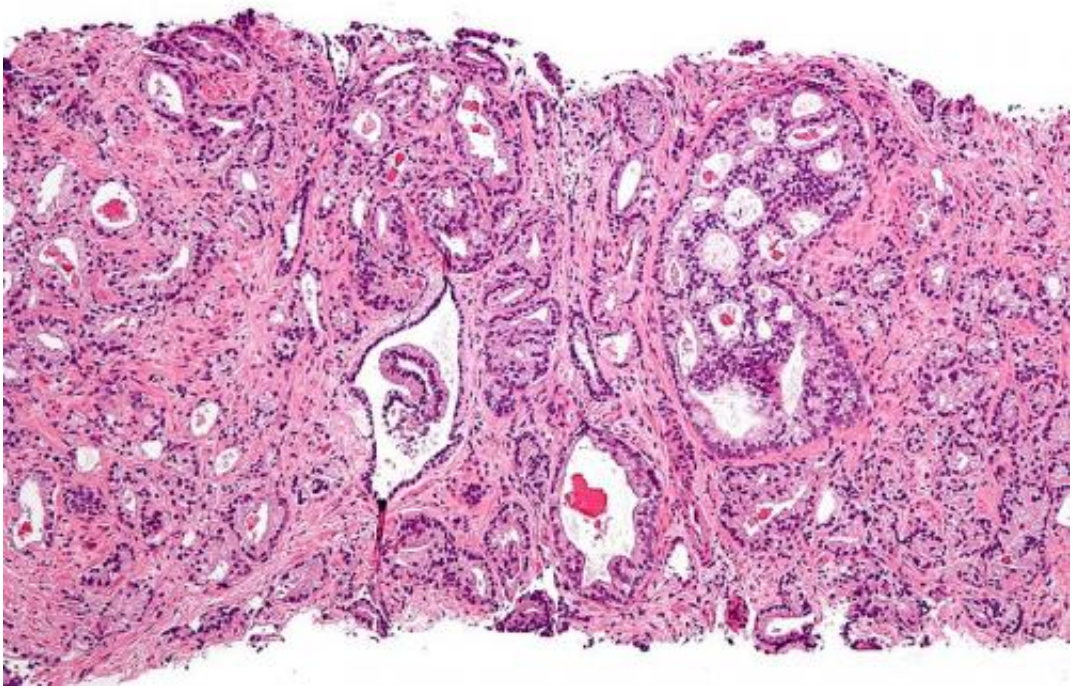
New molecules may offer treatment option for some aggressive prostate cancers

April 2 2017



Micrograph showing prostatic acinar adenocarcinoma (the most common form of prostate cancer) Credit: Wikipedia, CC BY-SA 3.0

Novel molecules called selective androgen receptor degraders (SARDs) may offer the next generation of treatment options for advanced prostate cancer, a new industry-sponsored study reports. The results of this research will be presented Saturday, April 1, at ENDO 2017, the 99th annual meeting of the Endocrine Society, in Orlando, Fla.

"If successful in the clinic, the novel highly potent SARDs discovered in this program could be used to treat many of the most aggressive and currently untreatable forms of prostate cancer," said senior author and principal investigator Ramesh Narayanan, Ph.D., associate professor and director of the Center for Cancer Drug Discovery at the University of Tennessee Health Science Center in Memphis, Tenn.

"The clinical success of new AR-targeted therapies in patients with castration-resistant prostate cancer emphasizes the continued importance of the AR signaling axis in the disease," he said. Using a rationale-based drug discovery approach and preclinical models that included cells, xenografts and patient-derived samples, Narayanan and his colleagues developed a series of SARDs that degrade all forms of the androgen receptor (AR) and may provide advanced treatment options to men with castration-resistant prostate cancer.

The unique pharmacology of the SARDs enables them to bind, antagonize and degrade the AR along with mutants and splice variants (AR-SVs) and inhibit the growth of aggressive prostate cancers that are unresponsive to other androgen pathway inhibitors.

"In most cases, the AR promotes the growth of prostate cancer, and currently available AR antagonists do not provide sustained treatment. After a brief period of treatment, the cancer often relapses due to alterations (mutations or splices) in the AR. The altered AR promotes the robust growth of the cancer," Narayanan said.

By contrast, "the molecules our group has discovered not only inhibit the AR, but they also degrade the AR and hence may have the potential to provide a more sustained treatment option than a conventional antagonist," he added.

"Unlike other hormone receptors, the AR is difficult to degrade,"

Narayanan explained. "The SARDs we have developed degrade the AR at pharmacologically achievable concentrations. Moreover, the molecules degrade spliced forms of the AR that do not contain a binding pocket, which was a surprise to the investigators."

Narayanan noted that, in most cases, advanced prostate cancers that relapse from AR antagonists are treated with chemotherapy. But for patients who don't respond to AR antagonists or who relapse, it's important to find new drugs with distinct mechanisms of action that can provide targeted sustained therapy.

He said that strengths of the study include its validation in multiple models and its reproducibility in multiple environments, but he added that the molecules are still in the preclinical stage and that clinical data are not yet available.

"Clinical development of these compounds will be initiated later this year," he added.

Provided by The Endocrine Society