Cincinnati Children's

2015 Research Annual Report

# Nephrology and Hypertension

RESEARCH AND TRAINING DETAILS

*Click to view members*

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| Faculty | **15** |
| Joint Appointment Faculty | **1** |
| Research Students | **8** |
| Support Personnel | **9** |
| Direct Annual Grant Support | **$1,595,374** |
| Direct Annual Industry Support | **$120,539** |
| Peer Reviewed Publications | **53** |

CLINICAL ACTIVITIES AND TRAINING

| | |
|---|---|
| Clinical Staff | **17** |
| Clinical Fellows | **7** |
| Inpatient Encounters | **4,500** |
| Outpatient Encounters | **4,400** |

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# Research Highlights

## Prasad Devarajan, MD

Dr. Devarajan has continued with a wide spectrum of approaches to kidney health and disease processes, spanning from molecular, genomic and proteomic approaches to human observational and clinical trials. Dr. Devarajan is the director of the National Institutes of Health (NIH) funded P50 Center of Excellence in Nephrology, a unique multi-disciplinary research program designed to support basic, translational, and clinical research on critical pediatric kidney diseases that have major unmet needs. The proposal includes several research projects in the areas of acute kidney injury, proteinuric kidney disease and lupus nephritis, with participation from recognized teams of investigators from multiple disciplines. Also included are high-resource cores and labs, led by internationally recognized experts. These resources include: the Gene Expression Core, Proteomics and the Biomarker Laboratory. Dr. Devarajan is also the nephrology lead investigator for several NIH-funded prospective clinical studies. He has established a Kidney Biomarker Laboratory which now performs more than 40 distinct assays for acute and chronic kidney disease biomarkers. Dr. Devarajan's ground-breaking research on biomarkers and new therapeutic targets in kidney diseases has yielded over 20 publications and several patent applications during the last fiscal year. Dr. Devarajan also directs the Nephrology Clinical Laboratory, a national resource that performs now over 50 specialized tests of kidney disease that require expert specialized interpretation. We had an exceptional year of growth in the past year, performing over 40,000 individual clinical tests, representing a 25% increase from previous years.

## Stuart L. Goldstein, MD

Dr. Goldstein is the director of the Center for Acute Care Nephrology (CACN), and has had a very productive research year, with achievements that spanned the scope of the center's research missions. The nephrotoxic medication acute kidney injury (AKI) reduction project, NINJA, which resulted in a 42 percent reduction in AKI at Cincinnati Children's, has been spread to US pediatric centers. The CACN also is coordinating the largest prospective pediatric AKI study ever undertaken: "Assessment of Worldwide AKI, Renal angina and Epidemiology in Children (AWARE)". In addition, the CACN coordinates the DIRECT study, which is a genome wide association study for nephrotoxic medication associated AKI; and the NICHD sponsored Pediatric Opportunistic Pharmacokinetic Study arm of the Pediatric Trials Network. In addition to continuous renal replacement and apheresis therapies, the CACN recently introduced the use of specialized novel techniques such as aquapheresis and the Molecular Adsorbent Recirculating System for liver support, making us one of less than five pediatric centers in the country that offer all of these techniques. In addition, the CACN demonstrated unparalleled commitment to education via the simulation course, which was offered to more than 100 RNs and MDs from all over the world during the past year. This course is funded by extramural grants, and is unique among children's hospitals.

## Elizabeth C. Jackson, MD

Dr. Jackson is the director of the Healthy Bladder Clinic and continues her active research program in optimizing the management of nocturnal enuresis. She has completed a randomized prospective trial comparing the effectiveness of the voice recordable alarm with the buzzer alarm for nocturnal enuresis. She has also completed an evaluation of the two-day versus the one-day metabolic stone profile in children. Preliminary findings suggest that more than half the children with a 48 hour urine collection have a significant abnormality that would have been missed if only 24 hours of urine had been tested.

## Bradley Dixon, MD

Dr. Dixon and his laboratory studies the effect of high concentrations of salt and urea, known as hyperosmolality, on the ability of cells in the kidneys and urinary tract to protect themselves from these hostile conditions and carry out normal biological processes such as cell division and metabolism under such stress. Dr. Dixon's research currently focuses on

how kidney cells can detect hyperosmolality in the environment around them in order to switch on vital cellular programs to withstand these conditions. He, and his collaborators both at Cincinnati Children's and the UC College of Medicine, are investigating how primary cilia act as sensors of hyperosmolality in kidney cells. Dr. Dixon is also involved in translational research focusing on the diagnostic evaluation of patients with thrombotic microangiopathies as well as certain forms of nephrotic syndrome, through his work in the Nephrology Clinical Laboratory. The significant increase in testing volume during last fiscal year was largely driven by requisitions from clinicians across the United States and around the world, highlighting Cincinnati Children's role as a national and international leader in highly complex clinical testing and the Nephrology Clinical Laboratory's contribution to that role.

## Mark Mitsnefes, MD MS

Dr. Mitsnefes' research interest has been to define biologic targets for interventions to prevent progression of cardiovascular disease in children with chronic kidney disease, through epidemiological and translational studies. Dr. Mitsnefes is a co-investigator and co-chair of the Cardiovascular Subcommittee in the multicenter NIH funded study of chronic kidney disease in children, the CKiD study. In one published study, the CKiD investigators examined the effect of blood pressure control on frequency of left ventricular hypertrophy (LVH). This study indicated that better BP control over time was associated with regression of LVH. Another landmark study showed a high prevalence of chronic kidney disease in obese teenagers, as evidenced by novel biomarkers.

