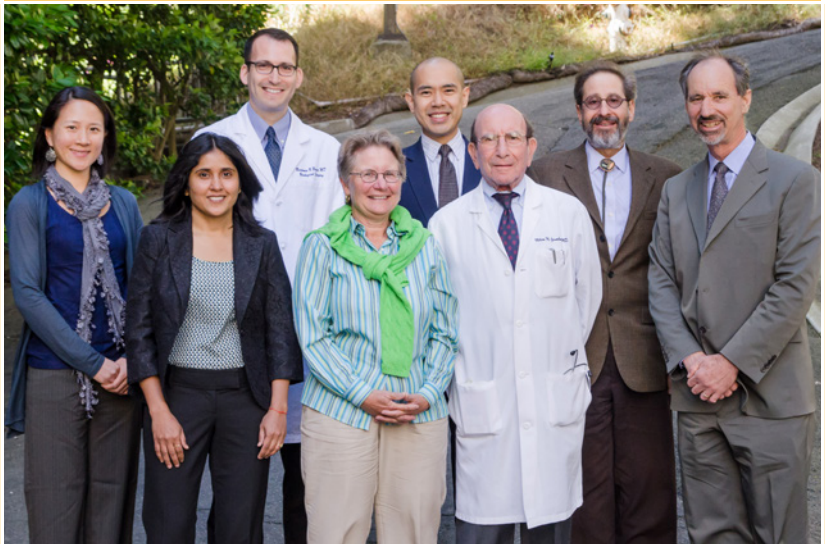
UCSF UROLOGY *KURe Career Development Program*

UNIVERSITY OF CALIFORNIA, SAN FRANCISCO | SCHOOL OF MEDICINE | 2013

UCSF KURe Career Development Team

Front row: **Scholars**; Nadia Roan, Shweta Choudhry. **Mentors**; Jeanette Brown, Mel Grumbach, Laurence Baskin. *Second row:* **Scholars**; Ben Breyer, Tom Chi. **Mentor**: Marshall Stoller.



INSIDE THIS ISSUE

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.

Career Development Program Supports Innovative Research

Now in its fifth year, the UCSF multidisciplinary K12 Urologic Research (KURe) Career Development Program continues to nuture talented young scientists.

We are delighted to report that the K12 grant from the National Institutes of Health (NIH) that supports this program has been renewed for another five years—a strong endorsement of the work we have accomplished so far. The NIH grant is supplemented by generous support from the UCSF Department of Urology, which sees the development of these young professionals as a vital part of its educational mission.

The goal of this program is ambitious—to develop the young faculty who will serve as future leaders in the field of benign urologic diseases. Our KURe scholars have an impressive record of publications in prominent journals, presentations at national specialty society meetings, and even popular media attention. This reflects the level of talent represented by our program participants: fourth-year scholars Shweta Choudhry, PhD, and Hillary Copp, MD, MS; third-year scholars Benjamin Breyer, MD, and Thomas Chi, MD, and first year scholar Nadia Roan, PhD. The success of the program also owes much to the mentors and advisors who guide these young faculty members. They bring top-flight expertise in fields ranging from epidemiology to genetics to clinical outcomes research—expertise that enriches the work of the KURe program.

> We are extremely excited to have another 5 years of NIH funding to train the future leaders in urologic research!
>
> – Laurence Baskin, MD.

KURe scholars receive departmental support and research facilities for their work. Scholars receive faculty appointments at UCSF and 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 Translational Science Training Program.

We hope you enjoy this overview of the exciting work supported by this program.

—Laurence Baskin, MD, Chief of Pediatric Urology, KURe Program Director.

Defining the Genetics of Hypospadias

Fourth-year KURe scholar Shweta Choudhry, PhD, has expanded her studies of hypospadias, a male birth defect in which the urethral opening is abnormally placed along the underside of the penis. Affecting approximately 1 per 250 male newborns, it is one of the most common congenital malformations. Genetics likely plays a significant role in the condition, since it shows strong aggregation in families.

