Nephrology and Hypertension

Division Photo

First row: M. Lo, R. Malatesta, E. Jackson, P. Devarajan, K. Czech, M. Mitsnefes, L. Patterson. Back row: J. Bissler, J. Goebel, C.F. Strife, D. Hooper, B. Laskin, E. Nehus. Not pictured: B. Dixon and E. Abraham.

Division Data Summary

Research and Training Details	
Number of Faculty	9
Number of Joint Appointment Faculty	1
Number of Research Fellows	6
Number of Support Personnel	15
Direct Annual Grant Support	$1,012,587
Direct Annual Industry Support	$115,487
Peer Reviewed Publications	29

Clinical Activities and Training	
Number of Clinical Staff	27
Number of Clinical Fellows	6
Number of Other Students	6
Inpatient Encounters	4,614
Outpatient Encounters	4,190

Significant Publications

Dixon BP, Lu L, Chu A, Bissler JJ. RecQ and RecG helicases have distinct roles in maintaining the stability of polypurine.polypyrimidine sequences. Mutat Res 2008;643:20-8.

This is the first study to reveal that helicase activity can greatly modify DNA replication fidelity and that such helicases may be involved in human diseases.

Weaver DJ, Kimball TR, Witt SA, Glascock BJ, Khoury PR, Kartal J, Mitsnefes MM. Sub-clinical systolic dysfunction in pediatric patients with chronic kidney disease. J Pediatrics 2008;153:565-9.

This is the first study to demonstrate the presence of sub-clinical systolic dysfunction in children with chronic kidney

disease.

Abraham EC, Wilson AC, Goebel J. Current kidney allocation rules and their impact on a pediatric transplant center. Am J Transplant 2009;9:404-8.

This is the first study to demonstrate the effects of changes in kidney allocation rules in the United States on pediatric transplant recipients.

Brunskill EW, Aronow BJ, Georgas K, Rumballe B, Valerius MT, Aronow J, Kaimal V, Jegga AG, Yu J, Grimmond S, McMahon AP, Patterson LT, Little MH, Potter SS. Atlas of gene expression in the developing kidney at microanatomic resolution. Dev Cell 2008;15:781-91.

This is the first study to describe a comprehensive gene expression atlas of the developing kidney.

Haase M, Haase-Fielitz A, Bellomo R, Devarajan P, Story D, Matalanis G, Reade MC, Bagshaw SM, Seevanayagam N, Seevanayagam S, Doolan L, Buxton B, Dragun D. Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery: a pilot double-blind, randomized controlled trial. Crit Care Med 2009;37:39-47.

This is the first study to demonstrate the utility of sodium bicarbonate as a reno-protective agent after cardiac surgery, and the utility of the novel biomarker NGAL to assess early responses to treatment of acute kidney injury.

Division Highlights

Bradley Dixon, MD

Understanding the risk of cancer after bladder reconstruction surgeries:
Children born with abnormal urinary tracts often also develop chronic kidney damage early in life. These children may require reconstructive surgery of their small, stiff-walled bladders before they can receive a kidney transplant to prevent damage to the new kidney. Bladders that have been reconstructed are at a higher risk for developing cancer later in a patient's life. Dr. Bradley Dixon, Assistant Professor of Nephrology at CCHMC, is studying the possible reasons for this increased risk of cancer. His research has shown that high concentrations of waste products such as urea in the urine may prevent the reconstructed bladder from recognizing that its genetic code may have been damaged, leading to cancer development.

Kimberly Czech, MD, PhD

Understanding the mechanisms of kidney failure in children with nephrotic syndrome:
Children with nephrotic syndrome caused by a disease called focal segmental glomerulosclerosis (FSGS) are at high risk for developing kidney failure. To better understand this disease, Dr. Kimberley Czech, Assistant Professor of Nephrology at CCHMC, is exploring the mechanisms of disease progression. Using microarray methods, she has determined which genes are turned on or off in FSGS. Currently, she is employing proteomic techniques to determine what specific proteins are lost in the urine of children with FSGS. The results will lead to improved diagnostic tools and treatments.

