UT SOUTHWESTERN MEDICAL CENTER NEWS

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Researchers at UT Southwestern identify novel class of drugs for prostate cancers that disrupts growth signaling

DALLAS – May 28, 2013 – A new study on prostate cancer describes a novel class of drugs developed by UT Southwestern Medical Center researchers that interrupts critical signaling needed for prostate cancer cells to grow.

In men with advanced prostate cancer, growth of cancer cells depends on androgen receptor signaling, which is driven by androgens, such as testosterone. To thwart tumor growth, most patients with advanced prostate cancer receive drugs that block the production of androgen or block the receptor where the androgen binds. Unfortunately, such treatments invariably fail and patients die of prostate cancer with their androgen receptor signaling still active and still promoting tumor growth.

In the new study, available online at *Nature Communications*, a team of researchers led by Dr. Ganesh Raj, associate professor of urology at UT Southwestern, found that they could disrupt androgen receptor signaling using a novel class of drugs called peptidomimetics. This therapeutic agent consists of an engineered small protein-like chain designed to mimic peptides that are critical for androgen receptor function. The peptidomimetic agents block the activity of the androgen receptor even in the presence of androgen by attacking the protein in a different spot from where the androgen binds.

"We are hopeful that this novel class of drugs will shut down androgen receptor signaling and lead to added options and increased longevity for men with advanced prostate cancer," said Dr. Raj, the senior author of the study.

Dr. Raj compared the action that takes place to a lock and key mechanism. In prostate cancer, the androgen receptor (lock) is activated by the androgen (key) resulting in a signal that causes prostate cancer proliferation. In advanced prostate cancer, despite drugs targeting either the lock (androgen receptor) or the key (androgen production), there can be aberrant keys that open the lock or mutated locks that are always open, resulting in cancer cell proliferation. Instead of trying to block the lock or the key, peptidomimetics uncouple the lock and key mechanism from the proliferation signal. Thus, even with the androgen receptor activated, the prostate cancer cells do not receive the signal to proliferate and do not grow.

The researchers tested their drug in mouse and human tissue models. The novel drug proved

(MORE)

non-toxic and prevented androgen receptor signaling in cancer cells. The response is highly promising and suggests that peptidomimetic targeting of prostate cancer may be a viable therapeutic approach for men with advanced disease.

Further testing is needed before a drug could move to Phase 1 clinical trials that involve human participants.

"Most drugs now available to treat advanced prostate cancer improve survival rates by three or four months," Dr. Raj said. "Our new agents may offer hope for men who fail with the current drugs."

These findings represent the development of a first-in-class agent targeting critical interactions between proteins. Other cellular and disease processes eventually could also be targeted with peptidomimetics, the scientists said.

Other UT Southwestern researchers involved in the study are Preethi Ravindranathan, a technician in Dr. Raj's laboratory, Dr. Jer-Tsong Hsieh, professor of urology, and Dr. Jung-Mo Ahn, visiting associate professor of urology. Researchers from University of Texas at Dallas; the First Affiliated Hospital of Medical College of Xi'an Jiaotong University, Urology Institute of Xi'an Jiaotong University; Dame Roma Mitchell Cancer Research Laboratories and Adelaide Prostate Cancer, Research Center, University of Adelaide and Hanson Institute also contributed to the research.

The Prostate Cancer Foundation, the Dorothy and James Cleo Thompson Foundation, and the Robert A. Welch Foundation funded the research.

Visit the Department of Urology or the Harold C. Simmons Cancer Center to learn more about treatment for prostate cancer at UT Southwestern, including highly individualized treatments at the region's only National Cancer Institute-designated center.

About UT Southwestern Medical Center

UT Southwestern, one of the premier academic medical centers in the nation, integrates pioneering biomedical research with exceptional clinical care and education. The institution's faculty has many distinguished members, including five who have been awarded Nobel Prizes since 1985. Numbering more than 2,700, the faculty is responsible for groundbreaking medical advances and is committed to translating science-driven research quickly to new clinical treatments. UT Southwestern physicians provide medical care in 40 specialties to nearly 90,000 hospitalized patients and oversee more than 1.9 million outpatient visits a year.

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