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1868

Defining the Genetics of Hypospadias ... continued

Environmental factors, including maternal diet, hormone levels, and exposure to endocrine-disrupting chemicals, may also contribute to hypospadias.

Choudhry and her colleagues published a study in a 2012 issue of the Journal of Urology that used specialized genomic analysis to look for additional methyl molecules (methylation) in foreskin samples of 12 hypospadias and 8 control subjects. Methylation is significant because it is known to affect gene expression. Choudhry's team detected changes in methylation patterns in several parts of the genome, suggesting that these areas may be important in the development of hypospadias.

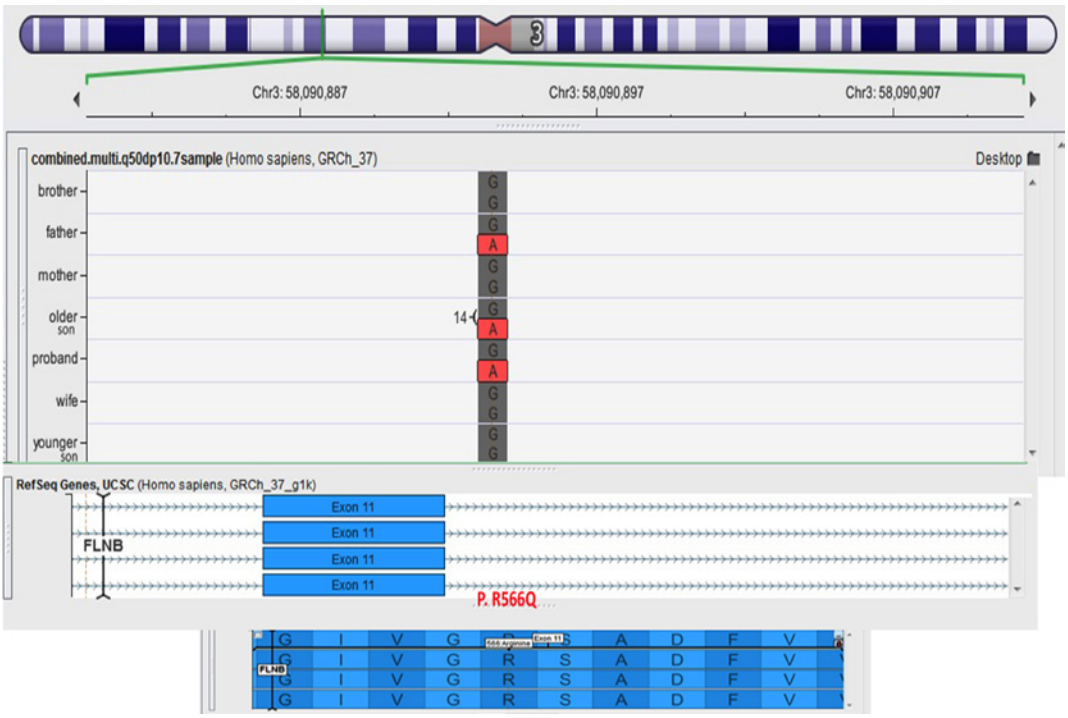
Choudhry, who has an extensive background in genetic epidemiology and molecular genetics, has also applied advanced genetic sequencing to identify mutations that may cause hypospadias. She and her colleagues have been recruiting hypospadias patients and healthy controls to contribute to a tissue bio-bank, and now have over 400 tissue samples available for genetic studies.

With the latest gene sequencing technology, Choudhry and her team have performed whole-genome sequencing of eight severe hypospadias patients and whole-exome (the coding region of DNA) sequencing of seven members of a multigenerational Caucasian family with a high incidence of hypospadias. So far, the team has identified potential causal mutations in the DLX6 and FLNB genes that will be confirmed in large population sample. This work will help decipher the developmental steps that govern normal urethral development. Understanding which genes and variants cause hypospadias will help inform men with hypospadias about potential risks to their offspring.

