Pediatric Insights

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An Update from the Division of Pediatric Nephrology

In This Issue

UPMC CHILDREN'S HOSPITAL OF PITTSBURGH

New R01 Grant to Study microRNA in Acute Kidney Injury

UPMC Children's Hospital of Pittsburgh Division of Pediatric Nephrology researchers **Sunder Sims-Lucas, PhD**, and **Jacqueline Ho, MD**, were awarded a four-year R01 grant from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), which is part of the National Institutes of Health (NIH).

Drs. Sims-Lucas and Ho's new grant will fund research into how the microRNA (miRNA) cluster 17~92 may work to protect against the renal damage that results from an acute kidney injury (AKI). Their study will probe the role of miR-17~92 and its ability to protect and possibly repair the renal microvasculature after AKI.

AKI affects a substantial portion of hospitalized patients (approximately 20%) and an even greater number of critically ill patients (~50%). At present, there are no treatments outside of supportive measures to halt or reverse an AKI and the damage it inflicts on the kidney. Once an individual suffers an AKI, they are at significant risk for both another AKI and the development of chronic kidney disease (CKD). Finding an effective treatment for AKI is of the utmost importance to blunt the short- and long-term morbidity and mortality associated with AKI and subsequent CKD.

Previous studies in the laboratories of Dr. Sims-Lucas and Dr. Ho have shown that several of the miRNAs in the 17~92 cluster (17; 18a; 19a/b; 20a; 92a) are required for the normal development and function of the kidney. However, little is currently known about how these miRNAs function in the renal microvasculature. Additionally, there are two other gaps in the scientific knowledge that need to be addressed in order to develop therapies targeted at the renal microvasculature. The first is a better understanding of the molecular mechanisms that drive endothelial repair after AKI; the second, whether it is possible to modulate the capacity of the renal microvasculature for repair after AKI.

Preliminary data from the researchers in a knockout model of AKI in mice where miR-17~92 is deleted in endothelial cells show a high susceptibility to ischemic-reperfusion injury. The researcher's central hypothesis is that miR-17~92 promotes endothelial cell repair after an injury and protects against AKI. The thrust of the R01 grant will attempt to understand the requirement for endothelial miR-17~92 during renal injury and repair, and to determine whether miR-17~92 is sufficient by itself to protect against renal injury associated with AKI.

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Kidney Transplantation Research: New Findings in Antibody-Mediated Rejection

Paul Fadakar, MD, is an assistant professor of pediatrics in the Department of Pediatrics at the University of Pittsburgh School of Medicine, and an attending nephrologist in the Division of Pediatric Nephrology at UPMC Children's Hospital of Pittsburgh. Dr. Fadakar joined the Division in 2018 after completing his nephrology fellowship training at UPMC Children's. During his fellowship, Dr. Fadakar's research focused on translational investigations of transplant immunology at the Thomas E. Starzl Transplantation Institute.

Dr. Fadakar's work involved ongoing projects in the laboratory of Diana M. Metes, MD, investigating the role of T follicular helper cells in antibody-mediated rejection (ABMR) in renal transplant recipients.

One of those research projects in which Dr. Fadakar was a collaborator was published in October in the *Journal of the American Society of Nephrology* (JASN) under the title of "Coordinated Circulating T Follicular Helper and Activated B Cell Responses Underlie the Onset of Antibody-Mediated Rejection in Kidney Transplantation."[1]

Research Summary

A leading cause of kidney transplant allograft failure is antibody-mediated rejection, a chronic attack upon the allograft tissues caused by antibodies directed against donor-specific HLA molecules, blood group antigen isoagglutinins, or endothelial cell antigens.[2]

