock of our Simulation Core Faculty.

INTERNAL MEDICINE RESIDENCY

Eileen Reynolds, MD, Program Director
C. Christopher Smith, MD, Senior Associate Program Director

Career choices of graduating residents – Last year, 9 of our graduating residents chose a career in generalism (primary care practice, general internal medicine fellowships and hospital medicine). Most of our residents choose to go on to subspecialty fellowships; in 2008-2009 36 residents applied for subspecialty positions, with phenomenal success. In 2009, 78% (28/36) matched with their top choice on their rank list, 97% (35/36) in one of their top two rank list programs, and 100% in their top three. In 2009, eight residents chose cardiology, 7 chose gastroenterology, and the remaining spread over all the subspecialties of medicine plus allergy.

Educational Innovation Project – In 2006, we were selected to participate in the ACGME's Educational Innovation Project (EIP), a national initiative intended to promote innovation. The basis of BIDMC's project proposal lay in (1) a reorganization of the existing inpatient medical service into geographically-based clinical micro-systems, in order to facilitate experiential learning in health systems quality and safety; in conjunction with (2) a standardized rotation designed to provide a foundational knowledge base in principles of health care quality, patient safety, and medical error analysis.

Early outcome measures, as summarized in an article by program directors Anjala Tess et al, demonstrate significant improvements in residents' awareness of and participation in health care quality-related issues since inception of these EIP-based program changes. Currently, our geographical admitting system allows housestaff to care for 90% of their inpatients on a single medical floor; residents are leading 16 longitudinal QI projects in the inpatient and outpatient settings; and housestaff perform 2/3 of all adverse event reviews in the department.

In 2009, associate program directors Julius Yang MD, PhD and Anjala Tess, MD led the our first multidisciplinary QI retreat, a retreat focused on the application of Lean principles to the routine patient care practices within our unit-based clinical microsystems. The retreat experience brought a new recognition of unintended process waste and opportunities for enhanced efficiency, while demonstrating the powerful benefits of interprofessional education of physicians and nurses.

Anjala Tess, MD, Associate Program Director, Internal Medicine Residency

ACES: Alternating Call and Elective Schedule – In 2009 we reorganized resident clinical rotations into a new model where upper level residents alternate rotations between "call" rotations (core inpatient and ICU) and "elective/ambulatory rotations" (Alternating Call and Elective Schedule – ACES). In this model

resident continuity practice no longer takes place on call blocks and instead is focused in the non-call blocks. In addition to weekly continuity practice sessions during the non-call blocks, residents participate in one week immersion "practice weeks" that provide time for daily practice, didactics and quality improvement work in the outpatient setting. We anticipate this model will enhance resident satisfaction with primary care practice, will decrease burnout and will improve continuity of patients with their primary care provider.

Claudia Denkinger, MD PhD DTMH MSc

As part of this reorganization, and led by Drs. Carol Bates (primary care program director) and Anjala Tess, we embarked on a redesign of our electives, moving to merged models where residents have ambulatory experiences built into each rotation. We continue to offer electives in a variety of care delivery models, in public health and health policy and hospital medicine.

New Tracks in the Residency Program – In 2009 we planned and implemented two new tracks in the program – a Global Health Track and a Medical Education Track, which join our long-established Primary Care Track.

Medical Education Track – In 2009 the Department introduced a novel Clinician Educator Track for its medical residents. Six interns per year will enter this two and a half year track, which allows residents to develop the skills necessary to become leaders in medical education. Directed by C. Christopher Smith, MD, who also directs the Rabkin Fellowship in Medical Education, the track will create a small group of residents who develop the knowledge and skills necessary to be successful teachers and learn how to effectively design and assess new curricular offerings, how to evaluate learners and programs and how to investigate and disseminate important educational curricular and research topics. The program features a comprehensive, longitudinal curriculum, active skills practice, and direct observation and feedback by master teachers.

Global Health Track – In 2009 we created a new Global Health Track, which combines the opportunity to do clinical and scholarly work in Global Health with a longitudinal curriculum and coursework. Track participants will participate in one of two formal courses: The Harvard Global Health Effectiveness Program or the Harvard Humanitarian Initiative—Humanitarian Studies Course. We have joined with residents and faculty in other programs to sustain a hospital-wide program, and we aim to prepare residents in this track for a career in Global Health.

