



TOP FIVE NEPHROLOGY RESEARCH STUDIES OF 2010

To formulate new clinical strategies designed to better prevent, diagnose, treat and cure disease associated with the kidney and bladder we must learn more about basic cellular and molecular programs responsible for urogenital development and pathogenesis.

In 2010, active collaboration between clinical and basic scientists in the Section of Nephrology fueled new research, providing novel data regarding opportunities to reduce comorbidity, develop best-practice testing, enhance treatment effectiveness and assess patient outcomes.





FIRST-YEAR RESPONSE TO RHGH THERAPY IN CHILDREN WITH CKD: A NATIONAL COOPERATIVE GROWTH STUDY REPORT

A clear definition of the appropriate growth response during recombinant human growth hormone (rhGH) treatment has never been established in the pediatric chronic kidney disease (CKD) population. In this study, which appears in *Pediatric Transplant*, investigators present data from Genentech's National Cooperative Growth Study (NCGS) on the first-year growth response in prepubertal children with CKD.

Using NCGS data, investigators constructed response curves for the first year of rhGH therapy in 270 (186 males, 84 females) naïve-to-treatment, prepubertal children with CKD prior to transplant or dialysis. At all ages, the first-year mean height velocity (HV) was greater than the mean pretreatment HV. The mean (- 2SD) for HV in children on rhGH treatment was similar to the mean pretreatment HV.

These growth plots will be useful to clinicians for assessing a patient's first-year growth response. We propose that a HV below the mean (- 1SD) is an inadequate response. These curves may help identify patients with a suboptimal growth response due to confounding medical factors and/or non-compliance.

Mahan JD, Warady BA, Frane J, Rosenfeld RG, Swinford RD, Lippe B, Davis DA. First-year response to rhGH therapy in children with CKD: a National Cooperative Growth Study Report. Pediatr Transplant. 2010 Feb;14(1):93-9.

STEROID-AVOIDANCE REGIMEN COULD DECREASE COMORBIDITY WHILE MAINTAINING COMPARABLE REJECTION RATES

Children receiving non-steroid immunosuppressant medications post-renal transplantation may experience similar clinical outcomes with less comorbidity than those who receive post-transplant steroid treatment. These are the findings of a retrospective study comparing one-year outcomes in 22 pediatric renal transplant recipients.

The study, which appears in *Pediatric Transplantation*, compares an immunosuppression regimen using sirolimus and cyclosporine (steroid-avoidance group) with prednisone (steroid group).

Findings showed that at one year, both groups had similar graft survival, acute rejection and estimated glomerular filtration rate. Children in the steroid-avoidance group had better linear growth, less excessive weight gain and were less likely to have an increase in antihypertensive medication use. However, this same patient group was more likely to be started on lipid lowering medications and erythropoiesis-stimulating agents and potentially be susceptible to developing cyclosporine-induced nephrotoxicity exacerbated by sirolimus.

Iorember FM, Patel HP, Ohana A, Hayes JR, Mahan JD, Baker PB, Rajab A. Steroid avoidance using sirolimus and cyclosporine in pediatric renal transplantation: one year analysis. Pediatr Transplant. 2010 Feb;14(1):93-9.

COL4A5 PHENOTYPES ARE MORE DIVERSE THAN PREVIOUSLY REALIZED; TESTING SHOULDN'T BE DISCOUNTED

Patients who present with glomerulopathy with an X-linked inheritance pattern should be considered for COL4A5 mutation testing, even if their symptoms aren't consistent with X-linked Alport syndrome (XLAS). A study appearing in *Kidney International* suggests that the range of phenotypes associated with COL4A5 mutations is more diverse than previously realized.

After examining a pedigree of 117 individuals across seven generations, investigators identified eight affected males with end-stage-renal-disease and 11 carrier or obligate carrier females. Genetic sequencing revealed a missense mutation in four affected males and four female obligate carriers that was absent in six asymptomatic male family members and 198 unrelated individuals. Although COL4A5 mutations typically cause XLAS, the affected males in this study had clinical and pathological features inconsistent with the classic presentation of XLAS.



Overall, findings emphasize that COL4A5 mutation analysis should be considered when glomerulonephritis presents in an X-linked inheritance pattern, even with a presentation distinct from Alport syndrome.

Becknell B, Zender GA, Houston R, Baker PB, McBride KL, Luo W, Hains DS, Borza DB, Schwaderer AL. Novel X-linked glomerulopathy is associated with a COL4A5 missense mutation in a non-collagenous interruption. Kidney Int. 2010 Sep 29. [Epub ahead of print]