## Edward Nehus, MD MS

Dr. Nehus' research interest is in comparative effectiveness research with special emphasis on long-term outcomes of pediatric kidney transplant recipients. He has ongoing research efforts in many areas, including steroid use in pediatric kidney transplant, chronic kidney disease in obesity, and pharmacokinetic alterations that occur in children receiving continuous renal replacement therapy.

## Michael Bennett, PhD

Dr. Bennett is the director of the Biomarker Laboratory and co-director of the Center of Excellence in Pediatric Nephrology Proteomics Core. His primary research interests include biomarkers and mechanisms of nephrotic syndrome and lupus nephritis. An exciting ongoing project that has continued this past year is the validation and addition of new candidates to an investigational panel of biomarkers that can distinguish steroid sensitive from steroid resistant nephrotic syndrome. This panel has the potential to assist physicians in the early diagnosis of steroid resistance and help them to tailor more appropriate treatment plans for patients with this serious and progressive disease.

## David Hooper, MD MS

Dr. Hooper's research interests lie in improving clinical outcomes for children with kidney disease through the design of reliable healthcare systems. His primary focus is to combine clinical outcomes research with quality improvement methodology to reliably prevent cardiovascular disease, the leading cause of long-term death and disability in children with kidney disease. During the past year, Dr. Hooper led the effort to develop a clinical registry for the chronic kidney disease, dialysis and kidney transplant patients capably of tracking process of care and outcomes in near real time for more than 30 different measures. He has led the Kidney Transplant Innovation Team in implementing practice change such as routine 24-hr ambulatory blood pressure monitoring and quality of life and psychosocial assessment for all kidney transplant recipients. Furthermore he has led the design of a sophisticated comprehensive web-based pre-visit planning tool that integrates medical record data, medication pharmacokinetic data and patient adherence data to provide decision support in kidney transplant care. Dr. Hooper is extending the reach of Cincinnati Children's Hospital Medical Center by applying the lessons learned in reliable care at Cincinnati Children's to develop a learning health network for children with a kidney transplant throughout the United States.

## Rene Vandevoorde, MD

Dr. Van De Voorde is the medical director of Dialysis. His research interest lies in the different sequelae of chronic kidney disease in children with a focus on end stage renal disease and dialysis. He participates in multi-center studies or registry based analysis of interventions and outcomes. Particular areas of interest include anemia management, bone and mineral disease, growth, psychosocial development, and associated morbidities of dialysis. He is the lead investigator for studies looking at the safety and efficacy of drugs in advanced chronic kidney disease specifically in children. Our dialysis unit also participates in a multi-center study examining factors to reduce the rate of infections in children receiving dialysis. The successes of this collaboration has spawned additional investigations into the risk of peritonitis in infants who have much higher risk, interventions to reduce the rate of blood stream infections with hemodialysis catheters, and the overall cost of dialysis related infections.

## Jens Goebel, MD

Dr. Goebel is the clinical director of the Division of Nephrology and medical director of Kidney Transplantation. His research interests focus on a better understanding of immune mechanisms affecting transplant outcomes. He has continued to advance knowledge about immunosuppressive agents used in pediatric kidney transplantation, and about renal issues in pediatric bone marrow transplantation. Examples for the former include the use of pharmacogenetics to better predict patients' responses to drugs such tacrolimus or mycophenolate and the application of advanced immune phenotyping to further characterize possibly tolerogenic effects of sirolimus. Examples for the latter are ongoing work in pediatric bone marrow transplantation to further characterize the role of BK virus as a significant pathogen in that field and to develop novel insights into thrombotic microangiopathy, a dreaded complication seen in patients who receive bone marrow transplants. Dr. Goebel also remains actively involved in work focusing on adherence and quality improvement in pediatric kidney transplantation, and he continues his role as center-PI for the CKiD study, a large, NIH-sponsored effort to better understand the effects of chronic kidney disease in children over time.

## Donna Claes, MD MS

By creating a highly reliable, clinical care delivery system, Dr. Claes' academic interest is to significantly slow the rate of decline in kidney function over time in pediatric chronic kidney disease (CKD) patients at Cincinnati Children's by focusing on the improved treatment of common associated comorbidities – such as hypertension and proteinuria. Dr. Claes has lead a team composed of clinical providers, outcome managers, and data analysts to first define the overall quality of care we wish to achieve in this patient population and then build the necessary framework and decision support tools to process and assimilate relevant outcome data over time. As there are no national benchmarks to compare the rate of pediatric CKD progression across the US by center – especially in regards to the management of these common comorbidities associated with CKD progression - Dr. Claes' vision is for Cincinnati Children's to become the leader in pediatric CKD care delivery. Dr. Claes is also the site PI for multi-center clinical and pharmacologic studies directed at the pediatric nephrotic syndrome patient population, including the NIH funded longitudinal study, CureGN.