Primary Care Track – BIDMC's primary care track has a long history of training future academic general internists as well as leading primary care doctors. Interns may join as early as the match, and last year, bucking the national trend, we had 47 residents in the primary care program across all three years. Last year's graduates pursuing primary care careers are now in general medicine fellowship, palliative care fellowship, and in practice in a community health center and an area private practice.

Our residents are actively involved in the Society of General Internal Medicine: BIDMC residents serve as the resident associate member for the Society's Education Committee, write a column for the SGIM Forum newsletter, and present and regularly win awards in the abstract and clinical vignette competitions. Our 2008 – 2009 chief resident, Shani Herzig, won the 2009 Lipkin award for the best research abstract presentation by a fellow.

Resident Research – Believing that scientific discovery is an integral to being a physician, the Department endeavors to expose every resident to research. An intensive elective

Residents at a Medical Grand Rounds lecture

course directed by Ken Mukamal prepares residents for clinical, translational, education or health care quality research, supported by elective time and faculty mentorship. The Department is proud of the success its residents have achieved. A 2009 *JAMA* article by Andrea Phelps, with Holly Prigerson and colleagues, and Gastroenterology paper by four residents, Brian Hyett, Fernando Martinez, Brian Gill and Shilpa Mehra, collaborating with three BIDMC gastroenterologists, were just two of the 46 publications to which residents contributed in just 2008 and 2009 (two years total), testimony to the initiative our residents have taken in their research projects and to their mentorship and support from the Department and the greater Boston research community.

TEACHING HONORS AND AWARDS

The Herrman L. Blumgart Teaching Award is given to the faculty member who has contributed the most to both housestaff education and professional development during the past academic year, as voted by the housestaff.

Alexander Carbo, MD

The Katherine Swan-Ginsburg Award is given to the senior resident who is voted by his/her housestaff colleagues to best embody Kathy's qualities of intelligence, courage, dignity, and compassion.

Heidi Blake, MD

The Elmer Hinton Award is given by the Department to an intern and junior resident who have formed outstanding physician-patient relationships.

Michelle Dossett, MD, PhD
Christine Mullowney, MD

The Lowell McGee Award is voted upon by the housestaff to recognize the senior resident who has contributed the most to the education of his/her fellow house officers.

Jed Gonzalo, MD

The James L. Tullis Award is bestowed by the Department to the intern and junior resident who have shown the greatest intellectual growth and enthusiasm for learning.

Douglas Hsu, MD
John Szumowski, MD, MPH

The Nursing Excellence Award is given to a nurse chosen by housestaff vote who best exemplifies the qualities of compassion, dedication and excellence in nursing, and who is gifted at improving housestaff understanding of the care of medical patients and the importance of good physician-nurse collaboration.

Alice Bradbury, RN

The Steven E. Weinberger, MD Award recognizes a senior member of the medical housestaff who has contributed unselfishly to the residency program.

Katherine Neal, MD

The Robert C. Moellering, Jr., MD Teaching Award recognizes a junior faculty member who best embodies the qualities of Dr. Moellering, our previous Chief of Medicine, as a teacher, clinician and researcher.

Booker Bush, MD

The Fellow Teaching Award, awarded for the first time in 2006, is given to the fellow, chosen by housestaff vote, who is considered to be the most outstanding teacher of the medical residents.

Graham Snyder, MD

The Mentorship of Resident Research Award is chosen by the Department's Education Committee; this award recognizes a faculty member who has significantly contributed to the growth and development of the research skills and experiences of the housestaff.

Gordon Strewler, MD

Resident as Teacher Award as nominated by the Harvard Medical School students who rotate on the medicine clerkships at BIDMC, this award recognizes a resident noted to be a most outstanding teacher.

Chethan Gangireddy, MD, MPH

2009 Harvard Medical School Teaching Awards

S. Robert Stone Award for Excellence in Teaching

Peter Clardy, MD

An Excellence in Tutoring Award was presented this year to Harvard Medical School tutors in Year 1 and Year 2 who received a perfect score of 1.0 in their evaluations by students. They include:

Residents

Suma S. Magge, MD
Yuheng Ruan, MD
Anita Vanka, MD

Faculty

Alexander R. Carbo, MD
John Danziger, MD
Sean Gilman, MD
Steve M. Kappler, MD
Alan C. Moss, MD
Laura K. Rock, MD
Helen M. Shields, MD
Joseph D. Zibrak, MD

