

2015 Research Annual Report

Pediatric Urology

RESEARCH AND TRAINING DETAILS



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Faculty	6
Joint Appointment Faculty	2
Research Fellows	1
Support Personnel	15
Direct Annual Grant Support	\$220,768
Direct Annual Industry Support	\$41,738
Peer Reviewed Publications	18

CLINICAL ACTIVITIES AND TRAINING

Clinical Staff	11
Clinical Fellows	4
Clinical Students	2
Inpatient Encounters	751
Outpatient Encounters	16,494

Research Highlights

Joo-Seop Park, PhD, and Eunah Chung, PhD

Drs. [Park](#) and Chung presented their two studies at the 13th [International Workshop on Developmental Nephrology](#) in Salt Lake City, 2015. Their first one was titled “Context-specificity of b-catenin gene regulatory networks in kidney and bladder cells”. Wnt/b-catenin signaling plays pivotal roles in various biological contexts. Transcriptional outcome caused by Wnt/b-catenin signaling is cell type-specific. Little is known about how the context-specific responses can be achieved. In this study, they performed genome-wide mapping of b-catenin in various cell types. Through motif analysis on cell type-specific binding sites of b-catenin, they found that b-catenin complex interacts with different sets of transcription factors present in various cell types. They showed that, in the bladder, urothelium, b-catenin complex interacts with Fox and AP1 and these interactions contribute to urothelium-specific response of Wnt/b-catenin signaling. Their second study was titled “Notch2 gene regulatory networks in the embryonic kidney”. Premature depletion of nephron progenitors causes renal agenesis or low nephron endowment that is linked to high blood pressure and chronic renal diseases. In this work, they presented a molecular mechanism of how premature depletion of nephron progenitors is inhibited during kidney development. They found that Six2, a transcription factor present in nephron progenitors, blocks premature depletion of nephron progenitors by preventing nephron progenitors from responding to differentiation signals.

Elizabeth C. Jackson, MD

Dr. [Jackson](#) presented results of her study entitled, “[Two Consecutive 24-hour Urines Improve Detection of Hypercalciuria, Elevated Supersaturation of Calcium Oxalate, and Excessive Urinary Sodium in Children With Urinary Symptoms or Signs,](#)” at the [PAS meeting](#) in San Diego, CA. The objective was to determine how often the diagnosis of hypercalciuria or elevated supersaturation of calcium oxalate (SS CaOx) or excessive urinary sodium might be missed if only a single 24-hour urine collection was obtained compared with two consecutive 24-hour urines in children. 302 symptomatic children ages 3-22 years, average age 13, collected two consecutive 24 hour urine samples for metabolic stone profile performed through the Litholink Corporation. The results showed that hypercalciuria in 63 children (21%) would potentially have been missed based on one collection only. The data suggests that two consecutive 24 hour urines detect more useful information for managing children with symptoms or signs of hypercalciuria without being overly burdensome for most families.

Elizabeth A. Mann, PhD

Dr. Mann’s study entitled, “[Chronic Social Defeat, But Not Restraint Stress Alters Bladder Function in Mice](#)” was published in *Physiology & Behavior*. The study sought to address the occurrence of voiding disorders and lower urinary tract symptoms in children 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. Results from this study showed that social defeat, in contrast to restraint stress, provides a model of psychological stress to further examine the interplay of behavior and bladder dysfunction.

W. Robert DeFoor, MD

Dr. [DeFoor](#) was recognized as a collaborator on the ground breaking [New England Journal of Medicine](#) article that presented the results of the [RIVUR Study](#) (Randomized Intervention for Children with Vesicoureteral Reflux). This prospective, randomized, multi-center National Institutes of Health (NIH) study was performed over five years and looked at infectious and renal scarring outcomes of children with vesicoureteral reflux. The study confirmed current practice that the proactive management of reflux with antibiotic prophylaxis decreased the risk of urinary tract infections. Dr. DeFoor served as the principal investigator for the study at Cincinnati Children’s Hospital Medical Center, and was responsible for all aspects of the study at Cincinnati Children’s.