## Elif Erkan, MD MS

Dr. Erkan's research focus is to understand the mechanisms underlying the detrimental effects of proteinuria in glomerular diseases and to examine the protein-protein interactions involved in protein endocytosis in the proximal tubule. She investigates the mechanism of albumin endocytosis in proximal tubule epithelial cells and determines how albumin overload may contribute to tubular apoptosis/autophagy in glomerular diseases. The goal is to dissect the molecular pathways and specific protein-protein interactions involved in cross-talk between apoptosis and autophagy in glomerular disease particularly in focal segmental glomerulosclerosis (FSGS). She has also initiated collaborations to understand the metabolic derangements that may play a role in progressive nature of FSGS by examining the urinary metabolomics of patients with FSGS. In addition, she seeks to determine the effect of insulin induced signaling pathways in albumin endocytosis in the proximal tubule. She has demonstrated a novel pathway linking insulin signaling to albumin endocytosis through downstream insulin mediator protein kinase B (Akt) in proximal tubule epithelial cells.

### Brian Siroky, PhD

Dr. Siroky and his laboratory is focused on understanding the mechanisms of renal cyst and tumor formation that occur in the inherited disease tuberous sclerosis complex (TSC), and the identification of targeted therapies for these lesions. In a published study, he showed that TSC-associated renal angiomyolipomas originate from a specialized vascular cell, the pericyte, and may respond to therapies that target angiotensin II receptor signaling, a vascular cell signaling pathway. He is also interested in the structural and functional relationship between renal epithelial primary cilia, which are specialized cellular organelles whose dysfunction is linked to cystogenesis, and mTOR signaling, the pathway that is dysregulated in TSC. Dr. Siroky also collaborates on a project studying the mechanisms by which renal epithelial cells sense and adapt to a hyperosmolal microenvironment, specifically the role of the primary cilium in this process.

### If you build it, they will come - a banner year for the Center for Acute Care Nephrology (CACN)

Under the direction of Dr. Stuart Goldstein, the Center for Acute Care Nephrology (CACN) provides nephrology care for the sickest critically ill children. In addition to continuous renal replacement (CRRT) and apheresis therapies, the CACN recently introduced the use of specialized novel techniques such as aquapheresis and the Molecular Adsorbent Recirculating System for liver support, making us one of less than five pediatric centers in the country that offer all of these techniques. During the past year, the demand for CACN services rose by about 100 percent, making for an exceptionally busy clinical service. Incredibly, despite this dramatic increase in clinical volume, the CACN continued to demonstrate continuous improvement in care delivery and outcomes for patients. This was convincingly demonstrated by showing significant increases in both CRRT circuit life as well as percentage of patients achieving the desired 24 hour fluid goal. In addition, the CACN demonstrated unparalleled commitment to education via the simulation course, which was offered to more than 100 RNs and MDs from all over the world during the past year. This course is funded by extramural grants, and is unique among children's hospitals. Dr. Goldstein received the 2015 Cincinnati Children's Clinical Care Faculty Achievement Award.

### The Nephrology Clinical Laboratory – exceptional growth and demand for this national resource

The Nephrology Clinical Laboratory directed by Dr. Prasad Devarajan is a national resource that now performs over 50 specialized tests of kidney disease that require expert specialized interpretation. We had an exceptional year of growth in the past year, performing over 40,000 individual clinical tests, representing a 25 percent increase from previous years and an annual revenue of over $2 million. This growth was due in part to the addition of new tests to the Clinical Laboratory's test menu such as an assay to detect PLA2R autoantibodies, which is important in the evaluation of children and adults with nephrotic syndrome. In addition, we witnessed a remarkable increase in the volume of tests performed through the thrombotic microangiopathy testing program launched in the previous year. The increase in testing volume was largely driven by requisitions from clinicians outside of Cincinnati Children's in adult and pediatric health care institutions across the United States and around the world, highlighting Cincinnati Children's role as a national and international leader in highly complex clinical testing and the Nephrology Clinical Laboratory's contribution to that role.

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# Division Publications


1. Abraham AG, Mak RH, Mitsnefes M, White C, Moxey-Mims M, Warady B, Furth SL. **Protein energy wasting in children with chronic kidney disease**. *Pediatr Nephrol*. 2014; 29:1231-8.

2. Basu RK, Donaworth E, Siroky B, Devarajan P, Wong HR. **Loss of matrix metalloproteinase-8 is associated with worsened recovery after ischemic kidney injury**. *Ren Fail*. 2015; 37:469-75.

3. Basu RK, Kaddourah A, Terrell T, Mottes T, Arnold P, Jacobs J, Andringa J, Goldstein SL, Prospective Pediatric

AKIRG. **Assessment of Worldwide Acute Kidney Injury, Renal Angina and Epidemiology in critically ill children (AWARE): study protocol for a prospective observational study**. *BMC Nephrol*. 2015; 16:24.

4. Basu RK, Wong HR, Krawczeski CD, Wheeler DS, Manning PB, Chawla LS, Devarajan P, Goldstein SL. **Combining functional and tubular damage biomarkers improves diagnostic precision for acute kidney injury after cardiac surgery**. *J Am Coll Cardiol*. 2014; 64:2753-62.

5. Bennett MR, Nehus E, Haffner C, Ma Q, Devarajan P. **Pediatric reference ranges for acute kidney injury biomarkers**. *Pediatr Nephrol*. 2015; 30:677-85.

6. Bucholz EM, Whitlock RP, Zappitelli M, Devarajan P, Eikelboom J, Garg AX, Philbrook HT, Devereaux PJ, Krawczeski CD, Kavsak P, Shortt C, Parikh CR, Consortium T-A. **Cardiac biomarkers and acute kidney injury after cardiac surgery**. *Pediatrics*. 2015; 135:e945-56.

7. Burri R, Promerova M, Goebel J, Fumagalli L. **PCR-based isolation of multigene families: lessons from the avian MHC class IIB**. *Mol Ecol Resour*. 2014; 14:778-88.