MEDICINE HOUSESTAFF

Interns

Alexandra Bailey, MD
Lisa Battaglia, MD
Evan Berg, MD
Aimee Boegle, MD
Demetrio Castillo, MD
Emily Clarke, MD
Avnish Deobhakta, MD
Amy Devlin, MD
Michelle Dossett, MD, PhD
Grace Farris, MD
Sarah Freedman, MD
Lauren Frost, MD
Neil Gheewala, MD
Jennifer Giuseffi, MD
Aaron Goldberg, MD
Andrea Goldberg, MD
Jordana Goren, MD
John Greenland, MD, PhD
Aric Hall, MD
Eric Heckman, MD
Brian Hobbs, MD
Douglas Hsu, MD
Romina Ilic, MD
Richard Kalman, MD
Vivek Kalra, MD
Russell Kerbel, MD
Eric Kerns, MD
Steven Kim, MD
Andrea Klayman, MD
Jennifer Lacy, MD
Joseph Ladapo, MD, PhD
Deborah Leong, MD
Piro Lito, MD, PhD
Katherine Lynch, MD
Susan Mackie, MD
Robert Meisner, MD, PhD
Cassandra Murphy, MD
Tracey Newlove, MD
Sarah Nicolai, MD
Brian O'Neill, MD, PhD
Pranith Perera, MD
Lindsey Petty, MD
Christine Pham, MD
Abid Qureshi, MD
Radha Rajasingham, MD
Elena Resnick, MD
Elizabeth Sandman, MD
Benjamin Schlechter, MD
Andrew Schutzbank, MD
Lauren Scott, MD
Sonali Shah, MD
Siddharth Sura, MD, MPH
Hector Tamez Aguilar, MD, MPH
Katherine Troy, MD
Byron Vaughn, MD
Karoly Viragh, MD
Talley Whang, MD
Brett Williams, MD
Hilary Womble, MD
Rebecca Zeitlin, MD
Audrey Zinchuk, MD
Omar Zuriya, MD

Junior Residents

Jorge Barrero, MD
Kristina Berglund, MD
Katherine Cahill, MD
Sharon Chou, MD
Alicia Clark, MD
Kristin Cox, MD
Bradley Crotty, MD
Katherine Dudley, MD
Bonnie Dunne, MD
Lisa English, MD
Adam Fein, MD
Jesse Foote, MD
Kelly Graham, MD
Stephen Kaplan, MD
Jiwon Kim, MD
Lindsay Kim, MD
Ramanan Kumareswaran, MD
Mary LaSalvia, MD
Barbara LeVarge, MD
Margaret Lippincott, MD
Fernando Martinez, MD
Matthew McGuiness, MD
Mary McKenzie, MD
Shilpa Mehra, MD
Daniel Meyer, MD
Carlos Montes, MD
Christine Mullowney, MD
Mihran Naljayan, MD
Kim-Son Nguyen, MD
Jennifer Nierman, MD
Elizabeth O'Donnell, MD
Catherine Parker, MD
Catherine Pelo, MD
Amanda Powell, MD
Ali Poyan Mehr, MD
Emily Rostholder, MD
Sachin Shah, MD
John Szumowski, MD, MPH
H. Claire Taylor, MD
Sumeet Tewani, MD
Melissa Tukey, MD
Joel Wedd, MD, MPH
Adam Weston, MD
Joseph Wright, MD
Charlotte Wu, MD
Daniel Zandman, MD

Medicine/Dermatology

Arash Mostaghimi, MD, MPP

Senior Residents

JoEllyn Abraham, MD
Jessica Bartfield, MD
Martin Black, MD
Heidi Blake, MD
Anthrony Breu, MD
Laurie Caines, MD
Meghan Cooper, MD
Natalie Cusano, MD
Eric Davis, MD
Ethan Ellis, MD
Asghar Fakhri, MD
Lauren Fishbein, MD, PhD
Katherine Frachetti, MD
Chethan Gangireddy, MD, MPH
Sagar Garud, MD, MPH
Elizabeth Gaughan, MD
Brian Gill, MD
Jed Gonzalo, MD
Matthew Hill, MD
Matthew Hitron, MD
Janice Hwang, MD
Rakhi Kheraj, MD
Yoon Ju Kim, MD
Catherine Lau, MD
Giovanna Leddy, MD
Erika Lee, MD
Grace Lopez, MD
Suma Magge, MD
Diane McNally, MD
Katherine Neal, MD
Ashish Nimgoankar, MD
Eric Osborn, MD, PhD
Matthew Parker, MD
Christine Peoples, MD
Andrea Phelps, MD
Yuri Pride, MD
Erin Rafferty, MD
Ranjan Ray, MD, PhD
Yuheng Ruan, MD
Sarah Schellhorn, MD
Kerri Shafer, MD
Katherine Van Loon, MD, MPH
Anna Varghese, MD
Tanya Weinstock, MD
Melissa Wendt, MD
Benjamin Wertheimer, MD
Benjamin Young, MD
Rachel Yung, MD
Matthew Yurgelun, MD

