

SCIENTIFIC STANDOUT Lily Wu

Developing a better understanding of prostate cancer biology

ily Wu grew up in a house of engineers. While her science is just as exacting, Wu took a different path—cancer research."I was always quite keen on biology in animals and in people, so I thought I would become either a biologist or a doctor," said Wu, who did both.

She earned her doctorate and medical degrees concurrently in six years through a UCLA program designed to increase the numbers of physician-scientists. She's quick to point out that what she does is not so dissimilar from what the engineers in her family are doing.

"The engineers are always working on ways to improve upon things," said Wu, who is an associate professor of urology. "I spend my time thinking about how to improve cancer care and make things better for patients. My dad and I always joke that he builds and fixes cars and I fix people."

Born in China, Wu and her family escaped the cultural revolution by fleeing to Hong Kong in 1967 when she was 7. They lived in Hong Kong for nearly a decade, moving to the United States in 1975, when Wu was 16.

They lived in Davis, Calif., where Wu attended high school. She graduated in 1983 from the University of California, Berkeley. She then studied at the University of California, San Francisco for a year before joining the MD/PhD program at UCLA.

After earning her degrees and completing her residency, she received a prestigious Howard Hughes Medical Institute fellowship for four years to hone her research skills. She then joined the UCLA faculty in 1998. Now an associate professor of urology and pharmacology, Wu's research is aimed at developing a better understanding of cancer biology and improving gene-based therapy.

Specifically, Wu is re-engineering a microscopic common cold virus so it can deliver a genetic payload to cancer cells. The payload, in turn, performs a range of tasks to help manage the cancer. Using positron emission tomography (PET), the clinician can image tiny prostate cancer metastases that can't be seen using traditional imaging tools. It also can be made toxic to destroy the cancer cells.

Wu believes linking the imaging and treatment steps is the most powerful aspect of her work. One day she will be able to locate these tiny metastases in humans and kill them at the same time, while watching it all on a PET scanner.

"I'm a person for whom seeing is believing," Wu said. "And that is what imaging allows me to do. I can visualize the entire treatment process—the engineered virus getting to the cancer, treating it and making it go away. If what you're doing is working, you'll see it right away. If it's not working, you can change course."

Currently, physicians don't know if a treatment is attacking the cancer cells until they use traditional imaging methods such as CT scanning to show a decrease in tumor size. That can take months. And if the treatment isn't working, the patient is subjected to a toxic therapy that is not helping.

In Wu's initial studies in mice, she used the engineered virus to deliver a specially designed gene called "sr39tk," which has two functions—to produce PET signals and provide a dormant killing function that can be activated later. Wu was able to show that the sr39tk was successfully produced in the prostate tumor and emitted a strong PET signal. Then, she gave a drug to the same animal that activated the killing function and watched the PET signal disappear, meaning the disease was gone. Now she's working to refine the process, make it more efficient and reproduce the same results in patients.

Her work was initiated five years ago with the support of an interdisciplinary grant from UCLA's Jonsson Comprehensive Cancer Center. Since then, Wu codeveloped TSTA, two-step transcriptional amplification method, which increased the expression of the genetic payload inside the cancer cell—in effect boosting the imaging signals and killing activity of the engineered virus.

Recently, Wu was able to show that the targeted strategy she developed works for treating lymph node metastases. Her research suggests that lymph nodes are where the cancer first goes when it spreads, before it moves to other vital organs. The critical next stage of her research is to image and kill the cancer cells at the lymph nodes, preventing spread to other organs, the metastatic stage of the disease that is often fatal.

She hopes to translate this work into human subjects within the next two years.

"It's very gratifying to see our work move from the concept stage to validation stage in animals," Wu said. "I'm excited that translating our work to people is in sight."

llan Pantuck always knew he wanted to be a physician. His father was an anesthesiologist, his mother a chemist. Together they did research for Columbia University on how diet and nutrition impacted drug metabolism.

In Pantuck's case, the apple didn't fall far from the tree.

Pantuck also is a doctor and researcher. One of his focuses has been to study how natural products and pomegranate juice can prevent the onset or recurrence of prostate cancer by stabilizing the levels of prostate specific antigen or PSA, a biomarker that indicates the presence of cancer.

"I grew up in a house where the topic of dinner conversation was how Brussels sprouts, cabbage and charcoal-broiled beef affected the activity of certain enzymes in the body," said Pantuck, director of the Genitourinary Oncology Program Area at UCLA's Jonsson Comprehensive Cancer Center and an associate professor of urology.

"Since then, we have learned there are foods that can affect the way these same enzymes metabolize potential

SCIENTIFIC STANDOUT Allan Pantuck

cancer causing substances, such as the chemicals in cigarette smoke," he added. "Some foods activate them and some cause them to be excreted without causing any harm. In a way, what I'm doing is an extension of what my parents were doing."

The pomegranate study, which showed that an eightounce glass of juice daily kept levels of PSA stable in men with prostate cancer, garnered international coverage, which wasn't surprising. A glass of juice keeping cancer at bay is big news.

Published in *Clinical Cancer Research*, the study found that the juice increased by nearly four-fold the length of time that PSA levels in prostate cancer patients remained stable. The study involved 50 men who had undergone surgery or radiation, but who quickly experienced increases in PSA. Pantuck measured "doubling time," how long it takes for PSA levels to double, a signal that the cancer is progressing. They observed an increase in doubling times from 15 months to 54 months.

But what Pantuck likes to point out about the study is its truly "translational" nature, a hallmark of research at the Jonsson Cancer Center. Pantuck is the only urologist in the country to hold a master's degree in clinical research, and he bridges the gap between the basic research in the laboratories and the clinical research that involves patients.