Dr. Choudhry is an associate professor of urology at UCSF. Her mentors include: John Witte, PhD (career mentor), Laurence Baskin, MD (lead research mentor), June Chan, ScD (co-mentor), and Peter Carroll (mentor and co-principal investigator).

Shweta Choudhy, PhD. Fourth year KURe Scholar.

Peter R. Carroll, MD, MPH, Professor and Chair, Department of Urology. Co-Investigator and Mentor UCSF KURE program



Detecting Genetic Abnormalities in Hypospadias on Chromosome 3: Potential causal mutation in exon 11 of FLNB gene in the affected members of a three generation family with hypospadias.

Exploring the Causes of Urinary Stones

Third-year KURe scholar Thomas Chi, MD, is continuing his study of urinary stones, a condition that affects up to 12 percent of Americans at some point in their lifetime. Chi is collaborating with his urology faculty mentors, Marshall Stoller, MD, and Katja Brückner, PhD, as well as researchers from the Buck Institute for Research on Aging to develop fruit fly models that closely mirror human stone formation. Because the life cycle of this fly (*Drosophila melanogaster*) is so short, scientists can rapidly track the effects of dietary and environmental changes and genetic variations on stone formation.

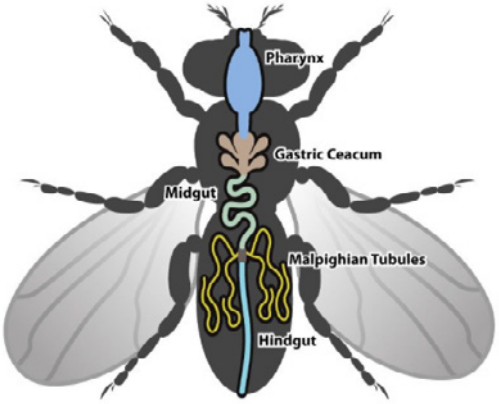
Development of the *Drosophila* model has provided a springboard for collaborations with many other researchers. Chi is working with a research team from the US Geological Services, which tracks the levels of many toxins and pollutants by geographic area, to examine the role that heavy metals may play in urinary stones. Chi is also collaborating with researchers at Children's Hospital of Oakland, who are conducting a study of the relationship to diet and its effect on urine and stone risks.

Chi and his colleagues have recently been studying how strontium, a heavy metal chemically similar to calcium, is incorporated into urinary stones. In collaboration with UC Berkeley, researchers use a football field-sized electron accelerator called a synchrotron to perform advanced x-ray imaging that characterizes the molecular composition of strontium and other elements in stone samples. In a recent study, this imaging tool detected strontium in all calcium-based stone samples, an intriguing finding since strontium cannot be detected with standard laboratory stone analyses. This finding should improve scientists' understanding of early stone formation and of ways to prevent and treat the condition. Chi is planning additional studies to examine the role of other heavy metals in stone formation.

Other work is focused on patients with cystinuria, who frequently form urinary stones due to a genetic defect that affects metabolism. Although they account for a small percentage of urinary stone patients, UCSF sees a relatively high number of these individuals, who can require frequent surgeries for stone removal. Chi has shown that the genetic mutation in cystinuria involves the same transporter mechanism in both humans and *Drosophila*, and is working to develop a fly model that will allow researchers to learn more about this disease.

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

Thomas Chi, MD, is Third Year KURe scholar and Assistant Professor of Urology at UCSF. His research is focused on understanding and treating kidney stones.



Drosophila have two pairs of Malpighian tubules (shown in yellow), which are the equivalent to the human kidney. Over 85% of the transporters are preserved between *Drosophila* species which allows researchers to understand how stones form at the cellular and genetic level using the fly model.

Dr. Tom Chi's Experimental Fruit Flys that are being used to better understand the etiology of kidney stone formation.

Semen Components and HIV Infection

First-year KURe scholar Nadia Roan, PhD, is exploring how factors in human semen influence the infection efficiency of human immunodeficiency virus (HIV). This is the latest in a series of research projects she has conducted on how host factors interact with microbes in the genital tract.