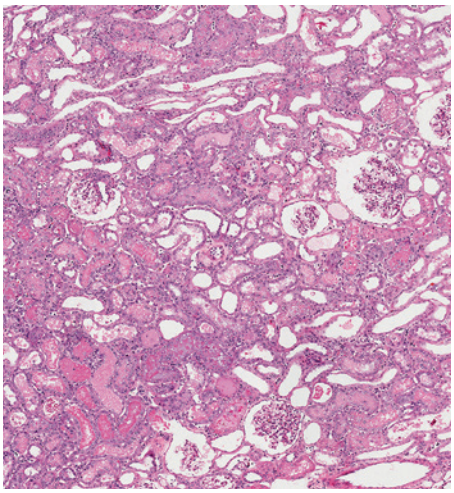
While much has been uncovered about how ABMR functions, many of the basic cellular and molecular pathways that lead to donor-specific antibody responses in the host are not well understood. Uncovering these processes and pathways may lead to more effective antirejection protocols and therapeutic targets.

The study in which Dr. Fadakar was a participant examined aspects of T follicular helper cells (TFH) and B cells, and their interactions and signaling in kidney transplant patients experiencing antibody-mediated rejection.

"Our study isolated a cohort of 20 individuals from a larger population of kidney transplant patients who were both positive for ABMR and the presence of donor-specific antibodies. We looked at these individuals' levels of TFH and B cells compared to other kidney transplant patients. We uncovered a number of important observations in how the T cells and B cells interact and signal, and what the products of those interactions are," says Dr. Fadakar.

According to the clinical implications summary from the paper, "... the authors identified highly coordinated responses of circulating TFH cells and activated B cells at phenotypic, functional, and transcriptional levels in patients with antibody-mediated rejection. The levels of circulating TFH cell and B cell activation were predictive of DSA pathogenicity, histologic severity, and allograft loss. This study provides novel mechanistic insights into the cellular and molecular processes underlying antibody-mediated rejection and a rationale for monitoring and therapeutic targeting of circulating TFH cell–B cell interaction during antibody-mediated rejection."

"For decades, the University of Pittsburgh and UPMC Children's have been pioneering leaders in transplantation medicine — for children and adults — built upon the seminal work of Dr. Thomas Starzl and many other colleagues.



Our new research is an extension of that legacy, another building block on the path toward the day when the complication of rejection in organ transplantation is a distant memory," says Dr. Fadakar.

References

[1] Louis K, Macedo C, Bailly E, et al. Coordinated Circulating T Follicular Helper and Activated B Cell Responses Underlie the Onset of Antibody-Mediated Rejection in Kidney Transplantation. *JASN.* October 2020; 31(10): 2457-2474.

[2] Singh N, Pirsch J, Samaniego M. Antibody-Mediated Rejection: Treatment Alternatives and Outcomes. *Transplant Rev.* 2009; 23(1): 34-46.

New Research Finding: KGF Protective in Cyclophosphamide Bladder Injury

UPMC Children's Hospital of Pittsburgh Division of Pediatric Nephrology researchers studying the mechanisms that lead to cyclophosphamide bladder injury (CBI) showed in a paper[1] published in January 2020 in the *American Journal of Pathology* that Keratinocyte Growth Factor (KGF) plays a role in mitigating and recovering from CBI. Division Chief **Carlton M. Bates, MD**, is the senior author on the paper and Director of the Bates Laboratory and the team that worked on the research.

Cyclophosphamide (CP) is a chemotherapeutic agent used to treat various forms of cancer. CP also is used to treat nephrotic syndrome and rheumatological diseases, including systemic lupus erythematosus, because of its suppressive effects on the immune system.

However, CP has, among other toxicities, the potential to injure the bladder urothelium causing acute and possibly life-threatening hemorrhagic cystitis and bladder cancer years after treatment.

Dr. Bates' CBI research is funded by a National Institutes of Health (NIH) R01 grant[2] that he was awarded in 2019 to study the "Role of FGFR2 Signaling in Bladder Injury and Regeneration."

Dr. Bates' study in a mouse model, showed that KGF, given prior to CP, blocked CP-driven apoptosis and accelerated regeneration of urothelial cells in the bladder. KGF also led to higher fidelity repair of bladder urothelium after CP when compared with vehicle treatment.

