

# UW Urology News

The Newsletter of the  
University of Washington Department of Urology



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## News from the Chairman

Paul H. Lange, MD, FACS



Dear alumni and friends,

This will be my last message in this newsletter as Chairman of this department. By now it should come as no surprise that I am stepping down from that role July 1<sup>st</sup>. After 19 years, it's time and the timing is what I actually intended for many years. Publicly I had been telling the faculty and prospective residents that I would probably step down in July of '08 but privately I hoped to do so a year earlier to mitigate the problems that occur with "lame-duck" Chairs. (That little lie is palatable I hope because I am not leaving). I intend to continue to do the things I love most for the foreseeable future: taking care of patients, doing surgery, teaching, and doing research (in my case on circulating stem cells in prostate cancer). I also hope to further increase the endowment level of this department - a necessity if we are to keep up with our academic peers and continue to function at the high level that we have achieved. As

such, I may be calling on some of you who are now reading this column.

Though I have had time to collect my thoughts, I must still admit to dreading, and thus procrastinating, writing this message. How does one send an appropriate parting comment after so many years? My deadline has past and my taskmaster, Mike Porter, who is doing such a fantastic job getting this newsletter out, is bearing down on me. It does not help that it is a beautiful Sunday and Easter besides.

I could reminisce about all of the wonderful things that have happened to this department while I have been here. For example we are currently in the top five in NIH research funding

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## Training the Next Generation of Scientists: The HUB Lab's Success Story

Dr. Jim Bassuk has a success story to tell. In 1998, he was recruited into the department by Drs. Rich Grady, Mike Mitchell and Paul Lange for the purpose of creating a urologic research laboratory at Seattle Children's Hospital. This initiative was successful and culminated in 2004 when Dr. Bassuk created the Program in Human Urothelial Biology. Known in Seattle as "The HUB Lab", the Program is supported by multiple NIH grants and has earned an international reputation for its pioneering work with positive and negative regulators of urothelial cell proliferation. The laboratory is staffed with scientists whose qualifications and training include bioengineering, urology and

nephrology, pharmacology, protein chemistry, molecular and cell biology, histology and microscopy, and bioinformatics. Partnerships have been built with collaborators of the hospital and the university for the purpose of translating bench science discoveries into new tools for the clinician to better manage, and ultimately treat, a variety of conditions such as interstitial cystitis, urethral stricture, and hypospadias.

One little known secret for the Program's success is the constant presence of undergraduate students in the lab's research efforts. "To me, undergrads are much more than bottle washers and gophers", says Dr. Bassuk. "They each have their own research project and typi-

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# UW Neurourology Laboratory

## Claire C. Yang, MD



The Neurourology Laboratory was founded at the University of Washington in 1995 by the late Dr. William E. Bradley, a prominent neurologist who spent his career in investigating the neurophysiology of the genitourinary tract. He is best known to urology for developing the artificial urinary sphincter and the inflatable penile prosthesis. The Neurourology Laboratory is dedicated to continuing his vision of genitourinary neurophysiology research. In addition to NIH funding, the Lab receives support from the Bradley Family Foundation.

The primary research objective of the Neurourology Laboratory is to investigate and define the neurologic factors of genitourinary function, in health and disease. Although the majority of the work is centered on electrodiagnostic techniques, other methods, standard and experimental, are used as well. Urologists consider the field of "neurourology" primarily to involve bladder function and dysfunction. However, neurourology is also the study of the nervous system and how it mediates sexual function (male and female), as well as its contributions to chronic pelvic pain (e.g., interstitial cystitis, chronic prostatitis).

Currently, our main project is developing and validating a method to measure autonomic innervation of erectile tissue. Except for certain cardiac tests, there are no techniques to measure autonomic

innervation of the viscera and internal organs. Many instances of erectile dysfunction are attributed to neuropathy (e.g., injury of the cavernous nerves during prostatectomy, neuropathy due to diabetes), but because the autonomic innervation to the penis cannot be measured, neurogenic erectile dysfunction is a diagnosis of exclusion. We are validating a technique to measure penile autonomic innervation in men with spinal cord injury and men following radical pelvic surgery. If successful, this method can be used to diagnose neurogenic ED, as well as document recovery with treatment. This technique is also applicable to women, and we have recently published preliminary reports on its feasibility.