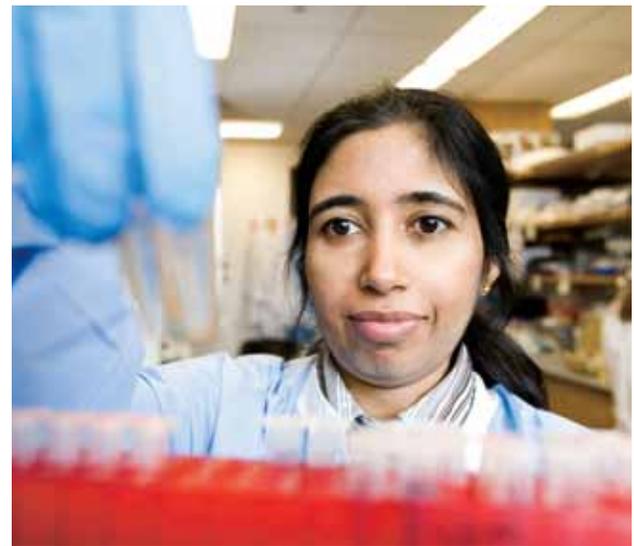
STUDY IDENTIFIES A UNIQUE MODEL OF CONGENITAL OBSTRUCTIVE NEPHROPATHY

A mouse model identified by investigators at Nationwide Children's Hospital may provide new insight into the development and treatment of congenital obstructive nephropathy (CON), the most common cause of kidney failure in children. The unique mutant mouse termed "megabladder" (mgb) shows traits similar to those observed in children with CON. Like children, these mice develop signs of lower urinary tract obstruction in utero secondary to a nonfunctional over-distended bladder, with signs of kidney failure evident shortly after birth. Kidney development in these mice occurs while the urinary tract obstruction progressively worsens, in a manner similar to that observed during late gestation in human CON.

In addition to these human similarities, mgb mice show physical traits not seen in other animal models. Mgb mice develop a progressive pattern of fibrosis, which investigators believe most likely reflects the gradual development of hydronephrosis seen in these animals. Myofibroblasts also appear early in mgb mice, a fact that could provide new evidence for understanding how kidneys develop and become diseased.

Using the mgb model, investigators could manipulate key molecular pathways associated with chronic renal failure, search for biomarkers associated with kidney disease and assess the impact surgical and therapeutic strategies have on CON.

Ingraham SE, Saha M, Carpenter AR, Robinson M, Ismail I, Singh S, Hains D, Robinson ML, Hirseli DA, Koff SA, Bates CM, McHugh KM. Pathogenesis of Renal Injury in the Megabladder Mouse: A Genetic Model of Congenital Obstructive Nephropathy. Pediatr Nephrol. 2010 June;25(6):1125-30.



TARGETING PODOCYTES MAY IMPROVE CLINICAL GLUCOCORTICOID EFFECTIVENESS IN NEPHROTIC SYNDROME

Targeting podocytes may provide new opportunities for improving the clinical effectiveness of glucocorticoids in the treatment of nephrotic syndrome, according to recent research.

Oral glucocorticoids are the most common treatment for nephrotic syndrome; yet neither the target cells nor the mechanism by which glucocorticoids lead to remission have been clearly identified.

The study, which appears in the American Journal of Physiology – Renal Physiology, showed that mouse podocytes express key components of the glucocorticoid-receptor complex. Short-term, high-dose glucocorticoid treatment resulted in similar changes in gene expression and glucocorticoid-receptor phosphorylation to that of long-term, low-dose glucocorticoid treatment, thus providing a molecular rationale for the known efficacy of pulse glucocorticoid therapy in nephrotic syndrome.

Findings suggest that negative feedback mechanisms, such as inducing the HSP90-binding immunophilin FKBP51 or downregulating the glucocorticoid-receptor could provide new opportunities to manipulate responsiveness and clinical effectiveness.

Guess A, Agrawal S, Wei CC, Ransom RF, Benndorf R, Smoyer WE. Dose- and time-dependent glucocorticoid receptor signaling in podocytes. Am J Physiol Renal Physiol. 2010 Oct;299(4):F845-53.

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Along with the nephrology research advances, the Section of Nephrology at Nationwide Children's provides specialized primary and consultative care for children with kidney and urinary tract problems through age 21. All forms of dialysis are available for children with renal failure or toxin/poisoning. In cooperation with The Ohio State University, Nationwide Children's offers living-related and cadaveric transplantation for infants, children and adolescents.

CONDITIONS TREATED:

- :: Urinary tract infection
- :: Urolithiasis
- :: Hypercalciuria
- :: Enuresis
- :: Urinary tract disorders
- :: Hypertension
- :: Hematuria/Proteinuria
- :: Metabolic bone disease
- :: Acute renal failure
- :: Chronic renal failure
- :: Disorders of mineral metabolism
- :: End-stage renal disease
- :: Familial renal disorders
- :: Fluid and electrolyte imbalances
- :: Glomerulonephritis
- :: Kidney transplantation
- :: Nephrotic syndrome
- :: Renal tubular disorders
- :: Syndromes with renal involvement
- :: Voiding disorders

CLINICS:

Nephrology Clinic

Outpatient Care Center, 5th Floor
555 S. 18th Street
Columbus, OH 43205
Phone: (614) 722-4360
Fax: (614) 722-6482

Dialysis Services

Nationwide Children's Hospital
700 Children's Dr.
Columbus, OH 43205
Phone: (614) 722-4850
Fax: (614) 722-4858
Mon.-Fri. 8 a.m. – 3:30 p.m.

For emergencies, please contact the Hospital Operator at (614) 722-2000 and ask for the Dialysis Services on call.

Metabolic Bone Clinic

Outpatient Care Center
5th Floor, Suite B
555 S. 18th Street
Columbus, OH 43205
Phone: (614) 722-4360
Fax: (614) 722-6482

Information Needed: patient's age, date of birth, and chronic medical condition(s); bone density, or DEXA scan report (if done)

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