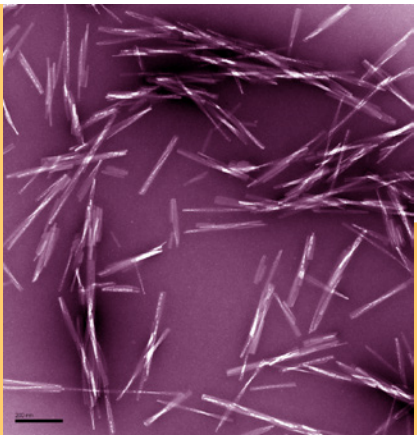
Roan is investigating how the semen components she has identified and characterized, called amyloids, promote HIV transmission. She previously demonstrated that semen amyloids help HIV attach to cellular targets. More recently, she found that semen amyloids may also induce inflammation, which can increase susceptibility to HIV infection. Roan is also examining how these amyloids alter the effectiveness of anti-HIV microbicides that are used to reduce the risk of infection, and is screening for compounds that can inhibit the ability of semen amyloids to enhance infection. The long-range goal of this work is to help develop a new class of microbicides that target both HIV and the naturally-occurring factors in semen that promote HIV infectivity and viral replication.

In a second line of investigation, Roan is working to understand the role semen amyloids play in human reproduction. She has found that peptides that produce amyloids are present in a variety of non-human primates, and that semen amyloids affect sperm function. Understanding the role semen amyloids play in reproduction may lead to new ways to enhance fertility or to new methods of contraception.

Roan is an assistant professor of urology at UCSF and a visiting scientist at the Gladstone Institute for Virology and Immunology, where she had initiated much of her HIV research under the mentorship of Dr. Warner Greene. She has been interested for many years in understanding the effects of host factors on microbial pathogens of the genital mucosa, first studying this process in the most common sexually transmitted bacterium, Chlamydia trachomatis, and then transitioning to the study of HIV. Roan completed her doctorate in biological and biomedical sciences at Harvard Medical School and received her undergraduate degree in molecular and cellular biology at UC Berkeley. She has received many awards throughout her professional career, most recently the 2013 Hellman Family Award for Early-Career Faculty, the 2012 Early Career Award of Excellence in Basic Research from the Centers for AIDS Research, and the 2012 Gladstone Institute of Virology and Immunology Award for Scientific Excellence.

Dr. Roan is an assistant professor of urology at UCSF. Her mentors include: Ruth Greenblatt, MD (career mentor); Warner Greene, MD PhD (lead research mentor); Laurence Baskin, MD and Linda Giudice, MD PhD MsC (co-mentors).

Nadia Roan, PhD, is an assistant professor of urology at UCSF and a visiting scientist at the J. David Gladstone Institutes. Her research focuses on understanding the effects of semen and semen-derived factors on HIV transmission and reproduction.



Amyloids derived from the major components of the semen coagulum form fibrillar structures (pictured) that markedly enhance HIV infection.

