Pediatric Insights

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An Update from the Division of Pediatric Nephrology

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 15th nationally by *U.S. News and World Report* in pediatric nephrology.

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UPMC CHILDREN'S HOSPITAL OF PITTSBURGH

Researching the Origins and Drivers of Kidney Development and Chronic Kidney Disease

While much is known about the origins and processes of kidney development, there remain gaps in our understanding of the basic science and molecular mechanisms of kidney formation — normal and abnormal. The same can be said for various kidney pathologies and the causes of renal failure and chronic kidney disease. Unfortunately, there also exists a very limited arsenal of therapies to slow the progressive loss of renal function in individuals with chronic kidney disease.

The laboratory of Jacqueline Ho, MD, assistant professor and director of the Pediatric Nephrology Fellowship Program in the Division of Pediatric Nephrology, is pursuing new lines of research into the role of microRNAs (miRNAs) and how they may regulate kidney development and disease processes. Dr. Ho's lab has also begun basic science studies on how certain in utero exposures, specifically maternal diabetes and hypoxia, may affect kidney development and how this might impact the risk of chronic kidney disease in the child.

MicroRNAs and Kidney and Nephron Formation

As Dr. Ho explains, approximately a third of the cases of chronic kidney disease (CKD) they see in the Division are attributable to congenital anomalies of the kidney and urinary tract, with renal dysplasia/hypoplasia being the leading cause of renal failure. There is also a wide variation from individual to individual in the quantity of nephrons in their kidneys. Individuals with fewer nephrons may be predisposed to CKD because of a relative lack of renal reserve in the face of various disease processes, acute injuries, and perhaps even the aging process. "The nephron has and needs a very complicated, three-dimensional structure to work appropriately.

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Dr. Ho and colleagues from the Division of Pediatric Nephrology have recently begun working with the University of Pittsburgh Center for Biologic Imaging (CBI) on imaging studies of the kidney.[2] The novel technology they have developed allows for the imaging of whole organs and other structures at the cellular level, achieving heretofore unheard of levels of resolution and detail. "The technology the CBI has worked to develop effectively allows us to image the entire kidney at the cellular level. We can actually count the number of nephrons in the kidney and see other structures in amazing detail and clarity," says Dr. Ho. More about the CBI and their imaging technology can be found at **Pittmed.health.pitt.edu/story/voyages-fantastic**.

Cellular and Molecular Drivers of Nephronophthisis

Nephronophthisis (NPHP) is a highly heterogeneous disease with genetic origins that mainly affects a pediatric population, but the condition can also manifest in older individuals during adolescence or even later in one's 20s or 30s. A multigene disorder, there are currently more than 30 identified genes known to be causative of the condition, but an individual only needs a mutation in a single gene for disease to occur. Although NPHP has long been considered a "ciliopathy," caused by a dysfunction in cilia, recent gene identification in humans has linked the pathogenesis of NPHP to defective DNA damage response signaling, resulting in genome instability and cell-cycle defects.

"This is for sure a disease that presents itself on a broad spectrum, and one in which the underlying pathomechanisms are not well understood," says Rannar Airik, PhD, a research specialist in pediatric nephrology who is currently an assistant professor of pediatrics and developmental biology at UPMC Children's and the University of Pittsburgh. Dr. Airik joined the Division in 2015 after previous appointments and fellowships at the University of Michigan and Boston Children's Hospital.

Dr. Airik's lab is currently focused on deciphering the mechanisms of chronic kidney disease resulting from NPHP using knockout murine models of *SDCCAG8, CEP164,* and *FAN1* — genes known to cause NPHP in humans. Dr. Airik's postdoctoral research was responsible for identifying for the first time the role of these three specific genes in NPHP, and specifically how DNA damage response and instability drives degenerative phenotypes of tubular atrophy and interstitial fibrosis that result from mutations in these target genes.

