Researchers discover a potential target for therapy for patients with a deadly prostate cancer

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A monoclonal antibody targeting a well known cell surface protein inhibited prostate cancer growth and metastasis in an aggressive form of the disease that did not respond to hormone therapy, according to a study by researchers with the UCLA Department of Urology and UCLA's Jonsson Comprehensive Cancer Center.

The researchers also found that the protein, N-cadherin, is up regulated or turned on in prostate cancer that does not respond to hormone therapy, known as castration resistant disease. The results of the study, done in cell lines and mouse models, were confirmed in humans after researchers examined tissue from dozens of men who died from prostate cancer, said Dr. Robert Reiter, a professor of urology, a Jonsson Cancer Center scientist and senior author of the study.

"This therapy may be particularly useful in men who are failing the newest forms of treatment that target the androgen receptor, which regulates testosterone," said Reiter, who is director of the cancer center's Specialized Program of Research Excellence (SPORE) in prostate cancer. "This could potentially offer an effective alternative or addition to those hormone therapies."

The study appears Nov. 7, 2010 in the early online edition of the peer-reviewed journal *Nature Medicine*.

The study represents a translational effort by Reiter and his team to take their basic science observations and transform them into new therapies for this aggressive form of prostate cancer to be tested in clinical trials. Observations made in those future clinical trials also could be used in the laboratory to refine potential therapies.

Reiter and his team first found that the N-cadherin gene was up regulated in castration resistant prostate cancer, presenting a potential target for therapy. The findings in cell lines and mouse models were confirmed by studying tissue from men who died from their castration resistant disease. Researchers then found that the up regulation is required to maintain castration resistant prostate cancers, meaning that the turning on of the pathway may be a cause of the hormone therapy resistance, making it an even more attractive target for therapy.

Armed with a hypothetical target at which to aim molecular therapies, Reiter and his team set out to develop novel therapeutics to block N-cadherin. They developed two monoclonal antibodies to test on their cell lines and animal models and found that the antibodies slowed the growth in their prostate cancer cell lines and mouse models and blocked the spread of castration resistant prostate cancer in mouse models. Reiter said this finding may mean the antibodies could potentially be used to block the spread of prostate cancer in men diagnosed with this aggressive form of the castration resistant disease, making it easier to treat and potentially improving outcomes in this patient population. It could also be effective in preventing men treated for early stage disease from progressing to castration resistance since the antibodies prevented that progression in the cell lines and mouse models, Reiter said.

"We believe these findings show that the up regulation of N-cadherin is one of the mechanisms that leads to castration resistance and it could be targeted perhaps in conjunction with other pathways already being studied that lead to resistance," Reiter said. "These findings may provide

us with yet another way to treat these cancers."

Although many men have indolent or slow growing prostate cancers that often are only observed over time, a significant percent of patients present with castration resistant disease or later develop castration resistance, which is very difficult to treat effectively. It would be very useful to have another tool in the arsenal to fight this type of prostate cancer, Reiter said.

The next step for Reiter and his team is to improve the antibodies and understand the mechanism by which N-cadherin works to promote resistance. Human clinical trials testing the antibodies would be opened in the future.

Reiter said his findings were somewhat surprising.

"We didn't think we'd see the level of activity that we did," he said. "And we didn't think the antibodies would block castration resistance."

Provided by University of California - Los Angeles