8. Chawla LS, Goldstein SL, Kellum JA, Ronco C. **Renal angina: concept and development of pretest probability assessment in acute kidney injury**. *Crit Care*. 2015; 19:93.

9. Devarajan P. (2015) **Acute kidney injury in children: Clinical features, etiology, evaluation, and diagnosis**. UpToDate. Waltham, MA, UpToDate. .

10. Devarajan P. (2015) **Prevention and management of acute kidney injury (acute renal failure) in children**. UpToDate. Waltham, MA, UpToDate. .

11. Devarajan P, Murray P. **Biomarkers in acute kidney injury: are we ready for prime time?**. *Nephron Clin Pract*. 2014; 127:176-9.

12. Dong M, Fukuda T, Cox S, de Vries MT, Hooper DK, Goebel J, Vinks AA. **Population pharmacokinetic-pharmacodynamic modelling of mycophenolic acid in paediatric renal transplant recipients in the early post-transplant period**. *Br J Clin Pharmacol*. 2014; 78:1102-12.

13. Erkan E. **Rebuttal to "ezetimibe treatment should be considered for patients with sitosterolemia"**. *Pediatr Nephrol*. 2014; 29:1471.

14. Goldstein S, Bagshaw S, Cecconi M, Okusa M, Wang H, Kellum J, Mythen M, Shaw AD, Group AXI. **Pharmacological management of fluid overload**. *Br J Anaesth*. 2014; 113:756-63.

15. Goldstein SL. **Renal recovery at different ages**. *Nephron Clin Pract*. 2014; 127:21-4.

16. Goldstein SL, Nolin TD. **Lack of drug dosing guidelines for critically ill patients receiving continuous renal replacement therapy**. *Clin Pharmacol Ther*. 2014; 96:159-61.

17. Jackson EC. **Urinary tract infections in children: knowledge updates and a salute to the future**. *Pediatr Rev*. 2015; 36:153-64; quiz 165-6.

18. Jodele S, Davies SM, Lane A, Khoury J, Dandoy C, Goebel J, Myers K, Grimley M, Bleesing J, El-Bietar J, Wallace G, Chima RS, Paff Z, Laskin BL. **Diagnostic and risk criteria for HSCT-associated thrombotic microangiopathy: a study in children and young adults**. *Blood*. 2014; 124:645-53.

19. Jodele S, Laskin BL, Dandoy CE, Myers KC, El-Bietar J, Davies SM, Goebel J, Dixon BP. **A new paradigm: Diagnosis and management of HSCT-associated thrombotic microangiopathy as multi-system endothelial**

**injury**. *Blood Rev*. 2015; 29:191-204.

20. Kaddourah A, Goldstein SL. **Renal replacement therapy in neonates**. *Clin Perinatol*. 2014; 41:517-27.

21. Kaddourah A, Uthup S, Madueme P, O'Rourke M, Hooper DK, Taylor MD, Colan SD, Jefferies JL, Rao MB, Goebel J. **Prevalence and predictors of aortic dilation as a novel cardiovascular complication in children with end-stage renal disease**. *Clin Nephrol*. 2015; 83:262-71.

22. Kellum JA, Devarajan P. **What can we expect from biomarkers for acute kidney injury?**. *Biomark Med*. 2014; 8:1239-45.

23. Koral K, Li H, Ganesh N, Birnbaum MJ, Hallows KR, Erkan E. **Akt recruits Dab2 to albumin endocytosis in the proximal tubule**. *Am J Physiol Renal Physiol*. 2014; 307:F1380-9.

24. Koyner JL, Cerda J, Goldstein SL, Jaber BL, Liu KD, Shea JA, Faubel S, Acute Kidney Injury Advisory Group of the American Society of N. **The daily burden of acute kidney injury: a survey of U.S. nephrologists on World Kidney Day**. *Am J Kidney Dis*. 2014; 64:394-401.

25. Krawczak M, Goebel J. **Causality of incest: a reply to ten Kate**. *Int J Legal Med*. 2014; 128:747.

26. Kwiatkowski DM, Menon S, Krawczeski CD, Goldstein SL, Morales DL, Phillips A, Manning PB, Eghtesady P, Wang Y, Nelson DP, Cooper DS. **Improved outcomes with peritoneal dialysis catheter placement after cardiopulmonary bypass in infants**. *J Thorac Cardiovasc Surg*. 2015; 149:230-6.

27. Lagos-Arevalo P, Palijan A, Vertullo L, Devarajan P, Bennett MR, Sabbisetti V, Bonventre JV, Ma Q, Gottesman RD, Zappitelli M. **Cystatin C in acute kidney injury diagnosis: early biomarker or alternative to serum creatinine?**. *Pediatr Nephrol*. 2015; 30:665-76.

28. Laskin BL, Mitsnefes MM, Dahhou M, Zhang X, Foster BJ. **The mortality risk with graft function has decreased among children receiving a first kidney transplant in the United States**. *Kidney Int*. 2015; 87:575-83.

29. Laskin BL, Nehus E, Goebel J, Furth S, Davies SM, Jodele S. **Estimated versus measured glomerular filtration rate in children before hematopoietic cell transplantation**. *Biol Blood Marrow Transplant*. 2014; 20:2056-61.

30. Menon S, Kirkendall ES, Nguyen H, Goldstein SL. **Acute kidney injury associated with high nephrotoxic medication exposure leads to chronic kidney disease after 6 months**. *J Pediatr*. 2014; 165:522-7 e2.