Chief Medical Residents

Suzanne Baumwell, MD
Stephanie Heon, MD
Shoshana Herzig, MD
Matt Kinsey, MD
Anita Vanka, MD

DEPARTMENT OF MEDICINE FELLOWS, 2008-2009

Cardiovascular Medicine
Anne-Marie Anagnostopoulos, MD
Riya Chacko, MD
Andre Dejam, MD
Francesca Nesta Delling, MD
Airley Fish, MD, MPH
Daniel Kramer, MD
David Leder, MD
Emerson Liu, MD
Ali Mahajerin, MD
Angela Morello, MD
Nisha Parikh, MD, MPH
Ali Rahimi, MD, MPH
Anne Riley, MD
Alex Tan, MD
Amit Thosani, MD
Connie Tsao, MD
Meghan York, MD

Cardiology Interventional
Amjad Almahameed, MD, MPH
Jonathan Bridges, MD
Randall Harada, MD
Claudia Hochberg, MD
Jan Pattanayak, MD
Xin Yang, MD

Cardiac Non-Invasive
Jonathan Chan, MD
Michael Chuang, MD
Joyce Meng, MD

Cardiac Electrophysiology
Alena Goldman, MD
Jeff Hsing, MD
Yuval Konstantino, MD
Kapil Kumar, MD
Sinjin Lee, MD
Karen Thomas, MD

Endocrinology, Diabetes and Metabolism
Chuanyun Gao, MD
Jennifer Gong, MD
Susan Herzlinger-Botein, MD
Eyiuche Okeke, MD
Jill Paulson, MD
Judy Shih, MD, PhD
Laura Sweeney, MD
Linus Tsai, MD, PhD

Gastroenterology
Laren Becker, MD
Paola Blanco, MD
Wissam Bleibel, MD
Filippo Cremonini, MD
Glen Doherty, MD
Nielsen Fernandez-Becker, MD
Sarah Flier, MD
Tahereh Ghaziani, MD
Steven Kappler, MD
Michelle Lai, MD
Laura Noddin Rosenberg, MD
Nuri Ozden, MD
Rishi Pawa, MD
Paul Sepe, MD
Sanjeev Tummala, MD

Gerontology
Amanda Berling, MD
Rebecca Brown, MD
Yosef Glassman, MD
Fernando Kawai, MD
Scott Kaiser, MD
Dae Hyun Kim, MD
Diane McMullin, MD
Mark Simone, MD
Foy White-Chu, MD

Hematology-Oncology
Kelly Bodio, MD
Gregory Britt, MD
Elizabeth Buchbinder, MD
Andrea Bullock, MD
Jessica Clement, MD
Erin DeRose, MD
Gregg Fine, MD
Brett Glotzbecker, MD
Ayad Hamdan, MD
Erin Hofstatter, MD
Rodney Jamil, MD
Michelle Lau, MD
Katarina Luptakova, MD
Susan Pandya, MD
Akash Patnaik, MD
David Portnoy, MD
Elizabeth Riley, MD
Sarah Scott, MD
Tanya Siddiqi, MD
Ryan Sullivan, MD

Infectious Disease
Catharina Armstrong, MD
Erica Blood, MD
Adrian Gardner, MD
Shikha Garg, MD
Ingrid Katz, MD
Daniel Leung, MD
John Love, MD
Lynn Matthews, MD
Anton Peleg, MD
Mai Pho, MD
Todd Pollack, MD
Graham Snyder, MD
Robin Wigmore, MD
David Yassa, MD

Nephrology
Nisha Bhatt, MD
Marta Hristova, MD, PhD
Ajay Kher, MD
Manish Maski, MD
Preeti Rout, MD
Sailaja Ventrapragada, MD
Seth Wright, MD