Larry Patterson, MD

A new understanding of how a kidney stops growing:
The kidney develops by branching and growth at the tips of the branches. The length of time that branching continues before it ends determines ultimate kidney size and function. A research team lead by Larry Patterson, MD, Associate Professor of Nephrology at CCHMC, has shown that a shift in the balance of cell fates causes the end of kidney development. This shift in fates favors differentiation over maintenance of kidney stem cells leading to exhaustion of the stem cell pool and loss of any potential for further renal growth. Dr. Patterson is exploring how to manipulate this shift in balance, which could enable us to promote kidney growth and function when its development goes awry.

John Bissler, MD

A transplant drug stops the growth of kidney tumors:
The basic cellular pathway that is disrupted in kidney and lung tumors of the tuberous sclerosis complex and a sporadic disease called lymphangioleiomyomatosis is the same pathway that is suppressed by the transplant drugs sirolimus and everolimus. A research team led by Dr. John Bissler, the Clark D. West Endowed Chair and Professor of Nephrology at CCHMC, demonstrated that sirolimus reduced the volume of renal tumors and improved the lung manifestations in patients with lymphangioleiomyomatosis. Following up on these studies, Dr. Bissler has an ongoing clinical trial examining different dosing regimes of sirolimus to optimize the effectiveness while reducing side effects. Dr. Bissler has also partnered with industry to launch a placebo controlled clinical trial that, if successful, will be used to support the FDA approval of everolimus in tuberous sclerosis patients. At the bench, the Bissler Laboratory is

conducting pre-clinical trials using human angiomyolipoma cells to see if there are better combination drug approaches to treat this devastating disease, and working with different tuberous sclerosis complex-related renal cystic disease models to understand better how cells go from normal renal structures to cysts and cancers.

Division Collaboration

Collaboration with Developmental Biology;

Collaborating Faculty: A. Kuan;

Co-investigator for study entitled "Global gene expression atlas of the developing kidney"

Co-investigator for study entitled "Glomerulosclerosis in human FSAs and mouse models"

Co-investigator for study entitled "Implications of JNK pathways in renal IRI"

Collaboration with Clinical Pharmacology

Collaborating Faculty: A. Vinks

Co-investigator for study entitled "Pharmacogenetics of mycophenolic acid in kidney transplant patients"

Collaboration with Rheumatology

Collaborating Faculty: H. Brunner

Co-investigator for study "Early prediction of Lupus Nephritis using advanced proteomics"

Collaboration with Cardiology

Collaborating Faculty: C. Krawczeski

Co-investigator for study entitled "Novel biomarkers for acute renal failure"

Co-investigator for study entitled "Adioponectin and Cardiovascular disease in the CKID children"

Collaboration with Epidemiology and Biostats

Collaborating Faculty: S. Salsbury; L. Martin

Co-investigator on Tuberous Sclerosis Complex natural history study

Co-investigator for study entitled "Adioponectin and Cardiovascular disease in the CKID children"

Collaboration with Interventional Radiology

Collaborating Faculty: J. Wansapura

Co-investigator on Tuberous Sclerosis Complex natural history study

Collaboration with Bioinformatics

Collaborating Faculty: M. Wagner

Co-investigator for study entitled "Early prediction of Lupus Nephritis using advanced proteomics"

Collaboration with Preventive Cardiology

Collaborating Faculty: E. Urbina

Co-investigator for study entitled "Modifying dietary behavior in adolescents with elevated blood pressure"

Faculty Members

Prasad Devarajan, MD, Professor

John J. Bissler, MD, Professor

Kimberly Czech, MD, PhD, Instructor

Bradley P. Dixon, MD, Assistant Professor

Jens Goebel, MD, Associate Professor Clinical

Elizabeth Jackson, MD, Associate Professor Clinical

Paul McEnery, MD, Professor Emeritus

Mark Mitsnefes, MD, Associate Professor Clinical

Larry Patterson, MD, Research Associate Professor

C. Frederic Strife, MD, Professor

Trainees

- **Donald Weaver, MD,** PL-3,
- **Amy Wilson, MD,** PL-3,
- **David Hooper, MD,** PL-2,
- **Elizabeth Abraham, MD,** PL-2,
- **Benjamin Laskin, MD,** PL-1,
- **Megan Lo, MD,** PL-1,

Significant Accomplishments

A simple new lab test predicts acute kidney failure and its clinical consequences