Dr. DeFoor collaborated with Drs. [Alberto Pena](#) and [Andrea Bischoff](#) from the Cincinnati Children’s [Colorectal Center](#) in a

review of patients with cloacal anomalies treated at our institution using our novel collaborative multi-disciplinary approach. These female patients have quite complex pelvic anatomy and often severely dysfunctional bladders which puts them at high risk for kidney injury. The rate of chronic kidney disease (CKD) progression was monitored over a ten year period. The analysis found that with aggressive and proactive bladder management coordinated with a bowel program, the degree of renal impairment remained stable for nearly all the children. No girls with chronic kidney disease stages 1 to 3 progressed to a higher (worse) stage of CKD during the follow-up period. Only one child with stage 4 CKD progressed to needing a renal transplant (CKD stage 5). This [manuscript](#) was published in the *Journal of Urology* which has the highest impact factor in the field of urology. Further collaborative projects with the colorectal team included an analysis of risk factors for end stage renal disease in children with anorectal malformations. This project resulted in a manuscript being published in the pediatric surgery literature.

Dr. DeFoor also served as principal or co-investigator on six extramural funded clinical trials sponsored by industry. This included one surgical randomized controlled trial looking at the efficacy of Botulinum A toxin (“Botox”) injections into the bladder muscle in children with spina bifida and neurogenic bladder. These children require lifelong intermittent catheterization of their bladder due to spinal cord nerve injury and often suffer from urinary incontinence and recurrent urinary tract infections. Major surgery to divert the urinary stream is often required to protect the kidneys and/or allow them to come out of diapers. Botox injection is a minimally invasive, short outpatient procedure that has the potential to improve bladder function and decrease urinary incontinence in these children with almost no side effects. This will possibly allow them to avoid a major abdominal surgery and weeks in the hospital for convalescence.

W. Robert DeFoor, MD, and Elizabeth Jackson, MD

Dr. DeFoor and [Dr. Jackson](#) collaborated with the [Surgical Weight Loss Program for Teens](#) at Cincinnati Children’s Hospital. Both worked with [Dr. Thomas Inge](#) from Bariatric Surgery, and with [Dr. John Asplin](#), a prominent national nephrologist and recognized kidney stone expert from Chicago, to perform the study. The team recruited severely obese patients considering weight loss surgery to assess their risks of developing kidney stones after the procedure. Multiple previous reports in adults had found an increased risk of oxalate reabsorption with resultant kidney stone formation after gastric bypass but no studies had previously been performed in children. The [study](#) found that the current procedure employed at Cincinnati Children’s called a “gastric sleeve” had significantly lower urinary metabolic changes in certain key indices that predispose children to forming stones than the older “Roux-en-Y gastric bypass” procedure. This work was published in a prominent peer-reviewed obesity journal.

Significant Publications

Bansal D, Cost NG, Bean CM, [Minevich EA](#), [Noh PH](#). [Pediatric urological laparoendoscopic single site surgery: single surgeon experience](#). *J Pediatr Urol*. 2014 Dec;10(6):1170-5.

The aim was to assess the feasibility and outcomes of pediatric urological laparoendoscopic single site (LESS) surgery. A retrospective review was performed of all children who underwent LESS surgery at a single pediatric institution from September 2010 to July 2013. Patient demographics, intraoperative details, narcotic usage, and complications were reviewed. The umbilicus was used as the surgical site in all cases. All procedures were performed with a flexible tip laparoscope, a multichannel port, standard 3- or 5-mm laparoscopic instrumentation, and articulating instruments. Sixty-one patients (50 male, 11 female) were identified. Procedures included 18 orchidopexies, 15 nephrectomies, 11 varicocelectomies, nine nephroureterectomies, four partial nephrectomies, one ureterectomy, one ureterolithotomy, one orchiectomy, and one utricule excision. The ureterolithotomy was converted to open surgery for failure to progress. The utricule excision was converted to conventional laparoscopy by adding one accessory port and one skin puncture because of the close proximity of the vas deferens to the utricule. Intraoperative complications included one vas deferens injury during orchidopexy in a postpubertal male. Postoperative complications occurred in

six patients: five grade II and one grade IIIb. Pediatric urological LESS procedures are technically feasible, safe, and effective. Further evaluation is warranted to better define its role in pediatric urological surgery.

Bansal D, Cost NG, Bean CM, **Vanderbrink BA**, Schulte M, **Noh PH**. **Infant robot-assisted laparoscopic upper urinary tract reconstructive surgery.** *J Pediatr Urol.* 2014 Oct;10(5):869-74.

