New drugs, new ways to target androgens in prostate cancer therapy

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Prostate cancer cells require androgens including testosterone to grow. A recent review in the *British Journal of Urology International* describes new classes of drugs that target androgens in novel ways, providing alternatives to the traditional methods that frequently carry high side effects.

"In many ways, therapies for prostate cancer have led the way in the fight against the disease," says E. David Crawford, MD, investigator at the University of Colorado Cancer Center and review co-author. "The first effective oral therapy for any cancer was estrogen which was described in 1941. The first cancer biomarker that allowed diagnosis and staging was prostatic acid phosphatase back in 1938. Then there was little progress for over four decades."

During those 40 years, in which early work in prostate cancer led to Nobel prizes for researchers Charles Huggins and Andrew Schally, other cancer types capitalized on this research, notably developing hormone therapies targeting estrogen in breast cancer. But work in prostate cancer stalled.

"What we realized is that production of androgens like testosterone depends on an intact system in which the brain recognizes hormone levels, signals the pituitary to increase or decrease production, and the pituitary in turn sets the testes in motion. Additionally, by targeting the production of androgens by the testes, we could break that system at many other points," Crawford says.

For example, estrogen is similar enough to testosterone that administering estrogen to patients tricked the brain into thinking testosterone hormone levels were high – with high presumed hormone levels, the brain sent no production signal to the pituitary. But estrogen therapy led to side effects including breast enlargement.

The next class of drugs, known as luteinizing hormone releasing hormones or LHRHs, intervened in this signaling chain at the level of the pituitary. Just as estrogen keeps the brain from signaling for more testosterone, LHRHs keep the pituitary from passing messages to the testes.

"Because the effects of LHRHs are reversible, this allowed us to use hormone-targeting therapies much earlier in the disease," Crawford says. "But LHRHs lead to an initial spike in testosterone, before it decreases." Most patients can withstand this spike, but for some, for example those with bone metastasis in the back, a spike in testosterone could flare the disease and lead to spinal complications.

"It was only about ten years ago that somebody was able to make a usable antagonist," Crawford says. Instead of first spiking and then lowering testosterone, these LHRH antagonists lead to an immediate drop.

And instead of targeting the signaling pathway that leads to the production of androgens including testosterone, androgen antagonists like Enzalutamide (formerly known as MDV3100), currently in phase III clinical trials, target cells' ability to trap testosterone that exists in the body – it doesn't matter how much testosterone is floating around, as long as prostate cancer cells are unable to grab it. Specifically, Enzalutamide and other androgen antagonists are easier to "catch" than the androgens themselves, and so cells grab Enzalutamide and are then unable to grab testosterone.

Also new to the field are drugs that block the production of androgens from all sources which of course includes the testes, but also includes blocking the smaller amounts produced by the adrenals and even by the cancer itself. This class of drugs is called androgen biosynthesis inhibitors, and the first approved is a drug called abiraterone or Zytiga.

"Targeting cells' androgen receptors is a new and exciting development in the field of prostate cancer therapy," Crawford says. "As these new drugs make their way from the lab to clinic, we expect the ability to offer androgen antagonists to patients whose cancers have resisted other treatments."

Provided by University of Colorado Denver