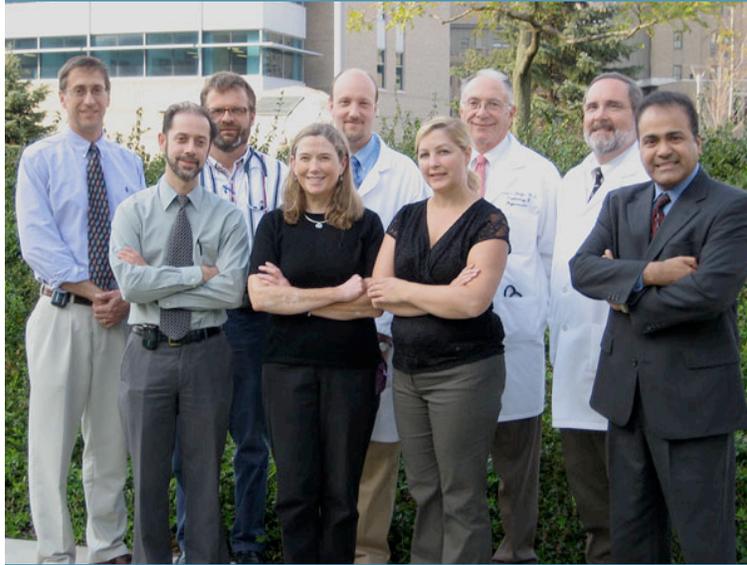


Nephrology and Hypertension

Division Photo



Back Row: L Patterson, J Goebel, B Dixon, C.F. Strife, J Bissler; **Front Row:** M Mitsnefes, E Jackson, K Czech, P Devarajan

Division Data Summary

Research and Training Details

Number of Faculty	9
Number of Research Fellows	2
Number of Research Students	5
Number of Support Personnel	13
Direct Annual Grant Support	\$1,206,219
Direct Annual Industry Support	\$89,941
Peer Reviewed Publications	37

Clinical Activities and Training

Number of Clinical Staff	3
Number of Clinical Fellows	6
Inpatient Encounters	2766
Outpatient Encounters	3350

Faculty Members

- Prasad Devarajan, MD**, Professor
- John J. Bissler, MD**, Associate Professor
- Bradley P. Dixon, MD**, Research Instructor
- Jens Goebel, MD**, Associate Professor Clinical
- Elizabeth Jackson, MD**, Associate Professor Clinical
- Mark Mitsnefes, MD**, Associate Professor Clinical

Larry Patterson, MD, Research Associate Professor

C. Frederic Strife, MD, Professor

Kamyar Zahedi, MD, Research Assistant Professor

Trainees

- Hsaio Lai, MD, PGY-3,
- Kimberly Czech, MD, PhD, PGY-3,
- Donald Weaver, MD, PGY-2,
- Amy Wilson, MD, PGY-2,
- David Hooper, MD, PGY-1,
- Elizabeth Abraham, MD, PGY-1,

Significant Accomplishments in FY08

Nephrology and Hypertension -- Research Highlights

A simple new lab test predicts acute kidney failure: 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, radio-contrast administration, sepsis, nephrotoxic medications, subjects admitted to intensive care units, and even patients randomly presenting to the emergency room. Their results have recently been published in prestigious medical journals such as *Lancet* and *Annals of Internal Medicine*. 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. It is anticipated that these simple new tests will become widely accessible to the medical community 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 transplant drug proves effective in treating kidney tumors: One goal of medical research is to understand disease mechanisms in order to develop new and more effective treatments. This was true for the kidney and lung manifestations of tuberous sclerosis complex and a sporadic disease called lymphangioleiomyomatosis. The cell-signaling pathway that is disrupted in both these diseases is the same pathway that is suppressed by the transplant drug called sirolimus. A research team led by Dr. John Bissler, the Clark D. West Endowed Chair in Nephrology at CCHMC, conducted a study to determine whether sirolimus had any effect on the kidney tumors called angiomyolipomas and the lung manifestation called lymphangioleiomyomatosis found in both diseases. After one year of treatment with sirolimus, the average size of angiomyolipomas was reduced by nearly 50 percent in patients. Sirolimus also improved lung function in the lymphangioleiomyomatosis patients. These results have recently been published in *New England Journal of Medicine*. Dr. Bissler is now conducting a study to identify an optimum dosing schedule for this strategy, to understand the mechanisms of this response, and to identify biomarkers that predict the best response. Research in Dr. Bissler's laboratory is also looking at drug combinations to further optimize the treatment of these patients.