With Dr. Richard Berger, several studies on the autonomic nervous system factors and male chronic pelvic pain/chronic prostatitis have been conducted. Electrodiagnostic tests have shown that there are signs of autonomic nervous system changes in men with chronic pelvic pain, and that these signs are perhaps more important in understanding the chronicity of the symptoms, than end organ findings. Associating these electrodiagnostic results with serum and urine metabolites of autonomic neurotransmitters is the subject of future studies.

A secondary area of research is in female sexual function. We are collaborating with Dr. Ken Maravilla, Director of MRI Research at UW, on studies using func-

tional MRI (fMRI) in evaluating the brain response to sexual arousal in women with sexual arousal disorder, along with corresponding pelvic anatomic studies. Histologic studies on female genital erectile tissue with Dr. Chris Cold, a pathologist at Marshfield Clinics in Marshfield, Wisconsin, are ongoing as well.

Lastly, because of our research in chronic pelvic pain, we are a center in the NIH-sponsored Urological Pelvic Pain Cooperative Research Network (UPPCRN), enrolling subjects into multi-center clinical trials for treatment of painful bladder syndrome/interstitial cystitis. Along with Dr. Jane Miller, and Dr. John Krieger, who is directing the UW site for the chronic pelvic pain/chronic prostatitis trials, UW Urology has been a significant contributor to the UPPCRN studies.

We are currently enrolling subjects for the following studies:

1. Spinal cord injury and erectile dysfunction-nerve testing Contact Brenda 206-598-3293
2. Interstitial cystitis/painful bladder syndrome Contact Sharon 206-

## Announcements

- The Society of Basic Urologic Research has named **Dr. Daniel Lin** as recipient of the 2007 Young Investigator Award
- The American Physiological Society-Cardiovascular Section named **Dr. Kanchan Chitale** as the recipient of the 2006 Young Investigator Award. Dr. Chitale was also honored by the Sexual Medicine Society of North America with an Award for Top 10 Basic Science Abstracts
- **Dr. James Kuan** is the recipient of the 2007 AUA/Gyrus ACMI Prize Essay Contest, 2nd prize Clinical Research Category, to be awarded at the Annual Meeting of the AUA in Anaheim, for his paper "Renal injury mechanisms in motor vehicle collisions: analysis of the Crash Injury Research and Engineering Network (CIREN) dataset"
- We are happy to announce the results of the 2007 resident match. **Laura Leddy** will graduate from the University of Virginia School of Medicine in June. She is Originally from Greenwich, CT. **Christopher Welty** will graduate from Vanderbilt University School of Medicine in June. He is originally from San Diego, CA.
- The UW Urology Website has been updated. Visit <http://depts.washington.edu/uroweb/index.html> to get the latest news about the department, view previous editions of this newsletter, or to get information about patient referrals

# UW Male Infertility and Prostatitis Research

**Charles (Chip) H. Mueller, PhD, HCLD (ABB)**

Sperm dysfunction and male chronic pelvic pain are the focus of research and clinical tests in the 11<sup>th</sup> floor labs directed by Chip Muller. Since 1983, he has directed the University of Washington Clinical Andrology Lab, first situated in the Department of Obstetrics and Gynecology, and moved in 1993 to the Department of Urology. Here, in collaboration primarily with Drs. Rick Berger, John Amory, Stan McKnight, John Krieger and Claire Yang, the labs have obtained NIH, industrial, and private funding to study topics such as drug and toxicant effects on human sperm, prostatitis, HIV in semen, vasectomy efficacy, ion channels in monkey sperm, and fertility of mice with gene knock-outs.

## CLINICAL TESTS AND RESEARCH IN THE MFL

The clinical lab, known as the Male Fertility Lab (MFL), is a full-service clinical andrology lab, one of only a small number of its kind in the US. Today, most semen analyses are performed either by general clinical labs or by In Vitro Fertilization (IVF) labs, where, in most cases only a rudimentary test is performed. In contrast, the Male Fertility Lab offers a wide range of advanced sperm function tests in addition to computer-assisted semen analysis. Men with idiopathic infertility (those with a normal semen analysis, normal partner, and no known abnormalities or exposures) benefit from tests which measure the ability of their sperm to perform several of the critical steps needed for fertilization and early embryonic development:

- **Acrosome Reaction** tests or sperm **Hyperactivated Motility** tests can identify fertilization-related sperm dysfunctions, and possible in vitro treatments



Present and former students and technologists of the Muller Lab. From far right: Pilar Cordero Roman (MFL Medical Technologist), Tiffany Tang, Erin Pagel and Alison Lane (Research Technologists). Far left: Priya Subramanian (Research Technologist). The lab supports and trains 2 - 5 student researchers or lab helpers per year.

that may assist sperm function prior to Intra-Uterine Insemination (IUI) or IVF.