Our aim was to assess the outcomes of infant robot-assisted laparoscopic (RAL) upper urinary tract reconstruction. The medical records of all infants who underwent RAL upper urinary tract reconstruction were reviewed. Patients less than one year of age at surgery were included. Patient demographics, intraoperative details, narcotic usage, and complications were reviewed. Ten infants met the study criteria. There were five right and five left-sided procedures. Eight pyeloplasties (four right, four left) and two ureteroureterostomies (one right single system, one left duplex system) were performed. The median age was eight months (range 3-12 months). Median weight was 7.7 kg (range 5.8-10.9 kg). Median operative time was 128 min (range 95-205 min). There was no significant blood loss or intraoperative complications. One (10%) patient received a regional block. Eight (80%) patients did not receive postoperative narcotics. Median hospital stay was one day (range 1-2). Median follow-up was 10 months (range 3-18 months). Complications included one urinary leak, one ileus, and one urinary tract infection. Hydronephrosis improved in all patients. Infant RAL upper urinary tract reconstruction is technically feasible, safe, and effective. It can be applied for duplication anomalies and single system obstructions in infants.

Riachy E, **Defoor WR**, **Reddy PP**, Alam S, **Noh PH**, **Sheldon C**, **Minevich EA**. **Endoscopic treatment with dextranomer/hyaluronic acid for persistent incontinence after continent urinary reconstruction.** *J Endourol.* 2015 Feb;29(2):137-40.

To determine the applicability and long-term outcome of endoscopic injection of dextranomer/hyaluronic acid (Dx/HA) to correct incontinence in patients who had previously undergone continent urinary reconstruction. A retrospective cohort study was performed of all patients who underwent Dx/HA injection at our institution from January 2001 to June 2011. All patients had adequate bladder capacity and compliance on maximized medical therapy before injection. "Success" was defined as either "continence" (daytime dry interval three hours) or "improvement" (daytime dry interval two hours). A total of 22 children (16 females and six males) had Dx/HA injections for persistent incontinence from either bladder neck (7), Mitrofanoff (10), or both (5). Median age at injection was 13 years (range four-21). Children underwent an average of 1.6 injection sessions per patient with an average of 2.6 mL of Dx/HA per session. At a median follow-up of 72 months (range four-104), 19 (86.4%) patients had successful results (16 continent, three improved). For those incontinent from bladder neck, 42% became continent after one, 75% after two, and 83% after three injections, with a success rate of 91% (10 continent, one improved). For those incontinent from Mitrofanoff, 20% became continent after one, and 73% after two injections, with a success rate of 86% (11 continent, two improved). Endoscopic injection of Dx/HA to correct residual incontinence in selected children after urinary reconstruction appears to be safe and effective, achieving a dry interval in more than two-thirds of patients.

Jackson E. **Between a rock and a hard place: getting families to change behaviors to reduce pediatric stone disease recurrence.** *J Urol.* 2014 Nov;192(5):1324-5.

The rapidly increasing incidence of stones in adults and children during the last 25 years is consistent with the effects of our rapidly changing lifestyle during the last 25 years. The good news is that lifestyles can be changed. The bad news is that changing lifestyles is difficult and documentation that changing lifestyles makes a difference in stone recurrence in children is largely lacking. Even the rate of stone recurrence is not known in children.

DeFoor W, Hazelwood L. **Unilateral ureteral reimplantation and management of contralateral low grade or resolved vesicoureteral reflux.** *J Urol.* 2014 Nov;192(5):1508-12.

New contralateral vesicoureteral reflux after unilateral ureteral reimplantation is well described in the literature. Management of high grade vesicoureteral reflux with resolved contralateral reflux is less extensively studied. Most surgeons perform a bilateral procedure in these cases. We report the results when an open procedure was deferred on the contralateral side. A retrospective cohort study was performed of all patients with unilateral vesicoureteral reflux undergoing ureteral reimplantation performed by one surgeon between 2003 and 2012. Resolved or low grade contralateral reflux was observed if the kidney was normal. Dextranomer/hyaluronic acid copolymer injection was also offered for persistent grade I contralateral reflux. Outcomes were abstracted from the medical record and compared to those in patients undergoing bilateral ureteral reimplantation. Of 78 patients undergoing unilateral ureteral reimplantation 15 met inclusion criteria. Median age was 5.5 years, and median followup was 7.6 years. Extravesical detrusorrhaphy was performed in all cases. The 15 study patients initially had contralateral reflux that either resolved (8) or persisted as grade I (7). Six patients had results on two cystograms that were negative for contralateral reflux before ureteral reimplantation. Length of stay was one day less and costs were 59% lower for patients undergoing unilateral vs bilateral ureteral reimplantation. Postoperatively two of 15 patients (13%) had an afebrile urinary tract infection. All 15 patients had normal contralateral kidneys on postoperative ultrasound. Observation of contralateral resolved or low grade vesicoureteral reflux at unilateral ureteral reimplantation is feasible, with minimal morbidity and a shorter hospital stay compared to performance of bilateral ureteral reimplantation. This approach appears to be a reasonable option to discuss with parents during preoperative counseling.