31. Moledina DG, Parikh CR, Garg AX, Thiessen-Philbrook H, Koyner JL, Patel UD, Devarajan P, Shlipak MG, Coca SG, Consortium T-A. **Association of Perioperative Plasma Neutrophil Gelatinase-Associated Lipocalin Levels with 3-Year Mortality after Cardiac Surgery: A Prospective Observational Cohort Study**. *PLoS One*. 2015; 10:e0129619.

32. Navarro MN, Goebel J, Hukelmann JL, Cantrell DA. **Quantitative phosphoproteomics of cytotoxic T cells to reveal protein kinase d 2 regulated networks**. *Mol Cell Proteomics*. 2014; 13:3544-57.

33. Nehus E, Furth S, Warady B, Mitsnefes M. **Correlates of leptin in children with chronic kidney disease**. *J Pediatr*. 2014; 165:825-9.

34. Nehus EJ, Mouksassi S, Vinks AA, Goldstein S. **Meropenem in children receiving continuous renal replacement therapy: clinical trial simulations using realistic covariates**. *J Clin Pharmacol*. 2014; 54:1421-8.

35. Nolin TD, Aronoff GR, Fissell WH, Jain L, Madabushi R, Reynolds K, Zhang L, Huang SM, Mehrotra R, Flessner MF, Leypoldt JK, Witcher JW, Zineh I, Archdeacon P, Roy-Chaudhury P, Goldstein SL. **Pharmacokinetic assessment in**

**patients receiving continuous RRT: perspectives from the kidney health initiative**. *Clin J Am Soc Nephrol*. 2015; 10:159-64.

36. Paoli S, Mitsnefes MM. **Coronary artery calcification and cardiovascular disease in children with chronic kidney disease**. *Curr Opin Pediatr*. 2014; 26:193-7.

37. Prowle JR, Calzavacca P, Licari E, Ligabo EV, Echeverri JE, Bagshaw SM, Haase-Fielitz A, Haase M, Ostland V, Noiri E, Westerman M, Devarajan P, Bellomo R. **Combination of biomarkers for diagnosis of acute kidney injury after cardiopulmonary bypass**. *Ren Fail*. 2015; 37:408-16.

38. Roeder E, Henrionnet C, Goebel JC, Gambier N, Beuf O, Grenier D, Chen B, Vuissoz PA, Gillet P, Pinzano A. **Dose-response of superparamagnetic iron oxide labeling on mesenchymal stem cells chondrogenic differentiation: a multi-scale in vitro study**. *PLoS One*. 2014; 9:e98451.

39. Sarnak MJ, Katz R, Newman A, Harris T, Peralta CA, Devarajan P, Bennett MR, Fried L, Ix JH, Satterfield S, Simonsick EM, Parikh CR, Shlipak MG, Health ABCS. **Association of urinary injury biomarkers with mortality and cardiovascular events**. *J Am Soc Nephrol*. 2014; 25:1545-53.

40. Selewski DT, Massengill SF, Troost JP, Wickman L, Messer KL, Herreshoff E, Bowers C, Ferris ME, Mahan JD, Greenbaum LA, MacHardy J, Kapur G, Chand DH, Goebel J, Barletta GM, Geary D, Kershaw DB, Pan CG, Gbadegesin R, Hidalgo G, Lane JC, Leiser JD, Song PX, Thissen D, Liu Y, Gross HE, DeWalt DA, Gipson DS. **Gaining the Patient Reported Outcomes Measurement Information System (PROMIS) perspective in chronic kidney disease: a Midwest Pediatric Nephrology Consortium study**. *Pediatr Nephrol*. 2014; 29:2347-56.

41. Siroky BJ, Yin H, Dixon BP, Reichert RJ, Hellmann AR, Ramkumar T, Tsuchihashi Z, Bunni M, Dillon J, Bell PD, Sampson JR, Bissler JJ. **Evidence for pericyte origin of TSC-associated renal angiomyolipomas and implications for angiotensin receptor inhibition therapy**. *Am J Physiol Renal Physiol*. 2014; 307:F560-70.

42. Smits TA, Cox S, Fukuda T, Sherbotie JR, Ward RM, Goebel J, Vinks AA. **Effects of unbound mycophenolic acid on inosine monophosphate dehydrogenase inhibition in pediatric kidney transplant patients**. *Ther Drug Monit*. 2014; 36:716-23.

43. Sutherland SM, Byrnes JJ, Kothari M, Longhurst CA, Dutta S, Garcia P, Goldstein SL. **AKI in hospitalized children: comparing the pRIFLE, AKIN, and KDIGO definitions**. *Clin J Am Soc Nephrol*. 2015; 10:554-61.

44. Sutherland SM, Goldstein SL, Alexander SR. **The prospective pediatric continuous renal replacement therapy (ppCRRT) registry: a critical appraisal**. *Pediatr Nephrol*. 2014; 29:2069-76.

45. VanDeVoorde RG, 3rd. **Acute poststreptococcal glomerulonephritis: the most common acute glomerulonephritis**. *Pediatr Rev*. 2015; 36:3-12; quiz 13.

46. Varnell CD, Jr., Goldstein SL, Yee DL, Teruya J, Guyer KE, Siddiqui S, Jefferies JL. **Age-related differences in urinary 11-dehydroxythromboxane B2 between infants, children, and adolescents: another example of developmental hemostasis?**. *Pediatr Blood Cancer*. 2014; 61:2074-6.

