To begin, could you provide a brief overview of congenital obstructive nephropathy (CON)?

CON is the most common cause of chronic kidney disease in children, and is among the top three diagnoses leading to paediatric end-stage renal disease. It is often grouped with congenital aplasia/hypoplasia/dysplasia, and other anomalies of the urinary system, as a heterogeneous entity: congenital anomalies of the kidney and urinary tract. Such anomalies are relatively common, affecting up to 2 per cent of pregnancies, and are responsible for 51 per cent of paediatric chronic kidney disease in North America. Among the varying diagnoses of congenital anomalies of the kidney and urinary tract, obstructive disease carries the greatest risk for developing end-stage renal disease.

What are the morphological events responsible for normal urinary tract development?

The bladder develops when the urorectal septum grows caudally, dividing the cloaca into the primitive urogenital sinus and rectum. As development progresses, the primitive urogenital sinus becomes divided into three regions, including a superior presumptive bladder, a middle pelvic urethra and a lower definitive urogenital sinus. During expansion of the superior presumptive bladder, the mesonephric and ureteric ducts are incorporated into the posterior wall of the developing bladder, connecting it to the developing kidneys. In males, the pelvic urethra becomes the membranous and prostatic urethra while the definitive urogenital sinus develops into the penile urethra. In females, the pelvic urethra becomes the membranous urethra while the definitive urogenital sinus becomes the vestibule of the vagina. In this manner, urine produced in the kidney is passed down the ureters to be stored in the bladder until voiding through the urethra.

How was the megabladder (mgb) mouse model developed?

The mgb mouse occurred as a result of a random transgene insertion/translocation during the production of a mouse model of lens development. Since my background is in gastrointestinal and urogenital development, a colleague asked me to examine the animals and determine the cause of the phenotype. Upon opening the abdomen it was obvious that the urinary bladders of the mice were grossly enlarged, carrying 12-15 ml of urine versus the more normal 0.2-0.5 ml. In addition, the bladder wall was translucent, suggesting a developmental defect in the thick muscular coat known as the detrusor smooth muscle. Based on these initial observations, I determined that the mice had a bladder defect that made them unable to pass urine. After discussions with my clinical colleagues, I realised that these animals represented a potential model of CON.

Do gender-specific differences in muscle development affect the pathogenesis of CON?

At this point we do not believe that gender-specific differences in detrusor smooth muscle development directly affect the pathogenesis of CON. Gender may play a critical role, however, in kidney response to congenital obstruction. Our studies suggest that the kidneys respond to chronic pressure by eliciting an adaptive response that includes an orchestrated balance between transforming growth factor beta (TGF-β)-directed pathogenesis, retinoic acid-mediated remodelling/repair and steroid hormone modulation. The precise role that steroid hormone modulation plays in kidney adaptation may have a gender basis.

How can the insights gained from studying the mgb mouse model be applied to humans?

The mgb mouse provides several unique insights into the mechanisms intrinsic to lower urinary tract development and pathogenesis. Genetic defects associated with long-range regulatory domains have the potential to alter the level of gene expression in a temporal and spatially specific manner. Standard genetic approaches to identify disease-specific loci may overlook these regulatory domains since they often occur at great distances from their given gene target. The mgb mouse highlights the importance of long-range transcriptional regulatory domains in modulating quantitative trait loci, and suggests these ‘hidden’ genetic elements may play a key role in many human diseases.

Finally, what is your proudest achievement to date?

I have worked diligently to create a research programme where physicians and basic scientists actively collaborate in cutting-edge translational research to enhance the health of children with kidney and urinary tract diseases. The success of the research programme at Nationwide Children’s Hospital and The Ohio State University is evidenced by our publication record and funding successes. However, I am most proud of the more than 35 trainees who have passed through my lab on the way to successful careers of their own.
Megabladder mouse

A project at Nationwide Children’s Hospital and The Ohio State University, USA, has developed a unique megabladder mouse that is helping researchers uncover new diagnostic biomarkers and therapeutic approaches.

The kidneys play a crucial role in many essential functions in the human body such as filtering waste from blood to produce urine, controlling blood pressure, and regulating the balance of salt and minerals. Damage to the kidneys can impair these vital exchanges. Paediatric nephrology, the study of kidney function in children, has found more than half of all children presenting with chronic kidney failure worldwide suffer from urinary tract malformations and congenital obstructive nephropathy (CON).

CON is the most common cause of chronic kidney disease in children and one of the leading aetiologies associated with paediatric end-stage renal disease. In spite of prompt surgical intervention and medical management, CON often results in impaired kidney function and eventual renal failure in children. CON represents a significant societal burden in terms of morbidity and mortality, with annual costs amounting to $1.5 billion in the US.

NATURAL AFFINITIES

As one of the foremost institutes in the study of paediatric nephrology in the US, Nationwide Children’s Hospital (NCH) in Columbus, Ohio, which also runs a kidney transplant programme, provides all forms of treatment for children with kidney disease. At the heart of NCH’s research is the Nephrology and Urology Research Affinity Group (NURAG), conceived in 2004 by Dr Kirk McHugh, Professor at The Ohio State University (OSU). The group was created to allow basic scientists and clinicians to exchange knowledge about the development and pathogenesis of kidneys and the urinary tract. As Director of NURAG and head of NCH’s research wing, McHugh is currently leading the ‘Model of Congenital Obstructive Nephropathy – Biomarker and Therapeutic Development’ project, which aims to broaden understanding of CON.