Division Publications

1. Avery DI, Herbst KW, Lendvay TS, Noh PH, Dangle P, Gundeti MS, Steele MC, Corbett ST, Peters CA, Kim C. **Robot-assisted laparoscopic pyeloplasty: Multi-institutional experience in infants**. *J Pediatr Urol*. 2015; 11:139 e1-5.
2. Bansal D, Cost NG, Bean CM, Minevich EA, Noh PH. **Pediatric urological laparoendoscopic single site surgery: single surgeon experience**. *J Pediatr Urol*. 2014; 10:1170-5.
3. Bansal D, Cost NG, Bean CM, Noh PH. **Pediatric laparo-endoscopic single site partial nephrectomy: feasibility in infants and small children for upper urinary tract duplication anomalies**. *J Pediatr Urol*. 2014; 10:859-63.
4. Bansal D, Cost NG, Bean CM, Vanderbrink BA, Schulte M, Noh PH. **Infant robot-assisted laparoscopic upper urinary tract reconstructive surgery**. *J Pediatr Urol*. 2014; 10:869-74.
5. Barthold JS, Wang Y, Kolon TF, Kollin C, Nordenskjold A, Olivant Fisher A, Figueroa TE, BaniHani AH, Hagerty JA, Gonzalez R, Noh PH, Chiavacci RM, Harden KR, Abrams DJ, Kim CE, Mateson AB, Robbins AK, Li J, Akins RE, Jr., Hakonarson H, Devoto M. **Phenotype specific association of the TGFBR3 locus with nonsyndromic cryptorchidism**. *J Urol*. 2015; 193:1637-45.
6. Brunskill EW, Park JS, Chung E, Chen F, Magella B, Potter SS. **Single cell dissection of early kidney development: multilineage priming**. *Development*. 2014; 141:3093-101.
7. Cost NG, DeFoor WR, Jr., Crotty EJ, Geller JI. **The initial experience with RENAL Nephrometry in children, adolescents, and young adults with renal tumors**. *Pediatr Blood Cancer*. 2014; 61:1434-9.
8. Cost NG, Liss ZJ, Bean CM, Geller JI, Minevich EA, Noh PH. **Prechemotherapy robotic-assisted laparoscopic radical nephrectomy for an adolescent with Wilms tumor**. *J Pediatr Hematol Oncol*. 2015; 37:e125-7.
9. Cost NG, Noh PH. **Rhabdomyosarcoma, Pediatric (Sarcoma Botryoides)**. In: LG Gomella, ed. *The 5-minute Urology Consult*. Philadelphia, PA: Wolters Kluwer; 2015:448-449.

