Nephrology and Hypertension

Division Details

Division Data Summary

Research and Training Details

Number of Faculty	**10**
Direct Annual Grant Support	**$1,948,472**
Direct Annual Industry Support	**$356,055**
Peer Reviewed Publications	**75**

Division Photo

Row 1: D Claes, N Xiao, H Shin, M Mitsnefes, S Menon
Row 2: M Bennett, J Bissler, L Pleasant, S Goldstein, P Devarajan
Row 3: D Hooper, R VanDeVoorde, B Dixon, J Goebel, E Nehus

Significant Accomplishments

NIH Pediatric Center of Excellence in Nephrology

Prasad Devarajan, MD, director of Nephrology and Hypertension, was awarded a prestigious five-year, $3.7 million Center of Excellence (P50) grant by the National Institute of Diabetes and Digestive and Kidney Diseases. Ours is one of only three such centers that were funded. The Center will fund groundbreaking translational research projects in three areas of unmet need, including acute kidney injury, nephrotic syndrome, and lupus kidney disease. It will bring together investigators performing cutting-edge bench-to-bedside research from several divisions within Cincinnati Children's, including Nephrology, Cardiology, Critical Care, Rheumatology, Developmental Biology, and Bone Marrow Transplant. The Center will include funding for innovative Research Cores in Genomics, Proteomics, and Biomarker Development, to support the primary focus areas. The Center will also incorporate an Administrative Core, and an Enrichment Core for the training of future pediatric nephrology researchers.

Nephrology Clinical Laboratory launches new tests for atypical HUS

Hemolytic uremic syndrome, or HUS, is a serious disease that can lead to kidney failure and even death. Some forms of HUS (known as atypical HUS) are associated with defects in the regulation of the complement system, a portion of the immune system, and are even more lethal if not correctly identified and treated. After caring for several patients with atypical HUS for whom the testing required sending samples to other institutions, taking weeks and even months to complete, Bradley Dixon, MD, wanted to make identification of these atypical forms of HUS easier and faster. He developed several blood tests to rapidly evaluate such patients, which have now been launched by the Nephrology Clinical Laboratory. These tests can quickly assay for the most common causes of atypical HUS, identify conditions that can closely resemble atypical HUS, and help clinicians rapidly

treat the disease to improve patient outcomes. The Clinical Laboratory has already become a regional resource for HUS testing in the Tri-state area, and remains a national leader in performing unique tests for the diagnosis of other complement disorders, acute kidney injury, and chronic kidney disease.

Nephrology Research leads to FDA Approval of New Drug for Tuberous Sclerosis

April 29, 2012 was a very good day for patients with a tumor predisposition syndrome called tuberous sclerosis complex. People affected with this disease develop renal tumors called angiomyolipomata. Until this last April, only surgery or endovascular procedures could help control individual tumors; however, many patients have bilateral, multifocal kidney involvement that was previously untreatable. Work pioneered here, including an eleven-country, placebo-controlled trial led by John Bissler, MD, has changed the outcome for these patients. The trial demonstrated that the drug Everolimus caused significant shrinkage of the renal tumors in patients suffering from tuberous sclerosis renal disease. The significance of these findings led the Food and Drug Administration to approve Everolimus for the treatment of patients with tuberous sclerosis complex. In the recent Tuberous Sclerosis Consensus Conference, Everolimus was recommended as the first line of therapy for these tumors. This represents the first approved drug that can alter the progressive nature of these tumors, and offers new hope for patients with Tuberous Sclerosis renal disease.

Division Highlights

Another banner year for the Kidney Transplant Team

The multi-disciplinary Kidney Transplant Center at Cincinnati Children's has been in existence since 1965, and has performed over 500 kidney transplants in children. Recent years have seen an explosion of activities, thanks to novel protocols that optimize the care of children with the most complex malformations, antibody-mediated rejection and BK virus nephropathy. Despite the complexity, Cincinnati Children's kidney transplant program, directed by Dr. Jens Goebel, continues to achieve patient and graft survival rates that are at or above the national benchmarks, while the lengths of stay for the initial transplant surgery are shorter than the national average. These successes have now established our program as one of the premier transplant centers in the Midwest, and more than half of our patients come from distant cities and states. We now perform 20-25 kidney transplants each year, which places us within the top five busiest pediatric kidney transplant centers in the country. During the past year, we performed our first combined heart-kidney transplant successfully, with an excellent outcome. We also performed successful kidney transplants for several fetal care center “graduates” who had prenatal interventions for severe developmental anomalies of the kidneys and urinary tract. In addition, Dr. David Hooper has led the transformation of our kidney transplant program to comprehensively track and improve outcomes for our patients. We have standardize the measurement, reporting, and classification of blood pressure by RN’s and MD’s across 6 clinic locations in addition to prototyping, refining and implementing a sophisticated visit planning process that includes decision support. We also started the first dedicated kidney transplant clinic. These interventions have contributed to an increase in the percentage of patients in our population with controlled blood pressure from under 50% to nearly 70%.