Pathomechanical Hallmarks of NPHP

While NPHP is highly heterogeneous, the clinical picture of the disease has certain commonalities, including tubular cysts and progressive interstitial scarring or fibrosis of the affected kidneys. Since the diseased kidneys display classic features of chronic kidney disease, NPHP represents an ideal genetic model to study the underlying mechanisms of this degenerative condition. "NPHP is an autosomal recessive disease, so it requires two alleles of a gene to be mutated in order to manifest. While the disease mechanisms remain largely enigmatic, it has been established, that the proteins encoded by NPHP genes localize to the primary cilium or centrosome. This shared subcellular localization is thought to unite the clinical phenotype of the condition," says Dr. Airik.

Accordingly, the current thinking postulates that NPHP proteins function in the cilium or at the centrosome, which in ciliated cells forms the base of the cilium. The ciliary axoneme is essentially a microtubular extension of the centrosome, that forms at the apical side of the renal tubular epithelial cells and protrudes into the tubular lumen. Various chemical and mechanical signals in this space are perceived by the primary cilium, which interprets them and relays to the cytoplasm. Dysregulation of this signaling axis precipitates NPHP. Although, this model of NPHP pathogenesis is widely accepted, recent gene identification in humans has challenged it, and linked the pathogenesis of NPHP to defective DNA damage response signaling, resulting in genome instability and cell-cycle defects. These findings have provided new insights to NPHP proteins' role in the primary cilium and cell cycle regulation.

"During my postdoctoral research, we discovered that, in addition to ciliary and centrosomal localization, some NPHP proteins localize to the nucleus where they participate in DNA replication and repair. Being normally components of the DNA replication machinery, their absence leads to destabilized replication forks, activation of DNA damage response, and ultimately to cellular senescence which underpins tubular atrophy and interstitial fibrosis in NPHP, and in chronic kidney disease in general."

Chronic Kidney Disease and the *FAN1* Gene

Dr. Airik's past work with the *FAN1* gene has led to his securing a new NIH RO1 grant to continue his research into interrogating the role of DNA damage response signaling in the development of chronic kidney disease.

FAN1, a DNA structure-specific endonuclease, functions at DNA repair and replication fork stabilization. Individuals with mutations in *FAN1* gene develop a form of chronic kidney disease, known as karyomegalic tubulo-interstitial nephritis, in their thirties. The affected kidneys display features of aged kidneys, suggesting that *FAN1* is required to protect kidneys from premature senescence.

"DNA damage repair is a very important component of the aging kidney required to avoid chronic kidney disease. Defective DNA repair via genetic mutation appears to be one of the culprits based on our *FAN1* knockout model. We're very interested in how the process of DNA repair through this pathway affords a protective function in the kidney, and are investigating how dysregulation of the process could be targeted therapeutically in order to slow or halt fibrotic progression and CKD," says Dr. Airik.

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Should Lactated Ringer's Become the Default Intravenous Solution?

Michael L. Moritz, MD
Professor of Pediatrics, University of Pittsburgh School of Medicine

Intravenous fluids play a critical role in the management of acutely ill patients as a bolus infusion for resuscitation, a continuous maintenance fluid, and as a vehicle to administer medications. It is now well established that acutely ill patients are at risk for developing hospital-acquired hyponatremia due to numerous stimuli for arginine vasopressin secretions (AVP), and that isotonic solutions should be used and hypotonic solutions should be avoided in order to prevent hospital-acquired hyponatremia.[1] One area of controversy is whether isotonic intravenous solutions should be 0.9% saline (normal saline) versus a balanced electrolyte solution (lactated Ringer's or Plasma-Lyte).[2] There has been a growing concern that 0.9% saline has a supraphysiologic chloride concentration and may result in untoward complications, such as hyperchloremic metabolic acidosis, renal vasoconstriction, delayed micturition, hyperkalemia, and an increased incidence of acute kidney injury and need for renal-replacement therapy. No well-conducted clinical trials have been able to demonstrate the superiority of a balanced solution over 0.9% saline in clinical practice until two recent studies published in the *New England Journal of Medicine*.