This initial study points in the direction of KGF being a potential therapeutic agent that could be given in tandem with cyclophosphamide to mitigate its potential toxicities and bladder damage. More studies will need to be conducted to better understand the mechanisms by which KGF can act against cyclophosphamide-induced bladder injury, and Dr. Bates and colleagues are currently working on additional research as part of their NIH R01 study.

Further Reading

[1] Narla ST, Bushnell DS, Schaefer CM, Nouraie M, Bates CM. Keratinocyte Growth Factor Reduces Injury and Leads to Early Recovery From Cyclophosphamide Bladder Injury. *Am J Pathology.* 2020; 190(1): 108-124.

[2] Role of FGFR2 Signaling in Bladder Injury and Regeneration. Project number: R01DK121493. Principal investigator: Carlton M. Bates, MD.

About the Division

The Division of Pediatric Nephrology at UPMC Children's Hospital of Pittsburgh provides a full range of services for the evaluation and management of children with simple or complex nephrologic or urologic disorders. UPMC Children's is ranked 13th nationally by *U.S. News and World Report* in pediatric nephrology.

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For a referral or consultation, please contact us at 412-692-5182. Visit us online at **CHP.edu/Nephrology**.

Basic Science Update: New Findings in Vesicoureteral Reflux

UPMC Children's Hospital of Pittsburgh Division of Pediatric Nephrology researcher **Melissa J. Anslow, MD**, published new findings this year in the journal *Pediatric Research* on her research into the mechanisms and pathways of vesicoureteral reflux (VUR). Dr. Anslow's basic science laboratory is focused on congenital anomalies of the kidney and urinary tract. In 2018, Dr. Anslow was awarded a two-year K-12 institutional career development grant to pursue her research into how microRNAs (miRNAs) contribute to increased rates of VUR. Dr. Anslow has created a transgenic mouse model with a knockout of the *Dicer* enzyme responsible for miRNA formation. Among other functions, miRNA regulates gene expression post-transcriptionally.

Previous work by Dr. Anslow in her animal models showed significantly higher rates of VUR in mice that lack the *Dicer* enzyme, implicating miRNAs for the first time in the development of VUR.

"We have good evidence for miRNAs role in VUR and the broader spectrum of kidney development. My continuing research is working to pinpoint which miRNAs are responsible for VUR development and the signaling pathways in which they work," says Dr. Anslow.

New Research Summary

Dr. Anslow's new research examined what role miRNAs play during the development of ureteric bud induction and formation of the vesicoureteral junction (VUJ). Normal development of these structures is key to the prevention of VUR.

It is known that ureteric bud induction is regulated by signaling pathways from the peri-Wolffian duct stromal cells, but what has been unclear is if miRNAs expressed in the peri-Wolffian duct stroma have any influence or regulatory properties that, if disrupted or otherwise modulated, could negatively affect either or both ureteric bud induction or the VUJ.

To test this hypothesis, Dr. Anslow and colleagues created a knockout mouse model with no miRNA expression in the critical peri-Wolffian duct stroma. They then examined the ureteric bud induction for defects, and also the presence of VUR by way of cystogram, along with screening for any potential gene expression irregularities that may have arisen from the knockout of miRNAs.

"Our study found that while gene expression seemed to be unaffected in the knockout model, there were marked changes in the ureteric bud induction sites, and the knockout animals experienced high rates of VUR compared to our control groups. This tells us that, indeed, miRNAs play a critical role in the peri-Wolffian duct stroma to regulate normal development and prevent VUR. We will be further exploring aspects of miRNA regulation and pathways in our continuing VUR research," says Dr. Anslow.

Reference

Anslow MJ, Bodnar AJ, Cerqueira DM, Bushnell D, Shrom BE, Sims-Lucas S, Bates CM, Ho J. Increased Rates of Vesicoureteral Reflux in Mice From Deletion of Dicer in the Peri-Wolffian Duct Stroma. *Pediatr Res.* 2020; 88: 382–390.