About 4 million people die of acute kidney failure each year. They die primarily because the current diagnosis of acute kidney failure is woefully delayed, crippling our ability to institute potentially effective therapies in a timely manner. A research team led by Dr. Prasad Devarajan, the Louise M. Williams Endowed Chair, Professor and Director of Nephrology at CCHMC, has identified a new biomarker called neutrophil gelatinase-associated lipocalin (NGAL), which appears in the urine and blood of patients up to three days before the current tests for acute kidney failure become positive. Dr. Devarajan's team has validated the biomarker in a wide variety of pediatric and adult patient populations, including those undergoing heart surgery, kidney transplantation, sepsis, nephrotoxic agents, subjects admitted to intensive care units, and even patients randomly presenting to the emergency room. In these patients, early NGAL measurements also predict long-term clinical outcomes such as dialysis requirement, length of hospital stay, and death. In addition, Dr. Devarajan has partnered with industry collaborators to design standardized clinical laboratory-based point-of-care kits that can measure NGAL in a drop of urine or blood and provide quantitative results in 30 minutes or less. These simple new tests have already been launched worldwide, and will also become available in the US within the next year. The availability of an early biomarker like NGAL could revolutionize medical care and save lives, by providing clinicians with a desperately needed tool for predicting acute kidney failure in hospitalized and ambulatory subjects, allowing for accurate risk assessment, optimizing resource utilization, providing timely therapies, monitoring the response to therapies, and providing a kidney safety marker for future drug development.

A new way to personalize immunosuppression management

Mycophenolate mofetil (MMF), a commonly used anti-rejection medication, is associated with gastrointestinal and hematological toxicity. Reducing the dosage may minimize toxicity but can also increase the risk of transplant rejection. To understand how to use MMF more effectively, Jens Goebel, MD, medical director of kidney transplantation, is leading a multi-center collaborative project that builds on pilot work demonstrating an association between genetic variants in the main MMF-metabolizing enzyme uridine glucuronyl transferase and the risk of MMF-associated toxicity. Ultimately, researchers expect these efforts to allow prediction of individual patients' responses to MMF and prospective personalization of drug dosing to avoid toxicity.

Getting to the heart of the matter in chronic kidney disease

Heart disease is the 2nd leading cause of death among children with kidney failure. A research team led by Mark Mitsnefes, MD, Associate Professor of Nephrology at CCHMC, has shown that early markers of cardiovascular disease such as left ventricular hypertrophy and increased thickness of carotid artery, are already apparent at early stages of kidney insufficiency in children. Currently, Dr. Mitsnefes is leading a multi-center effort to better understand the development of cardiovascular abnormalities in children with chronic kidney disease. Ultimately, researchers expect that identifying risk factors associated with cardiac and vascular problems will allow them to treat and prevent these conditions in children with chronic kidney disease.

Division Publications

1. Schmithorst VJ, Altes TA, Young LR, Franz DN, Bissler JJ, McCormack FX, Dardzinski BJ, Brody AS. **Automated algorithm for quantifying the extent of cystic change on volumetric chest CT: initial results in Lymphangioleiomyomatosis.** *AJR Am J Roentgenol.* 2009; 192: 1037-44.
2. Abraham EC, Wilson AC, Goebel J. **Current kidney allocation rules and their impact on a pediatric transplant center.** *Am J Transplant.* 2009; 9: 404-8.
3. Haase-Fielitz A, Bellomo R, Devarajan P, Story D, Matalanis G, Dragun D, Haase M. **Novel and conventional serum biomarkers predicting acute kidney injury in adult cardiac surgery--a prospective cohort study.** *Crit Care Med.* 2009; 37: 553-60.

