

2014 Research Annual Report

Pediatric Urology



Division Summary

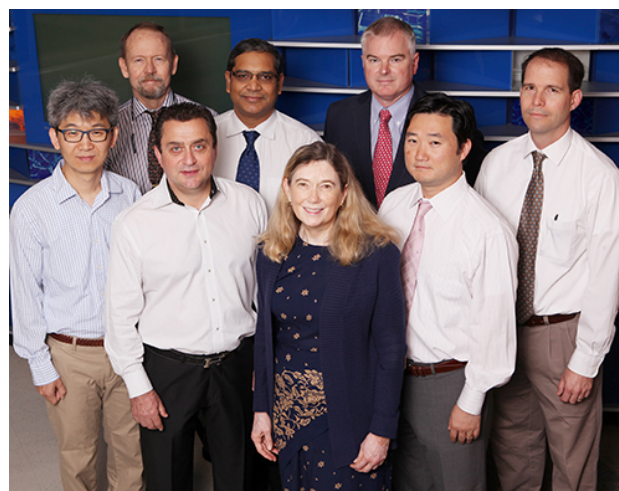
RESEARCH AND TRAINING DETAILS

Number of Faculty	6
Number of Joint Appointment Faculty	2
Number of Research Fellows	2
Number of Support Personnel	15
Direct Annual Grant Support	\$220,768
Direct Annual Industry Support	\$111,775
Peer Reviewed Publications	23

CLINICAL ACTIVITIES AND TRAINING

Number of Clinical Staff	11
Number of Clinical Fellows	3
Number of Other Students	2
Inpatient Encounters	919
Outpatient Encounters	16,908

Division Photo



Row 1: J Park, E Minevich, E Jackson, P Noh, B VanderBrink

Row 2: C Sheldon, P Reddy, W DeFoor

Significant Accomplishments

Top-ranked clinical services

Our division was ranked fourth in the nation among all pediatric urology programs ranked by *US News and World Report*. Our national reputation is linked to institutional and divisional strategic goals for clinical expansion. The Center for Disorders of Sex Development (DSD) provides specialized care for children with congenital chromosomal, gonadal or anatomical variations of sex development. We also are part of the NIH-funded Translational Research Network (TRN) with six other hospitals who offer DSD services.

Our Urogenital Center cares for children with highly complex genitourinary conditions involving abnormalities of the bladder, urethra, vagina, and anorectum. The Stone Center began clinical operations this year. The Stone Center offers comprehensive, cost effective, and coordinated care management of patients with stone disease of the urinary system. We are also working with the Cancer and Blood Diseases Institute and Gynecology to support oncofertility efforts for male oncology patients. We continued outcomes improvement work, sustaining renal function for all patients with posterior urethral valve. We kicked off a Rapid Cycle Improvement Collaborative (RCIC) team with the Division of Nephrology, aimed at providing nephrotoxic drug education to parents of children with Chronic Kidney Disease (CKD). These important patient safety efforts will expand in FY 2015.

Surgeons Share Expertise Overseas

Partnering with Global Health, **Pramod Reddy, MD**, traveled to India and **Eugene Minevich, MD**, traveled to Israel to perform complex urological surgeries. Several faculty members also were invited to present at international pediatric urological conferences: **W Robert DeFoor, Jr, MD, MPH**, in Germany; Minevich in Germany, Dubai, and India; **Paul Noh, MD**, in Germany; Reddy in Germany and India; and **Brian VanderBrink**,

MD, in Germany.

Leadership and Recognition

Joo-Seop Park, PhD, received an NIH grant for his study on cell fate regulation of nephron progenitors. The goal of this study is to determine the roles of Six2 and Hox proteins in Notch 2-mediated transcriptional activation in nephrogenesis. The leaders of the North Central Section of the American Leadership Association (AUA) selected DeFoor to participate in the 2014-2015 AUA Leadership Program. The program selects urologists who have demonstrated effective leadership skills within organized medicine or the community. Minevich served as the co-chair of the pediatric urology portion of the Friends of Israel Urological Symposium in Israel. Minevich also served as the chairperson of the “Fall Congress,” the annual meeting of the Society of Pediatric Urology, in Las Vegas.