New R01 Grant to Study microRNA in Acute Kidney Injury *Continued from Page 1*

Further Reading

Previously published work from Dr. Sims-Lucas and Dr. Ho that informs their new R01 are listed below. More details and the full abstract of the new grant can be found on the NIH RePORTER website.

The Role of MIR-17~92 in Nephron Progenitors. 5R01DK103776-05. Principal Investigator: Jacqueline Ho, MD.

The Role of Sirtuin 5 in Acute Kidney Injury. 1R56DK121758-01. Principal Investigator: Sunder Sims-Lucas, PhD.

Chiba T, Peasley KD, Cargill KR, Maringer KV, Bharathi SS, Mukherjee E, Zhang Y, Holtz A, Basisty N, Yagobian SD, Schilling B, Goetzman ES, Sims-Lucas S. Sirtuin 5 Regulates Proximal Tubule Fatty Acid Oxidation to Protect Against AKI. *J Am Soc Nephrol.* 2019 Dec; 30(12): 2384-2398.

Marrone AK, Stolz DB, Bastacky SI, Kostka D, Bodnar AJ, Ho J. MicroRNA-17~92 Is Required for Nephrogenesis and Renal Function. *J Am Soc Nephrol.* 2014 Jul; 25(7): 1440-1452

Hemker SL, Cerqueira DM, Bodnar AJ, Cargill KR, Clugston A, Anslow MJ, Sims-Lucas S, Kostka D, Ho J. Deletion of Hypoxia-Responsive microRNA-210 Results in a Sex-Specific Decrease in Nephron Number. *FASEB J.* 2020 Mar 5. doi: 10.1096/fj.201902767R. Epub ahead of print.

Phua YL, Chen KH, Hemker SL, Marrone AK, Bodnar AJ, Liu X, Clugston A, Kostka D, Butterworth MB, Ho J. Loss of miR-17~92 Results in Dysregulation of Cftr in Nephron Progenitors. *Am J Physiol Renal Physiol.* 2019 May 1; 316(5): F993-F1005.

New Maintenance Fluid Guidelines Gaining Traction in Hospitals

In November 2018, the American Academy of Pediatrics (AAP) published the first-ever clinical practice guidelines in the United States for the use of intravenous maintenance fluids in children. The new, evidence-based guidelines are meant, in part, to reduce or prevent hospital-acquired hyponatremia and its associated morbidities and mortalities. The literature shows approximately a 15% to 30% rate of hyponatremia in hospitalized children and adults.

Michael L. Moritz, MD, FAAP, clinical director and director of dialysis in the Division of Pediatric Nephrology at UPMC Children's Hospital of Pittsburgh, was the senior author on the committee that established the guidelines, which in part reflect a clinical practice change that Dr. Moritz has pioneered and studied for the past 15 years: namely, the use of isotonic fluids over those of a hypotonic concentration.

The *Key Action Statement* from the new guidelines, "Recommends that patients 28 days to 18 years of age requiring maintenance IVFs should receive isotonic solutions with appropriate potassium chloride and dextrose because they significantly decrease the risk of developing hyponatremia."[1]

"Hypotonic fluids have, unfortunately, been the standard of care in pediatrics for more than 50 years, primarily based on tradition and not evidence. I introduced the concept of avoiding hypotonic fluids and using isotonic fluids to prevent hyponatremia about 15 years ago. Since then, numerous studies in thousands of children have demonstrated that isotonic fluids decrease the incidence of hyponatremia from greater than 20% to less than 5%," says Dr. Moritz.

Survey to Assess Isotonic Fluid Use

Now that the new clinical guidelines have been in place for nearly 18 months, are they being implemented by physicians and hospitals?