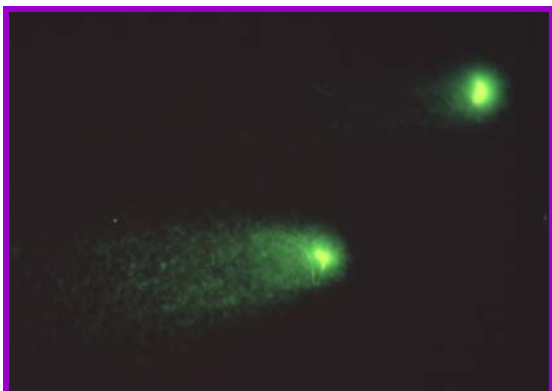
- **Sperm Recovery and Overnight Survival** test has a high predictive value for pregnancy success using IUI.
- **Reactive Oxygen Species** and **Anti-Oxidant** tests are performed to determine levels of oxidative stress. Sperm have high proportions of easily oxidized membrane lipids, and no DNA repair mechanisms, and thus are highly susceptible to oxidative damage. These tests are recommended for men with idiopathic infertility, those with high concentrations of leukocytes or immature germ cells (either of which may cause oxidative stress) in semen, and for men with prolonged infertility post-vasovasostomy.
- **Sperm DNA Fragmentation** tests are used in cases of high oxidative stress, idiopathic infertility, and recurrent spontaneous abortion. Sperm with damaged DNA often have normal fertilization potential,

but may lead to early embryonic death or embryonic malformations.

We are presently developing purification methods that separate sperm with damaged DNA from undamaged sperm. Because of studies such as these, the MFL enjoys an excellent national and international reputation as a first-rate research-oriented andrology lab.

The Male Fertility Lab has a very busy **Sperm Cryopreservation Program** that gives men with pending cancer therapy or reproductive surgery an option of storing their sperm for later use. As opposed to a sperm bank, this service is for patient clients, and does not sell donor sperm. Working with Rick Berger, Ivan Rothman and Claire Yang, we also have the capacity and techniques needed to extract, purify and freeze sperm from the testes. This has proven to be a critically important asset for some cancer patients. We interact intensely with the SCCA, Children's Hospital, and private clinical practices.

The MFL is very active in providing clinical semen analysis data for NIH and industry-sponsored trials of new drugs or vasc-



Two human spermatozoa exhibiting DNA fragmentation in the COMET assay. The sperm with the longer "Comet" tail is highly damaged.

## Infertility and Prostatitis research, continued from page 3

tomy techniques. For example, working with Dr. John Amory (UW General Internal Medicine), our lab played the key role in determining that a new potential male contraceptive (quite effective in mice) had no effect on human sperm formation or function. With Dr. John Krieger, we detailed the sperm and leukocyte changes accompanying early stages of HIV infection. As a key part of an international multi-center trial, with Dr. Rick Berger, we helped show the importance of variations in surgical procedure for vasectomy effectiveness. As part of this study, Dr. Muller traveled to Nepal to train lab technologists from Kathmandu and Sri Lanka. The MFL has been a major contributor to several past and ongoing clinical trials of new pharmaceuticals, including 5-alpha-reductase inhibitors and anti-depression drugs.

The laboratory is certified as a CLIA-approved Medical Test Site through the State of Washington. The Cryopreservation program is regulated and licensed by the FDA. Dr. Muller is licensed as a Director of High Complexity Laboratories through the American Board of Bioanalysts. The MFL reports clinical results and bills through the Dept. of Laboratory Medicine systems. (For further information, contact the MFL at 206-543-9504 or [androl@u.washington.edu](mailto:androl@u.washington.edu)).

### BASIC AND TRANSLATIONAL RESEARCH IN SPERM FUNCTION AND PROSTATITIS

Dr. Muller's background in comparative reproductive endocrinology led to his studies of mouse sperm maturation and in vitro fertilization, and eventually to studies of human sperm function and biochemistry. When the opportunity arose to study the effects of chronic pelvic pain (prostatitis) in collaboration with Dr. Rick Berger, he naturally thought of using sperm and seminal fluid biochemical markers as indicators of the disease process. This approach has paid off, with recent novel results showing an increased amount of DNA fragmentation in sperm of men with prostatitis compared to controls without pain, and elevated levels of a macrophage-specific cytokine in seminal plasma of the affected men.