Research Highlights

Joo-Sep Park, PhD

Dr. Park was awarded an RO1 NIH Grant for his project entitled, “Genome-wide mapping of Notch2 in embryonic kidneys identifies Six2 and Hox proteins as Notch signal modifiers.” Mesenchymal nephron progenitors give rise to various types of epithelial cells found in the nephron. Once they undergo mesenchymal-to-epithelial transition, they need to be further differentiated to establish proper segmental identities. It is known that Notch signaling plays important roles in nephron segmentation, but little is known about gene regulatory networks controlled by Notch. To address this, Dr. Park and his team performed genome-wide mapping of Notch2 binding in embryonic kidneys. They found that Notch2 and Six2 share common targets of cis-regulatory elements associated with genes regulating nephron differentiation. Dr. Park’s motif analysis revealed that Hox proteins are important components of Notch2 gene regulatory network. The in vitro analyses show that Six2 and Hox proteins form a complex with Rbpj and Notch2 and that they regulate Notch activity. In addition, a cis-regulatory element bound by both Six2 and Notch2 can drive a transgenic reporter in differentiating nephrons in vivo. Taken together, the data suggest that Six2 and Hox proteins participate in the Notch2 gene regulatory network.

Elizabeth C. Jackson, MD

Dr. Jackson presented preliminary results on her bedwetting alarm study entitled, “A prospective randomized comparison of buzzer and voice alarms for nocturnal enuresis,” at the First Annual Pediatric Urology meetings in Las Vegas, 2013. She enrolled 200 children and randomized them to a buzzer or voice alarm, and the data showed that the type of alarm made no difference in the success rate. The study had a 50% success rate and was offered to all patients who wet at least two nights a week. The study was funded by The Children’s Hospital Gift Shop Junior Co-operative Society.

Susan Council, MSN, RN III, CPN

Susan led an RCIC project entitled, “Nephrotoxic Drug Education.” The project idea originated in the Urology Division, and the objective was to increase patient and family awareness about nephrotoxic drugs, and to reduce the occurrence of kidney injury and disease progression in at risk children. The target population was patients who have Chronic Kidney Disease (CKD). With input from parents, and a panel of experts in Urology, Nephrology, and Pharmacy, a wallet card was developed that identified commonly encountered outpatient medications that can cause kidney injury. The card displays medications in a ‘stoplight’ format, identifying drugs that should be avoided, used with caution, or safely administered in patients with existing kidney disease. The card could be carried in a purse or wallet as reference tool, and could be presented to other providers and pharmacies, increasing awareness and opening an avenue for discussion about the patient’s

preexisting renal dysfunction. The wallet card project will be expanded to other patient populations, including Nephrology. Additionally, more education will be developed and available on an interactive patient and family website.

Elizabeth A. Mann, PhD

Dr. Mann led a study entitled, "Chronic Social Defeat, But Not Restraint Stress Alters Bladder Function in Mice." The aim of the study was to prove that voiding disorders and lower urinary tract symptoms in children may occur in the absence of any neurological or structural reason. Studies of voiding disorders have shown an association with increased incidence of behavioral issues as well as a past history of childhood abuse. The results showed that social defeat, in contrast to restraint stress, provides a model of psychological stress to further study the interplay of behavior and bladder dysfunction. Future study will provide information on signalling pathways and biomarkers that may be used in diagnostic and therapeutic trials, and eventually lead to improved outcomes for children presenting with voiding dysfunction.

Significant Publications

Wang J, **Park JS**, Wei Y, Rajurkar M, Cotton JL, Fan Q, Lewis BC, Ji H, Mao J. **TRIB2 acts downstream of Wnt/TCF in liver cancer cells to regulate YAP and C/EBPalpha function.** *Mol cell*. 2013 Jul 25;51(2):211-25.

Dysregulation of Wnt signaling is closely associated with human liver tumorigenesis. However, liver cancer-specific Wnt transcriptional programs and downstream effectors remain poorly understood. Here, we identify tribbles homolog 2 (TRIB2) as a direct target of Wnt/TCF in liver cancer and demonstrate that transcription of Wnt target genes, including TRIB2, is coordinated by the TCF and FoxA transcription factors in liver cancer cells. Altogether, our study uncovers a regulatory mechanism underlying liver cancer-specific Wnt transcriptional output, and suggests that TRIB2 functions as a signaling nexus to integrate the Wnt/beta-catenin, Hippo/YAP, and C/EBPalpha pathways in cancer cells.