47. Wang Z, Ma S, Wang CY, Zappitelli M, Devarajan P, Parikh C. **EM for regularized zero-inflated regression models with applications to postoperative morbidity after cardiac surgery in children**. *Stat Med*. 2014; 33:5192-208.

48. Warady BA, Abraham AG, Schwartz GJ, Wong CS, Munoz A, Betoko A, Mitsnefes M, Kaskel F, Greenbaum LA, Mak RH, Flynn J, Moxey-Mims MM, Furth S. **Predictors of Rapid Progression of Glomerular and Nonglomerular Kidney Disease in Children and Adolescents: The Chronic Kidney Disease in Children (CKiD) Cohort**. *Am J Kidney Dis*. 2015; 65:878-88.

49. Webb TN, Ramratnam M, Evans RW, Orchard T, Pacella J, Erkan E. **Atherosclerotic renal artery stenosis as a cause for hypertension in an adolescent patient**. *Pediatr Nephrol*. 2014; 29:1457-60.

50. Weir MR, Burgess ED, Cooper JE, Fenves AZ, Goldsmith D, McKay D, Mehrotra A, Mitsnefes MM, Sica DA, Taler SJ. **Assessment and management of hypertension in transplant patients**. *J Am Soc Nephrol*. 2015; 26:1248-60.

51. Xiao N, Devarajan P, Inge TH, Jenkins TM, Bennett M, Mitsnefes MM. **Subclinical kidney injury before and 1 year after bariatric surgery among adolescents with severe obesity**. *Obesity (Silver Spring)*. 2015; 23:1234-8.

52. Xiao N, Jenkins TM, Nehus E, Inge TH, Michalsky MP, Harmon CM, Helmrath MA, Brandt ML, Courcoulas A, Moxey-Mims M, Mitsnefes MM, Teen LC. **Kidney function in severely obese adolescents undergoing bariatric surgery**. *Obesity (Silver Spring)*. 2014; 22:2319-25.

53. Zappitelli M, Greenberg JH, Coca SG, Krawczeski CD, Li S, Thiessen-Philbrook HR, Bennett MR, Devarajan P, Parikh CR, Translational Research Investigating Biomarker Endpoints in Acute Kidney Injury C. **Association of definition of acute kidney injury by cystatin C rise with biomarkers and clinical outcomes in children undergoing cardiac surgery**. *JAMA Pediatr*. 2015; 169:583-91.

# Faculty, Staff, and Trainees

## Faculty Members

**Prasad Devarajan, MD**, Professor

**Leadership** Louise M. Williams Endowed Chair; Director, Division of Nephrology and Hypertension; Director, Clinical Nephrology Laboratory; CEO, Dialysis Unit; Director, Nephrology Fellowship Training Program

**Research Interests** Pathogenesis, biomarkers, and novel therapies of acute kidney injury; pathogenesis and biomarkers of focal segmental glomerulosclerosis; pathogenesis and biomarkers of lupus nephritis.

**Michael Bennett, PhD**, Assistant Professor

**Leadership** Director, Biomarker Laboratory

**Research Interests** Biomarker discovery in acute and chronic kidney disease; focal segmental glomerulosclerosis.

**Donna Claes, MD**, Assistant Professor

**Research Interests** Clinical trails in nephrotic syndrome and chronic kidney disease.

**Bradley P. Dixon, MD**, Assistant Professor

**Research Interests** DNA damage and repair; cell biology of the augmented bladder; atypical hemolytic uremic syndrome and thrombotic thrombocytopenic purpura.

**Elif Erkan, MD**, Associate Professor

**Research Interests** Mechanisms of proteinuna - induced kidney damage.

**Jens Goebel, MD**, Professor

**Leadership** Medical Director of Transplantation; Clinical Director, Nephrology; Associate Division Co-Director

**Research Interests** Advancing basic and translational investigations into immunological aspects especially relevant to the field of transplantation.

**Stuart Goldstein, MD**, Professor

**Leadership** Director, Center for Acute Care Nephrology; Medical Director, Pheresis Service; Associate Division Co-Director

**Research Interests** Acute kidney injury; end stage renal disease; multi-organ dysfunction syndrome; continuous renal replacement therapy; cardio-renal syndrome; nephrotoxic medication injury.

**Elizabeth Jackson, MD**, Associate Professor

**Leadership** Director, Healthy Bladder Clinic

**Research Interests** Nocturnal enuresis; kidney stones; lower urinary tract dysfunction.

**Paul McEnery, MD**, Professor Emeritus

**Research Interests** Glomerulonephritis; vitamin D resistant rickets; end stage renal disease.

**Mark Mitsnefes, MD**, Professor

**Leadership** Program Director, Clinical Translational Research Center

**Research Interests** Cardiovascular abnormalities and risk factors for increased cardiac morbidity and mortality in children with CKD; evaluation of LVH; cIMT; hypertension.

**Edward Nehus, MD**, Assistant Professor

**Leadership** Associate Director, Nephrology Fellowship Program

**Research Interests** Comparative effectiveness research with special emphasis on long-term outcomes of pediatric kidney transplant recipients.

**C. Frederic Strife, MD**, Professor Emeritus

**Research Interests** Clinical aspects of glomerulonephritis and dialysis.

**Rene Vandevoorde, MD**, Assistant Professor

**Leadership** Medical Director, Dialysis Unit

**Research Interests** Chronic kidney disease; dialysis including infant dialysis; epidemiology of renal diseases; medical education.