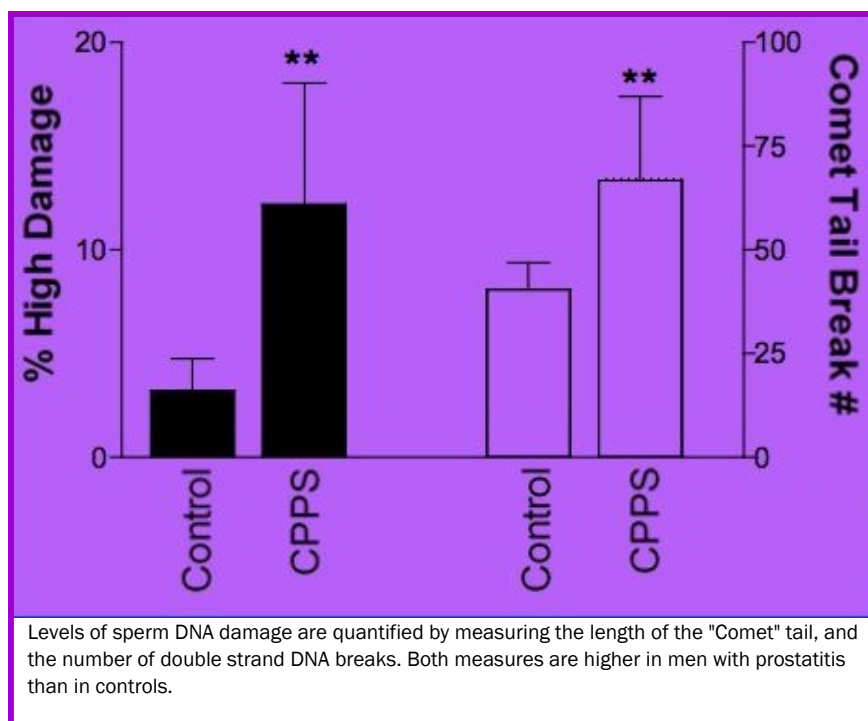
Men with non-bacterial chronic pelvic pain syndrome (CPPS) present with debilitating pain of unknown origin, and no culturable urogenital pathogens. It is a frustrating malady for both patient and clinician, with no proven effective treatment. Our goal in studying this syndrome is to elucidate a possible etiology, and therefore point to specific op-

tions for therapy. We have focused on oxidative stress as a likely contributor to the symptoms. Men have a perfect marker for oxidative stress: the sperm cell. Sperm are easily damaged and cannot repair oxidized (fragmented) DNA. As seen in the chart, sperm from men with CPPS have higher levels of DNA damage than do those from controls without pain. Originally, we believed that the number or type of leukocytes present in expressed prostatic secretions or semen might hold a key to pelvic pain or levels of oxidative stress, but found that these were largely unrelated. Even though leukocytes (primarily neutrophils and macrophages) in these fluids can exert tremendous levels of oxidative stress, it is difficult to determine levels of leukocytes or oxidative stress within urogenital tissues. In addition, epithelial cells may contribute to oxidative stress under certain conditions. Whichever its source, oxidative stress likely induces neuroinflammation, resulting in the painful destruction and re-growth of sensory neurons. Approaches we have taken to link inflammation to pain are to measure specific cytokines and chemokines in blood and seminal fluid, and to measure Nitric Oxide and its related free radicals in seminal fluid and urine. For example, we find that Nitric Oxide in seminal fluid is highly correlated with suprapubic pain and urinary symptoms

in men with CPPS. This is interesting, because many now believe that male interstitial cystitis is a component of, or confused with, prostatitis.

We recently found that the chemokine, Macrophage Chemotactic Protein 1, is elevated in men with CPPS, compared to controls, regardless of the presence of absence of prostatic fluid inflammation. This discovery was part of the medical research project of UW medical student Krister Freese. It is an important finding, because dozens of other cytokines and chemokines we and others have studied either have no relationship to CPPS symptoms, or are closely related to levels of inflammation regardless of pain symptoms. We propose that MCP1 may be a biomarker for CPPS, and may play a role in the development of this syndrome.

