Focusing on Prostate Cancer Research

cientists nationwide are toiling to pinpoint the causes of prostate cancer and find better ways to prevent, detect and treat the disease. At UCLA's Jonsson Cancer Center, researchers are focusing on this cancer with the help of a prestigious national grant that ranks their program among the best in the country.

The National Cancer Institute designated the UCLA prostate cancer program as a site of research excellence in October 2002, making it one of a few institutions nationwide tapped to focus on this disease.

The designation as a Specialized Program of Research Excellence (SPORE) includes a five-year, \$11.5 million grant to further expand UCLA's renowned prostate cancer program, pulling in researchers and clinicians from a variety of disciplines to work together to uncover the mysteries of prostate cancer.

Already, within the first year of the SPORE, one basic science discovery is being moved into a clinical trial, a prime example of the program's focus on translational research, said Dr. Jean deKernion, chairman of the UCLA department of urology, director of the Clark Urology Center and head of the prostate cancer SPORE.

"This is exactly what this SPORE is supposed to do," said deKernion, referring to the study of an experimental drug shown in UCLA lab and animal studies to target a cell signaling pathway involved in the development of prostate cancer. "We will see important things coming from the prostate cancer SPORE within the next three to five years—actual clinical applications such as this clinical trial."

Dr. Robert Reiter, co-principal investigator of the study with Dr. Charles Sawyers, said the clinical trial is for patients with localized prostate cancer who are at high risk for recurrence after surgery. UCLA lab studies have shown that some patients with prostate cancer have lost PTEN, a tumor suppressor gene. In some patients, when PTEN is lost, a gene called mTOR located downstream in the cell signaling pathway gets turned on and may be driving the cancer. Reiter, Sawyers and their colleagues want to test a drug that they believe targets mTOR.

In this early phase study, a drug called CCI779 will be administered to study volunteers for eight weeks prior to surgery. The prostate will then be removed and researchers will study samples from patients to determine if the drug hit mTOR, its target. Researchers will follow patients, measuring PSA levels and monitoring for recurrences. If they're successful, they may be able to decrease the numbers of recurrences expected in these patients, Reiter said.

"This is a very scientifically oriented studied, not a conventional drug company study at all," said Reiter. "This study is entirely a product of the prostate cancer program here."

The UCLA prostate cancer SPORE focuses on two major areas, deKernion said. Researchers are identifying new molecu-

lar targets for therapies—attempting to fix what's broken in the prostate cancer cell—like Reiter, Sawyers and their colleagues are doing. SPORE investigators also are studying nutritional strategies to prevent the disease and impede tumor growth.

"We believe nutrition will play a critical role in the future in preventing prostate cancer," said Dr. William Aronson, an associate clinical professor of urology, a Jonsson Cancer Center researcher and one of the investigators heading up a nutrition study. "Nutrition also may play a role, either alone or combined with other treatments, for patients with existing prostate cancer."

SPORE grants are designed to promote collaboration among the best scientific minds. The grants bring together researchers

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who might not otherwise have a chance to work together on their far-flung academic campuses and in their large medical institutions, deKernion said. The goal is to translate basic research from the laboratories into patient care much more quickly and effectively. Funding is offered at UCLA to young researchers just starting out and to scientists ready to take their basic lab discoveries into the clinic. Additionally, those involved in the UCLA prostate cancer SPORE collaborate with researchers at other prostate cancer SPOREs across the nation.

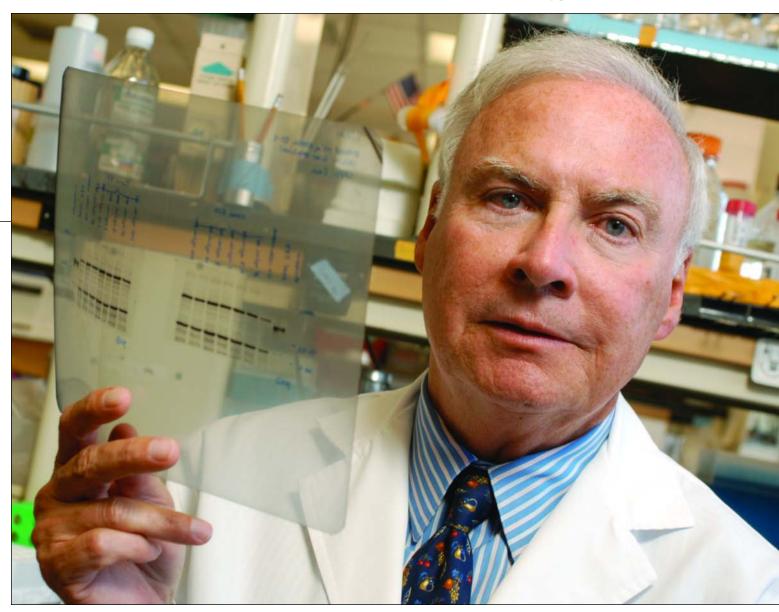
"We're bringing together the best of our laboratory scientists and clinical researchers to move the most promising concepts forward for clinical evaluation in patients with prostate cancer," deKernion said.