**David Hooper, MD**, Assistant Professor

**Research Interests** Reliable and innovative chronic disease management; cardiovascular outcomes following kidney transplantation.

**Brian Siroky, PhD**, Instructor

**Research Interests** Inherited renal cystic diseases; primary cilia biology; mammalian target of rapamycin (mTOR) signaling; tuberous sclerosis complex; polycystic kidney disease.

### Trainees

- **Stella Shin, MD**, PL-3
- **LaTawnya Pleasant-Griffin, MD**, PL-3
- **Keri Drake, MD**, PL-2
- **Gilad Hamdani, MD**, PL-2
- **Mary Avendt, MD**, PL-1
- **Orville Bignall, II, MD**, PL-1
- **Oded Volovelsky, MD**, PL-1

# Grants, Contracts, and Industry Agreements

**Grant and Contract Awards** **Annual Direct**

### Bennett, M / Brunner, H

**Innovative Efficacy Measures of Lupus Nephritis Therapies**

National Institutes of Health

| | | |
|---|---|---|
| U01 AR065098 | 7/26/2013-6/30/2016 | $148,962 |

## Devarajan, P

**Critical Translational Studies in Pediatric Nephrology**

National Institutes of Health

| | | | |
|---|---|---|---|
| P50 DK096418 | | 9/21/2012-8/31/2017 | $622,525 |
| | Devarajan, P | Administrative Core | $66,745 |
| | Devarajan, P | Gender Supplement | $25,667 |
| | Devarajan, P | Summer Supplement | $66,745 |
| | Bennett, M | Pilot & Feasibility Study I (Administrative Core) | $50,000 |
| | Erkan, E | Pilot & Feasibility Study II (Administrative Core) | $50,000 |
| | Devarajan, P | Proteomics Core | $103,824 |
| | Potter, S | Genomic Core | $51,134 |
| | Potter, S | Primary Research Core | $107,266 |
| | Brunner, H | Lupus Nephritis Core | $101,144 |

**Novel Serum and Urinary Biomarkers of Diabetic Kidney Disease**

National Institutes of Health(Yale University School of Medicine)

| | | |
|---|---|---|
| R01 DK096549 | 9/1/2012-9/30/2014 | $5,773 |

**Novel Biomarkers in Cardiac Surgery to Detect Acute Kidney Injury**

National Institutes of Health(Yale University School of Medicine)

| | | |
|---|---|---|
| R01 HL085757 | 4/12/2012-3/31/2017 | $23,435 |

**Research Training in Pediatric Nephrology**

National Institutes of Health

| | | |
|---|---|---|
| T32 DK007695 | 7/1/2014-6/30/2019 | $147,956 |

**Progression of Acute Kidney Injury to Chronic Kidney Disease**

National Institutes of Health(Yale University School of Medicine)

| | | |
|---|---|---|
| U01 DK082185 | 9/19/2013-6/30/2018 | $20,000 |

## Goebel, J

**Pediatric Trial Network: Rapid Start Network for Federally Funded Contracts (RSN-C)**

National Institutes of Health(Duke University)

| | | |
|---|---|---|
| | 10/1/2011-8/31/2015 | $1,000 |

## Goldstein, S

**Antibiotic Safety in Infants with Complicated Intra-Abdominal Infections**

National Institutes of Health(Duke University)

| | | |
|---|---|---|
| HHSN2752010000031 | 5/7/2014-9/23/2017 | $16,401 |

**Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care**

National Institutes of Health(Duke University)

| | | |
|---|---|---|
| HHSN2752010000031 | 2/27/2013-2/24/2017 | $10,934 |

**Reduction of Nephrotoxic Medication-Associated Acute Kidney Injury in Children**

Agcy for Healthcare Research and Quality

| | | |
|---|---|---|
| R18 HS023763 | 4/1/2015-3/31/2018 | $320,172 |

**Recombinant Erythropoietin Protects Against Kidney Disease (REPAKD)**

National Institutes of Health(Children's Hosp & Reg Med Ct-Seattle)

| | | |
|---|---|---|
| R01 DK103608 | 9/17/2014-8/31/2019 | $10,432 |

## Mitsnefes, M

**Cardiovascular Disease in Children with Chronic Kidney Disease**

National Institutes of Health

| | | |
|---|---|---|
| K24 DK090070 | 7/1/2011-6/30/2016 | $154,579 |

**Chronic Kidney Disease in Children (CKiD III)**

National Institutes of Health(Children's Mercy Hospital)

| | | |
|---|---|---|
| U01 DK066143 | 8/1/2013-7/31/2018 | $113,205 |

| | |
|---|---|
| **Current Year Direct** | **$1,595,374** |

## Industry Contracts

| | |
|---|---|
| **Dixon, B** | |
| Covance, Inc | $18,560 |
| **Dixon, B** | |
| Diapharma Group Inc | $17,064 |
| **Goldstein, S** | |
| Gambro Renal Products, Inc | $35,582 |
| International Serious Adverse Events | $7,854 |
| **Pleasant-Griffin, L** | |
| Mallinckrodt Pharmaceuticals | $38,500 |
| **VanDeVoorde II, R** | |
| AMAG Pharmaceuticals | $2,979 |
| **Current Year Direct Receipts** | **$120,539** |
| **Total** | **$1,715,913** |

# Insights into Cell Growth, Cell Death Offer New Pathways to Treat Kidney Disease

Elif Erkan, MD, MS

RESEARCH AND TRAINING DETAILS

| | |
|---|---|
| Faculty | 15 |
| Joint Appointment Faculty | 1 |
| Research Students | 8 |
| Support Personnel | 9 |
| Direct Annual Grant Support | $1.5M |
| Direct Annual Industry Support | $120,539 |
| Peer Reviewed Publications | 53 |

Koral K, Li H, Ganesh N, Birnbaum MJ, Hallows KR, Erkan E. Akt recruits Dab2 to albumin endocytosis in the proximal tubule. *Am J Physiol Renal Physiol*. 2014;307(12):F1380-1389.