Our future studies in prostatitis will develop from these points. Our approach of combining novel andrology lab tools with the study of prostatitis have been fruitful and enlightening. The Andrology and Prostatitis Research labs welcome collaborations and student projects. Please contact us at [cmuller@u.washington.edu](mailto:cmuller@u.washington.edu).



## News from the Chair, continued from page 1

among Urology departments in the nation, and one of a handful with a Training Grant also. Our graduates are constantly demonstrating that we trained them well and quite a few have chosen the academic life for themselves. We have greatly increased our clinical activity – a requirement to meet our increased teaching load, and for the generation of financial resources. We find ourselves at the cutting, burning edge in many of our clinical fields including oncology, pediatrics, trauma, laparoscopy/robotics, female urology, stone disease, and erectile dysfunction. To that end we have tripled the faculty, and, more importantly, populated it with very wonderful, skilled, and dedicated people. In short we have successfully fulfilled our duty as exemplified in our department motto: “to cure, to comfort, to teach, and to wonder.” I am proud to have been associated with these successes and I hope that you are also.

I could ruminate about the challenges we now face. We know that the US medical care system, particularly as it relates to reimbursement, is broken, and increasingly academia is called upon to shoulder a disproportionately heavy burden of this dysfunctional system. For example, we are seeing an increasing number of poorly insured or unin-

sured patients and the number of hard, risky, or lengthy surgeries that we do is increasing at the same time the reimbursement level is going down. The salary disparities between academia and private practice seem to be widening, making it harder for the younger people who feel called to the academia challenge to persevere. Granted, academic surgeons have always “paid” for the privilege of this higher calling with lower salaries, but this situation is made even more difficult than in the past because “making your salary” takes longer, leaving less time for teaching and research, which itself is inadequately remunerated, if at all. I am grateful that the faculty have remained resolute in the face of these challenges. We try to do our part, and we have made some progress, by increasing private resources, such as endowments, to help pay for these labors of love.

What is most important now is to remind ourselves that we need to concentrate on the future rather than “fondle” the past, and face the future with optimism. Here this task will be made easier by many things. For the immediate future the department will be in very competent hands with Bill Ellis as Acting Chairman. Hopefully, soon the

Department will have a new permanent Chair selected from a pool of candidates that is large and impressive. Among that pool are Bill Ellis and Hunter Wessells. Thus, we will soon receive new energy, different ideas, and renewed resources from the Chair recruitment negotiation process with the medical school and hospitals. But most of all we have what can best be seen rather than described, as it is found in the faces of the young and idealistic residents and faculty who permeate this department. The best word that would describe this scene is the word that should have been the 5<sup>th</sup> mission of our department. And that word (which would follow those missions of to cure, comfort, teach, and wonder) is to confidently hope: to hope for the continued and better development of those Urologists that will follow us, to hope for better and more available cures for our diseases, and to hope for the enhanced attractiveness of the urologic calling. Hope is what we should remember we are and should be about. I look forward to continuing to do my duty in that mission and I trust that you who are reading this – friends, alumni, or staff – can also do your part.

## Upcoming Events

<p><b>UW Urology Graduation Banquet</b></p>	<p><b>June 2, 2007</b> <b>Seattle Yacht Club</b></p>
<p><b>Northwest Urological Society</b> <b>Vancouver, B.C.</b></p>	<p><b>December 7-9, 2007</b> <b>Westin Bayshore.</b></p>

**Change of Address? Feedback?**  
**Updates? Story ideas?**  
**Questions?**

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## HUB Lab, continued from page 1

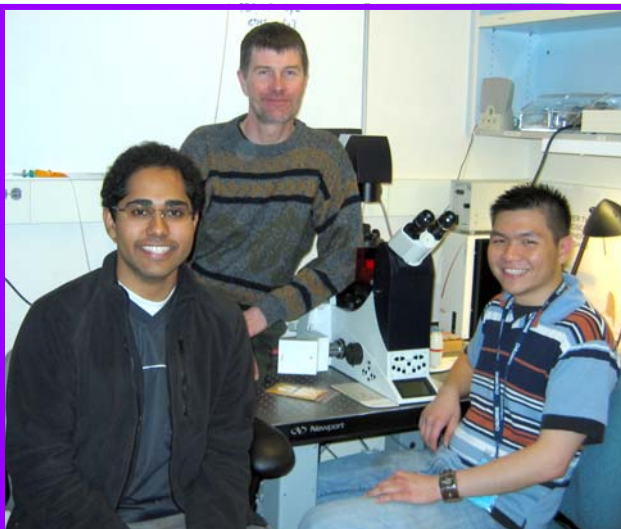
cally earn first authorships on manuscripts submitted to high impact journals.” Five students have completed the mandatory 2-year commitment to the HUB Lab where they are hired on as per-diem staff. “I expect not to see my students in the lab during finals week”, says Dr. Bassuk, who adds that summer and school breaks provides blocks of time where the research effort can be intensely focused. Because time management is the number one barrier that undergrads face early on in their matriculation, Dr.