Pulmonary, Critical Care and Sleep Medicine
Asha Anandaiah, MD
Abdul Basit, MD
Jay Blachandran, MD
Batt Bianchi, MD, PhD
John Brehm, MD
Angela J. Carbonetti, MD
Josalyn Cho, MD
Carolyn E. Come, MD
Vanessa J. Craig, MD
Laura Crotty, MD
Trustin Ennacheril, MD
Maha Farhat, MD
Lee Gazourian, MD
Alexander Geyer, MD
Andrew J. Goodwin, MD
Sarah Grant, MD
Charles C. Hardin, MD
Megan Hardin, MD
Jeffrey Haspel, MD
Umakanth Khatwa, MD
Shamsa Kazani, MD
Peggy Lai, MD
Andrew Lim, MD
Jonathan Oren Lipton, MD, PhD
Amy Markezich, MD
Amy Nuernberg, MD
Robert Owens, MD
Avignat S. Patel, MD
Jeremy Richards, MD
K. Akaya Smith, MD
William Stigler, MD
Anil Trindade, MD
Patrick J. Troy, MD
Vladamir Vinarsky, MD
Emily Wan, MD
Tracy Wanner, MD

Renal Transplant
Manasa Ujire, MD

Rheumatology
Sonali Desai, MD
Roumey Ishizawar, MD
Martin Kriegel, MD, PhD
Yvonne Lee, MD
Katherine Liao, MD
Thorvardur Love, MD
Susan Ritter, MD
Ki-Shul Shin, MD

Megan Hardin, MD, Pulmonary Fellow

Division of Continuing Medical Education

The CME Division in the Department of Medicine at BIDMC has 3 directors – Sanjiv Chopra, MD, Martin J. Abrahamson, MD and Mark Zeidel, MD. Drs. Chopra and Abrahamson, in addition to serving as course directors of 2 annual Internal Medicine courses, and CME online courses, also assist in the planning and organization of new course offerings directed by members of the Department.

ANNUAL INTERNAL MEDICINE COURSES

- Update and Review of Internal Medicine – a collaborative effort with the University of New Mexico. This 6-day course is held annually in Santa Fe and attracted 240 attendees in 2008. The course consistently gets outstanding reviews.
- Update in Internal Medicine – this is the flagship course of the Department of Medicine and is held annually in Boston. This 7-day course had 525 attendees in 2008 from 50 states and 15 countries abroad. Sixty percent had attended the course multiple times. This course has the largest attendance of any of the Internal Medicine courses sponsored by the Department of Continuing Medical Education at HMS. This course has consistently received accolades.

Martin J. Abrahamson, MD, Co-director
Sanjiv Chopra, MD, Co-director
Mark L. Zeidel, MD, Co-director

DEPARTMENT OF MEDICINE COURSES, 2008

Many senior members of our distinguished faculty serve as directors of outstanding courses, most of which are held annually. These include the following:

- Advanced Diagnostic Bronchoscopy: Armin Ernst, MD, Heinrich Becker, MD and Raphael Bueno, MD (BWH)
- Advances in Gastroenterology – 2008: J. Thomas LaMont, MD, Stephen Goldfinger, MD (MGH) and Richard Blumberg, MD (BWH)
- Nephrology 2008: Burton Rose, MD and Mark Zeidel, MD
- HIV Update: Contemporary Issues in Management: Peter Weller, MD and Lori Panther, MD
- Endobronchial Ultrasound – An Interdisciplinary Training Course: Armin Ernst, MD, David Feller-Kopman, MD and Malcolm Decamp, MD
- Primary Care Internal Medicine: Principles and Practice: William Taylor, MD, Charles Hatem, MD, John Goodson, MD (MGH), Albert Mulley, MD (MGH) and Richard Pels, MD (Cambridge)
- Emergency Medicine Into the 21st Century: Stephen Traub, MD, David Peak, MD and Jessica Radin Peters, MD (BWH)
- The Patient Safety Imperative: Saul Weingart, MD, Hans Kim, MD and David Bates, MD (BWH)
- Current and Emerging Therapies in Gastrointestinal Motility and Functional GI Disorders: Anthony Lembo, MD, Braden Kuo, MD (MGH) and Hiroshi Mashimo, MD (VAMC)
- The Management of Pleural Diseases including Medical Thoracoscopy: Armin Ernst, MD and David Feller-Kopman, MD
- Enhancing the Safety of Parenteral and Enteral Nutrition: Bruce Bistrian, MD with Drs. Blackburn and Driscoll
- Boston Live Endoscopy Course: Ram Chuttani, MD and Doug Pleskow, MD
- ECGs in Clinical Practice: Pearls and Pitfalls: Ary Goldberger, MD, Peter Zimetbaum, MD and Mark Josephson, MD
- Healthy Kitchens, Healthy Lives: Caring for Our Patients and Ourselves: course directors David Eisenberg, MD and Mark Erickson. A unique feature of the course was hands on learning of healthy cooking techniques and provision of scores of recipes in the syllabus. Many of the attendees subsequently commented that they had shared these techniques and recipes and motivated many of their patients.