More than half of children diagnosed with CON will progress to end-stage kidney disease, even if they undergo surgical intervention. Unfortunately, existing biomarkers are unable to identify those who will progress to this stage. “It is clear that some of the changes in the kidney observed during CON are irreversible,” explains McHugh. “This highlights the importance of developing better prognostic and diagnostic markers for the disease.”

UNIQUE MOUSE MODEL

Animal models play a major role in the study of the pathogenesis of human diseases. To this end, McHugh developed the megabladder (mgb) mouse, a highly unique model that is the first of its kind worldwide. The mgb mouse was created through the insertion of an exogenous piece of DNA into the genome of a laboratory mouse. The transgene randomly inserted into a region of Chromosome 16 and translocated to a specific domain on Chromosome 11. “The 1 megabase of Chromosome 16 carried four functional genes with it, resulting in their over expression in these animals,” reveals McHugh. “The insertion site occurred in a gene-free region, and as a result did not directly disrupt any genes on Chromosome 11.”

The mgb mouse shows a defect in bladder smooth muscle development, which results in the animal developing CON. The mouse has restricted urine flow, which leads to an abnormally enlarged urinary bladder, hence the ‘megabladder’ name. The mgb mouse also develops hydronephrosis, or distension of the kidney with urine. Once born, the mgb mouse develops chronic kidney disease and progressive renal failure, which eventually leads to death. The mgb mouse model closely mirrors the health situation confronting children suffering from CON, and thus allows the NCH researchers to study the disease in the laboratory. “The identification of factors responsible for the pathogenic changes in renal function provides a platform for the evaluation of pharmacological, surgical and therapeutic strategies designed to prevent and treat the development of progressive renal failure,” elucidates McHugh.
An improved understanding of congenital obstructive nephropathy will bring better surgical and therapeutic approaches, as well as renewed hope for the numerous children suffering from the disease around the world.

**POSITIVES AND NEGATIVES**

To identify the genetic defect at work in the mgb mouse, the scientists first generated a bacterial artificial chromosome (BAC) library from the animal. The library was then screened for a specific stretch of the transgene that is not usually found in mice. This procedure demonstrated that the transgene was located in a specific part of Chromosome 16. McHugh and his colleagues then performed a fluorescence in situ hybridisation (FISH) analysis of metaphase spreads of mgb mouse chromosomes, which showed there were three copies of the transgene in heterozygotic mgb mice (mgb+-), and four in homozygotic mgb mice (mgb-/-). This proved that a translocation event had taken place.

Next, the team used custom-made Affymetrix Expression Arrays to verify the over expression of the four genes on Chromosome 16 and to identify the under expression of a target gene located on Chromosome 11. The latter turned out to be myocardin, which plays an important role in determining muscle cells in cardiac and smooth muscle tissue.

**PROTECTIVE LINING**

Work in McHugh’s lab showed that changes in the expression of certain genes in the mgb-/- mouse were primarily restricted to a single cell layer called the urothelium, the lining found throughout the urinary tract. In mgb-/- kidneys, the urothelium underwent significant cell division while producing proteins to protect the obstructed organ from damage. A gradual increase in pressure in the renal pelvis of the mgb-/- mice with CON caused a gradual enlargement of the renal urothelium and production of a less mature urothelial phenotype.

Although the longevity of female mgb-/- mice was relatively normal, male mgb-/- mice died at five to six weeks of age due to renal failure. McHugh believes transient high pressure obstruction and/or chronic inflammation may drive the molecular balance away from retinoic acid-mediated renal remodelling and repair towards end-stage renal disease through transforming growth factor beta-mediated pathogenesis. He speculates that the changes that take place as the kidney adapts to severe pressure could alter the functionality of the urothelium and thus leave the kidney more susceptible to infection. “The mgb-/- mouse model of CON demonstrates that a chronic, low-pressure obstruction results in significant renal remodelling that may in turn prime the kidney for continued disease progression if left untreated”.

**IMPROVED APPROACHES**

The multidisciplinary approach championed by NURAG is allowing the scientists and physicians at NCH to pursue cutting-edge translational research projects related to the kidney and urinary tract, while the mgb mouse model has helped the researchers to pursue a broad range of genetic and molecular approaches to characterise the progression of renal pathogenesis associated with CON.

An improved understanding of CON will bring better surgical and therapeutic approaches, as well as renewed hope for the numerous children affected by the disease around the world. Affirming the outstanding progress made by McHugh and his team, the *US News and World Report* has ranked NCH among the top 10 best children’s hospitals for paediatric nephrology in the US for consecutive years.

Looking ahead, the research group will continue to investigate CON and the molecular pathways associated with renal adaptation following the development of the disease. “We hope to identify more useful diagnostic and prognostic markers of renal injury, thereby helping paediatric nephrologists and urologists to make better treatment and surgical decisions,” concludes McHugh.

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**MODEL OF CONGENITAL OBSTRUCTIVE NEPHROPATHY – BIOMARKER AND THERAPEUTIC DEVELOPMENT**

**OBJECTIVES**

- To better understand paediatric congenital obstructive nephropathy (CON)
- To uncover new diagnostic biomarkers and develop novel therapeutic approaches

**PARTNERS**

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**FUNDING**

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**DR KIRK McHugh** is a senior member of the research team and Director of the Nephrology and Urology Research Affinity Group at Nationwide Children’s Hospital and OSU. Over the past 10 years, McHugh has worked diligently to create a research programme where physicians and basic scientists actively collaborate in cutting-edge translational research designed to enhance the health of children with disease of the kidney and urinary tract. His current endeavours are focused on better understanding CON in children using a unique megabladder mouse model.