

Division of Nephrology



Vikas P.
Sukhatme, MD, PhD,
Chief

● *Overview*

The Nephrology Division's activities are organized under the leadership of Dr. Sukhatme, 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. The Division has research and clinical interfaces with Ob-Gyn, cardiology, gastroenterology, immunology, pathology, pulmonary medicine, hematology-oncology, and surgery. New faculty added over the last year include Drs. Parikh, Egbuna, Mutter, Danziger, and Friedman. They have added new research dimensions and begun new clinical initiatives in the division as detailed below.

● *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 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 (Danziger). The largest clinic practices are those of Drs. Cohen, Danziger, D'Elia, Hoenig, Epstein, Lecker, Pavlakis, Mandelbrot, Roshan, Stanton, Steinman and Williams. Drs. Stanton, D'Elia, Hoenig, 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. Epstein has a particular interest in high-risk pregnancies and renal disease. Dr. Kaldany has developed a number of ESRD programs abroad, especially in the Middle East.

● *Quality Improvement*

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 first quarter of 2007, it was four days. In addition, our office staff has improved their customer service skills, registration skills, and customer service ratings from considerably less than perfect scores to perfect scores of 100%, 100% and 5.0 respectively.

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 we hope will translate into fewer preventable complications which we can assess as we track the future results.

Simulation procedures – The Division is developing a program within the Simulation Center to systematize its instructional techniques 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.

● *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 91 fellow graduates now include 68 academic physicians, of which 14 are full professors, 14 associate professors, 23 assistant professors, 9 nephrology division chiefs, 2 vice-chairmen, and 3 associate deans.



●
● Dr. Danziger and Lisa Dumouchel, NP discuss a patient while in Medical Specialties.

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 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 the Transplant Clinic while on the Transplant Service, and the Peritoneal Dialysis Clinic while on the Dialysis Service. In the second year, the

research-oriented fellows spend four weeks on the clinical service and the remaining time in a research laboratory of their choice.

A broad array of didactic activities have been organized. These include conferences with Dr. Rose, pathology sessions with Dr. Stillman, a Monday series of conferences that include journal clubs, basic science and research, a clinical conference every Friday, weekly rounds with Dr. Sukhatme, Epstein or Brown, and joint laboratory research conferences twice each month. In addition, Drs. Pavlakis and Mandelbrot, in conjunction with the surgical transplant team, hold weekly transplant and immunology conferences and kidney/pancreas intake conferences. Other faculty with major educational roles include: Cohen, Roshan, Danziger, Stanton, Hoenig, Lecker, Williams and Steinman. A "Distinguished Visiting Professors" program designed to expose faculty and fellows to world leaders in Nephrology has been initiated.

● *Research Activities*

These activities encompass a wide array of both basic and translational investigations with studies that include patients with renal disease, normal volunteers, animal models and cultured cells. Research categories include: physiology and treatment of acute renal failure, molecular mechanisms of cell injury and cell metabolism, ion transport and water excretion, cellular transduction mechanisms, mechanisms of muscle wasting and intracellular protein breakdown, preeclampsia, glomerular pathology, the cellular immunology of organ transplantation, autoimmune disorders, mammalian gene regulation, kidney cancer, endothelial biology, tumor angiogenesis, vascular leak, atherogenesis, diabetic nephropathy and fibrosis.

Ion and water transport – The laboratories of Drs. Alper, Zeidel, Hill, Mathai, MacIver and Epstein are active in this area, with studies on: the molecular physiology of bicarbonate transport in cell pH and volume regulation; cell biology of urothelium; potassium homeostasis in red cell hemoglobinopathies and in secretory epithelia; how water, protons and small non-electrolytes cross biological membranes; how intracellular

Research Funding • AY'07

Federal Direct.....	1,511,349
Federal Indirect.....	655,165
Other Direct.....	650,167
Other Indirect.....	48,972

signaling pathways modulate the secretion of chloride by rectal glands of elasmobranchs.

Vascular biology – endothelial specific genes, preeclampsia, vascular leak, tumor angiogenesis, purinergic signaling. Dr. Sukhatme's research efforts aim at understanding the molecular, cellular, and network mechanisms that govern small and large vessel formation during development and relating these findings to human diseases characterized by abnormal vessel formation or function or an altered systemic angiogenic state. Zebrafish are being used to discover novel genes critical in vessel development. Sukhatme and Parikh are 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). 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 – 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.

Acute renal failure, 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. Dr. Parikh has initiated studies on markers and mechanisms in acute renal failure.

States of muscle atrophy – Dr. Lecker's research explores the molecular mechanisms behind the muscle wasting which occurs in uremia and other illnesses such as cancer, sepsis and diabetes. Dr. Lecker's studies have identified a group of "atrogenes" that are coordinately regulated during wasting. A collaboration with Drs. Hanai and Sukhatme has shed new light into the mechanisms of statin induced myopathy.