4. Nyakeriga AM, Fichtenbaum CJ, Goebel J, Nicolaou SA, Conforti L, Chougnet CA. Engagement of the CD4 receptor affects the redistribution of Lck to the immunological synapse in primary T cells: implications for T-cell activation during human immunodeficiency virus type 1 infection. *J Virol.* 2009; 83: 1193-200.
5. Haase M, Haase-Fielitz A, Bellomo R, Devarajan P, Story D, Matalanis G, Reade MC, Bagshaw SM, Seevanayagam N, Seevanayagam S, Doolan L, Buxton B, Dragun D. Sodium bicarbonate to prevent increases in serum creatinine after cardiac surgery: a pilot double-blind, randomized controlled trial. *Crit Care Med.* 2009; 37: 39-47.
6. Sise ME, Barasch J, Devarajan P, Nickolas TL. Elevated urine neutrophil gelatinase-associated lipocalin can diagnose acute kidney injury in patients with chronic kidney diseases. *Kidney Int.* 2009; 75: 115-6; author reply 116.
7. Devarajan P. The strong silent type: the distal tubule to the rescue. *Crit Care Med.* 2009; 37: 2129-30.
8. Lu JC, Coca SG, Patel UD, Cantley L, Parikh CR, Edelstein C, Devarajan P, Garg A, Shlipak M, Zappatelli M, Murray P, Koyner J, Swaminathan M, Dent C, Wang Z. Searching for genes that matter in acute kidney injury: a systematic review. *Clin J Am Soc Nephrol.* 2009; 4: 1020-31.
9. Siroky BJ, Czyzyk-Krzeska MF, Bissler JJ. Renal involvement in tuberous sclerosis complex and von Hippel-Lindau disease: shared disease mechanisms? *Nat Clin Pract Nephrol.* 2009; 5: 143-56.
10. Weaver DJ, Jr., Kimball TR, Koury PR, Mitsnefes MM. Cardiac output and associated left ventricular hypertrophy in pediatric chronic kidney disease. *Pediatr Nephrol.* 2009; 24: 565-70.
11. Jackson EC. Nocturnal enuresis: giving the child a "lift". *J Pediatr.* 2009; 154: 636-7.
12. Prausa SE, Fukuda T, Maseck D, Curtsinger KL, Liu C, Zhang K, Nick TG, Sherbotie JR, Ellis EN, Goebel J, Vinks AA. UGT genotype may contribute to adverse events following medication with mycophenolate mofetil in pediatric kidney transplant recipients. *Clin Pharmacol Ther.* 2009; 85: 495-500.
13. Bennett MR, Ravipati N, Ross G, Nguyen MT, Hirsch R, Beekman RH, Rovner L, Devarajan P. Using proteomics to identify preprocedural risk factors for contrast induced nephropathy. *Proteomics Clin Appl.* 2008; 2: 1058-1064.
14. Devarajan P. Neutrophil gelatinase-associated lipocalin (NGAL): a new marker of kidney disease. *Scand J Clin Lab Invest Suppl.* 2008; 241: 89-94.
15. Ma Q, Devarajan P. Induction of proapoptotic Daxx following ischemic acute kidney injury. *Kidney Int.* 2008; 74: 310-8.
16. Nguyen MT, Dent CL, Ross GF, Harris N, Manning PB, Mitsnefes MM, Devarajan P. Urinary aprotinin as a predictor of acute kidney injury after cardiac surgery in children receiving aprotinin therapy. *Pediatr Nephrol.* 2008; 23: 1317-26.
17. Dixon BP, Lu L, Chu A, Bissler JJ. RecQ and RecG helicases have distinct roles in maintaining the stability of polypurine.polypyrimidine sequences. *Mutat Res.* 2008; 643: 20-8.
18. Devarajan P. Neutrophil gelatinase-associated lipocalin--an emerging troponin for kidney injury. *Nephrol Dial Transplant.* 2008; 23: 3737-43.
19. Goldstein SL, Devarajan P. Progression from acute kidney injury to chronic kidney disease: a pediatric perspective. *Adv Chronic Kidney Dis.* 2008; 15: 278-83.
20. Lewis AG, Kohl G, Ma Q, Devarajan P, Kohl J. Pharmacological targeting of C5a receptors during organ preservation improves kidney graft survival. *Clin Exp Immunol.* 2008; 153: 117-26.
21. Brunskill EW, Aronow BJ, Georgas K, Rumballe B, Valerius MT, Aronow J, Kaimal V, Jegga AG, Yu J, Grimmond S, McMahon AP, Patterson LT, Little MH, Potter SS. Atlas of gene expression in the developing kidney at microanatomic resolution. *Dev Cell.* 2008; 15: 781-91.
22. Stabach PR, Devarajan P, Stankewich MC, Bannykh S, Morrow JS. Ankyrin facilitates intracellular trafficking of alpha1-Na+-K+-ATPase in polarized cells. *Am J Physiol Cell Physiol.* 2008; 295: C1202-14.
23. Koyner JL, Bennett MR, Worcester EM, Ma Q, Raman J, Jeevanandam V, Kasza KE, O'Connor MF, Konczal DJ, Trevino S, Devarajan P, Murray PT. Urinary cystatin C as an early biomarker of acute kidney injury following adult cardiothoracic surgery. *Kidney Int.* 2008; 74: 1059-69.
24. Lavery AP, Meinzen-Derr JK, Anderson E, Ma Q, Bennett MR, Devarajan P, Schibler KR. Urinary NGAL in premature infants. *Pediatr Res.* 2008; 64: 423-8.
25. Weaver DJ, Jr., Kimball T, Witt SA, Glascock BJ, Khoury PR, Kartal J, Mitsnefes MM. Subclinical systolic dysfunction in pediatric patients with chronic kidney disease. *J Pediatr.* 2008; 153: 565-9.
26. West CD, Bissler JJ. Nephritic factor and recurrence in the renal transplant of membranoproliferative glomerulonephritis type II. *Pediatr Nephrol.* 2008; 23: 1867-76.
27. Calvo-Garcia MA, Campbell KM, O'Hara SM, Khoury P, Mitsnefes MM, Strife CF. Acquired renal cysts after pediatric liver transplantation: association with cyclosporine and renal dysfunction. *Pediatr Transplant.* 2008;