10. Craig MP, Grajevskaja V, Liao HK, Balciuniene J, Ekker SC, Park JS, Essner JJ, Balciunas D, Sumanas S. **Etv2 and fli1b function together as key regulators of vasculogenesis and angiogenesis**. *Arterioscler Thromb Vasc Biol*. 2015; 35:865-76.
 11. DeFoor W, Hazelwood L. **Unilateral ureteral reimplantation and management of contralateral low grade or resolved vesicoureteral reflux**. *J Urol*. 2014; 192:1508-12.
 12. Jackson E. **Between a rock and a hard place: getting families to change behaviors to reduce pediatric stone disease recurrence**. *J Urol*. 2014; 192:1324-5.
 13. Jackson EC. **Urinary tract infections in children: knowledge updates and a salute to the future**. *Pediatr Rev*. 2015; 36:153-64; quiz 165-6.
 14. Noh PH, Cost NG. **Sacral Agenesis, Urologic Consideration**. In: LG Gomella, ed. *The 5-Minute Urology Consult*. Philadelphia: Wolters Kluwer; 2015:450-451.
 15. Noh PH, Cost NG. **Testis, Tumor And Mass, Pediatric, General Considerations**. In: LG Gomella, ed. *The 5-Minute Urology Consult*. Philadelphia: Wolters Kluwer; 2015:510-511.
 16. Riachy E, Defoor WR, Reddy PP, Alam S, Noh PH, Sheldon C, Minevich EA. **Endoscopic treatment with dextranomer/hyaluronic acid for persistent incontinence after continent urinary reconstruction**. *J Endourol*. 2015; 29:137-40.
 17. VanderBrink BA. **Editorial comment**. *J Urol*. 2015; 193:648-9.
 18. VanderBrink BA, Sivan B, Levitt MA, Pena A, Sheldon CA, Alam S. **Epididymitis in patients with anorectal malformations: a cause for urologic concern**. *Int Braz J Urol*. 2014; 40:676-82.
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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.

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**
- **Kimberly Kennedy, RNII, CPN**
- **Odile Kennedy, MSN, CNP**
- **Tammy Lingsch, MSN, CNP**
- **BJ Manz, MSN, CNP**
- **Katie Mueller, MSN, CNP**
- **Renee Niehaus, RNII, BSN, CPN**
- **Nan Tobias, MSN, CNP**

Trainees

- **Zachary Liss, MD**, PL-7, Wayne State University School of Medicine, Detroit, Michigan
 - **Katherine Corbyons, MD**, PL-6, University of Florida College of Medicine, Gainesville, Florida
 - **Mukunda Ramachandra, MBBS**, PL-4, Karnataka Institute of Medical Sciences, Karnataka, India
 - **Zaheer Alam, MBBS**, PL-4, Hamdard College of Medicine and Dentistry, Karachi, Pakistan
 - **Nathalie Kremer, MD**, PL-7, Heinrich-Heine-University Faculty of Medicine, Düsseldorf, Germany
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Grants, Contracts, and Industry Agreements

Grant and Contract Awards

Annual Direct

Park, J

Cell Fate Regulation of Nephron Progenitors

National Institutes of Health

R01 DK100315

1/1/2014-12/31/2018

\$217,500

Reddy, P

Short-Term Outcomes of Genitoplasty in DSD

National Institutes of Health (University of Oklahoma)

7/5/2015-4/30/2018

\$3,268

Current Year Direct

\$220,768

Industry Contracts

DeFoor, W

Allergan, Inc.

\$20,869

Noh, P

Watson Laboratories, Inc

\$1,192

Reddy, P

Pfizer, Inc.

\$19,677

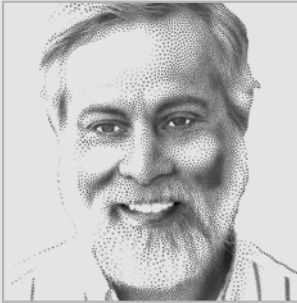
Current Year Direct Receipts

\$41,738

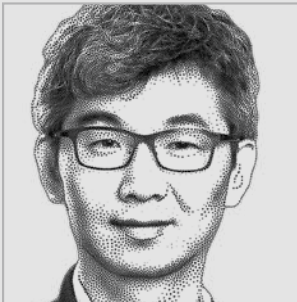
Total

\$262,506

Single-Cell Analysis Changes Understanding of Organ Development



Steven Potter, PhD



Joo-Seop Park, PhD

PUBLISHED ONLINE JULY 22, 2014

Development

Researchers examining early kidney development used a recently developed single cell RNA-sequence strategy to create a new atlas of gene expression patterns that has already led to a significant finding on the nature of organ development.

The study, published online in July 2014 in the journal *Development*, included senior author Steven Potter, PhD, Division of Developmental Biology; Joo-Seop Park, PhD, Division of Urology, and research associate Eunah Chung. The study reports that during organogenesis in mice, single cells often express genes related to several developmental pathways — not just a single, predetermined fate. This finding provides powerful evidence of a concept called multilineage priming.

During early development, cells partially activate multiple programs, priming them for their next step in development. This is followed by a combination of gene repressions, which turn off the genes associated with various possible lineages until each cell settles upon its ultimate state. “This was a surprise,” Potter says. “We had expected that cells would just gradually fire up the correct program as they assumed their differentiated state.”