Training Background and Mentors

The University of California, San Francisco (UCSF) is renowned as one of the premier health sciences campuses in the world, in part due to our outstanding training programs in basic, translational, and clinical sciences and their close alignment with the many superb research activities. UCSF is in a unique position to translate basic science discoveries into public health and clinical practices and was chosen as one of the first 12 academic institutions selected to be part of the NIH's national clinical & translational science consortium. The UCSF Clinical & Translational Sciences Institute (CTSI) established in 2006, has integrated laboratory- based and clinical research training programs in the comprehensive and coordinated UCSF Clinical Translational Science Training Program. The UCSF Multidisciplinary K12 (KURe) Urologic Career Training Program has been fully integrated since its inception in 2009 within the CTSI providing the translational/multidisciplinary research environment to facilitate the successful development of young scholars interested in pursuing academic careers in the study of benign urological diseases. The anchor of the KURe program will be the department of Urology at UCSF, chaired by Dr. Peter Carroll (Co PI). Drs. Laurence Baskin, Gerald Cunha (Laboratory Science) and Jeanette Brown (Clinical Studies) are the Program Director and Program Co-Directors, respectively. A 12 member Advisory Committee interfaces with the KURe scholars, program leaders and over 60 UCSF mentors with the core mentors within the department of urology. These mentor/ scientists have outstanding well-funded research programs and have a proven track record of mentoring junior faculty. We presently have 5 outstanding KURe scholars and their mentoring teams at UCSF. In conjunction with the resources of the CTSI, UCSF Department of urology and NIH, our scholars have met their goals as defined by their formalized career development plans. This is reflected in their publication record, internal funding record and the pending NIH grants from our senior scholars. The anticipated outcome of the KURe remains excellence in training with the ultimate goal of independent funding for our scholars. We are committed to nurturing our present and future cadre of UCSF KURe Scholars that will discover and expand knowledge, test innovations, and become the future leaders in the field of benign urologic research.

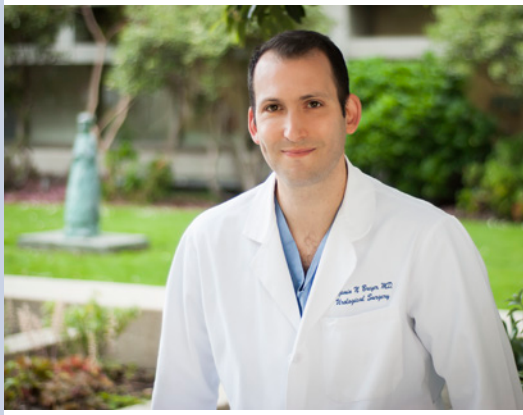
The Competitive renewal was submitted and received a score of 20.

It was funded at Counsel for an additional 5 years.

Nadia Roan has received independent funding and will graduate the KURe.

Voiding Problems and Mood Disorders

Benjamin Breyer, MD, began his KURe research career with an examination of the relationship between HIV infection and lower urinary tract symptoms (LUTS), such as frequent or urgent urination. Now in his third year as a KURe scholar, Breyer has shifted his research focus to the relationship between LUTS and sexual dysfunction in mood disorders and anxiety. He is leading a study of the effect of post-traumatic stress disorder (PTSD) on LUTS and sexual dysfunction in U.S. veterans who have served in Afghanistan and Iraq. This work is based on data from the Veterans Administration hospitals and is being performed in conjunction with two experts in PTSD: Karen Seal, MD, and Thomas Neylan, MD. Breyer is also conducting a study of depression, suicide and LUTS in a broader population, using data gathered through the CDC's National Health and Nutrition Examination Survey (NHANES).



Benjamin N. Breyer, MD, MAS is and Assistant Professor of Urology and Third Year KURe Scholar. Dr. Breyer is studying of the effect of post-traumatic stress disorder on Lower Urinary tract Symptoms and sexual dysfunction in U.S. veterans who have served in Afghanistan and Iraq.

Consumer Product-Related Genital Injuries

Breyer's other research interest is the prevention and treatment of genital trauma. He has fielded a variety of media inquires in response to his ongoing investigations with professor Jack McAninch, MD, on genitourinary injuries from common consumer products. Using data from the U.S. Consumer Product Safety Commission National Electronic Injury Surveillance System, Breyer has reviewed emergency department records to track the epidemiology of adult and pediatric genitourinary injuries from such objects as toilet seats, zippers and personal grooming. The research team is currently reviewing genital injuries related to bicycling, other sports, and playground equipment.

Dr. Breyer is an assistant professor of urology at UCSF. His 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).