Mineral ion homeostasis – New efforts by Dr. 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 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



- A snapshot from MD simulation of AQP1/H2O system. Only one monomer of the water channel is shown for clarity. Note the single file arrangement of water molecules inside the channel.

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.

Diabetic nephropathy/ESRD clinical studies – Ongoing trials include: prevention of catheter related infections and the use of long-lasting RBC stimulating agents (Brown), the efficacy and safety of sulodexide on type 2 diabetics with overt proteinuria and renal insufficiency (Cohen and Williams), and the utility of 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.

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.

● Awards and Honors

Dr. Seth Alper was an invited speaker at the Frontiers in Epithelial Transport (Phys Soc), Manchester, UK and at the Satellite Symposium of the 7th Annual Meeting of the German Neuroscience Society, Gottingen, Germany. He delivered the Robert W. Schrier Endowed Lectureship at the Annual Meeting of the American Society of Nephrology, San Diego, CA. Dr. George Bayliss was awarded the George Altman, MD and Harriet Altman Annual Nephrology Traveling Fellowship

● Faculty

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

given in Dr. Ted Steinman's honor. Dr. Gabor Bodonyi-Kovacs received an Amgen Nephrology Fellowship Award. Dr. Ogo Egbuna received an NIH-NIDDK career development award, and the Pfizer-Merck-HST Clinical Investigator training program award. Dr. Franklin Epstein received the Edward W. Gibbs award of the New York Academy of Sciences. Dr. S. Ananth Karumanchi received the Preeclampsia foundation's Hope Award, the American Society of Hypertension's Young Scholar Award, and was inducted into the American Society of Clinical Investigation. Dr. Walter Mutter was selected to speak at the 2006 Brigham and Women's Hospital and Harvard Medical School Nephrology Fellows Research Forum. Dr. Terry Strom received the 2006 Homer Smith Award by the American Society of Nephrology. Dr. Vikas P. Sukhatme was appointed the first Chief, Division of Interdisciplinary Medicine and Biotechnology, Beth Israel Deaconess Medical Center and Vice-Chair of Medicine for Interdepartmental and Translational Programs, Beth Israel Deaconess Medical Center. Dr. Mark Williams presented "Complex World of Diabetic ESRD" at the Trans-Atlantic Renal Council Annual Meeting, Newark, N.J.

● *Selected Publications*

- Deaglio S, Dwyer KM, Gao W, Friedman D, Usheva A, Erat A, Chen JF, Enjyoji K, Linden J, Oukka M, Kuchroo VK, Strom TB, Robson SC. Adenosine generation catalyzed by CD39 and CD73 expressed on regulatory T cells mediates immune suppression. *J Exp Med* 2007; 204:1257-65.
- Friedman DJ, Rennke HG, Csizmadia E, Enjyoji K, Robson SC. The vascular ectonucleotidase ENTPD1 is a novel renoprotective factor in diabetic nephropathy. *Diabetes* 2007 [Epub ahead of print].
- Gensure RH, Zeidel ML, Hill WG. Lipid raft components cholesterol and sphingomyelin, increase H⁺/OH⁻ permeability of phosphatidylcholine membranes. *Biochem J* 2006; 398:485-495.
- Leopold JA, Dam A, Scribner AW, Liao R, Diane E, Handy DE, Stanton RC, Pitt B, Loscalzo J. Aldosterone impairs vascular reactivity by decreasing glucose-6-phosphate dehydrogenase activity. *Nature Med* 2007; 13:189-197.
- Levine RJ, Lam C, Qian C, Yu K, Maynard SE, Sachs BP, Sibai B, Epstein FH, Romero R, Thadhani R, Karumanchi SA. Soluble endoglin and other angiogenic factors in preeclampsia. *N Engl J Med* 2006; 355:992-1005.
- Mamonov AB, Coalson RD, Zeidel ML, Mathai JC. Water and deuterium oxide permeability through aquaporin 1: MD predictions and experimental verification. *J Gen Physiol* 2007; 130:111-116.
- Patlolla V, Zhong X, Reed G, Mandelbrot DA. Efficacy of anti-IL-2 receptor antibodies compared to no induction and to antilymphocyte antibodies in renal transplantation. *Am J Transplantation* 2007; 7:1832-1841.
- Venkatesha S, Toporsian M, Lam C, Mammoto T, Kim YM, Bdoiah Y, Lim KH, Yuan HT, Libermann TA, Stillman IE, Roberts D, D'Amore PA, Epstein FH, Sellke F, Romero R, Sukhatme VP, Letarte M, Karumanchi SA. Soluble endoglin contributes to the pathogenesis of preeclampsia. *Nature Med* 2006; 12:642-49.
- Williams ME, Lacson E Jr, Teng M, Ofsthun N, Lazarus JM. Hemodialyzed type 1 and type 2 diabetic patients in the U.S.: Characteristics, glycemic control, and survival. *Kidney Int* 2006; 70:1503-9.
- 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 Ca²⁺ signaling. *Am J Physiol Renal Physiol* 2007; 292:F930-45.