

UCSF KURe Scholars group: Thomas Chi, MD, Ben Breyer, MD, Shweta Choudhry, PhD and Hillary Copp, MD, MS



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The UCSF KURe program is supported by a NIH funded K12 grant, an institutional research and academic career development award. Candidates from across the nation interested in career development are invited to apply.

Four Talented Scholars Participate in Career Development Program

Now in its second year, the UCSF multidisciplinary K12 Urologic Research (KURe) Career Development Program is providing mentoring and research funding to four young scientists as they work to add to our understanding of benign urologic diseases.

The KURe program is supported by a K12 grant from the National Institutes of Health--an institutional research and academic career development award. Funding from the UCSF Department of Urology supplements the KURe program.

Second-year scholars Shweta Choudhry, PhD and Hillary Copp, MD, MS, and first-year scholars Benjamin Breyer, MD, and Thomas Chi, MD,

work with career and research mentors selected from the UCSF faculty.

KURe scholars receive departmental support and research facilities for their

Translational Science Training Program. An annual progress report and review ensure that each scholar is progressing toward research independence.

The UCSF program is designed to launch the careers of scientists who will lead urology research in the years to come.

– Laurence Baskin, MD, chief of pediatric urology at UCSF and KURe program director.

work. Scholars, who receive faculty appointments at UCSF, spend a minimum of half their time in research activities. They also participate in the campus-wide Clinical and Translational Science Institute and Clinical and

Scholars receive training in grant and manuscript writing as part of the program, so that they can receive independent research funding, ideally by the end of their third year as a KURe scholar. 

HIV and voiding problems

Lower urinary tract symptoms, such as having to urinate frequently or urgently, become more common with age, and they can seriously impact a person's quality of life. First-year KURe

scholar Benjamin Breyer's research has shown that men who are HIV positive are more likely to report lower urinary tract symptoms (LUTS). How HIV might increase the risk of LUTS is not clear. It

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Executive Committee: Gerald Cunha PhD, KURe Co Program Director, Laboratory Based Research
Jeanette S. Brown MD, KURe Co Program Director, Clinical Research
Peter Carroll, MD, MPH, KURe Co Principal Investigator

HIV and voiding problems ... continued

may be that the virus directly affects the central or peripheral nervous system, or that symptoms arise from side effects of HIV treatment, opportunistic infections, or inflammation.

Breyer used social networking sites in the design of his survey, recruiting men who have sex with men to participate in an Internet survey of urinary wellness by placing ads on Facebook and distributing them to community centers internationally. The men, who participated anonymously, rated their symptoms using the International Prostate Symptom Score, an 8-question tool commonly used to measure lower urinary tract function. The survey also gathered information about comorbid diseases, sexual practices, and ethnic and demographic information.

Approximately 2400 men completed the survey, which was conducted over four months in 2010. Breyer then analyzed

data on 1830 respondents aged 30 and older who were certain of their HIV status: 1507 of whom were HIV negative; 148 who were HIV positive but who did not have AIDS, and 175 who were HIV positive and had AIDS. Symptoms proved to be worst in people with HIV/AIDS, followed by those with HIV alone and those who were HIV negative.

HIV status was also found to contribute to LUTS in a study Breyer conducted with epidemiologist Stephen Van Den Eeden, PhD, of a subset of men enrolled in the California Men's Health Study led by Kaiser Permanente, Northern California. They looked at 41,414 HIV-negative and 256 HIV-positive men age 45 to 69, and, after adjusting for age, race/ethnicity, diabetes, smoking, and hypertension, found that being HIV-positive nearly doubled the odds of having LUTS.

In future work, Breyer plans to explore the role of local and systemic inflammation in LUTS and the link between LUTS and depression.

Dr. Breyer's KURe mentors include Jack McAninch, MD, and Peter Carroll, MD, MPH, (career mentors); Leslee Subak, MD (lead research mentor), Tom Lue, MD (co-lead research mentor). [U](#)



Ben Breyer, MD on the right with his mentors: Leslee Subak, MD, and Stephen Van Den Eeden, PhD.

Antibiotics for prenatally-detected urinary tract dilation

The widespread use of prenatal ultrasound has meant that many cases of urinary tract dilation are detected before birth. This imaging finding may indicate an obstruction of the flow of urine from the kidneys to the bladder, and it can occur anywhere along the upper or lower urinary tract (Figure). Second-year KURe scholar Hillary Copp, MD, MS, is examining the risks and benefits of the antibiotic prophylaxis that is routinely prescribed for these children after birth.

Urinary tract dilation appears on prenatal ultrasound in from 1.5 to 8% of fetuses, and the condition persists in about 1 in 200 births. Because the condition can spontaneously resolve, most specialists recommend watchful waiting rather than immediate surgery. Antibiotic prophylaxis is often recommended during this observation period to prevent urinary tract infection and pyelonephritis.

