

# Division of Nephrology



Mark L. Zeidel, MD,  
Interim Chief

## ● *Overview*

With the departure of our division chief, Vikas Sukhatme, to serve as the Academic Dean for the medical center, the Department and Division have begun a national search for a new Nephrology Division Chief. The Division provides expert care for patients with all varieties of renal disease, provides teaching and training in renal physiology, pathophysiology and the clinical care of patients for medical students, residents and fellows, and performs cutting-edge research in a broad spectrum of renal diseases. These activities are organized under the interim leadership of Dr. Mark Zeidel, as Division Chief, and Dr. Robert Brown, as the Clinical Chief. Drs. Brown and Mark Williams serve as dialysis Co-Directors and Dr. Martha Pavlakis is Director of Renal Transplantation. The Division has critical research and clinical interfaces with Ob/Gyn, cardiology, gastroenterology, immunology, pathology, pulmonary medicine, hematology-oncology, and surgery.

*New Programs* – Drs. Karumanchi, Friedman and Parikh are becoming increasingly closely affiliated with the multidisciplinary Center for Vascular Biology Research, and plan to move their laboratories into Research North with the Center. Dr. Alexander Goldfarb was recruited recently to bolster our care of end-stage renal disease patients, and to develop further our clinical research in this area.

## ● *Clinical Activities*

The Division's inpatient and outpatient activities encompass all aspects of renal disease diagnosis and management, including water and electrolyte disorders, acute and chronic kidney disease and the care of patients requiring hemodialysis, hemofiltration, home and in-center peritoneal dialysis, and renal or renal

and pancreas transplantation. In-house consultations are provided via the Consult service, the Dialysis service or the Transplant service.

As the Clinical Chief, Dr. Brown supervises the clinical program in nephrology and the fellowship program, and he serves as the Medical Director of the BIDMC Medical Specialties Clinic. He is also Co-Medical Director of the outpatient and inpatient dialysis units at BIDMC. A new clinic in preventive nephrology to vigorously address the needs of those with early-stage renal insufficiency has been established by Dr. John Danziger. Drs. Robert Stanton, John D'Elia, Melanie Hoenig, Bishan Roshan, and Williams, via their affiliation with the Joslin Clinic, have a particular interest in diabetic patients with renal disease. Dr. Williams also serves as Co-Director of Dialysis at BIDMC. Dr. Franklin Epstein has a particular interest in high-risk pregnancies and renal disease. Dr. Antoine 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.

## ● *Quality Improvement*

*Quality improvement in patient care* – The Division has initiated a Renal Dashboard to track its invasive procedures of central venous placement of hemodialysis catheters and renal biopsies, generally performed by fellows in training. The Dashboard allows us to review every procedure and analyze any complication sustained so as to consider changes in technique that may improve patient safety. So far, we have made several significant changes, which already appear to have resulted in fewer complications as we track our performance.

*Simulation procedures* – The Division is developing a program within the Simulation Center to systematize its instructional tech-

niques and to train new fellows in a simulated environment in the performance of central venous placement of dialysis catheters and renal biopsies. This program is expected to decrease unnecessary technical variation and to improve the safety of the training of new nephrology fellows to perform these invasive procedures for the first time. Real-time ultrasound is being added to dialysis catheter placement to improve the safety of this procedure as well.

*Clinical access and service* – In the first quarter of 2006, the average waiting time for a new patient appointment in nephrology was 14 days. In the second quarter of 2008, it is now 2.5 days.

### ● *Educational Programs*

The Division plays an active role in training fellows, residents and students. It has an enviable record in fellowship training. Since 1973, its 97 fellow graduates now include 70 academic physicians, of whom 17 are full professors, 14 associate professors, 23 assistant professors, 10 nephrology division chiefs, 2 vice-chairmen, and 3 associate deans.

During the first year, fellows spend time on the Consult, Dialysis and Transplant Services. The fellow sees patients and performs percutaneous kidney biopsies of native and transplant kidneys, places central venous catheters for dialysis, manages patients receiving continuous renal replacement therapies, peritoneal dialysis and hemodialysis, and learns to interpret renal pathology and radiology. The fellow cares for ambulatory patients in the weekly Nephrology Continuity Clinic throughout the year and participates in Transplant Clinic while on the Transplant Service. In the second year, the research-oriented fellows spend four weeks on the clinical service, remain in Continuity Clinic, take a second elective clinic, including outpatient hemodialysis and peritoneal dialysis clinics, and spend the remaining time in a research laboratory of their choice. The clinical fellow has a similar program except that only 4 months are in clinical research and the remaining 7 months on clinical rotations of their choosing.