Xu J, Liu H, **Park JS**, Lan Y, Jiang R. **Osr1 acts downstream of and interacts synergistically with Six2 to maintain nephron progenitor cells during kidney organogenesis.** *Development*. 2014 Apr 141(7):1442-52.

How Six2 maintains the nephron progenitor cells against Wnt-directed commitment is not well understood. We report here that Six2 is required to maintain expression of Osr1, a homolog of the Drosophila odd-skipped zinc-finger transcription factor, in the undifferentiated cap mesenchyme. Tissue-specific inactivation of Osr1 in the cap mesenchyme caused premature depletion of nephron progenitor cells and severe renal hypoplasia. We show that Osr1 and Six2 act synergistically to prevent premature differentiation of the cap mesenchyme. Furthermore, although both Six2 and Osr1 could form protein interaction complexes with TCF proteins, Osr1, but not Six2, enhances TCF interaction with the Groucho family transcriptional co-repressors. Moreover, we demonstrate that loss of Osr1 results in beta-catenin/TCF-mediated ectopic activation of Wnt4 enhancer-driven reporter gene expression in the undifferentiated nephron progenitor cells in vivo. Together, these data indicate that Osr1 plays crucial roles in Six2-dependent maintenance of nephron progenitors during mammalian nephrogenesis by stabilizing TCF-Groucho transcriptional repressor complexes to antagonize Wnt-directed nephrogenic differentiation.

Cost NG, **Noh PH**, Devarajan P, Ivancic V, **Reddy PP**, **Minevich E**, Bennet M, Haffner C, Schulte M, **DeFoor WR Jr**. **Urinary NGAL levels correlate with differential renal function in patients with ureteropelvic junction obstruction undergoing pyeloplasty.** *J Urol*. 2013 Oct;190(4 Suppl):1462-67.

Recent investigations described the use of NGAL, a sensitive biomarker for kidney injury, in the setting of ureteropelvic junction obstruction. We prospectively evaluated urinary NGAL levels in the affected renal pelvis and bladder of children with ureteropelvic junction obstruction undergoing unilateral dismembered pyeloplasty. Our hypothesis was that higher NGAL in the kidney and bladder would correlate with decreased ipsilateral

differential function. We found that bladder NGAL is increased in children with ureteropelvic junction obstruction. Renal pelvic and bladder normalized urinary NGAL levels correlate inversely with the relative function of the affected kidney in cases of unilateral ureteropelvic junction obstruction.

Bansal D, **Defoor WR Jr, Reddy PP, Minevich EA, Noh PH. Complications of robotic surgery in pediatric urology: a single institution experience.** *Urology*. 2013 Oct;82(4):917-20.

The objective is to report our analysis of complications on pediatric robotic urologic procedures. We found that pediatric robotic urologic procedures are safely performed with a relatively low complication rate and a low incidence of additional interventions owing to complications. Ongoing use of robotic technology in the pediatric population can be supported. Further reports are needed to validate our findings.

Noh PH, Vinson MA, Bansal D. LaparoEndoscopic Single Site orchidopexy for intra-abdominal testes in the pediatric population with a multichannel single port and flexible tip laparoscope. *J Endourol*. 2013 Nov;27(11):1381-83.

Our purpose is to assess the outcomes of pediatric LaparoEndoscopic Single Site (LESS) orchidopexy using a commercially available multi-channel single port (MCSP) and flexible tip laparoscope (FTL). We found that our initial experience with this technique was favorable with excellent outcomes. LESS orchidopexy is facilitated with a MCSP and FTL.