CLA's Jonsson Cancer Center is the only prostate cancer SPORE in Southern California, and one of only 11 in the United States. This year alone, an estimated 189,000 American men will be diagnosed with prostate cancer. More than 30,000 men will die, according to the American Cancer Society.

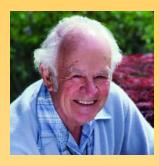
Five key projects form the core of the UCLA SPORE, most of which have their scientific roots in Jonsson Cancer Center labs. Four of the projects focus on cell surface antigens and cell signaling pathways implicated in prostate cancer. The goal is to develop targeted therapies that focus on what is broken in the cancer cell. The fifth project will explore the relationship between diet and prostate cancer.

The SPORE projects include:

- ★ Reiter and Dr. Owen Witte will focus on PSCA, or prostate stem cell antigen, which sits on the surface of prostate cancer cells in about 80 percent of men with the disease. The study will evaluate the role of PSCA in the cause and progression of prostate cancer and examine the affects of antibody therapy targeting PSCA. The study ultimately will lead to clinical trials using a monoclonal antibody against PSCA in men with high-risk prostate cancer. In laboratory models, the antibody —generated in Reiter's UCLA laboratory—has exhibited anti-tumor activity.
- ★ Sawyers, Reiter and pathologist George Thomas will test the drug rapamycin on a group of men whose prostate cancer cells lack PTEN, a gene that acts like a switch regulating access to a cell signaling pathway. UCLA researchers have discovered that cells lacking PTEN are more sensitive to rapamycin. About 20 percent of men with prostate cancer lack the PTEN gene. The study also seeks to develop and optimize techniques to determine the status of the PTEN gene in patients through prostate biopsies. Men are currently being recruited to take part in this study.
- ★ Drs. Pinchas Cohen and Peter Tontonoz will study the potential interactions of two key cell signaling pathways found to be important in prostate cancer development. The first involves growth factors known as insulin-like growth factors (IGFs) and their binding proteins (IGFBPs), recently



Prostate Cancer Risk Factors



The chances of getting prostate cancer go up as a man gets older.



For unknown reasons, prostate cancer is more common among African-American men than among white men. And African-American men are twice as likely to die of the disease.



Diet

Men who eat a lot of red meat or consume large quantities of high-fat dairy products seem to have a higher risk of prostate cancer. They also tend to eat fewer fruits and vegetables.

Doctors are not sure which of these factors causes the risk to go up.



Exercise

Getting enough exercise and keeping a healthy weight may help reduce prostate cancer risk.



Family history

Men with close family members—a father or brother—who have had prostate cancer are more likely to get it themselves, especially if their relatives were young when they got the disease.

recognized as critical regulators of prostate cancer development. The second is a family of retinoid receptors that include the retinoid X receptor (RXR) and the peroxisome proliferator activated receptor (PPAR). Evidence derived in UCLA labs indicates that the IGFBP and RXR pathways interact and synergize in inducing prostate cancer cell death. The researchers will attempt to use retinoids and IGFBPs to induce prostate cancer cell death, first in laboratory models and later in humans. Their goal is to develop less toxic, more effective treatments for men with advanced prostate cancer.

★ Drs. David Agus and Phillip Koeffler will focus on developing targeted therapies that inhibit the growth of prostate cancer. Their laboratory studies currently are evaluating the effectiveness of drugs that target and turn off a key growth-signaling pathway called the epidermal growth factor receptor (EGFR). The EGFR is a part of the HER kinase family of proteins that regulate cell growth and can stimulate the spread of tumors when over-expressed on cancer cells. Ultimately, these studies will lead to an understanding of the molecular mechanisms involved in the growth and treatment of prostate cancer. Other studies in the laboratory and in clinical trials will examine the effectiveness of using a monoclonal antibody to target a protein called HER-2/neu that controls cell growth.

"There are a lot of reasons to think that the risk for prostate cancer can be lowered through diet," said Glaspy, who also has studied a low-fat diet with fish oil supplements in women with breast cancer. "Men in Japan, where they eat more omega-3 fatty acids, have a much lower incidence of prostate cancer than men in American, where we consume more omega-6 fatty acids. That can't be a coincidence."

The UCLA Specialized Program of Research **Excellence in prostate cancer provides grants to** support innovative research. The following are the first SPORE grants awarded:

Career Development Awards

For promising young investigators for prostate cancer research:

- * George Thomas, Pathology
- * Christina Jamieson, Urology and Human Genetics
- * Anna Wu, Molecular and Medical Pharmacology

Developmental Research Program Awards

To fund the translation of promising basic research into the clinic:

- * Kathleen Sakamoto, Pediatrics
- * Ben Bonavida, Microbiology, Immunology and Molecular Genetics
- * Gang Zeng, Urology