A Distinguished Visiting Professor program has been initiated by Dr. Theodore 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 conferences with Dr. Burton Rose, pathology sessions with Dr. Isaac Stillman, a Monday series of conferences that include journal clubs, basic science and research, a clinical conference every Friday, weekly rounds with Dr. Zeidel, Epstein or Brown, and joint laboratory research conferences twice each month. In addition, Drs. Pavlakis and Didier Mandelbrot, in conjunction with the surgi-



● Nephrology Division

cal transplant team, hold weekly transplant & immunology conferences and Kidney/Pancreas intake conferences. There are also topic-oriented core curricular conferences held weekly and a joint Urology-Nephrology-Radiology-Pathology conference held every 3 months. Other faculty with major educational roles include: Drs. Cohen, Danziger, Goldfarb, Karumanchi, Friedman, Parikh, Mutter, D'Elia, Roshan, Williams, Stanton, Hoenig, Lecker, Williams and Steinman. 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*

<i>Research Funding • AY'07</i>	
Federal Direct .....	914,956
Federal Indirect .....	182,286
Other Direct .....	756,520
Other Indirect .....	33,583

Many of the Division's faculty members perform ground-breaking research in a wide variety of areas related to renal physiology and kidney disease.

*Ion and water transport* – The laboratories of Drs. Seth Alper, Zeidel, Warren Hill, Mathai

and Bryce MacIver and Epstein 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.

*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 novel anti-angiogenesis drug combinations for cancer therapy (Sukhatme). Dr. Karumanchi's research aims at understanding the pathophysiology of preeclampsia. A novel role for the orphan endothelial specific receptor Tie-1 in

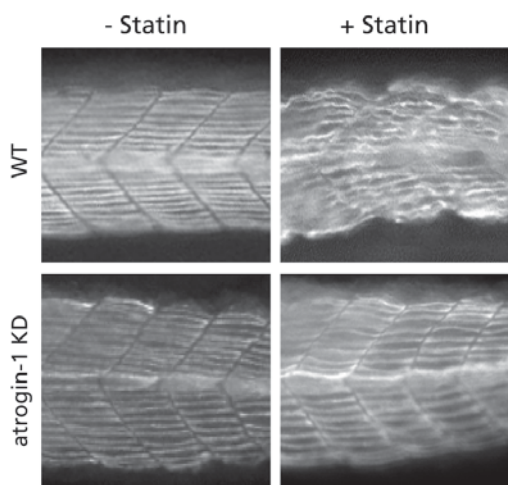
atherosclerosis has been elucidated (Chan and Sukhatme), as have downstream signaling pathways (Yuan, Karumanchi, Chan, and Sukhatme). Dr. Friedman's research focuses on the role of purinergic signaling (ectonucleotidases and purinergic receptors) in vascular disease. Using mouse models, he is investigating microvascular injury in diabetic nephropathy and large vessel disease in studies of arteriovenous fistula maturation and stenosis.

*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.

*Acute renal failure* – Dr. Parikh studies the biology of critical illness, focusing on endothelial molecular mechanisms that contribute to vascular leak. Additional studies in acute renal injury focus on a novel animal model of sepsis-induced ARF as well as a cohort study of acute renal failure patients at BIDMC.

*Chronic kidney disease and kidney hypoxia* – Dr. Epstein continues to investigate the degree of oxygenation of renal tissue in patients with chronic renal disease by magnetic resonance, that will test the hypothesis that hypoxia plays a key role in the progression of chronic renal failure.

*States of muscle atrophy* – Dr. Stewart 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. His work now focuses on the function



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 ● Atrogenin-1 mediates statin-induced muscle damage in zebrafish. Microscopic images of the muscle fibers in tails of zebrafish embryos show that those treated with lovastatin (top right) have muscle damage compared to untreated zebrafish (top left). In fish where atrogenin-1 has been knocked-down, the lovastatin did not cause as severe a defect.

of one of those genes, called atrogin-1. 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.