A continued surge of infants at the Dialysis Center

The Dialysis Unit at Cincinnati Children's, directed by Dr. Rene Vandevoorde, is among the 10 largest in the country. By far the most challenging and complex dialysis patients are infants. Over the past couple of years, this extremely demanding population has exploded, and we now care for several infants on home dialysis. The majority of these infants have come from outside the Cincinnati area, many referred via our Fetal Care program

and others because of lack of complex dialysis expertise at their home institutions. The care of these infants is optimized through a coordination of services orchestrated by the dialysis unit, bringing together their medical, surgical, nutritional, developmental, and psychosocial needs. New policies for aggressive feeding, hormonal, and dialytic treatments have already resulted in improved physical and mental development, and earlier kidney transplantation. Such initiatives have assured optimal care and set best practice care standards for this unique dialysis population.

An enormously successful year for the new Center for Acute Care Nephrology

The incidence of acute kidney injury has reached epidemic proportions globally, afflicting one third of critically ill children and often resulting in death or chronic kidney disease. Stemming the tide requires a concerted effort to develop optimal care for patients with or at risk for acute kidney injury. These urgent needs led to the launch of the Center for Acute Care Nephrology (CACN) in 2010, a collaborative effort between Nephrology, the Heart Institute, and Critical Care, directed by Dr. Stuart Goldstein. Our clinical accomplishments have included launching the first in-house consultative acute Pheresis Service, implementation of early proactive peritoneal dialysis in children at risk for acute kidney injury after cardiac surgery, development of intra-operative plasmapheresis for Heart Institute patients with high antibody sensitization undergoing heart transplantation, and implementation of the Nephrotoxic Medication Associated Injury Negated by Just In Time Action (NephroNINJA) project which has led to the avoidance of 900 days of nephrotoxic medication associated acute kidney injury days annually.

Expert and unique care for children and adults with Tuberous Sclerosis

We have now established the largest referral center for the management of kidney manifestations of tuberous sclerosis in the country. Under the leadership of Dr. John Bissler, we perform innovative embolization techniques for renal angiomyolipomas that complicate tuberous sclerosis, and have pioneered the use of steroid therapy to minimize post-embolization complications.

Significant Publications

Pai AL, Rausch J, Tackett A, Marsolo K, Drotar D, Goebel J. System for integrated adherence monitoring: real-time non-adherence risk assessment in pediatric kidney transplantation. Pediatr Transplant. 2012 Jun;16(4):329-34.

In this manuscript, which was accompanied by an editorial, we reported for the first time how a combined approach of using self-report, electronic pill bottle monitoring, and calculated standard deviation of drug trough levels can be used to predict medication adherence in school-age kidney transplant recipients.

Hooper DK, Fukuda T, Gardiner R, Logan B, Roy-Chaudhury A, Kirby CL, Vinks AA, Goebel J. Risk of tacrolimus toxicity in CYP3A5 nonexpressors treated with intravenous nicardipine after kidney transplantation. Transplantation. 2012 Apr 27;93(8):806-12.

This is the first manuscript to characterize the risk of a potentially toxic drug interaction in kidney transplant recipients with a common genotype who are treated simultaneously with intravenous nicardipine and tacrolimus. We also demonstrated that some large pediatric transplant programs are prescribing this drug combination in over 30% of their patients, suggesting the potential to change clinical practice and avoid tacrolimus over-exposure in a significant portion of patients.

Dixon BP, Henry J, Siroky BJ, Chu A, Groen PA, Bissler JJ. Cell cycle control and DNA damage response of conditionally immortalized urothelial cells. PLoS One. 2011 Jan 28;6(1):e16595.