PUBLISHED ONLINE SEPT. 24, 2014
*American Journal of Physiology - Renal Physiology*

One of the challenges for kidney specialists is protecting the kidney from too much protein, which can contribute to progressive damage that leads to end-stage renal disease. Proximal tubule epithelial cells internalize albumin by receptor-mediated endocytosis and undergo apoptosis – programmed cell death – when exposed to too much albumin, the primary protein in the filtrate.

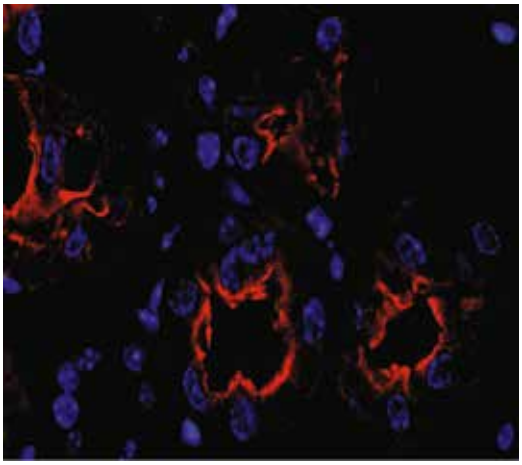
A team led by Elif Erkan, MD, MS, in the Division of Nephrology, has identified an interaction between receptors and proteins in the proximal tubule that support albumin endocytosis and cell survival. The link involves protein kinase B (Akt), a pivotal protein involved in cell survival, megalin-cubilin complex receptor and the endocytic adaptor disabled-2 (Dab2). Detailed findings appeared online Sept. 24, 2014, in the *American Journal of Physiology - Renal Physiology*.

Specifically, Erkan's team found that both Akt1 and Akt2 are involved in mediating albumin endocytosis in proximal tubule epithelial cells, and that Akt phosphorylates Dab2. In Akt1 and Akt2 knock-out mice, the location of Dab2 is shifted from the cell membrane to the perinuclear area of the proximal tubule indicating the role of Akt in trafficking of Dab2.

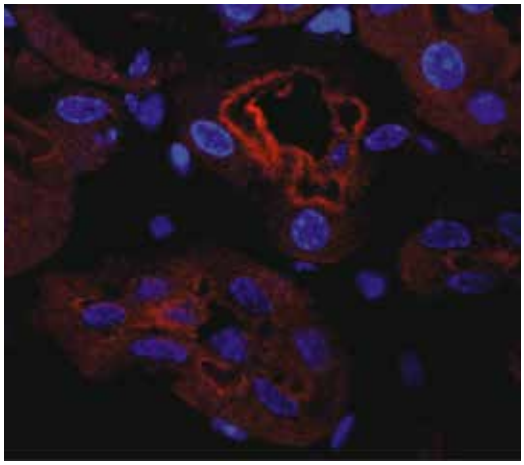
Erkan says the highlight of the work is the discovery of the link between the endocytic pathway and cell survival/cell death. "Because Akt mediates albumin endocytosis, its expression is down-regulated in tubular epithelial cells in kidney disease, leading to apoptosis" she says. "If we can figure out a way to up-regulate Akt in tubular epithelial cells, perhaps we can promote cell survival and prevent progression in glomerular diseases."

Erkan and her team are continuing to study the link between Akt and Dab2 in mice. Additional research may identify other potential targets or additional regulating roles for Akt in a search for novel pharmaceutical agents to reduce kidney damage.

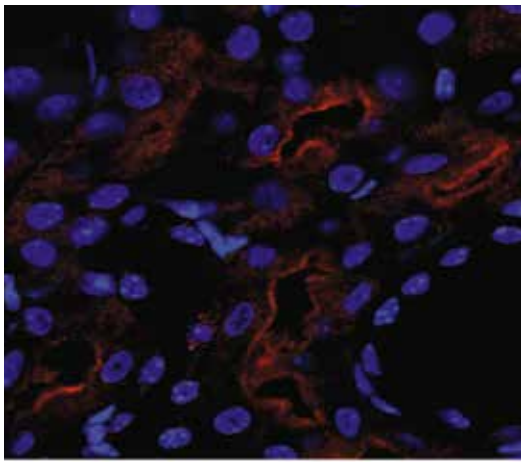
WT



AKT1KO



AKT2KO



Dab2 expression was examined in WT, Akt1 KO and Akt2 KO mice kidneys. Apical location of Dab2 was prominent in WT mouse proximal tubule cells in parallel with its function as an adaptor protein harboring receptor-mediated endocytosis. There was a decrease in apical location of Dab2 in Akt1 and Akt2 KO mice proximal tubule cells.

Up-regulating Akt in tubular epithelial cells may promote cell survival and prevent progression in glomerular diseases.