PROTAC shows efficacy against castration-resistant prostate cancer in preclinical studies

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An orally bioavailable androgen receptor PROTAC, developed using a protein degradation technology, was effective in lowering tumor burden in mice bearing human castration-resistant prostate cancer, according to data presented here at the AACR Annual Meeting 2017, April 1-5.

"More than 15 years ago, Professor Craig Crews of Yale University had an idea of targeting oncoproteins for degradation by essentially hijacking the endogenous ubiquitination and proteasome machinery. He pioneered the PROteolysis TArgeting Chimera (PROTAC) technology, a novel modality for degrading disease-causing proteins," said Taavi Neklesa, PhD, director of Biology at Arvinas, in New Haven, Connecticut.

Many men treated with androgen-deprivation therapy as first-line treatment for prostate cancer develop resistance to therapy over time. Subsequent treatment with enzalutamide (Xtandi) or abiraterone (Zytiga) is not always successful because amplifications and point mutations in the androgen receptor (to which androgens bind) lead to resistance to these therapeutics.

"Because up to two-thirds of patients develop resistance to enzalutamide or abiraterone as the androgen receptor evolves, there is an unmet need that the PROTAC technology can address. The protein degradation technology is well-suited to work in these cases of androgen receptor overexpression and mutations," Neklesa said.

PROTACs are small molecules with two heads – one side of the small molecule binds to the protein of interest and the other side binds to E3 ubiquitin ligase, which plays a role in a cellular process that signals the degradation of the protein. When applied to cancer cells, PROTAC brings the ubiquitin ligase to the proximity of the disease-causing protein , leading to its ubiquitination and subsequent degradation.

Neklesa and colleagues developed and tested the orally bioavailable AR PROTAC, which targets the androgen receptor, in cell lines and animal models. They found that AR PROTAC is very potent, degrading approximately 98 percent of the androgen receptors in the cell lines they tested, and requiring less than 1 nanomolar (nM) to degrade 50 percent of the androgen receptors. Degrading the proteins led to effective inhibition of prostate cancer cell proliferation. The investigators also observed a dose-dependent inhibition of tumor growth in mice bearing human castration-resistant prostate cancer, with a 10 mg/kg daily dose demonstrating maximal tumor growth inhibition and androgen receptor degradation.

One of the characteristics of resistant prostate tumors is that they start making their own androgens and outcompete the binding of enzalutamide, thus diminishing its efficacy. Because AR PROTAC molecules only need to bind to the androgen receptor transiently to induce degradation, they are capable of overcoming this challenge, Neklesa explained.

"For example, in vitro, if you keep adding androgens to the media containing prostate cancer cells, enzalutamide would not work anymore, but AR PROTACs do, because they don't need to constantly bind to the androgen receptor, which makes them very effective," he said.

"Our first goal was to show that AR PROTAC works in vivo, our second goal was to make it orally bioavailable, and our third goal is to take this

to the clinic. We are preparing to test AR PROTAC in patients in a clinical trial next year," Neklesa said.

Limitations of the study include that this technology is still not tested in humans, and the efficacy of AR PROTAC against prostate cancers that contain some altered forms of androgen receptor has not yet been evaluated, Neklesa explained.

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