This manuscript describes a new cell line originating from the lining of the bladder of a genetically modified

mouse that can be grown in culture. The unique aspect of this cell line is that it can be grown in culture indefinitely under one set of conditions ("immortalized" cells), but by slightly adjusting these growth conditions, the cells behave more like normal bladder cells. When they behave more like normal bladder cells, these cells are able to sense when their DNA is damaged, and activate the appropriate responses to this damage. This work will allow researchers to study the development of bladder cancer in a normal bladder cell population, as well as to study how to correct severe birth defects involving the bladder experienced by some children.

Moffett BS, Goldstein SL. Acute kidney injury and increasing nephrotoxic-medication exposure in noncritically-ill children. Clin J Am Soc Nephrol. 2011 Apr;6(4):856-63.

This is the first manuscript to describe the complete epidemiology of nephrotoxic medication associated acute kidney injury in children, demonstrating a doubling of AKI rates when children are exposed to 3 or more nephrotoxins. This finding serves as the foundation for identifying patients at risk, which is of major significance for improving outcomes of children by optimizing their medication exposure and decreasing acute kidney injury.

Nehus E, Furth S, Warady B, Mitsnefes M. Correlates of resistin in children with chronic kidney disease: the chronic kidney disease in children cohort. J Pediatr. 2012 Aug;161(2):276-80.

This is the first study to demonstrate that serum resistin is involved in the inflammatory milieu present in children with chronic kidney disease, therefore identifying resistin as potential biomarker that can be used to improve cardiovascular outcomes in this population.

Division Publications

1. Abraham BP, Frazier EA, Morrow WR, Blaszak RT, Devarajan P, Mitsnefes M, Bryant JC, Sachdeva R. **Cystatin C and neutrophil gelatinase-associated lipocalin as markers of renal function in pediatric heart transplant recipients**. *Pediatr Transplant*. 2011; 15:564-9.
2. Arikan AA, Zappitelli M, Goldstein SL, Naipaul A, Jefferson LS, Loftis LL. **Fluid overload is associated with impaired oxygenation and morbidity in critically ill children**. *Pediatr Crit Care Med*. 2012; 13:253-8.
3. Askenazi DJ, Goldstein SL. **Renal Conditions**. *Manual of Neonatal Care*. Philadephia: Lippincott Williams & Wilkins; 2011:350-376.
4. Askenazi DJ, Koralkar R, Levitan EB, Goldstein SL, Devarajan P, Khandrika S, Mehta RL, Ambalavanan N. **Baseline values of candidate urine acute kidney injury biomarkers vary by gestational age in premature infants**. *Pediatr Res*. 2011; 70:302-6.
5. Askenazi DJ, Montesanti A, Hunley H, Koralkar R, Pawar P, Shuaib F, Liwo A, Devarajan P, Ambalavanan N. **Urine biomarkers predict acute kidney injury and mortality in very low birth weight infants**. *J Pediatr*. 2011; 159:907-12 e1.
6. Bagshaw SM, Haase M, Haase-Fielitz A, Bennett M, Devarajan P, Bellomo R. **A prospective evaluation of urine microscopy in septic and non-septic acute kidney injury**. *Nephrol Dial Transplant*. 2012; 27:582-8.
7. Basu RK, Donaworth E, Wheeler DS, Devarajan P, Wong HR. **Antecedent acute kidney injury worsens subsequent endotoxin-induced lung inflammation in a two-hit mouse model**. *Am J Physiol Renal Physiol*. 2011; 301:F597-604.
8. Basu RK, Standage SW, Cvijanovich NZ, Allen GL, Thomas NJ, Freishtat RJ, Anas N, Meyer K, Checchia PA, Lin R, Shanley TP, Bigham MT, Wheeler DS, Devarajan P, Goldstein SL, Wong HR. **Identification of candidate serum biomarkers for severe septic shock-associated kidney injury via microarray**. *Crit Care*. 2011; 15:R273.
9. Bennett MR, Piyaphanee N, Czech K, Mitsnefes M, Devarajan P. **NGAL distinguishes steroid sensitivity in idiopathic nephrotic syndrome**. *Pediatr Nephrol*. 2012; 27:807-12.
10. Bissler JJ. **Polycystic Kidney Disease**. *Clinician's Manual of Pediatric Nephrology*. Singapore; Hackensack,

NJ: World Scientific Publishing Co; 2011:703-712.

