# 2014 Research Annual Report Nephrology and Hypertension

# Cincinnati Children's

# **Division Summary**

Number of Faculty	14
Number of Joint Appointment Faculty	1
Number of Research Students	7
Number of Support Personnel	10
Direct Annual Grant Support	\$2,259,578
Direct Annual Industry Support	\$471,967
Peer Reviewed Publications	45
CLINICAL ACTIVITIES AND TRAINING	
Number of Clinical Staff	18
Number of Clinical Fellows	6
Inpatient Encounters	3,580
Outpatient Encounters	4.580

### **Division Photo**



Row 1: D Claes, M Avendt, E Jackson, S Goldstein, E Erkan, K Drake Row 2: T Pleasant, J Goebel, M Bennett, R Bignall, P Devarajan Row 3: B Siroky, B Dixon, G Hamdani, R VanDeVoorde, D Hooper, O Volovelsky

# Significant Accomplishments

# New Test Panel Revolutionizes Diagnosis of Thrombotic Microangiopathy

A transformative advancement in diagnostic testing has further elevated the profile of Cincinnati Children's. Thrombotic microangiopathies are a group of disorders that cause damage to small blood vessels throughout the body, leading to organ damage and possibly death if not treated promptly. In the past, the required blood tests were available only piecemeal at different institutions. Through the efforts of Bradley Dixon, MD, in the Division of Nephrology and Hypertension, and his collaborators in the Cancer and Blood Diseases Institute and the Division of Human Genetics, all of these tests were brought under one roof at Cincinnati Children's. This platform of tests was made available for clinical use in September 2013, and has revolutionized the diagnostic testing of individuals with thrombotic microangiopathies. In recognition, Dr. Dixon received the Entrepreneurial Achievement Faculty Award in February.

# Multidisciplinary Stone Center Launched to Meet Soaring Demand

More than 625 children were treated last year for kidney and urinary tract stones at Cincinnati Children's, double the number from five years ago and more than triple the figure over the last decade. In response to this growing epidemic, the Stone Center was launched. The Center's multidisciplinary team includes physicians, nurses, dieticians, genetic counselors, and social workers from seven specialties. Under the direction of Prasad Devarajan, MD, Nephrology Division Director, the Center provides families of children with kidney stones coordinated care, education, treatment, prevention and research. Children are seen by a nephrologist, urologist, dietician, and genetics counselor. Research in stone disease includes a data base, evaluation of the

two-day versus one-day metabolic stone profile, stone risk before and after bariatric surgery, and development of a genetic chip to detect the common hereditary stone forming conditions. We are also one of the Coordinating Centers within the NIH-funded Rare Kidney Stone Consortium to test novel therapies for kidney stones.

# **Our Kidney Transplant Program Busiest in the Country**

Our Kidney Transplant Program, spearheaded by nephrologists Jens Goebel, MD, and David Hooper, MD, MS, is one of the most experienced in the country at treating complex diseases of the kidney and urinary tract. We have excellent outcomes, with 100 percent one-year post-transplant patient and graft survival rates. Last year, we performed 34 kidney transplants, more than any other center in the U.S. In recognition of the achievements of the kidney transplant program, Hooper received the Clinical Care Achievement Faculty Award in February.

# **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 NIH-funded P50 Center of Excellence in Nephrology, a unique multidisciplinary research program designed to support basic, translational, and clinical research on critical pediatric kidney diseases that have major unmet needs. The proposal includes three primary 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 gene expression, proteomics, and biomarker cores with core leaders of international repute to support the study of the three focus areas. In addition, six to eight pilot and feasibility projects will be funded in the three areas of research focus. Dr. Devarajan is the center PI and/or 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.

### 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 was associated with a 42% reduction in AKI, had four related publications this year. The CACN received pilot funding to spread NINJA to nine other 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)". The CACN published two landmark papers validating the Renal Angina risk stratification concept, with incorporation of urinary biomarkers. These demonstrate the utility of a simple risk stratification system to aid in directing biomarker measurement and guide therapies to support patients with AKI. In addition, the CACN coordinates the international pediatric contribution to the DIRECT study, which is a genome wide association study for nephrotoxic medication associated AKI; currently 15 pediatric centers have signed on to this project. The CACN is also coordinating the NICHD sponsored Pediatric Opportunistic Pharmacokinetic Study arm of the Pediatric Trials Network at Cincinnati Children's with two protocols that are active currently.