CURRENT CLINICAL ISSUES IN PRIMARY CARE MEDICINE

Sanjiv Chopra, MD serves as course director for Current Clinical Issues in Primary Care Medicine. Mark Aronson, MD and Gerald Smetana, MD are on the course committee and also serve as co-directors for these programs. Seven courses were held in 2008 in the following cities: Anaheim, Baltimore, Boston, Chicago, Fort Lauderdale, Houston and New York City. Each course is attended by 5000 to 9000 attendees. The courses held outside Boston are a collaborative effort with other major academic institutions. These include UCLA, Johns Hopkins, Northwestern University, University of Miami and Baylor College of Medicine and The University of Columbia College of Physicians and Surgeons. Many BIDMC faculty members speak each year at these courses and some have served as distinguished keynote speakers.

CME ONLINE

The following members of the Department of Medicine have developed interactive and engaging distance learning courses and contributed in a major fashion to the HMS CME Online initiative. Offerings include the following:

- Challenging Cases in Toxicology: Steve Traub, MD
- Chronic Hepatitis C: A Multifaceted Disease: Sanjiv Chopra, MD and Barry Kelleher, MD
- Clinical Challenges in Electrocardiography: Ary Goldberger, MD, Larry Nathanson, MD and Seth McClennen, MD
- Clinical Challenges in Chest Radiology: Phil Boiselle, MD and Richard Schwartzstein, MD
- Emergency Medicine 2006 Lifelong Learning and Self-Assessment (LLSA) Review: Stephen Traub, MD
- Managing Type 2 Diabetes: A Clinical Challenge: Martin Abrahamson, MD and Richard Beaser, MD
- Hypertension: Evidence-based Treatment and Clinical Challenges: Gerald Smetana, MD and John Goodson, MD (MGH)
- Management of Patients with Hyperlipidemia: J. Peter Oettgen, MD
- Nonalcoholic Steatohepatitis: Barry Kelleher, MD, Sanjiv Chopra, MD and Sangik Oh, MD
- Prostate Cancer for the Internist and General Practitioner: Marc Garnick, MD and Carolyn Lamb, MD
- HIV Infection for the Primary Care Provider: Howard Libman, MD and Paul Sax, MD
- Neurological Emergencies: Case Studies in Critical Diagnosis: Jonathan Edlow, MD and Steve Traub, MD
- Metastatic Case Studies in Breast, Colorectal, and Lung Cancers: Jeff Meyerhardt, MD, Lowell Schnipper, MD, Marc Garnick, MD and Steven Come, MD
- Venous Thrombosis: David Feinbloom, MD and Kenneth Bauer, MD
- Sudden Cardiac Death: A Focus on the ACLS Guidelines: Shamai Grossman, MD
- Management of Atrial Fibrillation: Peter Zimetbaum, MD and Joseph Germano, DO
- Breast Cancer for the Primary Care Provider: Steve Come, MD and Zsofia Stadler, MD