11. Blinder JJ, Goldstein SL, Lee VV, Baycroft A, Fraser CD, Nelson D, Jefferies JL. **Congenital heart surgery in infants: effects of acute kidney injury on outcomes**. *J Thorac Cardiovasc Surg*. 2012; 143:368-74.
12. Cavanaugh TM, Schoenemen H, Goebel J. **The impact of sirolimus on sex hormones in male adolescent kidney recipients**. *Pediatr Transplant*. 2012; 16:280-5.
13. Coca SG, Jammalamadaka D, Sint K, Thiessen Philbrook H, Shlipak MG, Zappitelli M, Devarajan P, Hashim S, Garg AX, Parikh CR. **Preoperative proteinuria predicts acute kidney injury in patients undergoing cardiac surgery**. *J Thorac Cardiovasc Surg*. 2012; 143:495-502.
14. Czech KA, Bennett M, Devarajan P. **Distinct metalloproteinase excretion patterns in focal segmental glomerulosclerosis**. *Pediatr Nephrol*. 2011; 26:2179-84.
15. Devarajan P. **Acute Kidney Injury**. *Pediatric Nephrology: A Handbook for Training Health Care Providers*. Singapore; Hackensack, NJ: World Scientific Publishing Co; 2011:159-194.
16. Devarajan P. **Acute Kidney Injury (AKI)**. *Clinician's Manual of Pediatric Nephrology*. Singapore; Hackensack, NJ: World Scientific Publishing Company; 2011:437-464.
17. Faubel S, Chawla LS, Chertow GM, Goldstein SL, Jaber BL, Liu KD. **Ongoing clinical trials in AKI**. *Clin J Am Soc Nephrol*. 2012; 7:861-73.
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20. Goebel J, Pai A. **Creating a monster: non-adherence underlying late transplant rejection**. *Pediatr Transplant*. 2012; 16:312-4.
21. Goldstein SL. **Acute kidney injury in children and its potential consequences in adulthood**. *Blood Purif*. 2012; 33:131-7.
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25. Goldstein SL. **A novel use for novel acute kidney injury biomarkers: fenoldopam's effect on neutrophil gelatinase-associated lipocalin and cystatin C**. *Crit Care*. 2011; 15:177.
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29. Hooper DK, Fukuda T, Gardiner R, Logan B, Roy-Chaudhury A, Kirby CL, Vinks AA, Goebel J. **Risk of tacrolimus toxicity in CYP3A5 nonexpressors treated with intravenous nicardipine after kidney transplantation**. *Transplantation*. 2012; 93:806-12.
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Devarajan P, Toto RM, Hsu CY, Greene TH, Mehta RL, Stokes JB, Thompson AM, Thompson BT, Westenfelder CS, Tumlin JA, Warnock DG, Shah SV, Xie Y, Duggan EG, Kimmel PL, Star RA. **Design of clinical trials in acute kidney injury: a report from an NIDDK workshop--prevention trials**. *Clin J Am Soc Nephrol*. 2012; 7:851-5.

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uric acid is associated with high blood pressure in pediatric hemodialysis patients. *Pediatr Nephrol*. 2011; 26:1123-8.

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Faculty, Staff, and Trainees

Faculty Members

Prasad Devarajan, MD, Professor

Leadership Louise M. Williams Endowed Chair; Director, Division of Nephrology & Hypertension; Director, Clinical Nephrology Laboratory; CEO, Dialysis Unit

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

John J. Bissler, MD, Professor

Leadership Director, Nephrology Fellowship Training Program; Associate Program Director for Research and Academic Careers; Clark D. West Chair of Nephrology

Research Interests Polycystic kidney disease, renal tumors, tuberous sclerosis complex, Renal Cell Biology

Bradley P. Dixon, MD, Assistant Professor

Leadership Assistant Director, Nephrology Fellowship Training Program

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

Jens Goebel, MD, Associate Professor

Leadership Medical Director of Transplantation; Clinical Director, Nephrology

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

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

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

- **Edward Nehus, MD**, PL-3
- **Rossana Malatesta-Muncher, MD**, PL-3
- **Ahmad Kaddourah, MD**, PL-2

- **Donna Claes, MD**, PL-2
- **Nianzhou Xiao, MD**, PL-1
- **Matthew O'Rourke, MD**, PL-1