Are Balanced Solutions Superior to 0.9% Saline in Clinical Practice? The SALT-ED and SMART trials

Two large trials recently published in the *New England Journal of Medicine* sought to address whether balanced solutions are superior to 0.9% saline in clinic practice; the data did suggest that there was a small benefit to balanced resuscitation solutions in comparison to normal saline.[3,4] The Saline Against Lactated Ringer's or Plasma-Lyte in the Emergency Department (SALT-ED) and Isotonic Solutions and Major Adverse Renal Events (SMART) trials involved almost 30,000 adult patients at one large tertiary care center in the United States. These were parallel pragmatic clinic trials where there was a waiver of informed consent, fluid allocation was unblinded to either normal saline or a balanced solution based on alternating calendar months, and the volume of the resuscitation solution and choice of balanced solution (either lactated Ringer's or Plasma-Lyte) was left to the discretion of the treating physician. In the SMART study, patients were admitted to one of five different ICUs. Both studies demonstrate an absolute decrease of about 1 percent for a composite of major adverse kidney events at 30 days, defined as death, new renal replacement therapy, or a persistent two-fold increase in serum creatinine. Neither study was able to demonstrate a statistically significant benefit to any one factor independently. The benefits of a balanced solution were seen primarily in critically ill patients with sepsis and those with preceding acute kidney injury and previous renal replacement therapy. Two groups of patients that fared better with 0.9% saline were patients admitted to the cardiac ICU or with traumatic brain injury.

Based on the findings of these two studies, many editorial commentaries and news outlets have recommended that balanced solutions be used in favor of normal saline.[5] Given that millions of hospitalized patients require fluid resuscitation, even a modest benefit, with a need to treat 100 patients to prevent one major adverse renal event, could potentially translate into a benefit to tens of thousands of patients yearly. By extension, practitioners may choose to use balanced solutions over normal saline for not only resuscitation fluids, but as maintenance fluids as well, as there is no obvious theoretical advantage to using normal saline over a balanced solution.

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Table 1. Composition of Commonly Used Resuscitation Fluids

Fluid	Sodium	Chloride	Potassium mEq/L	Calcium	Magnesium	Buffer	Osmolarity mOsm/L
Human plasma	135-145	95-105	3.5-5.3	4.4-5.2	1.6-2.4	23 – 30 bicarbonate	308[a]
Normal Saline							
0.9% NaCl	154	154	0	0	0	0	308
Balanced Solutions							
Lactated Ringer's	130	109	4	3	0	28 lactate	273
Plasma-Lyte	140	98	5	0	3	27 acetate & 23 gluconate	294

[a] The osmolality for plasma is 275-295 mOsm/kg

Lactated Ringer's *(Continued from Page 3)*

What's the Difference Between Balanced Solutions and Normal Saline?

Balanced solutions differ from normal saline in a few important ways. Foremost is that they have variable amounts of a buffering agent, such as lactate, acetate, or gluconate. Balanced solutions do not have bicarbonate, as it is not stable in polyvinyl chloride bags. Balanced solutions also have variable amounts of potassium, calcium, and magnesium, and have a lower sodium concentration and osmolarity in comparison to normal saline (See Table 1 on Page 3). 0.9% saline (Na 154 mmol/L) has the same sodium concentration as the aqueous phase of plasma, whereas Plasma-Lyte (Na 140 mmol/L) and lactated Ringer's (Na 130 mmol/L) are slightly hypotonic in relationship to plasma. Plasma is 93% aqueous and 7% anhydrous, consisting of proteins and lipids.

