Researchers identify novel class of drugs for prostate cancers

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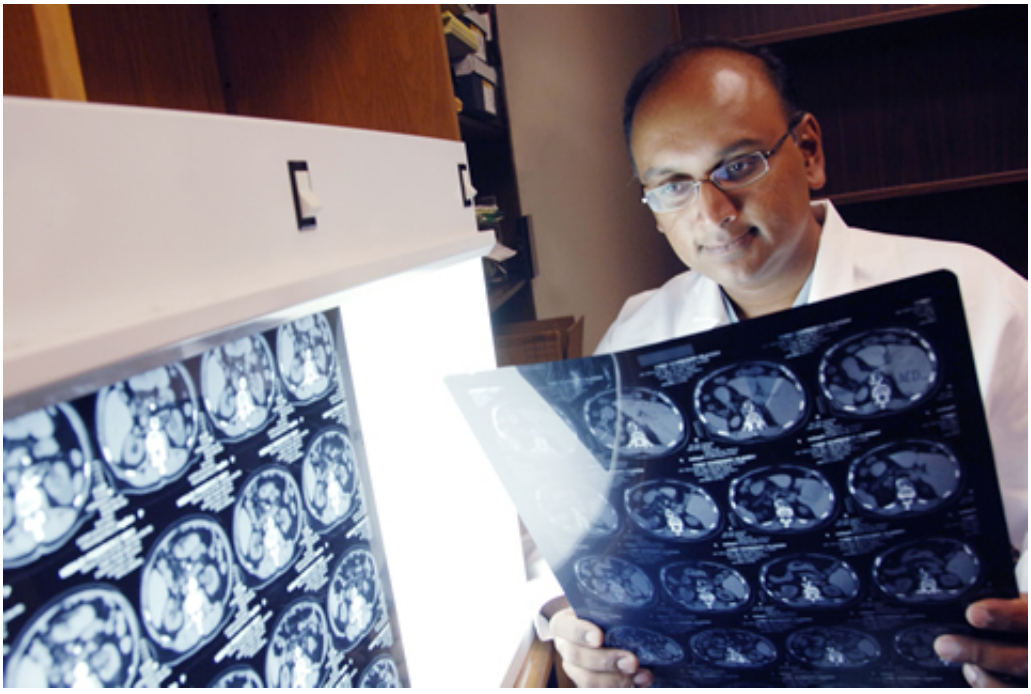

This is Dr. Ganesh Raj, an associate professor of urology at UT Southwestern Medical Center. Credit: UT Southwestern Medical Center

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 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.

Provided by UT Southwestern Medical Center

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