Division Collaboration

Heart Institute » Catherine Krawczeski

Co-investigator on studies entitled "Novel biomarkers in cardiac surgery to detect acute kidney injury" and "Ancillary Studies in the natural history of acute kidney injury" (Prasad Devarajan)

Rheumatology » Hermine Brunner

Co-investigator on studies entitled "Forecasters of progression of chronic kidney disease" and "Advanced Proteomics for the early prediction of lupus nephritis" (Prasad Devarajan)

Rheumatology » Hermine Brunner

Co-PI on study entitled "Biomarkers to distinguish classes of lupus nephritis" and Research Associate on "Advanced Proteomics for the early prediction of lupus nephritis" (Prasad Devarajan)

Developmental Biology » Steven Potter

Co-investigator on studies entitled "Glomerulosclerosis in human FSGS and mouse models" (Prasad Devarajan)

Hematology/Oncology » Sonata Jodele

Co-Investigator on study entitled "A Prospective Analysis of Clinical and Biochemical Markers for Pediatric Stem Cell Transplant-Associated Thrombotic Microangiopathy" (Prasad Devarajan)

Critical Care Medicine » Derek Wheeler

Use of Novel Urine and Blood Biomarkers to Optimize Fluid Dosing in Critically Ill Children with Acute Kidney Injury (Prasad Devarajan)

James M Anderson Ctr for Health Systems Excellence » Peter A. Margolis

Reliable Individualized Monitoring Improves Cholesterol Control in Kidney Transplant Recipients (David K. Hooper, Jens Goebel)

James M Anderson Ctr for Health Systems Excellence » Adam C. Carle

Quality of CVD Care in Adolescents (David K. Hooper, Mark Mitsnefes)

Clinical Pharmacology » Tsuyoshi Fukuda, Alexander Vinks, and Rhonda Gardiner

Risk of Tacrolimus Toxicity in CYP3A5 Non-Expressors Treated with Intravenous Nicardipine After Kidney Transplantation (David K. Hooper, Jens Goebel)

James M Anderson Ctr for Health Systems Excellence » Ashwini Roy-Chaudhury

Risk of Tacrolimus Toxicity in CYP3A5 Non-Expressors Treated with Intravenous Nicardipine After Kidney Transplantation (David K. Hooper, Jens Goebel)

James M Anderson Ctr for Health Systems Excellence; Behavioral Medicine and Clinical Psychology; Preventive Cardiology » Peter A. Margolis, Ahna Pai, and Elaine M. Urbina

A Reliable Blood Pressure Management System (David K. Hooper, Mark Mitsnefes, Jens Goebel)

Urology » William DeFoor, Pramod Reddy, and Paul Noh

Collect NGAL on hydronephrosis before and after repair (Prasad Devarajan)

Grants, Contracts, and Industry Agreements

Grant and Contract Awards		Annual Direct
DEVARAJAN, P		
Research Training in Pediatric Nephrology		
National Institutes of Health		
T32 DK 007695	07/01/07-06/30/12	$126,844
DIXON, B		
DNA Damage and Response in the Bladder Microenvironment.		
National Institutes of Health		
K08 DK 081737	07/01/11-04/30/15	$140,200
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/Translational Sciences & Training		
National Institutes of Health(University of Cincinnati)		
UL1 RR 026314	04/03/09-03/31/14	$1,463,314
SIROKY, B		
Environmental Carcinogenesis and Mutagenesis		
Tuberous Sclerosis Alliance		
TSA 05-11	12/15/11-12/14/13	$60,000
	Current Year Direct	**$1,948,472**

Industry Contracts	
BISSLER, J	
Novartis Pharmaceuticals	$215,069
Otsuka Pharmaceutical Development & Commercialization Inc.	$34,157
GOEBEL, J	
Abbott Laboratories	$3,080
Amgen, Inc.	$22,784
GOLDSTEIN, S	
Baxter Healthcare	$30,800
McGill	$19,250
VANDEVOORDE, R	
Abbott Laboratories	$16,824
AMAG Pharmaceuticals	$14,091
Current Year Direct Receipts	**$356,055**

Service Collaborations	
GOLDSTEIN, S	
Baxter Plasmalyte	$4,800
Watermark	$6,975
Current Year Direct	**$11,775**
Total	**$2,316,302**