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 is completing a randomized prospective trial comparing the effectiveness of the voice recordable alarm with the buzzer alarm for nocturnal enuresis. Preliminary results suggest that the voice alarm may lead to a lower dropout rate, and have been presented at national scientific meetings. Dr. Jackson is also evaluating 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's 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, a group of disorders which cause blood vessel inflammation and clotting leading to organ damage, through his work in the Nephrology Clinical Laboratory. Dr. Dixon is particularly interested in making clinical testing for the major forms of thrombotic microangiopathy more efficient and meaningful as well as investigating new tests for these disease processes.

## 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 published CKiD study analyzed sphingolipid levels. This is the first study indicating that ceramide levels are increased in children with CKD. One of the ceramides, lactosylceramide was identified as an independent predictor of lower systolic function in these children.

# 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. This past year, he completed a nationwide study of focal and segmental glomerulosclerosis (FSGS), the second leading cause of kidney failure in children. This study investigated national trends in FSGS leading to kidney transplant and analyzed risk factors for recurrence of disease. Dr. Nehus' research demonstrated that FSGS as a cause of pediatric kidney failure is on the rise, and that recurrence risk is highest in young, white children. He also has ongoing research efforts in many other 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 Cincinnati Children's 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. Additionally, Dr. Bennett's group has established reference values for Acute Kidney Injury Biomarkers in healthy children, which is a necessary step in bringing these markers from the bench into clinical practice.

### 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 by developing a learning health network for children with a kidney transplant throughout the United States.

### Rene Vandevoorde, MD

Dr. VanDeVoorde 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 include anemia management, bone and mineral disease, growth, psychosocial development, and associated morbidities of dialysis. He is the lead investigator for four studies looking at the safety and efficacy of drugs in advanced chronic kidney disease specifically in children: an intravenous iron supplement, a calcimimetic agent which binds the calcium-sensing receptor of the parathyroid gland, and a phosphate binder. Our dialysis unit is also one of 27 pediatric units examining factors to reduce the rate of infections in children receiving dialysis. This project has shown a 27% reduction in peritonitis rates in infants and children receiving peritoneal 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 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. In less than twelve months, 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's 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 recently published study, he provided evidence 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.

# Significant Publications

Ronco C, Garzotto F, Brendolan A, Zanella M, Bellettato M, Vedovato S, Chiarenza F, Ricci Z, **Goldstein SL**. Continuous renal replacement therapy in neonates and small infants: development and first in-human use of a miniturised machine CARPEDIEM. *Lancet*. 2014 24;383(9931):1807-13.

Continuous renal replacement therapy in neonates and small children: development and first-in-human use of a miniaturised machine (CARPEDIEM). The Lancet; 383:1807-13, 2014. This paper represents the culmination of

a 5-year project to develop, validate and apply a novel acute continuous renal replacement therapy (CRRT) platform specifically designed for the critically ill neonatal population with acute kidney injury (AKI). Prior to CARPEDIEM, all CRRT platforms had been designed for adults or larger children, requiring often label use in smaller pediatric populations, with system tolerances that represented a challenge to provision of optimal pediatric care for the most vulnerable populations. This report of the 3 kg child with severe AKI and multi-organ failure treated with CARPEDIEM highlights the importance of developing pediatric specific devices, as this child likely would not have survived using previous technologies.

Kupferman J, Aronson Friedman L, Cox C, Flynn J, Furth S, Warady B, **Mitsnefes MM**. BP Control and Left Ventricular Hypertrophy Regression in Children with CKD. *J Am Soc Nephrol*, 2014; 25(1):167-74.

This is the largest longitudinal study analyzing the effect of blood pressure on cardiac structure in children with chronic kidney disease stages 2-4. In this study, hypertension was found to be strongly associated with left ventricular hypertrophy. Importantly, any decrease in blood pressure also corresponded to regression of left ventricular hypertrophy over time, with a decline in the actual prevalence of left ventricular hypertrophy from 16% to 11% after the 4 year period of observation. The study concluded that regression of left ventricular hypertrophy can be accomplished with better blood pressure control.