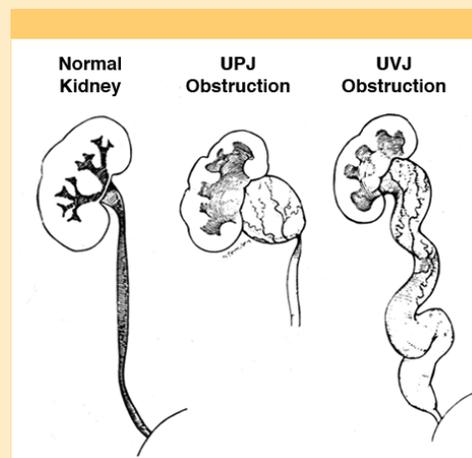
However, studies have suggested that there is a similar infection rate whether or not a child is receiving antibiotics (ranging from 0-36%) and there is also

evidence that resistant infections are more common in children on antibiotic prophylaxis.

The Prenatally-detected Urinary Tract Dilation (PNUT) study, which Copp developed with epidemiologist Stephen Van Den Eeden, PhD, will draw on a mother and child electronic medical record database from the Northern California Kaiser Permanente Medical Care Program. With 30,000 births each year in the study group, an average of 300 patients with urinary tract dilation should be diagnosed annually. Copp will retrospectively search the text of prenatal ultrasounds for key words that identify urinary tract dilation in the fetus. Once children are born, ultrasonography, voiding cystourethrograms and other diagnostic testing will be noted, along with whether or not antimicrobial prophylaxis was initiated. Compliance with antibiotic prophylaxis as measured through electronic pharmacy records will be examined. The study, which is in the data abstraction phase, should provide clues as to which children are more likely to develop UTIs, whether antibiotic

prophylaxis is helpful, and whether it is associated with treatment-resistant bacterial strains.

Dr. Copp's KURe mentors include Laurence Baskin, MD, Jeanette Brown, MD, Steve Hulley, MD, MPH (career mentors); Stephen Van Den Eeden, PhD (lead research mentor), Michael Cabana, MD, MPH (co-lead research mentor). [U](#)



Common causes of obstructive urinary tract dilation. UPJ = ureteropelvic junction, UVJ = ureterovesical junction

Genetic clues to hypospadias

Second-year KURe scholar Shweta Choudhry, PhD is studying the genetics of hypospadias, a birth defect of the male urethra in which the urethral opening is abnormally placed. The condition is classified as mild to severe, depending on where the opening is located along the penile shaft. Incidence figures for hypospadias range from as low as 1 in 4,000 in some countries to 1 in 250 boys born in the US, and there has been concern that the rate is rising.

The molecular events that lead to hypospadias remain largely unknown. There may be some genetic predisposition—seven percent of boys born with hypospadias have a father with the condition, and several genetic mutations are associated with a percentage of cases. Environmental exposures, including exposure to environmental estrogens, may also play a role in hypospadias. The condition can be induced in developing mice by in utero exposure to endocrine-disrupting chemicals with estrogenic or anti-androgenic activity. Prenatal exposure of mice to phthalates or estrogen also increases expression of genes that adversely affect male genitourinary development. In humans, some studies have suggested an increase in the incidence of hypospadias with exposure to farm chemicals, pesticides, phthalates and hair spray.

In an initial pilot study, Choudhry looked at the role of DNA methylation (the

addition of a methyl group to a cytosine-pyrimidine ring in DNA) in hypospadias. Changes in methylation levels of various genes have been associated in other studies with diseases such as cancer, autoimmune disease, mental disorders and diabetes.

Using BeadChip™ technology to probe DNA extracted from the foreskin tissue of 13 boys with severe hypospadias and 19 controls, Choudhry found a relationship between hypospadias and methylation of the CXorf6 gene, known to be important in the development of male genitalia. Choudhry hopes to confirm these findings in a larger sample and to add information on environmental exposures. Additional work in mouse models might provide clues to a possible cause-and-effect relationship.

Choudhry's second pilot study looked at genes that might be associated with hypospadias in 123 boys with the anomaly and 56 controls recruited from UCSF and Children's Hospital Oakland. Genotyping and analysis found association with genetic polymorphism in the 3' untranslated region of the ESR2 gene, an association she will attempt to confirm by expanding her sample size in future studies.