*Mineral ion homeostasis* – New efforts by Dr. Ogo Egbuna to understand mineral ion regulation by the calcium-sensing receptor independent of parathyroid hormone are under investigation, as are studies of the role of this receptor in immune cells.

*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 demonstrated.

*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. Alper 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.

*Diabetic nephropathy/ESRD clinical studies* – Ongoing trials include: the efficacy and safety of sulodexide on type 2 diabetics with overt proteinuria and renal insufficiency (Cohen and Williams), and an antibody to connective tissue growth factor in early diabetic nephropathy (Williams).

*Tolerance and rejection* – An understanding and clinical application of immune tolerance is the primary goal of the Strom laboratory. The balance of activated effector to regulatory cells can be manipulated through signals that are triggered by specially designed cytokine related Ig fusion proteins crafted in the Strom laboratory or through activation of select members of the T cell immunoglobulin family of proteins.

## ● Faculty

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

*Drug trials in renal transplantation* – Drs. Pavlakis, Mandelbrot, and Egbuna remain active in this area. Strategies to reduce calcineurin nephrotoxicity in renal transplant patients, the optimal management of hepato-renal patients, including liver transplantation, and IL-2 receptor blockade to prevent rejection of renal transplants are under investigation.

*Islet transplantation* – Islet Transplantation is at BIDMC as part of the Center for Islet Transplantation at Harvard Medical School. Dr. Pavlakis and colleagues are currently enrolling patients with diabetes who have received a kidney transplant.

*Anemia in renal failure* – Dr. Mutter is investigating the role of soluble erythropoietin receptor in the anemia of chronic kidney disease.

*Disparity in living kidney transplantation rates among African Americans*

– Drs. Egbuna, Mandelbrot and Pavlakis are involved in an NIH sponsored trial to reduce the rates of disparity in African Americans.

● *Selected Publications*

Charytan DM, Albich WC, Brown RS. Make your diagnosis: A pregnant woman with hyponatremia. *Kidney Intern* 2007; 72:1167-1169.

Clark JS, Vandorpe DH, Chernova MN, Heneghan JF, Stewart AK, Alper SL. Species differences in Cl<sup>-</sup> affinity and in electrogenicity of SLC26A6-mediated oxalate/Cl<sup>-</sup> exchange correlate with the distinct human and mouse susceptibilities to nephrolithiasis. *J Physiol* 2008; 586:1291-306.

Epstein, FH. Atlantic City Memories. *J Clin Invest* 2008; 118:1222-1223.

Goldfarb-Rumyantzev AS, Habib AN, Baird BC, Barenbaum LL, Cheung AK: The association of lipid-modifying medications with mortality in patients on long-term peritoneal dialysis. *Am J Kidney Dis* 2007; 50:791-802.

Mandelbrot DA, Pavlakis M, Danovitch GM, Johnson SR, Karp SJ, Khwaja K, Hanto DW, Rodrigue JR. The Medical Evaluation of Living Kidney Donors: A Survey of US Transplant Centers. *Am J Transplant* 2007; 7:2333-43.

Mathai JC, Tristram-Nagle S, Nagle JF, Zeidel ML. Structural determinants of water permeability through the lipid membrane. *J Gen Physiol* 2008; 131:69-76.

Nagle JF, Mathai JC, Zeidel ML, Tristram-Nagle S. Theory of passive permeability through lipid bilayers. *J Gen Physiol* 2008; 131:77-85.

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

Xu C, Rossetti S, Jiang L, Harris PC, Brown-Glaberman U, Wandinger-Ness A, Bacallao R, Alper SL. Human ADPKD primary cyst epithelial cells with a novel, single codon deletion in the PKD1 gene exhibit defective ciliary polycystin localization and loss of flow-induced Ca<sup>2+</sup> signaling. *Am J Physiol Renal Physiol* 2007; 292:F930-45.

Yuan HT, Shivalingappa V, Chan B, Deutsch U, Mammoto T, Sukhatme VP, Woolf AS, Karumanchi SA. Activation of the orphan endothelial receptor tie1 modifies tie2 mediated intracellular signaling and cell survival. *FASEB J* 2007; 21:3171-83.