**Nehus E, Goebel J**, Succop P, Abraham E. Focal segmental glomerulosclerosis in children: multivariate analysis indicates that donor type does not alter recurrence risk. *Transplantation*. 2013 96(6):550-4.

This retrospective study evaluated risk factors for recurrence of focal segmental glomerulosclerosis (FSGS) in pediatric kidney transplant recipients, with special emphasis on donor type (living vs. deceased donor). The study reported the novel findings that FSGS recurrence is highest in young, white children, whereas donor type was not independently associated with increased risk of recurrence.

# **Division Publications**

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- 3. Basu RK, Zappitelli M, Brunner L, Wang Y, Wong HR, Chawla LS, Wheeler DS, Goldstein SL. Derivation and validation of the renal angina index to improve the prediction of acute kidney injury in critically ill children. *Kidney Int.* 2014; 85:659-67.
- 4. Claes DJ, Yin H, Goebel J. Protective immunity and use of bortezomib for antibody-mediated rejection in a pediatric kidney transplant recipient. *Pediatr Transplant*. 2014; 18:E100-5.
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# 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

#### Trainees

- Ahmad Kaddourah, MD, PL-3
- Nianzhou Xiao, MD, PL-3
- Stella Shin, MD, PL-2
- LaTawnya Pleasant-Griffin, MD, PL-2
- Keri Drake, MD, PL-1
- Gilad Hamdani, MD, PL-1

# Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct
DEVARAJAN, P		
2014 Medical Student Summer Res	earch Program	
National Institutes of Health		
P50 DK 096418	06/01/14-08/31/14	\$28,000
Critical Translational Studies in Peo	diatric Nephrology	
National Institutes of Health		
P50 DK 096418	09/21/12-08/31/17	\$512,018
Novel Biomarkers in Cardiac Surge	ery to Detect Acute Kidney Injury	
National Institutes of Health(Yale Un	iversity School of Medicine)	
R01 HL 085757	04/12/12-03/31/17	\$17,393
Novel Serum and Urinary Biomark	ers of Diabetic Kidney Disease	
National Institutes of Health(Yale Un	iversity School of Medicine)	
R01 DK 096549	09/01/12-06/30/17	\$5,774

09/19/13-06/30/18		
		\$20,000
DIXON, B		
DNA Damage and Response in the Bladder Microenvironment.		
National Institutes of Health		
K08 DK 081737 07/01/11-04/30/15		\$136,922
GOLDSTEIN, S		
Drug Induced Renal Injury Consortium (DIRECT)		
International Serious Adverse Events Con		
05/01/13-04/30/15		\$23,077
Pediatric Kidney Disease: AKI and Acute Kidney Function Biomarkers Casey Lee Ball Foundation		
09/01/13-08/31/15		\$100,000
Pharmacokinetics of Understudied Drugs Administered to Children per S National Institutes of Health(Duke University)	tandard of Care	. ,
HHSN-2752010000031 02/27/13-06/25/15		\$8,085
Antibiotic Safety in Infants with Complicated Intra-Abdominal Infections National Institutes of Health(Duke University)		
HHSN-2752010000031 05/07/14-09/23/16		\$3,080
MITSNEFES, M		
Cardiovascular Disease in Children with Chronic Kidney Disease		
National Institutes of Health		
K24 DK 090070 07/01/11-06/30/16		\$158,114
Cincinnati Center for Clinical and Translational Sciences and Training		
National Institutes of Health(University of Cincinnati)		
UL1 TR 000077 04/30/09-03/31/15		\$1,247,115
	Current Year Direct	\$2,259,578
Industry Contracts		
BISSLER, J		
Novartis Pharmaceuticals		\$425,979
DIXON, B		
DIXON, B Otsuka Pharmaceutical Development		\$17,363
		\$17,363

GOLDSTEIN, S		
Gambro Renal Products, Inc		\$27,874
	Current Year Direct Receipts	\$471,967
	Total	\$2,731,545