Bassuk provides a guiding hand to help students succeed in all of their academic efforts. “My satisfaction occurs when my trainees achieve their goal of medical or graduate school admission – and of course having a few extra papers on hand for NIH progress reports doesn’t hurt either”, Dr. Bassuk adds with a smile.

The current crop of undergraduate researchers includes Mr. Kiran Dyamenahalli and Mr. Jun Blaine “JB” Amora, University of Washington students majoring in bioengineering and biochemistry, respectively. Kiran and JB joined the lab in 2004 and 2005 with freshman and junior status, respectively. Soon after, they began to collect prestigious scholarships such as the Mary Gates Undergraduate Research Endowment, the Howard Hughes Undergraduate Research Endowment, the Undergraduate Scholars in Research Program, and the National Aeronautics and Space Administration Science and Technology Scholarship Program. These scholarships provide a significant stipend to the student and often a significant stipend to the lab to cover supplies and travel costs. “Students like Kiran and JB represent the very best of the UW undergraduate population. They are extremely

bright and quite clever in their approach to research”, adds Dr. Bassuk.

Kiran’s role in the HUB Lab is to help create a functional epithelial tissue for the purpose of tissue engineered hypospadias repair, a translational project of the Program that is currently undergoing institutional review for its human subjects protocol. He has been able to generate and isolate abundant quantities of medically important growth regulators after expres-



University of Washington undergraduate researchers Kiran Dyamenahalli (left) and June Blaine Amora (right) flank Dr. Jim Bassuk (center) in the laboratory of the Program in Human Urothelial Biology located at Seattle Children’s Hospital.

sion in bacterial fermentations. Such regulators are biologically active on urothelial cells in vitro and in vivo and hold great promise as new clinical tools. Kiran has co-authored two 2007 publications in the *Journal of Molecular Biology and the Journal of Cellular Biochemistry*. His specific studies on the regulation of the squamous-transitional epithelial switch and the assessment of the utility of various scaffolds for tissue engineering keeps this talented young scientist busy throughout the academic year.

JB’s project is to better understand the type of interaction between the above-mentioned growth regulators with DNA. A combination of approaches has been used to apply electrophoretic and biophysical experimentation to the interaction of these polypeptide regulators with the minor groove of DNA. When added to cultures of human urothelial cells, these regulators migrate to the nucleus, interact with chromatin, and either turn on or turn off DNA synthesis. While the precise mechanism of what happens once these polypeptides gain entry to the cell nucleus is not yet clear, JB has been able to identify calcium and magnesium as essential co-factors for these processes. With only a few months

left before he heads off to medical school, JB has begun to write up his observations for publication.

In September of 2007, the HUB Lab will relocate to the newly created Seattle Children’s Hospital Research Institute and join the Center for Tissue and Cell Biology. Housed at 9<sup>th</sup> and Stewart within the biotech corridor between South Lake Union and downtown Seattle, the Institute will accommodate all clinical, basic and outcome research efforts of the hospital. Such efforts are part of a bold strategic plan to elevate Seattle Children’s Hospital to the top of all pediatric healthcare institutions. The Program is now entering into a new era where well-funded investigators will congregate within the state-of-the-art facility that the Institute has provided. “Being a founding principal investigator of the Institute is rewarding”, says Dr. Bassuk who adds that “The future of the HUB LAB is full of energetic expectations because of the vision of Drs. Grady, Mitchell and Lange”.

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## On the lighter side...



Will the real Bob Vessella please take one step forward? Dr. Vessella and his staff are pictured in this recently discovered photograph. Email Mike Porter (mporter@u.washington.edu) creative and/or humorous captions for this photo and we will include them in the next newsletter.

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