The History of Intravenous Solutions

British physician Sydney Ringer developed a 0.75% saline as a frog tissue preservation solution in the 1870s.[6] The fluid was slightly hypotonic, as frogs have a lower plasma sodium concentration (105 mmol/L) in comparison to humans. Dutch physiological chemist Hartog Jakob Hamburger developed 0.9% saline (154 mmol/L) in the 1890s, which has a similar sodium concentration to the aqueous phase of plasma in humans and mammals (151 mmol/L). 0.9% saline came into clinical practice in the 1910s. It was not until the 1930s that a version of Ringer's solution came into clinical practice, when American pediatrician Alexis Hartmann modified Ringer's solution by adding lactate in order to treat acidosis in children with diarrheal dehydration. Therefore, lactated Ringer's solution (sodium 130 mmol/L) is a hyponatremic solution in relationship to the aqueous phase of plasma and is known to contribute to hyponatremia.[7] Plasma-Lyte has a combined sodium, potassium, and magnesium concentration of 148 mmol/L, which is very similar to the sodium concentration of normal saline (154 mmol/L).

Which Balanced Solution Should Be Used, Lactated Ringer's or Plasma-Lyte?

The SALT-ED and SMART studies did not attempt to address which balanced solution is superior.[8] The study design and analysis pooled the data for lactated Ringer's and Plasma-Lyte together and did not evaluate the benefits and complications as separate variables. In both studies, there was significantly more hyponatremia associated with balanced solutions in comparison to normal saline, which is likely due to the use of lactated Ringer's. In the SALT-ED, 95 percent of patients received lactated Ringer's, and the serum sodium fell ($p < 0.001$). In the SMART study, on the other hand, only 44 percent received lactated Ringer's, with a significant variation of fluid choice in the five ICUs. 94 percent admitted to the medical ICU received lactated Ringer's, whereas a minority in the other four ICUs (surgical 38 percent, cardiac 24 percent, trauma 18 percent, and neurosurgical 2 percent) received lactated Ringer's. The incidence of hyponatremia in SMART was higher for balanced solutions (38.1 percent) compared to normal saline (35.5 percent) ($p=0.002$). The hyponatremic effect of balanced solution was seen even though the median volume of resuscitation fluids administered in both trials was relatively small at only 1000 mL.

Trading One Problem for Another: Hospital-Acquired Hyponatremia

It is encouraging that a simple change in fluid therapy from normal saline to a balanced solution could potentially translate into a clinical benefit with decreased acidosis and adverse renal events, but this might come at cost if lactated Ringer's is the solution that is used. Most practitioners are probably more familiar with lactated Ringer's than Plasma-Lyte and might assume that the fluids are equivalent. Lactated Ringer's is a hyponatremic solution and an increase in its use could increase the incidence of hospital-acquired hyponatremia. Hyponatremia is an independent predictor of hospital mortality and is associated with increased hospital costs, length of hospital stay, and rates of readmission. Hyponatremia can be difficult to treat, so preventive measures should be taken by avoiding intravenous fluids with free water, like lactated Ringer's. Further studies are underway to better evaluate the potential benefit and complications associated with different balanced solutions. Until the results of those studies are available, Plasma-Lyte would appear to be the preferred balanced resuscitation solution due to its higher sodium concentration.

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Protein-Protein Interactions in Nephrotic Syndrome and Cystic Fibrosis

Agnieszka Swiatecka-Urban, MD, FASN, is a tenured associate professor of pediatrics in the Division of Pediatric Nephrology with a secondary appointment in the Department of Cell Biology at the University of Pittsburgh. She joined the Department of Pediatrics and UPMC Children's Hospital of Pittsburgh in 2007. Dr. Swiatecka-Urban remains clinically active in pediatric nephrology while devoting most of her time to the basic science research of her laboratory, where she investigates aspects of nephrotic syndrome, protein-protein interactions, and the regulation of cell surface stability of transmembrane proteins, most notably in the mechanisms and pathways regulating the cystic fibrosis transmembrane conductance regulator (CFTR) and nephrin.

Dr. Swiatecka-Urban was a driving force in the creation of the Pittsburgh Nephrotic Syndrome Symposium in 2014 and remains one of the course directors for this CME-accredited, NIH-sponsored symposium, designed to tackle the current clinical challenges of nephrotic syndrome and expand the practice of evidence-based management of the condition.