Division Publications

1. Bansal D, Bean CM, Vanderbrink BA, Noh PH. **Infant robotic bilateral upper urinary tract surgery.** *Korean J Urol*. 2014; 55:288-91.
2. Bansal D, Cost NG, Bean CM, Riachy E, Defoor WR, Jr., Reddy PP, Minevich EA, Noh PH. **Comparison of pediatric robotic-assisted laparoscopic nephroureterectomy and laparoendoscopic single-site nephroureterectomy.** *Urology*. 2014; 83:438-42.
3. Bansal D, Cost NG, DeFoor WR, Jr., Reddy PP, Minevich EA, Vanderbrink BA, Alam S, Sheldon CA, Noh PH. **Infant robotic pyeloplasty: comparison with an open cohort.** *J Pediatr Urol*. 2014; 10:380-5.
4. Bansal D, Defoor WR, Jr., Noh PH. **Pediatric robotic assisted laparoscopic nephropexy: case study.** *Springerplus*. 2013; 2:321.
5. Bansal D, Defoor WR, Jr., Reddy PP, Minevich EA, Noh PH. **Complications of robotic surgery in pediatric urology: a single institution experience.** *Urology*. 2013; 82:917-20.
6. Bansal D, Riachy E, Defoor WR, Jr., Reddy PP, Minevich EA, Alam S, Noh PH. **Pediatric varicocelectomy: a comparative study of conventional laparoscopic and laparoendoscopic single-site approaches.** *J Endourol*. 2014; 28:513-6.
7. Brady RC, Ruth NM, Minevich EA, Johnson ND, Passo MH. **Severe Back and Pelvic Pain in a 14-Year-Old Boy.** *Infectious Diseases in Clinical Practice*. 2013; 21:377-379.
8. Cost NG, Cost CR, Geller JI, Defoor WR, Jr.. **Adolescent urologic oncology: current issues and future directions.** *Urol Oncol*. 2014; 32:59-69.
9. Cost NG, Noh PH. **Minimally invasive uro-oncology.** In: P Godbole, MA Koyle, DT Wilcox, eds. *Pediatric endourology techniques*. New York: Springer; 2014:301-321.
10. Cost NG, Noh PH, Devarajan P, Ivancic V, Reddy PP, Minevich E, Bennett M, Haffner C, Schulte M, DeFoor WR, Jr.. **Urinary NGAL levels correlate with differential renal function in patients with ureteropelvic junction obstruction undergoing pyeloplasty.** *J Urol*. 2013; 190:1462-7.
11. Cost NG, Sawicz-Birkowska K, Kajbafzadeh AM, Turchi A, Parigi GB, Guillen G, DeFoor WR, Jr., Apoznanski W. **A Comparison of Renal Function Outcomes After Nephron-sparing Surgery and Radical Nephrectomy for Nonsyndromic Unilateral Wilms Tumor.** *Urology*. 2014; 83:1388-93.

12. DeFoor W, Reddy PP. **Minimally Invasive Techniques to Approach Complications of Enterocystoplasty and Continent Catheterizable Channels.** In: P Godbole, MA Koyle, DT Wilcox, eds. *Pediatric endourology techniques*. London: Springer; 2014:287-299.
13. Defoor WR, Jr.. **New contralateral vesicoureteral reflux-is it double trouble?** *J Urol*. 2014; 191:291-2.
14. Khandelwal P, Brewer AJ, Minevich E, Miles L, Geller JI. **High-grade transitional cell carcinoma of the bladder in a 5-year-old boy successfully treated with partial cystectomy and intravesical bacillus Calmette-Guerin.** *J Pediatr Hematol Oncol*. 2014; 36:e234-6.
15. Minevich E, DeFoor W. **Urinary tract infection and vesicoureteral reflux.** In: GW Holcomb, JP Murphy, DJ Ostlie, eds. *Ashcraft's pediatric surgery*. London: Elsevier Saunders; 2014:733-748.
16. Minevich E, Sheldon CA. **Urinary tract reconstruction for continence and renal preservation.** In: MM Ziegler, RG Azizkhan, TR Weber, eds. *Operative pediatric surgery*. New York: McGraw-Hill; 2014:857-879.
17. Noh PH, Vinson MA, Bansal D. **LaparoEndoscopic Single Site orchidopexy for intra-abdominal testes in the pediatric population with a multichannel single port and flexible tip laparoscope.** *J Endourol*. 2013; 27:1381-3.
18. Vanderbrink BA. **Neonatal Obstructive Uropathy.** In: A Chishti, S Alam, S Kiessling, eds. *Kidney and urinary tract diseases in the newborn*. New York: Springer; 2014:211-220.
19. VanderBrink BA. **Fewer augments with fewer complications--laudable, but likely?** *J Urol*. 2013; 190:1159-60.
20. VanderBrink BA, Cain MP, Kaefer M, Meldrum KK, Misseri R, Rink RC. **Outcomes following Malone antegrade continence enema and their surgical revisions.** *J Pediatr Surg*. 2013; 48:2134-9.
21. VanderBrink BA, Levitt MA, Defoor WR, Alam S. **Creation of an appendicovesicostomy Mitrofanoff from a preexisting appendicocostomy utilizing the spilt appendix technique.** *J Pediatr Surg*. 2014; 49:656-9.
22. Wang J, Park JS, Wei Y, Rajurkar M, Cotton JL, Fan Q, Lewis BC, Ji H, Mao J. **TRIB2 acts downstream of Wnt/TCF in liver cancer cells to regulate YAP and C/EBPalpha function.** *Mol Cell*. 2013; 51:211-25.
23. Xu J, Liu H, Park JS, Lan Y, Jiang R. **Osr1 acts downstream of and interacts synergistically with Six2 to maintain nephron progenitor cells during kidney organogenesis.** *Development*. 2014; 141:1442-52.