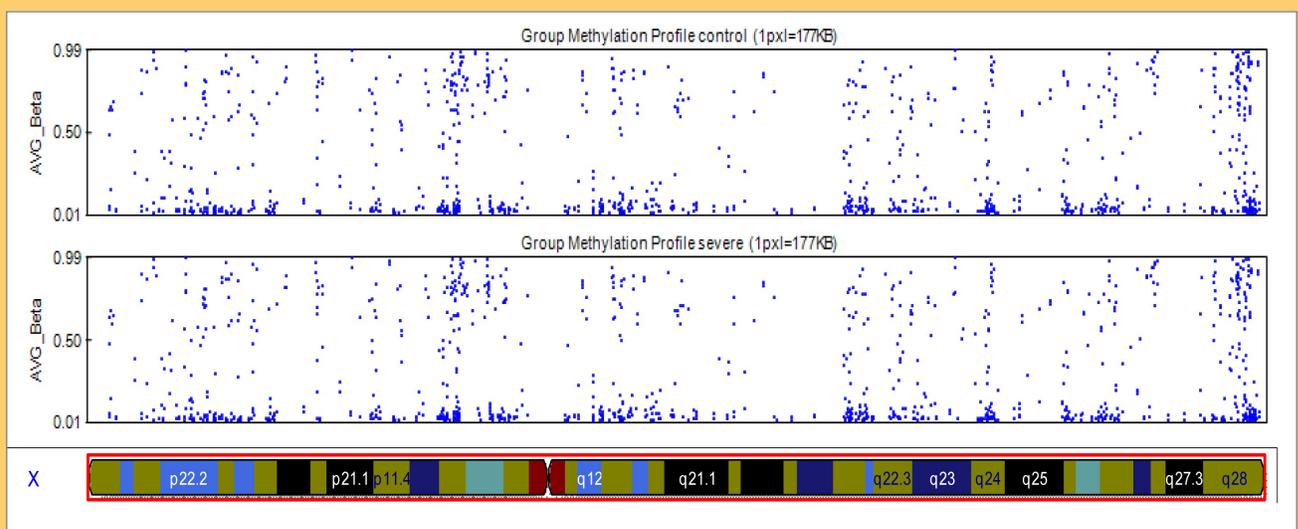
Dr. Choudhry's mentors include: John Witte, PhD (career mentor) Laurence Baskin, MD (lead research mentor), June Chan, ScD (co-mentor). [U](#)

Drosophila as a model for urinary stone disease

Thomas Chi, MD, who will become a KURe scholar in July 2011, is working with UCSF urology faculty mentor Marshall Stoller, MD, and researchers from the Buck Institute on Age Research to explore the fruit fly (*Drosophila melanogaster*) as a novel model for urinary stone disease. In people, up to 12 percent of Americans experience a kidney stone over the course of a lifetime. Urinary stones can be extremely painful, and more than half of patients require surgical treatment. Little is known about how stones form, and ways to treat and, more importantly, prevent them are limited.

Dr. Chi is working with two *Drosophila* experts, Pankaj Kapahi, PhD, of the Buck Institute on Age Research, and Katja Brueckner, PhD, a UCSF cell and tissue biologist, to develop fruit flies as a novel animal model for urinary stone disease. Scientists had previously observed that these insects form something that resembles stones in their tubules, which are the fly's kidney equivalent - structures that filter waste in their bodies. As a model for the study of urinary stones, *Drosophila* demonstrate some important benefits.

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DNA methylation genetic clues hypospadias



Letter from the Program Director

Laurence Baskin, MD

Training urologic research stars of the future is our goal! We are now starting our third year of the UCSF Multidisciplinary K12 Urologic Research (KURe) Career Development Program. As you can see from the newsletter, Dr. Ben Bryer our 1st year scholar is off to an amazing start with his study of voiding dysfunction in high risk populations. Our veterans Drs. Shweta Choudhry who is studying the etiology of hypospadias and Hillary Copp who is determining the need for antibiotic prophylaxis continue to be incredibly productive. We are especially excited to welcome Tom Chi, our 1st laboratory based surgeon scientist, along with his Drosophila friends into our program.

With the help of the incredibly supportive environment of the Urology Department and the Clinical and Translational Science Institute Postgraduate Educational Program we are looking forward to mentoring our new scholars. This unique program has been made possible by funding from the National Institute of Health with a generous supplement from the Urology Department.

We have high expectations for our scholars as they train to become the next generation of urologic leaders. We are presently recruiting additional future scholars committed to urologic research. If you have finished or are about to finish your urologic residency or doctoral studies and want to continue your career in urologic research please look us up. We have the commitment, environment and mentors to make it happen!

Sincerely,

Laurence S. Baskin, MD
Chief, Pediatric Urology, Department of Urology
Professor of Urology and Pediatrics, University of California, San Francisco

Drosophila ... continued

Their short lifespan of 30-45 days lets scientists observe the entire disease course. The flies can also be genetically manipulated to increase or decrease stone formation, giving insight into how and why stones form in the first place.

Researchers in this project have so far identified genetic mutations in the fly that cause the formation of different types of stones and are analyzing how their chemical composition compares to human stones. They have also shown that increasing protein in the fly's diet increases the amount of stones formed in the tubules.

Chi's team has also identified a fly gene related to vitamin D metabolism that may suppress stone formation and another relating to calcium metabolism that may increase formation, potentially pointing to transporters that could be manipulated as novel treatment targets for stone disease.

In future work, Dr. Chi plans to link his work in the fly to large scale human

epidemiologic studies to identify additional novel genetic targets for new treatments in stone disease. Chi will also explore the possible link between inflammation and kidney stone formation using this newly developed animal model.

Dr. Chi's KURe mentors include Marshall Stoller, MD (career mentor); Pankaj Kapahi, PhD (lead mentor), Katja Bruckner, PhD (co-mentor). 



Drosophila the "Fruit Fly". The green image is the fly injected with a fluorescent bisphosphonate which is stains for calcium.

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For more information about applying to the KURe Program please contact lbaskin@urology.ucsf.edu

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