Dr. Swiatecka-Urban also leads the Cure Glomerulonephropathy (CureGN) network cohort study at the University of Pittsburgh — a multicenter, prospective cohort observational study for patients with nephrotic syndrome.

Nephrin, the Slit Diaphragm, and Nephrotic Syndrome

Dr. Swiatecka-Urban's research related to nephrotic syndrome, a severe form of kidney disease responsible for approximately 20 percent of cases of pediatric kidney failure, has focused on the protein-protein interactions — specifically the protein nephrin — and how the integrity of the slit diaphragm between the kidney cells called podocytes is dynamically regulated by these protein interactions.

The slit diaphragm is an inter-podocyte junction, and the protein nephrin plays a critical role in regulating how the slit diaphragm functions. In nephrotic syndrome, the slit diaphragm is compromised functionally leading to a steady decrease in kidney function over time. The protein nephrin interacts with other proteins in cells of the slit diaphragm and plays a role in aspects of cell signaling.

"My research on nephrotic syndrome has been focused on identifying novel protein-protein interactions between nephrin, which is a protein that, in a manner, functions like a zipper between podocytes of the slit diaphragm. Podocytes have these different projections on them, the final ones which are finger-like in nature. Nephrin forms very tiny bridges between these finger-like projections, effectively sealing the filtration barrier," says Dr. Swiatecka-Urban.

Dr. Swiatecka-Urban's research has used a knockout zebra fish model to study the importance of nephrin in kidney formation and function, and its dysregulation leading to nephrotic syndrome.

Protein-Protein Interactions: CFTR and TGF-β Research

Beyond her nephrotic syndrome research but related to her broader interest in the regulation of cell-surface stability and intracellular trafficking of membrane proteins in epithelial cells, Dr. Swiatecka-Urban's studies have been successful in the characterization of the mechanisms and pathways that regulate the cystic fibrosis transmembrane conductance regulator (CFTR) in order to improve treatment strategies for cystic fibrosis.

Broadly speaking, Dr. Swiatecka-Urban has pursued and helped to uncover aspects of endocytic trafficking pathways of CFTR, protein-protein interactions that regulate CFTR cell surface stability, and lately the mechanisms of TGF-β1 as they relate to signaling in airway epithelial cells. She currently has several NIH-funded studies in progress, including an R01 grant studying high throughput screening for Dab2 inhibitors as stabilizers of CFTR.

Patients with cystic fibrosis have mutations in the CFTR gene that prevent the protein from getting into the plasma membrane and functions as a chloride channel, leading to impaired function.

"Many patients with cystic fibrosis have elevated levels of TGF-β1. Novel protein-protein interactions regulating CFTR and novel mechanisms of the cytokine TGF-β1 signaling are our most recent focus on research related to cystic fibrosis. We hypothesize that the elevated TGF-β1 levels are the roadblock for new treatments — recently FDA-approved molecules that are able to bring the mutant CFTR from inside the cell to the cell membrane but with limited efficiency. TGF-β1 seems to inhibit this process, and the goal is to develop some form of compound that will block or limit TGF-β1 effect," says Dr. Swiatecka-Urban.

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Kidney Development and CKD *(Continued from Page 1)*

"How well an individual's nephrons are made, and how many they have at birth, are likely big influences on a predisposition," says Dr. Ho. "To better understand both the formation and quantities of nephron development, we are studying the role of small molecules called microRNAs in transgenic mouse models," says Dr. Ho.

miRNAs are small, non-coding molecules that function in the regulation of post-transcription gene expression, and are known to be important in many biological and developmental processes of organs and organ systems. Dr. Ho and her colleagues are broadly interested in how miRNAs work to influence kidney and nephron development (both formation and quantity), and their implication in disease processes. In terms of their role in kidney development, miRNA research is really in its infancy, but the literature is growing. So, too, is the goal to develop novel regenerative therapies through the propagation and manipulation of nephron progenitors.