Faculty, Staff, and Trainees

Faculty Members

Pramod P. Reddy, MD, Professor

Leadership Division Director; The Curtis Sheldon and Jeffrey Wacksman Chair in Pediatric Urology

Research Interests Neuromodulation of voiding dysfunction in mouse model, Bladder dysfunction and epigenetic changes to bladder phenotype in patients with in-utero bladder outlet obstruction; patient reported outcomes in children with posterior urethral valves.

Shumyle Alam, MD, Assistant Professor

Research Interests Complex genitourinary reconstruction; neurogenic bladder; anorectal malformations; disorders of sexual development; renal transplant in the neurogenic bladder; general pediatric urology surgery; complex hypospadias; re-operative hypospadias.

W. Robert DeFoor, Jr, MD, MPH, Associate Professor

Leadership Director of Clinical Research; Director, Pediatric Urology Fellowship Program

Research Interests Robotic-assisted laparoscopic pediatric urologic surgery; Complex genitourinary reconstruction; clinical outcomes research; clinical trials; kidney stones; uro-oncology; vesicoureteral reflux,

prenatal hydronephrosis, posterior urethral valves.

Eugene A. Minevich, MD, Professor

Leadership Surgical Director, Stone Center

Research Interests Kidney stones; ESWL; complex genitourinary reconstructive surgery; microscopic hypospadias; general pediatric urology surgery; endoscopic treatment of VUR.

Paul H. Noh, MD, Associate Professor

Leadership Director, Minimally Invasive Surgery

Research Interests Minimally invasive laparoscopic surgery; minimally invasive robotic-assisted surgery; general pediatric urology surgery; prenatal evaluation and fetal care.

Curtis A. Sheldon, MD, Professor

Leadership Founding Director, Urogenital Center

Research Interests Ethics, Professionalism.

Brian A. VanderBrink, MD, Assistant Professor

Research Interests Spina bifida, genitourinary reconstructive surgery; neurogenic bladder; minimally invasive laparoscopic surgery; clinical trials.

Joint Appointment Faculty Members

Elizabeth C. Jackson, MD, Associate Professor (Division of Nephrology; Director of Healthy Bladder Clinic)

Research Interests Voiding dysfunction; overactive bladder; urinary tract infections; metabolic basis of stones; nocturnal enuresis; clinical outcomes research; clinical trials.

Joo-Seop Park, PhD, Assistant Professor (Division of Pediatric Urology; Division of Developmental Biology)

Research Interests Basic research on self-renewal and differentiation of progenitors during development of the mammalian kidney and bladder; studies transcriptional and epigenetic controls of cis-regulatory modules that act downstream of various signaling pathways.

Clinical Staff Members

- **Stephanie Boardman, MSPAS, PA-C**
- **Sharon Dickman, MSN, CNP, SANE-P**
- **Denise Ferguson, MSN, CNP**
- **Abbey Franklin, MSPAS, PA-C**
- **Odile Kennedy, MSN, CNP**
- **Tammy Lingsch, MSN, CNP**
- **BJ Manz, MSN, CNP**
- **Katie Mueller, MSN, CNP**
- **Nan Tobias, MSN, CNP**

Trainees

- **Christopher Bean, MD**, PL-7, MD - University of Mississippi School of Medicine; Spring Hill College, Mobile, Alabama
- **Zachary Liss, MD**, PL-6, MD - Wayne State University School of Medicine, Detroit, Michigan
- **Maher Sraj, MD**, PL-4, MD - Beirut Arab University, Beirut, Lebanon
- **Muhammad Kamran Khan, MD**, PL-4, MD - Ayub Medical College, Abbottabad, Pakistan

Division Collaboration

Urinary metabolic evaluations in morbidly obese children. (Urinary metabolic evaluations in morbidly obese children.)