12: 666-71.

28. Devarajan P. The future of pediatric acute kidney injury management--biomarkers. *Semin Nephrol.* 2008; 28: 493-8.
29. Devarajan P. NGAL in acute kidney injury: from serendipity to utility. *Am J Kidney Dis.* 2008; 52: 395-9.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards — Annual Direct / Project Period Direct

BISSLER, J

Tuberous Sclerosis Complex Natural History Study
Department of Defense - Army
W81XWH-06-1-0538 — 05/01/06 - 04/30/11 — $45,529 / $595,828

CZECH, K

Altered Gene Expression using Microarray in Focal Segmental Glomerulosclerosis
National Institutes of Health
F32 DK 079545 — 07/01/07 - 06/30/10 — $58,886 / $176,658

DEVARAJAN, P

Implications of the Ask1/Jnk Pathway in Arf
National Institutes of Health
R01 DK 069749 — 04/01/05 - 03/31/10 — $204,428 / $1,100,000

Early Prediction of Lupus Nephritis Using Advanced Proteins
Department of Defense - Army
W81XWH-07-1-0322 — 06/01/07 - 05/31/10 — $211,400 / $621,759

Research Training in Pediatric Nephrology
National Institutes of Health
T32 DK 007695 — 07/01/07 - 06/30/12 — $118,884 / $574,980

Novel Biomarkers in Cardiac Surgery to Detect Acute Kidney Injury
National Institutes of Health (Yale University School of Medicine)
R01 HL 085757 — 05/01/07 - 03/31/12 — $70,000 / $369,103

Ancillary Studies in the Natural History of Acute Kidney
National Institutes of Health (Yale University School of Medicine)
U01 DK 082185 — 09/01/08 - 06/30/13 — $17,962 / $92,004

GOEBEL, J

Noninvasive Markers and Transplant Outcome in Humans
National Institutes of Health (Mt. Sinai Medical Center)
U01 AI 063594 — 09/01/05 - 08/31/09 — $15,585 / $57,889

Health and Literacy in Child and Adult Assessment-Pediatrics
National Institutes of Health (University of North Carolina)
08/01/08 - 07/31/09 — $2,649 / $2,649

Chronic Renal Insufficiency in NAPRTCS Patients
National Institutes of Health (Children's Mercy Hospital-Kansas City)
U01 DK 066143 — 08/01/04 - 07/31/08 — $39,310 / $39,310

HOOPER, D

Prospective Individualized Dosing of Mycophenolate Mofetil
Kidney Foundation of Greater Cincinnati
07/01/08 - 06/30/09 — $10,000 / $10,000

MITSNEFES, M

Adioponectin and Cardiovascular Disease in the CKiD Children
National Institutes of Health
R01 DK 076957 — 09/01/07 - 08/31/10 — $172,500 / $525,000

SIROKY, B

The Role of Primary Cilia in Regulating Mammalian Target
PKD Foundation

07/01/08 - 06/30/10 $45,454 / $45,454

Current Year Direct **$ 1,012,587**

Industry Contracts

BISSLER, J
Novartis Pharmaceuticals $ 106,268

DEVARAJAN, P
Thrasos, Inc. $ 9,219

Current Year Direct Receipts **$ 115,487**

Total $1,128,074