To find out, Dr. Moritz and colleagues Alan M. Hall, MD, from the University of Kentucky College of Medicine, and Juan Carlos Ayus, MD, from the University of California Irvine School of Medicine, surveyed pediatric hospitalists across the United States. The results of their research were published in January in the journal *Frontiers in Pediatrics.*[2]

The anonymous and voluntary survey was distributed to physicians who are part of the American Academy of Pediatrics Section on Hospital Medicine. Responses from 402 individuals were elicited from the survey request, which equates to a 10.1% response rate. The broad conclusion of the survey showed that pediatric hospitalists are choosing to follow the new fluid guidelines.

Survey responses indicated that for patient populations age 1 year to 18 years, 87.8% of surveyed physicians were using the recommended isotonic fluids for their hospitalized patients. For patients age 28 days to 1 year, the usage rate was 66.3%. For those younger than 28 days, 10.6% of physicians indicated the use of isotonic fluids. It should be noted that the new fluid guidelines specifically exclude neonates younger than 28 days or who are in the NICU from receiving isotonic fluids.

The guidelines recommend the use of isotonic fluids; based on this survey, pediatric hospitalists are following the guidelines for patients outside of the neonatal period.

References

[1] Feld LG, Neuspiel DR, Foster BA, et al. Clinical Practice Guideline: Maintenance Intravenous Fluids in Children. *Pediatrics.* 2018; 142(6): e20183083. Epub ahead of print.

[2] Hall AM, Ayus JC, Moritz ML. How Salty Are Your Fluids? Pediatric Maintenance IV Fluid Prescribing Practices Among Hospitalists. *Front Pediatr.* 2020; 7: 549. Epub ahead of print.

Division Welcomes Cassandra Formeck, MD

In July, the Division of Pediatric Nephrology at UPMC Children's Hospital of Pittsburgh welcomed its newest faculty member, **Cassandra Formeck, MD**. Dr. Formeck completed her undergraduate studies in neuroscience at the University of Pittsburgh, followed by her medical degree from The Ohio State University College of Medicine and residency at Nationwide Children's Hospital.

In 2016, Dr. Formeck began a fellowship in pediatric nephrology at UPMC Children's, and subsequently became a postdoctoral scholar on the Division's NIH T32 training grant immediately prior to accepting her faculty position as an assistant professor.

Dr. Formeck gained an early interest in urinary tract pathology and physiology as an undergraduate, which led her to perform research on the neural regulation of urogenital tract function during postnatal development and following neural injury under the mentorship of William de Groat, PhD, at the University of Pittsburgh Department of Pharmacology and Chemical Biology. During medical school and residency, Dr. Formeck had the opportunity to investigate antimicrobial peptides and urinary tract immunity. In 2018, Dr. Formeck presented two abstracts at the American Society of Nephrology Kidney Week. Her research conducted at UPMC Children's as a fellow involved studies of hyponatremia associated with the development of sepsis and acute kidney injury epidemiology, risk factors, and prevention.

"Early in my medical training, I found myself drawn toward patients with complex renal issues. These patients tested my medical knowledge and engaged my critical thinking. Through residency and my exposure to the diversity of pediatric medicine, I found nephrology both compelling and fulfilling," says Dr. Formeck.

Dr. Formeck Awarded UPMC Children's Scholar's Program Award

Upon completing her fellowship, Dr. Formeck applied for and was awarded a UPMC Children's Scholar's Program grant. This competitive, internal two-year funding award supports early and junior faculty members with additional training on the path to becoming independent physician-scientists.

Dr. Formeck's research has been focused on acute kidney injury as a risk factor for subsequent infections in the critical care setting. With the funding support from the UPMC Children's Scholar's Program, Dr. Formeck will continue her AKI research and attempt to find causal pathways between acute kidney injury and subsequent infections, such as sepsis. Dr. Formeck will be working with the Center for Causal Discovery at the University of Pittsburgh, whose main interest is in using causal discovery methods to derive valid, novel, and significant causal relationships from large biomedical data sets to spur new insights and therapies.