Significant Publications in FY08

Bennett M, Dent CL, Ma Q, Dastrala S, Grenier F, Workman R, Syed H, Ali S, Barasch J, Devarajan P. Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study. *Clin J Am Soc Nephrol*. 2008 May;3(3):665-73.

This is the first study to validate a standardized laboratory platform for the measurement of a novel sensitive biomarker of acute kidney injury.

Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, Schmithorst VJ, Laor T, Brody AS, Bean J, Salisbury S, Franz DN. Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangioleiomyomatosis. N Engl J Med. 2008 Jan 10;358(2):140-51.

This is the first study to demonstrate the efficacy of a new treatment regimen for angiomyolipomas.

Devarajan P, Parikh C, Barasch J. Case 31-2007: a man with abdominal pain and elevated creatinine. N Engl J Med. 2008 Jan 17;358(3):312; author reply 3.

This is the first elucidation of a novel concept of using emerging biomarkers for the diagnosis and outcomes of acute kidney injury.

Nickolas TL, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, Buchen C, Khan F, Mori K, Giglio J, Devarajan P, Barasch J. Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury. Ann Intern Med. 2008 Jun 3;148(11):810-9.

This is the first demonstration of the utility of a novel biomarker for the prediction of acute kidney injury in a heterogeneous population.

Weaver DJ, Jr., Kimball TR, Knilans T, Mays W, Knecht SK, Gerdes YM, Witt S, Glascock BJ, Kartal J, Khoury P, Mitsnefes MM. Decreased maximal aerobic capacity in pediatric chronic kidney disease. J Am Soc Nephrol. 2008 Mar;19(3):624-30.

This is the first demonstration of decreased exercise tolerance in children with chronic kidney disease.

Division Collaboration

Collaboration with Developmental Biology

Collaborating Faculty: S. Potter

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

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: K. Dent; T. Kimball

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

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

Collaboration with Epidemiology and Biostats

Collaborating Faculty: S. Salisbury; L. Martin

Co-investigator on Tuberous Sclerosis Complex natural history study (DOD)

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

Collaboration with Interventional Radiology

Collaborating Faculty: J. Wansapura

Co-investigator on Tuberous Sclerosis Complex natural history study (DOD)

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"