Past work by Dr. Ho and colleagues uncovered the role of a cluster of miRNAs — miR-17~92 — in kidney development.[1] "In this experiment, the deletion of miR-17~92 in the animal model showed this miRNA cluster to be important in renal and nephron development. We saw a reduced capacity, or number of nephrons developed, and postnatally the animal models showed signs of renal disease," says Dr. Ho.

miRNAs and Disease Process

Another major area of focus of Dr. Ho's research, one that is beginning to take on more prominence, is a better understanding of miRNAs in the context of specific disease processes. This work is related to her past studies of miR-17~92. "We are also looking at models of acute kidney injury with our division, colleague **Sunder Sims-Lucas, PhD**, in relation to microRNAs. Clearly, we believe this is an important field of study, and our group is moving more along these lines of research to study how microRNAs may regulate disease processes."

Kidney Development, CKD, and In Utero Exposure to Diabetes and Hypoxia

While microRNAs are a primary focus of research for Dr. Ho, new, ongoing studies in her laboratory are investigating how certain in utero exposures may affect kidney development (nephrogenesis) or predispose one to future disease.

One such line of investigation, in collaboration with Dr. Sims-Lucas' laboratory, is delving into how and why children born to mothers with diabetes predisposes them to a higher risk of congenital anomalies of the kidney and urinary tract. "We don't yet know if the exposure to high glucose environments is causative. It may be a cluster of metabolic events that results from the diabetic milieu that is important for the development of pathology. It's an intriguing question, and one we hope to provide some answers to," says Dr. Ho.

Exposure to hypoxia in utero often leads to kidney malformation. The reasons are not specifically known at this time. However, an investigator in Dr. Ho's lab, Shelby Hemker, is studying the role of microRNA-210, which is induced in hypoxia, to better understand how this may impact nephron development and quantity.

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Nephronophthisis *(Continued from Page 2)*

Dr. Airik's new RO1 from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) seeks to better understand the damage response that occurs in *FAN1* deficient models to better characterize the process and identify targets of possible intervention.

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Acute Kidney Injury Research

Sunder Sims-Lucas, PhD, is an assistant professor of pediatrics in the Division of Pediatric Nephrology. A developmental biologist by training with a focus on the kidney, Dr. Sims-Lucas also holds appointments in the University of Pittsburgh Department of Developmental Biology, the Clinical and Translational Science Institute, and the Center for Critical Care Nephrology. Dr. Sims-Lucas operates a broad portfolio of research interests, many with related and interrelated themes.

His postdoctoral research at UPMC Children's focused on fibroblast growth factor receptors in kidney development, and upon joining the Division as full-time faculty in 2013, his laboratory began investigating aspects of the different types of developing vasculature, identifying a novel subset of endothelial progenitors that are critical for repair after an acute kidney injury (AKI).

Since his early days with the Division, Dr. Sims-Lucas' research has progressed and expanded into a host of related themes that deal with vasculature development, acute kidney injury, hypoxia and nephrogenesis, and endothelial progenitors in the developing kidneys and lungs and in their diseases, among others. The goal of much of this research is to ultimately develop new therapies that could be used to mediate acute kidney injury or help stimulate repair of injured kidney tissues following AKI.

Beyond his bench research responsibilities and interests, Dr. Sims-Lucas serves as the director of student research training at UPMC Children's. In this capacity, he oversees training programs for students in high school through to postdoctoral researchers. Dr. Sims-Lucas indicates that this year they have applied for NIH funding to train undergraduates from the current summer program at UPMC Children's (which he has run for the past four years) in a break-off program, placing them in various laboratories across the University of Pittsburgh to study the science of kidney formation and various diseases of the kidney.

Endothelial Progenitor Research and Acute Kidney Injury

The developing vasculature gives rise to many different types of mature vessels, and this has been a focus for the Sims-Lucas laboratory. Past work on the nature of vascular development by Dr. Sims-Lucas was able to identify a novel subset of endothelial progenitors which proved to be critical to normal formation. "Deleting a key gene for these progenitors in animal models caused endothelial cell malformation, leading to incorrectly formed vessels and making the model very susceptible to damage." In essence, what Dr. Sims-Lucas' research points to is that an individual may have a developmental insult that is sub-pathological in nature — until a secondary stressor like AKI occurs, leading to a further decline in kidney function.