New Paper Links AKI with Sepsis in Critically Ill Patients

In August, Dr. Formeck published a new paper[1] in the journal *Pediatric Critical Care Medicine* on the association between acute kidney injury and the subsequent development of sepsis in critically ill children. Joining Dr. Formeck on the study was Division of Pediatric Nephrology colleague Dana Y. Fuhrman, DO, and former Division Faculty Emily Joyce, MD The senior author on the paper is internationally-respected acute kidney injury expert John A. Kellum, MD, Endowed Chair in Critical Care Research, and Vice-Chair for Research in the Department of Critical Care Medicine at the University of Pittsburgh School of Medicine.

Dr. Formeck's study, a single-center retrospective analysis, examined data from more than 5,000 cases of children treated at UPMC Children's pediatric and cardiac critical care units, 255 of which were identified as having a stage 2 or 3 acute kidney injury (AKI).

"There has been a lot of discussion about the immunological components of having acute kidney injury and whether or not AKI predisposes one to severe infections — including sepsis. Our study was designed to specifically look at what associations or risks exist for AKI patients to develop sepsis. Both AKI and sepsis have high rates of morbidity and mortality, with AKI having no directed therapeutic treatment options at this time. Both are a challenge to treat, but if we know that AKI patients are susceptible to sepsis or other infections, we may be able to identify modifiable mediators that allows us to reduce the risk for subsequent infection and thereby reduce mortality in these patients," says Dr. Formeck

Of the 255 children identified with a stage 2 or 3 AKI, 18% went on to develop suspected sepsis, compared to 5.4% of critically ill children stage 1 or no AKI. When adjusting for other factors, children with stage 2/3 AKI had more than a two-fold increase in the risk of subsequent sepsis. Those with a stage 2 AKI were shown to exhibit a 1.79-fold increase in the odds of developing sepsis, while those with a stage 3 AKI showed a more than three-fold increase in odds – 3.24 to be exact.

"Not only have we shown that AKI increases the risk for subsequent infection in a heterogenous cohort of critically ill children, but our study also supports the concept of AKI as a clinically relevant immunocompromised state. More work will need to be done to further our findings," says Dr. Formeck.

Reference

[1] Formeck CL, Joyce EL, Fuhrman, DY, Kellum JA. Association of Acute Kidney Injury With Sepsis in Critically Ill Children. *Pediatr Crit Care Med.* 2020 Aug 27. Epub ahead of print.

Nephrology Clinical Trials Update

The Division of Pediatric Nephrology at UPMC Children's Hospital of Pittsburgh has a number of clinical trials open for pediatric nephrology patients. Below is current list of trials currently recruiting patients. Referring physicians who have patients that may be candidates for enrolling in any of the trials should contact 412-692-5182 for additional information including inclusion/exclusion criteria.

Newly Opened Trials at UPMC Children's

Sparsentan: A Randomized, Multicenter, Double-Blind, Parallel, Active-Control Study of the Effects of Sparsentan, a Dual Endothelin Receptor and Angiotensin Receptor Blocker, on Renal Outcomes in Patients With Primary Focal Segmental Glomerulosclerosis (FSGS).

Ongoing Clinical Studies

CURE-GN – Cure Glomerulonephropathy Network: Multicenter study examining the epidemiology, biomarkers, genetics, and patient-reported outcomes of four glomerular diseases: Minimal Change Disease (MCD), Focal Segmental Glomerulosclerosis (FSGS), Membranous Nephropathy (MN), and IgA Nephropathy (IgAN and IgAV).

CARE-DX: Utilization of dd-cfDNA to assess for rejection, monitor high risk pediatric patients via a surveillance protocol, and assess the response to therapy in patients with biopsy proven 1B rejection.

Ongoing Pharmaceutical Studies

Relypsa: A Phase 2, Open-Label, Multiple Dose Study to Evaluate the Pharmacodynamic Effects, Safety, and Tolerability of Patiromer for Oral Suspension in Children and Adolescents 2 to < 18 Years of Age with Chronic Kidney Disease and Hyperkalemia (EMERALD).