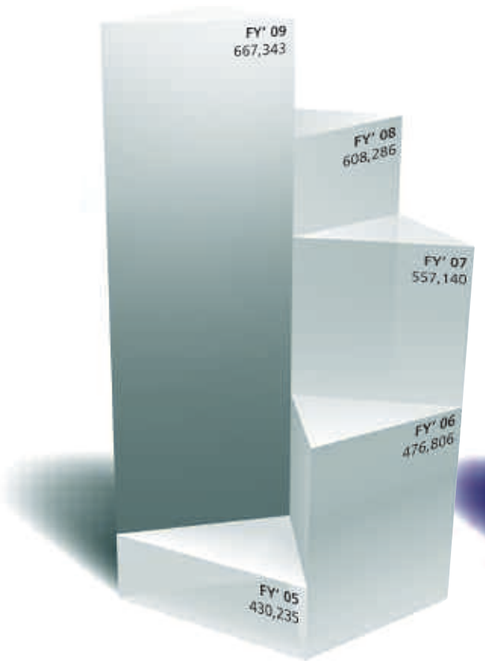
Research Funding for FY 2009

		Direct	Indirect
Allergy & Inflammation			
	Federal	999,832.00	647,051.00
	Non-federal	150,557.45	10,268.97
Cardiovascular Medicine			
	Federal	5,477,996.36	2,075,628.77
	Non-federal	3,572,751.28	593,987.59
Clinical Informatics			
	Federal	300,026.46	95,368.60
	Non-federal	199,656.00	17,970.00
Clinical Nutrition			
	Federal		
	Non-federal	109,295.82	99,924.95
Endocrinology, Diabetes and Metabolism			
	Federal	6,336,673.34	3,597,799.87
	Non-federal	3,541,643.97	1,084,494.09
Experimental Medicine			
	Federal	949,629.65	621,818.53
	Non-federal	796,730.44	14,341.92
Genetics			
	Federal	3,687,166.83	1,880,299.10
	Non-federal	2,367,744.97	235,540.83
General Medicine			
	Federal	7,466,308.95	1,360,398.38
	Non-federal	2,131,853.92	129,308.34
Gerontology			
	Federal	1,480,136.29	593,965.64
	Federal (HSL)	4,587,548.00	1,966,092.00
	Non-federal	1,617,602.95	151,781.47
	Non-federal (HSL)	663,207.00	79,393.00
Gastroenterology			
	Federal	5,219,417.68	2,249,703.94
	Non-federal	2,726,565.42	454,458.66
Hematology-Oncology			
	Federal	13,375,941.63	6,537,505.63
	Non-federal	11,154,496.51	1,558,829.61
Hemostasis and Thrombosis			
	Federal	2,259,015.26	1,007,996.78
	Non-federal	357,552.08	14,625.95

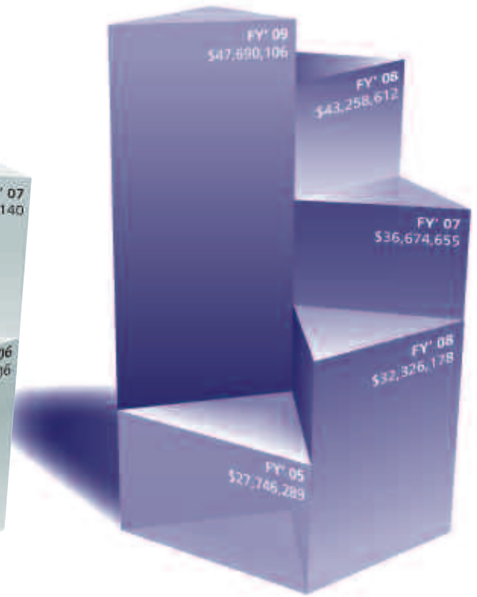
		Direct	Indirect
Infectious Diseases			
	Federal	1,510,009.96	635,016.21
	Non-federal	500,369.12	70,950.34
Interdisciplinary Medicine and Biotechnology			
	Federal	1,035,944.81	163,453.80
	Non-federal	1,240,296.32	37,630.79
Immunology			
	Federal	3,067,310.09	900,648.28
	Non-federal	468,865.65	116,255.00
Matrix Biology			
	Federal	1,093,742.73	583,469.00
	Non-federal	182,383.94	
Molecular and Vascular Medicine			
	Federal	1,093,224.20	691,503.87
	Non-federal	2,086,543.09	104,953.78
Nephrology			
	Federal	1,545,481.81	676,856.35
	Non-federal	967,194.35	64,292.12
Pulmonary, Critical Care and Sleep Medicine			
	Federal	1,775,933.90	1,027,090.79
	Non-federal	949,021.30	159,175.09
Rheumatology			
	Federal	2,480,632.84	1,260,249.07
	Non-federal	472,505.19	62,442.56
Signal Transduction			
	Federal	4,300,548.77	1,562,458.54
	Non-federal	1,253,535.42	312,358.98
Translational Research			
	Federal	1,936,117.60	
	Non-federal	8,700.00	
Transplant Immunology			
	Federal	2,016,627.03	1,379,251.23
	Non-federal	716,596.10	
Viral Pathogenesis			
	Federal	26,985,445.94	6,516,594.27
	Non-federal	6,016,231.77	419,345.94

