Prostate cancer's penchant for copper may be a fatal flaw

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Like discriminating thieves, prostate cancer tumors scavenge and hoard copper that is an essential element in the body. But such avarice may be a fatal weakness.

Researchers at Duke Medicine have found a way to kill prostate cancer cells by delivering a trove of copper along with a drug that selectively destroys the diseased cells brimming with the mineral, leaving non-cancer cells healthy.

The combination approach, which uses two drugs already commercially available for other uses, could soon be tested in clinical trials among patients with late-stage disease.

"This proclivity for copper uptake is something we have known could be an Achilles' heel in prostate cancer tumors as well as other cancers," said Donald McDonnell, Ph.D., chairman of the Duke Department of Pharmacology and Cancer Biology and senior author of a study published Oct. 15, 2014, in *Cancer Research*, a journal of the American Association of Cancer Research.

"Our first efforts were to starve the tumors of copper, but that was unsuccessful. We couldn't deplete copper enough to be effective," McDonnell said. "So we thought if we can't get the level low enough in cancer cells to kill them, how about we boost the copper and then use a drug that requires copper to be effective to attack the tumors. It's the old if-you-can't-beat-'em-join-'em approach."

McDonnell and colleagues searched libraries of thousands of approved therapies to identify those that rely on copper to achieve their results. Among those they found was disulfiram, a drug approved by the FDA to treat alcoholism. Disulfiram had at one time been a candidate for treating prostate cancer – it homes in on the additional copper in prostate cancer tumors – but it showed disappointing results in clinical trials among patients with advanced disease.

The Duke team found that the amount of copper cancer cells naturally hoard is not enough to make the cells sensitive to the drug. But when the Duke researchers added a copper supplement along with the disulfiram, the combination resulted in dramatic reductions in prostate tumor growth among animal models with advanced disease.

And there was another surprise: Androgens, the male hormones that fuel prostate cancer, increase the copper accumulation in the cancer cells. McDonnell said this finding could make the combination of disulfiram or similar compounds and copper especially beneficial for men who have been on hormone therapies that have failed to slow tumor growth.

"Unfortunately, hormone therapies do not cure prostate cancer, and most patients experience relapse of their disease to a hormone-refractory or castration-resistant state," McDonnell said. "Although tremendous progress has been made in treating prostate cancer, there is clearly a need for different approaches, and our findings provide an exciting new avenue to explore."

McDonnell said clinical trials of the combination therapy are planned in upcoming months.

Andrew Armstrong, M.D., associate professor of medicine, was involved with a recent study at Duke testing disulfiram in men with advanced prostate cancer.

"While we did not observe significant clinical activity with disulfiram in men with recurrent prostate cancer in our recent clinical trial, this new data suggests a potential way forward and a reason why this trial did not have more positive results," Armstrong said. "Further clinical studies are now warranted to understand the optimal setting for combining copper with disulfiram or similar compounds in men with progressive prostate cancer, particularly in settings where the androgen receptor is active."

Provided by Duke University Medical Center