Mentions in Consumer Media

Division Publications

1. Bissler JJ, McCormack FX, Young LR, Elwing JM, Chuck G, Leonard JM, Schmithorst VJ, Laor T, Brody AS, Bean J, Salisbury S, Franz DN. [Sirolimus for angiomyolipoma in tuberous sclerosis complex or lymphangiomyomatosis](#). *N Engl J Med*. 2008; 358: 140-51.
2. Jiang X, Kenerson H, Aicher L, Miyaoka R, Eary J, Bissler J, Yeung RS. [The tuberous sclerosis complex regulates trafficking of glucose transporters and glucose uptake](#). *Am J Pathol*. 2008; 172: 1748-56.
3. Kozlowski P, Bissler J, Pei Y, Kwiatkowski DJ. [Analysis of PKD1 for genomic deletion by multiplex ligation-dependent probe assay: absence of hot spots](#). *Genomics*. 2008; 91: 203-8.
4. Liu G, Bissler JJ, Sinden RR, Leffak M. [Unstable spinocerebellar ataxia type 10 \(ATTCT*\(AGAAT\) repeats are associated with aberrant replication at the ATX10 locus and replication origin-dependent expansion at an ectopic site in human cells](#). *Mol Cell Biol*. 2007; 27: 7828-38.
5. Robison JG, Bissler JJ, Dixon K. [Replication protein A is required for etoposide-induced assembly of MRE11/RAD50/NBS1 complex repair foci](#). *Cell Cycle*. 2007; 6: 2408-16.
6. Robison JG, Dixon K, Bissler JJ. [Cell cycle- and proteasome-dependent formation of etoposide-induced replication protein A \(RPA\) or Mre11/Rad50/Nbs1 \(MRN\) complex repair foci](#). *Cell Cycle*. 2007; 6: 2399-407.
7. Bagga A, Bakkaloglu A, Devarajan P, Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Joannidis M, Levin A. [Improving outcomes from acute kidney injury: report of an initiative](#). *Pediatr Nephrol*. 2007; 22: 1655-8.
8. Bennett M, Dent CL, Ma Q, Dastrala S, Grenier F, Workman R, Syed H, Ali S, Barasch J, Devarajan P. [Urine NGAL predicts severity of acute kidney injury after cardiac surgery: a prospective study](#). *Clin J Am Soc Nephrol*. 2008; 3: 665-73.
9. Bennett MR, Czech KA, Arend LJ, Witte DP, Devarajan P, Potter SS. [Laser capture microdissection-microarray analysis of focal segmental glomerulosclerosis glomeruli](#). *Nephron Exp Nephrol*. 2007; 107: e30-40.
10. Devarajan P. [Proteomics for biomarker discovery in acute kidney injury](#). *Semin Nephrol*. 2007; 27: 637-51.
11. Devarajan P. [Neutrophil gelatinase-associated lipocalin: new paths for an old shuttle](#). *Cancer Ther*. 2007; 5: 463-470.
12. Devarajan P. [Proteomics for the investigation of acute kidney injury](#). *Contrib Nephrol*. 2008; 160: 1-16.
13. Devarajan P. [Neutrophil gelatinase-associated lipocalin \(NGAL\): a new marker of kidney disease](#). *Scand J Clin Lab Invest Suppl*. 2008; 241: 89-94.
14. Han WK, Waikar SS, Johnson A, Betensky RA, Dent CL, Devarajan P, Bonventre JV. [Urinary biomarkers in the early diagnosis of acute kidney injury](#). *Kidney Int*. 2008; 73: 863-9.
15. Murray PT, Devarajan P, Levey AS, Eckardt KU, Bonventre JV, Lombardi R, Herget-Rosenthal S, Levin A. [A framework and key research questions in AKI diagnosis and staging in different environments](#). *Clin J Am Soc Nephrol*. 2008; 3: 864-8.
16. Nickolas TL, Barasch J, Devarajan P. [Biomarkers in acute and chronic kidney disease](#). *Curr Opin Nephrol Hypertens*. 2008; 17: 127-32.
17. Nickolas TL, O'Rourke MJ, Yang J, Sise ME, Canetta PA, Barasch N, Buchen C, Khan F, Mori K, Giglio J, Devarajan P, Barasch J. [Sensitivity and specificity of a single emergency department measurement of urinary neutrophil gelatinase-associated lipocalin for diagnosing acute kidney injury](#). *Ann Intern Med*. 2008; 148: 810-9.
18. Parikh CR, Devarajan P. [New biomarkers of acute kidney injury](#). *Crit Care Med*. 2008; 36: S159-65.
19. Parikh CR, Edelstein CL, Devarajan P, Cantley L. [Biomarkers of acute kidney injury: early diagnosis, pathogenesis, and recovery](#). *J Investig Med*. 2007; 55: 333-40.
20. Portilla D, Dent C, Sugaya T, Nagothu KK, Kundi I, Moore P, Noiri E, Devarajan P. [Liver fatty acid-binding protein as a biomarker of acute kidney injury after cardiac surgery](#). *Kidney Int*. 2008; 73: 465-72.
21. Suzuki M, Ross GF, Wiers K, Nelson S, Bennett M, Passo MH, Devarajan P, Brunner HI. [Identification of a urinary](#)