Statistical Snapshot for FY 2009

Work RVU



Payments



Illustrations: Matt Pickett

Clinical (FY09)

Discharges	16,389
Outpatient visits	266,602
Cardiac catheterizations	3,848
Endoscopies	23,266

Research (FY09)

Federal Direct Awards	$142,920,837
Nonfederal Direct Awards	$117,535,055
Total Direct	**$260,455,892**
Federal Indirect Awards	$42,207,363
Nonfederal Indirect Awards	$34,184,091
Total Indirect	**$76,391,454**
Total	**$336,847,346**

Departmental Organizational Overview

Administration

Mark L. Zeidel, MD
Chair, Department of Medicine

Mark Aronson, MD
Vice-Chair, Quality

Gordon Strewler, MD
Vice-Chair, Education

Peter Weller, MD
Vice-Chair, Research

Joanne Casella
Administrative Director

Marian McDermott
Financial Administrator

Clinical Divisions

Allergy and Inflammation
Peter Weller, MD, Division Chief
Courtney Ives, Division Administrator

Cardiovascular Medicine
Mark Josephson, MD, Division Chief
Daniel Ibanez, Division Administrator

Endocrinology, Diabetes and Metabolism
Barbara Kahn, MD, Division Chief
Elizabeth McDonnell, Division Administrator

Gastroenterology
J. Thomas Lamont, MD, Division Chief
Eileen Joyce, Division Administrator

General Medicine and Primary Care
Russell Phillips, MD, Division Chief
Louise Mackisack, Division Administrator

Gerontology
Lewis Lipsitz, MD, Division Chief
Karen Turnquist, Division Administrator

Hematology-Oncology
Lowell Schnipper, MD, Division Chief
Ellen Volpe & Kerry Brown, Division Administrators

Infectious Diseases
Peter Weller, MD, Division Chief
Ruth Colman, Division Administrator

Nephrology
Mark L. Zeidel, MD, Acting Division Chief
Courtney Ives, Acting Division Administrator

Pulmonary, Critical Care and Sleep Medicine
J. Woodrow Weiss, MD, Division Chief
Courtney Ives, Division Administrator

Rheumatology
George Tsokos, MD, Division Chief
Patricia Harris, Division Administrator

Research Divisions

Clinical Informatics
Charles Safran, MD, Division Chief

Clinical Nutrition
Bruce Bistrian, MD, Division Chief

Experimental Medicine
Jerome Groopman, MD, Division Chief

Genetics
Pier Paolo Pandolfi, MD, PhD, Division Chief

Hemostasis and Thrombosis
Barbara Furie, PhD and Bruce Furie, MD,
Division C0-Chiefs

Immunology
Cox Terhorst, PhD, Division Chief

Interdisciplinary Medicine and Biotechnology
Vikas Sukhatme, MD, PhD and Ary Goldberger, MD,
Division C0-Chiefs

Matrix Biology
Raghu Kalluri, MD, PhD, Division Chief

Molecular and Vascular Medicine
William Aird, MD, Division Chief and
J. Peter Oettgen, MD, Associate Chief

Signal Transduction
Lewis Cantley, PhD, Division Chief

Translational Research
Steven Freedman, MD, PhD, Division Chief

Transplant Immunology
Terry Strom, MD and Laurence Turka, MD,
Division C0-Chiefs

Vaccine Research
Dan Barouch, MD, PhD, Division Chief

Viral Pathogenesis
Norman Letvin, MD, Division Chief

The Department of Medicine gratefully acknowledges the Division Chiefs, administrators and partners from our affiliated sites for their contributions to this Annual Report.

Produced by: Beth Israel Deaconess Medical Center, Department of Medicine
Project Managers / Editors: Jane Hayward, BIDMC Media Services; Sara Cyr, Department of Medicine
Design and Layout: Matthew Pickett, Pickett Design
Photography: Bruce Wahl, Oran Barber, BIDMC Media Services; Marilyn Humphries, Fenway Health

Beth Israel Deaconess Medical Center

A teaching hospital of Harvard Medical School

Affiliated with Joslin Clinic

A research partner of
NCI CCC DANA-FARBER/HARVARD CANCER CENTER
A Comprehensive Cancer Center
Designated by the National Cancer Institute

Official hospital of the Boston Red Sox