"To improve human health, basic scientific discoveries must be translated into everyday applications," Pantuck said. "Such discoveries begin at 'the bench' with laboratory research—in which scientists study disease at a molecular or cellular level—then progress to the clinical level, or the patient's 'bedside."" Researchers are increasingly aware that this bench-tobedside approach is really a two-way street. Basic scientists provide clinicians with promising new tools that need to be tested in patients, and clinical researchers make novel observations about the nature and progression of disease that can stimulate new ideas for basic investigations. Pantuck sought a master's degree because he recognized that the increasing complexities of clinical research make it more difficult to translate new knowledge to the clinic and back again.

"I think clinical trial design is something you need advanced training to do well," he said.

The pomegranate study, beginning with a novel observation about the effects of the juice on prostate cancer in the laboratory, is a good example. Pantuck and his team took findings from the lab into the clinic to test in patients. Pantuck collected urine and blood samples from study volunteers and took them back into the lab to see if he could discover how the juice keeps PSA levels stable. Taking discoveries from the lab bench to the bedside

"We want to understand what is happening on a



molecular level," he said. "We need to understand what the pomegranate juice is doing to the prostate cancer, not just to the patient's PSA measurement."

Pantuck currently is recruiting men for the final phase of the study, which involves centers nationwide.

In addition, Pantuck was involved in a study that tested green tea extract and the drug Tarceva to determine if either prevented bladder cancer. The study, also based on research conducted in cancer center labs, was part of a program to prevent the recurrence and progression of smoking-related bladder cancer.

Pantuck attended Columbia University before going to Robert Wood Johnson Medical School. After his urology residency in New Jersey, Pantuck arrived at UCLA in 1999. He was attracted to the Westwood campus because of its renowned kidney cancer program.

"Cancer is a great challenge in terms of curing people," Pantuck said. "And for people we can't currently cure, I think it's important to improve their quality of life while seeking to discover the cures of the future." Pioneering discoveries and procedures to battle prostate cancer



SCIENTIFIC STANDOUT Robert Reiter

r. Robert Reiter is used to breaking new ground. Only a handful of scientists were doing prostate cancer research when he came to UCLA a dozen years ago.

In the lab, Reiter discovered prostate stem cell antigen, or PSCA, a cell surface protein found in about 95 percent of early stage prostate cancers and about 87 percent of prostate cancers that have spread to the bones. An antibody that targets PSCA has already been tested in early phase clinical trials.

As a surgeon, Reiter pioneered the use of the robotic prostatectomy at UCLA and he performs about 50 brachytherapy procedures a year, implanting radioactive seeds into the prostates of men with cancer.

As the new principal investigator for the Specialized Program for Research Excellence (SPORE) in prostate cancer, Reiter was responsible for writing the renewal for an \$11.5-million, five-year grant, first awarded in October 2002. The National Cancer Institute (NCI) was cutting back on large grants and many doubted that the proposal would be approved. But it was, and was among only a few prostate cancer SPOREs renewed over the summer.

Reiter serves as co-director of the Genitourinary Oncology Program Area at UCLA's Jonsson Comprehensive Cancer Center, overseeing the prostate program. He also is the first urologist to be elected to the American Society for Clinical Investigation, an organization that honors the accomplishments of physician-scientists.

Most recently, Reiter went back to school to earn a master's degree in business administration, all while juggling his surgical practice, research and administrative duties. The program strengthened his leadership capabilities and taught him managerial skills that can be applied to his roles in academic medicine. The business degree also will help him in his bench-to-bedside research.

"We took the discovery of PSCA from the lab all the way into clinical trials," said Reiter, a professor of urology. "It was a true example of translational research."

The prostate cancer SPORE also had success in translating research from the bench to the bedside, Reiter said. All five projects proposed in the initial grant proposal, based on discoveries in UCLA laboratories, were successfully translated into clinical trials. Studies included work on insulin growth factor binding protein-3 and an intervention study of a low-fat diet and fish oil supplements in men with early stage prostate cancer.

"We did everything we set out to do in the SPORE," Reiter said. "I think the program is very strong."

Going forward, Reiter is working with other scientists to develop PSCA as an imaging target to locate primary cancers and small metastases that are too tiny to be picked up by conventional imaging methods. He is studying the role of the androgen receptor in prostate cancer progression and metastasis. His laboratory also is collaborating with other scientists to study cancer stem cells in prostate cancer.

Reiter always wanted to be a surgeon, poring over books on the subject as a boy. His grandfather, an urologist, also influenced his decision to go into medicine. His focus on cancer came later.

"Cancer is an interesting disease. I liked the idea that if you could find it early and take it all out, you could cure people," Reiter said. "But I realized that surgery is not enough, which is why I focused my academic career on learning how cancer grows and finding new ways to target the disease with drugs that kill it without damaging the host."

Although he always thought he would pursue surgery and teaching in an academic medical center, it was not until he went to the NCI as a fellow in urologic oncology that he discovered an interest in research. There, he found that the laboratory work made his clinical practice more interesting, and vice versa. The synergy between research and clinical medicine continues to drive his career today.

After finishing medical school at Stanford, a residency at Baylor College of Medicine and the fellowship at the NCI, Reiter came to UCLA in 1995 to work in Dr. Owen Witte's lab. He spent a year doing prostate cancer research under the tutelage of Witte, a renowned scientist and Howard Hughes Medical Institute investigator.

Reiter said he sees UCLA patients becoming more invested in clinical trials as laboratory discoveries are translated into successful therapies, something for which the Jonsson Cancer Center has developed an international reputation. Those patients are becoming advocates for research.

"That will be helpful over the next several years, having those voices heard," Reiter said. "I'd like to see UCLA get the recognition that it deserves as a center for the complete care of prostate cancer from beginning to end." *