Rank	18-28 years	29-45 years	46-65 years	66+ years	All Ages
1	Sporting items (39.6%)	Sporting items (28.5%)	Sporting items (23.6%)	Furniture (19.5%)	Sporting items (30.1%)
2	Clothing items (8.7%)	Clothing items (8.8%)	Bathroom fixtures (10%)	Bathroom fixtures (15.6%)	Furniture items (9%)
3	Shaving items (8.1%)	Furniture (8.8%)	Clothing items (9.4%)	Climbing fixtures (10.9%)	Clothing items (8.7%)
4	Furniture (7.7%)	Shaving items (6.8%)	Furniture (7.4%)	Flooring (8.8%)	Shaving items (6.9%)
5	Bathing products (5.5%)	Bathing products (4.9%)	Shaving items (6.3%)	Sporting items (8.8%)	Bathroom fixtures (5.6%)
6	Climbing fixtures (3.6%)	Climbing fixtures (4.6%)	Climbing fixtures (5.3%)	Clothing items (5.9%)	Climbing fixtures (4.9%)
7	Sex Toys (2.6%)	Bathroom Fixtures (4.2%)	Bathing products (4.1%)	Bathing products (3.5%)	Bathing products (4.8%)

Antibiotic Use in Pediatric UTIs

Fourth-year KURe scholar Hillary Copp, MD, MS, continues her research on antibiotic resistance, antibiotic prescribing, and urine testing practice patterns in the management of pediatric urinary tract infections (UTIs).

At a plenary session of the 2013 meeting of the American Urological Association, she spoke on the continuing problem of microbial resistance to various antibiotics. Copp's data analysis has shown that some classes of broad-spectrum antibiotics are overused and that some narrow-spectrum drugs (e.g., trimethoprim/sulfamethoxazole) are prescribed in geographic regions where there are high rates of resistance.

The issue of pediatric UTI treatment is complex because many patients are treated in the outpatient setting, where culturing urine for specific bacteria and follow-up are challenging. With a grant from the NIH-sponsored Urologic Diseases in America project, Copp plans

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Hillary Copp, MD, MS, is an Assistant Professor and Fourth Year KURe Scholar. Dr. Copp's research is focused on antibiotic resistance, antibiotic prescribing, and urine testing practice patterns in the management of pediatric urinary tract infections.

Letter from the Program Director

Laurence Baskin, MD

Training urologic research stars of the future is our goal! We are now starting our sixth year of the UCSF Multidisciplinary K12 Urologic Research (KURe) Career Development Program. As you can see from the newsletter, we have just received another five years of funding from NIH to support our program!

Congratulations to our first year scholar Nadia Roan, who has received independent NIH funding. Nadia officially graduates from our UCSF KURe program but will continue on in the Department of Urology as an assistant professor. Nadia's seminal work focuses on how factors in human semen influence the infection efficiency of HIV.

Please enjoy the enclosed summaries of the unique projects of our four present scholars: Hilary Cop, Shweta Choudhry, Ben Breyer and Tom Chi.

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 doctorial 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

Antibiotic Use in Pediatric UTIs ... continued

to analyze the cost effectiveness of various treatment approaches using a combination of broad-spectrum and narrow-spectrum antibiotics without and without urine culture.

Copp has published an analysis of national prescribing patterns for pediatric UTIs from 1998-2007, using the National Ambulatory Medical Care Survey and National Hospital Ambulatory Medical Care Survey. Her research showed that one-third of antibiotics prescribed for the treatment of pediatric UTI were broad-spectrum. Her most recent work in Pediatrics demonstrates that that a substantial proportion of children with antibiotic-treated UTIs are not undergoing urine testing prior to antibiotic prescription.

Copp has also published an analysis of national patterns of antibiotic resistance, using data from The Surveillance Network®. She and her colleagues found that the most common uropathogen, Escherichia coli, was resistant to the most commonly prescribed antibiotic, trimethoprim-sulfamethoxazole, 24 percent of the time.

Dr. Copp is an assistant professor of urology at UCSF. Her KURe mentors include Laurence Baskin, MD, Jeanette Brown, MD, Steve Hulley, MD, MPH (career mentors); Stephen Van Den Eeden, PhD (research mentor), Michael Cabana, MD, MPH (research mentor).

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The KURe Newsletter is published by the Department of Urology to present developments made within the program.

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

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