Bariatric Surgery » Thomas Inge, MD

Nephrology, University of Chicago » John Asplin, MD

Evidence based clinical pathway for hemorrhagic cystitis. (William R. DeFoor, MD; Pramod Reddy, MD)

Bone Marrow Transplant and Immune Deficiency » Jodele Sonata, MD

Cloaca project and neurogenic bladder project looking at the long term outcomes. (Brian VanderBrink, MD; Pramod Reddy, MD; William R. DeFoor, MD; Eugene Minevich, MD)

Colorectal Center » Alberto Pena, MD and Jason Frischer, MD

Identification of Notch target genes during the formation of multiple organs. (Joo-Seop Park, PhD)

Developmental Biology » Rafael Kopan, PhD

Transcriptome analysis of Wnt signaling in liver development. (Joo-Seop Park, PhD)

Developmental Biology » Aaron Zom, PhD

Surgical outcomes with feminizing genitoplasty in DSD patients. (Brian vanderBrink, MD; Pramod Reddy, MD)

Pediatric & Adolescent Gynecology » Leslie Breech, MD

Oncofertility efforts in male Oncology patients. (William R. DeFoor, MD; Pramod Reddy, MD)

Pediatric & Adolescent Gynecology » Leslie Breech, MD

Oncology » Karen Burns, MD and Christine Phillips, MD

Education about nephrotoxic medications in patients with chronic kidney disease. (Pramod Reddy, MD)

Nephrology and Hypertension » Stuart Goldstein, MD

Urinary NGAL in ureteropelvic junction obstruction in children. (Paul Noh, MD)

Nephrology and Hypertension » Prasad Devarajan, MD

Robotic surgery for pediatric renal tumors. (Paul Noh, MD; William R. DeFoor, MD)

Oncology » James Geller, MD

Epidemiology and surgical approach to pediatric renal cell tumor. (William R. DeFoor, MD; Paul Noh, MD)

Oncology » James Geller, MD

Children's Oncology Group (National Organization) »

Renal rhabdomyosarcoma. (William R. DeFoor, MD)

Oncology » James Geller, MD

Pediatric General and Thoracic Surgery » Gregory Tiao, MD

Imaging for pediatric renal tumors. (William R. DeFoor, MD; Paul Noh, MD)

Oncology » James Geller, MD

Pediatric General and Thoracic Surgery » Roshni Dasgupta, MD

Radiology » Eric Crotty, MD

External fixator pelvic immobilization in bladder exstrophy patients. (Brian VanderBrink, MD; Pramod Reddy, MD)

Orthopaedics » Charles Mehlman, MD

Urinary outcomes with (1) kidney transplant for urological conditions and (2) infant posterior urethral valves. (Brian VanderBrink, MD; Pramod Reddy, MD)

Pediatric General and Thoracic Surgery » Gregory Tiao, MD

Develop a method to track a patient's radiation exposure from various radiology testing. (Pramod Reddy, MD)

Radiology » Brian Coley, MD

Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct

PARK, J

Cell Fate Regulation of Nephron Progenitors

National Institutes of Health

R01 DK 100315

01/01/14-12/31/18

\$217,500

REDDY, P

Short-term Outcomes of Genitoplasty in DSD

National Institutes of Health(University of Oklahoma)

R01 HD 074579

07/05/13-04/30/18

\$3,268

Current Year Direct

\$220,768

Industry Contracts

DEFOOR, W

Oceana Therapeutics, Inc.

\$34,374

JACKSON, E

Astellas Pharma Europe BV

\$10,780

NOH,P

Watson Laboratories, Inc

\$21,084

REDDY, P

Novartis Pharmaceuticals

\$24,362

VANDERBRINK, B

Astellas Pharma Europe BV

\$21,175

Current Year Direct Receipts

\$111,775

Total

\$332,543