Oxygenation and Hypoxia

Another central focus of Dr. Sims-Lucas' research is the role of oxygenation in hypoxia within the broader theme of vascular development and organ perfusion. Ischemic injury in AKI can very quickly cause cellular damage. "When they do become damaged through hypoxia, several interesting things happen. These cells undergo a differentiation back to an early developmental stage and begin expressing immature markers. The cells do this in order to become proliferative again, thus instigating a repair process, repopulating the damaged tubule in the kidney and subsequently re-differentiating to complete the repair process. So, we are very interested in how this process works, and why, and perhaps we can one day control or manipulate it to repair damage from AKI."

Gene Mediation and AKI

In progress research by Dr. Sims-Lucas and his laboratory is probing a family of genes called the sirtuins and their possible protective role in AKI. "The sirtuin genes have been linked to a number of processes related to aging, metabolic defects, and others, including tubule injury following AKI. *SIRT5* plays key roles in fatty acid oxidation which is a major energy source for the tubules of the kidney. Knocking out *SIRT5* in mouse models has led us to theorize two processes that may be driving a protective phenotype in AKI," says Dr. Sims-Lucas.

SIRT5 interacts with *SIRT1* and *3,* both of which are known to be protective sirtuins. Knocking out *SIRT5,* according to Dr. Sims-Lucas, may release *SIRT1* and *3* from a competitive inhibition. "In the models, we see this upregulation of *SIRT1* and *3* driving a protective phenotype such that the animals are not very susceptible to AKI."

The second hypothesis is that the creation of large amounts of reactive oxygen species as a consequence of fatty acid oxidation, coupled with a hypoxic state or degree of hypoxia in an AKI, is detrimental to the tubule cells. "*SIRT5* is thought to be largely a mitochondrial sirtuin, and it causes post-translational modifications, essentially cleaving off succinyl groups. What we believe is these models have accumulation of the post-translational modifications, which essentially then shunt fatty acid oxidation, to another organelle called the peroxisome. These peroxisomes then run fatty acid oxidation and we do not see as much reactive oxygen species production. This leads to our secondary mechanism of why we don't see as much injury in these animals. This is an exciting direction to study, these positive regulators of kidney injury. There are ways that we could potentially pharmacologically target these pathways and in the future test that in humans," says Dr. Sims-Lucas.

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Acute Kidney Injury Research *(Continued from Page 7)*

Kidney Precision Medicine Initiative

Dr. Sims-Lucas is part of the University of Pittsburgh team, led by primary investigator **John Kellum, MD**, professor of Critical Care Medicine and director of the Center for Critical Care Nephrology, working on the NIDDK's Kidney Precision Medicine Project. This large scale, multi-institutional collaboration is designed to find new therapies and interventions to treat both acute kidney injury and chronic kidney disease. The University of Pittsburgh is one of the recruitment sites that will be collecting biopsies from AKI patients to be used in the creation of a biobank and molecular atlas of AKI to elucidate the mechanisms and phenotypes of AKI, and to identify potential novel treatment approaches.

The University of Pittsburgh's grant for the project is called Phenotyping REnal Cases In Sepsis and surgery for Early Acute Kidney Injury (PReCISE AKI). The grant will facilitate the collection of biopsy and fluid (blood/urine) samples from patients with an early AKI and from those with more established cases to understand the specificity of clinical phenotypes between these kinds of cases, and if there are any predictors of injury resolution or future risk of developing chronic kidney disease.

References and Further Reading

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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 13th among children's hospitals and schools of medicine in funding for pediatric research provided by the National Institutes of Health (FY2017).

UPMC Children's Hospital of Pittsburgh is affiliated with the University of Pittsburgh School of Medicine and nationally ranked in nine clinical specialties by *U.S. News & World Report*.