The team also was surprised to see an abundance of genes with partially degraded noncoding RNA. All these findings are changing our understanding of early organ development, which in turn could lead to new ways to treat or prevent disease.

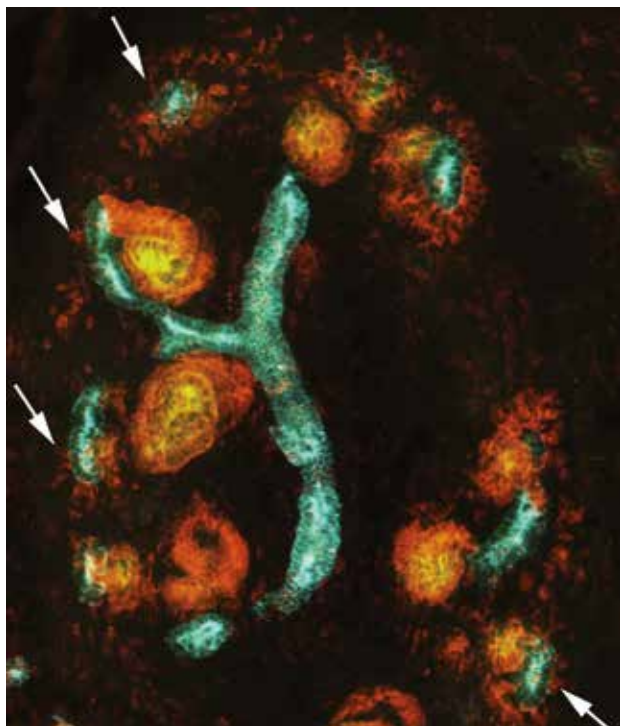
“As is common in science, this new data raises new questions,” Potter says. “How do cells decide which programs to test and how do they make their final decisions? We do not yet know, but new knowledge brings new power. We are moving steadily forward in our quest for groundbreaking therapeutic options.”

RESEARCH AND TRAINING DETAILS

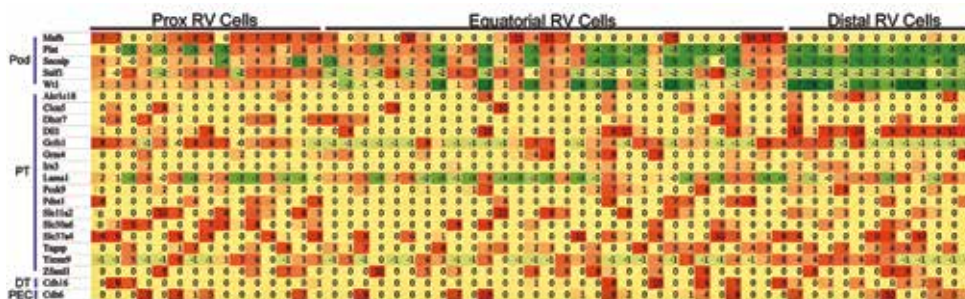
Faculty	6
Joint Appointment Faculty	2
Research Fellows	1
Support Personnel	15
Direct Annual Grant Support	\$220,768
Direct Annual Industry Support	\$41,738
Peer Reviewed Publications	18

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 Brunskill EW, Park JS, Chung E, Chen F, Magella B, Potter SS: Single cell dissection of early kidney development: multilineage priming. *Development* 2014, 141(15):3093-3101

“As is common in science, this new data raises new questions. How do cells decide which programs to test and how do they make their final decisions? We do not yet know, but new knowledge brings new power.”



This image shows unexpected Wnt4 expression in progenitor cells that appear to not yet be induced. Wnt4 is normally thought to be expressed only in cells that are induced. Researchers found that during organogenesis in mice, single cells often express genes related to numerous developmental pathways, which bolsters evidence of a concept called multilineage priming.



This heat map shows a diagram of single cells (each column) showing expression of multiple lineages, marked along the left. Individual RV cells express markers of multiple differentiated cell types. Genes normally expressed in differentiated Podocytes (Pod), proximal tubules (PT), distal tubules (DT) and parietal epithelial cells (PEC) are shown on the left. Red represents high expression and green low expression. The numbers represent approximate log, median baseline and normalized expression values.