- [proteomic signature for lupus nephritis in children](#). *Pediatr Nephrol*. 2007; 22: 2047-57.
22. Suzuki M, Wiers KM, Klein-Gitelman MS, Haines KA, Olson J, Onel KB, O'Neil K, Passo MH, Singer NG, Tucker L, Ying J, Devarajan P, Brunner HI. [Neutrophil gelatinase-associated lipocalin as a biomarker of disease activity in pediatric lupus nephritis](#). *Pediatr Nephrol*. 2008; 23: 403-12.
 23. Wheeler DS, Devarajan P, Ma Q, Harmon K, Monaco M, Cvijanovich N, Wong HR. [Serum neutrophil gelatinase-associated lipocalin \(NGAL\) as a marker of acute kidney injury in critically ill children with septic shock](#). *Crit Care Med*. 2008; 36: 1297-303.
 24. Zappitelli M, Washburn KK, Arikian AA, Loftis L, Ma Q, Devarajan P, Parikh CR, Goldstein SL. [Urine neutrophil gelatinase-associated lipocalin is an early marker of acute kidney injury in critically ill children: a prospective cohort study](#). *Crit Care*. 2007; 11: R84.
 25. Alam S, Goebel J, Pacheco MC, Sheldon C. [Papillary urothelial neoplasm of low malignant potential in a pediatric renal transplant recipient \(PUNLMP\): a case report](#). *Pediatr Transplant*. 2007; 11: 680-2.
 26. Laskin B, Goebel J. [Clinically "silent" weight loss associated with mycophenolate mofetil in pediatric renal transplant recipients](#). *Pediatr Transplant*. 2008; 12: 113-6.
 27. DeFoor W, Minevich E, Jackson E, Reddy P, Clark C, Sheldon C, Asplin J. [Urinary metabolic evaluations in solitary and recurrent stone forming children](#). *J Urol*. 2008; 179: 2369-72.
 28. Jackson EC. [Is lack of bladder inhibition during sleep a mechanism of nocturnal enuresis?](#). *J Pediatr*. 2007; 151: 559-60.
 29. Dent CL, Ma Q, Dastrala S, Bennett M, Mitsnefes MM, Barasch J, Devarajan P. [Plasma neutrophil gelatinase-associated lipocalin predicts acute kidney injury, morbidity and mortality after pediatric cardiac surgery: a prospective uncontrolled cohort study](#). *Crit Care*. 2007; 11: R127.
 30. Foster BJ, Mackie AS, Mitsnefes M, Ali H, Mamber S, Colan SD. [A novel method of expressing left ventricular mass relative to body size in children](#). *Circulation*. 2008; 117: 2769-75.
 31. Hirsch R, Dent C, Pfriem H, Allen J, Beekman RH, 3rd, Ma Q, Dastrala S, Bennett M, Mitsnefes M, Devarajan P. [NGAL is an early predictive biomarker of contrast-induced nephropathy in children](#). *Pediatr Nephrol*. 2007; 22: 2089-95.
 32. Lai HL, Kartal J, Mitsnefes M. [Hyperinsulinemia in pediatric patients with chronic kidney disease: the role of tumor necrosis factor-alpha](#). *Pediatr Nephrol*. 2007; 22: 1751-6.
 33. Mitsnefes MM. [Understanding carotid artery intima-media thickness in childhood: lessons from studies in children with renal transplants](#). *Pediatr Transplant*. 2008; 12: 377-80.
 34. Mitsnefes MM. [Cardiovascular complications of pediatric chronic kidney disease](#). *Pediatr Nephrol*. 2008; 23: 27-39.
 35. Weaver DJ, Jr., Kimball TR, Knilans T, Mays W, Knecht SK, Gerdes YM, Witt S, Glascock BJ, Kartal J, Khoury P, Mitsnefes MM. [Decreased maximal aerobic capacity in pediatric chronic kidney disease](#). *J Am Soc Nephrol*. 2008; 19: 624-30.
 36. Hartman HA, Lai HL, Patterson LT. [Cessation of renal morphogenesis in mice](#). *Dev Biol*. 2007; 310: 379-87.
 37. Potter SS, Hartman HA, Kwan KM, Behringer RR, Patterson LT. [Laser capture-microarray analysis of Lim1 mutant kidney development](#). *Genesis*. 2007; 45: 432-9.

Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct / Project Period Direct

Bissler, J

DNA Replication Fork: Pausing, Recombination & Disease

National Institutes of Health

R01 DK 061458

05/01/03 - 02/28/09

\$157,125 / \$1,025,002

Tuberous Sclerosis Complex Natural History Study

Department of Defense - Army

W81XWH-06-1-0538

05/01/06 - 05/31/09

\$182,117 / \$550,299

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

\$207,580 / \$621,759

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

\$42,000 / \$369,103

Research Training in Pediatric Nephrology

National Institutes of Health

T32 DK 007695 07/01/07 - 06/30/12

\$114,996 / \$574,980

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

\$5,600 / \$57,889

Lai, H**Mechanism of Termination of Kidney Development**

Kidney Foundation of Greater Cincinnati

07/01/07 - 06/30/08

\$10,000 / \$10,000

Mitsnefes, M**Adiponectin and Cardiovascular Disease in the CKiD Children**

National Institutes of Health

R01 DK 076957 09/01/07 - 08/31/10

\$175,000 / \$525,000

Strife, C**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

\$48,487 / \$104,480

Current Year Direct**\$1,206,219****Industry Contracts****Bissler, J**

Novartis Pharmaceuticals

\$ 11,550

Devarajan, P

Ross Products Divisions, Abbott Labs

\$ 22,715

Mitsnefes, M

Kings Pharmaceuticals Res & Dev, Inc

\$ 8,006

Strife, F

Medical City Dallas Hospital

\$ 700

Liutpold Pharmaceuticals

\$ 46,970

Current Year Direct Receipts**\$89,941****Total \$1,296,160**