Dicerna 201: A Phase 2 Placebo-Controlled, Double-Blind, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of DCR-PHXC Solution for Injection (subcutaneous use) in Patients with Primary Hyperoxaluria.

Cardinal: A Phase 2/3 Trial of the Efficacy and Safety of Bardoxolone Methyl in Patients with Alport Syndrome.

Eagle: An Extended Access Program To Assess Long Term Safety of Bardoxolone Methyl In Patients With Chronic Kidney Disease. *Provide continuing open-label treatment with bardoxolone methyl as part of this extended access program while collecting ongoing safety and tolerability data of bardoxolone methyl. Open to patients upon completion of the Cardinal study and who meet the other inclusion criteria.*

VX19-NEN801: A Study of the Prevalence of Apolipoprotein L1 (APOL1) Alleles Among Individuals With Proteinuric Kidney Disease Who Are of Recent African Ancestry or Geographic Origin.

VX19-147-101: A Phase 2a, Open-label, Single-arm, 2-Part Study to Evaluate the Efficacy, Safety, and Pharmacokinetics of VX–147 in Adults With APOL1-dependent Focal Segmental Glomerulosclerosis.

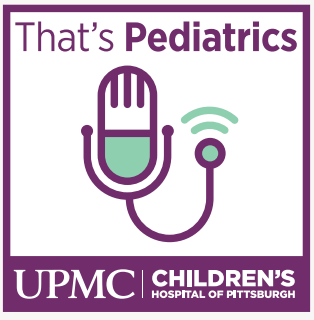
HECTORAL: Evaluate the effect of Hectorol® capsules in reducing elevated levels of intact parathyroid hormone (iPTH).

NAPRTCS Cystinosis Registry: This study will report the longitudinal and comparative epidemiology, care, and outcomes for North American children with all stages of chronic kidney disease, including those on dialysis and status post kidney transplant, with the ultimate goal of improving outcomes.

UPMC Children's Hospital of Pittsburgh Pediatric Research Podcast Series

UPMC Children's Hospital of Pittsburgh "That's Pediatrics" podcast series features interviews with the hospital's leading researchers and clinicians.

Episodes featuring pediatric nephrology faculty include compelling interviews with scientists at UPMC Children's Hospital who are performing innovative basic, translational, and clinical research. Subscribe to "That's Pediatrics" in iTunes or Google Play Music to have new episodes automatically download to your phone for free when they become available.



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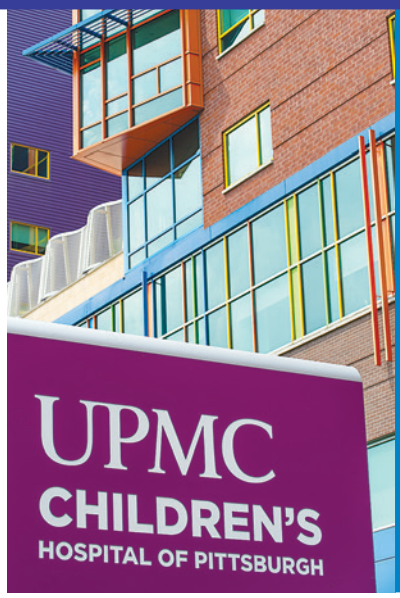

About UPMC Children's Hospital of Pittsburgh

Regionally, nationally, and globally, UPMC Children's Hospital of Pittsburgh is a leader in the treatment of childhood conditions and diseases, a pioneer in the development of new and improved therapies, and a top educator of the next generation of pediatricians and pediatric subspecialists. With generous community support, UPMC Children's Hospital has fulfilled this mission since its founding in 1890. UPMC Children's is recognized consistently for its clinical, research, educational, and advocacy-related accomplishments, including ranking 15th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2019) and ranking on *U.S. News & World Report's* Honor Roll of America's Best Children's Hospitals (2020–21).

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