New system finds prostate cancer spread earlier than conventional imaging

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Researchers at UCLA's Jonsson Comprehensive Cancer Center have developed a way to image the spread of a particularly dangerous form of prostate cancer earlier than conventional imaging in use today, which may allow oncologists to find and treat these metastases more quickly and give patients a better chance at survival.

The gene-based imaging system targets prostate cancers that have become resistant to androgen deprivation therapy, an aggressive form of the disease known as castration resistant prostate cancer. Once the hormone treatment is no longer working, the cancer will progress within 12 to 18 months and prognosis becomes grim, said Lily Wu, a professor of molecular and medical pharmacology, a Jonsson Cancer Center researcher and senior author of the study.

"Anytime you can detect cancer earlier, the chances of more effective control of the cancer increase and the outcomes for patients are better," Wu said. "Unfortunately, there is little that can be done to treat castration resistant prostate cancer once it has spread. In our study, we focused on finding ways to image these advanced metastatic prostate cancers accurately. "

The study appeared Sept. 21 in the early online edition of *Cancer Research*, a peer-reviewed journal of the American Association for Cancer Research.

Wu's team focused on using "control switches" of genes that are active

only in castration resistant prostate cancer, and linked these molecular switches to a "reporter" gene that can be easily imaged. The specific switch the team used in this study is the prostate specific enhancing sequence (PSES), an androgen-independent promoter in castration resistant prostate cancer that is more specific to that form of malignancy.

The PSES is derived from the prostate specific antigen and the prostate specific membrane antigen (PMSA) and is given a boost by the two-step transcriptional amplification system, which drives the expression of the imaging reporter genes, which glow under bioluminescent or positron emission tomography (PET) scanning. The system works well in the androgen depleted environment and is strongly specific to the prostate, two conditions that are most fitting for castration resistant prostate cancer.

"The engineered system exhibits greatly elevated transcriptional activity, androgen-independency and strong prostate cancer specificity, verified in cell culture and pre-clinical mouse models," said Ziyue Karen Jiang, a senior doctoral student in pharmacology who is supported by a Jonsson Cancer Center fellowship. "These advantageous features of the system elicit superior gene expression capability for castration resistant prostate cancer in comparison to the other systems, which are driven by androgen-dependent promoters."

Based on the favorable features shown in cell culture experiments, the research team expected the PSES-driven imaging system to be discriminating in detecting castration resistant prostate cancer and cancer that has spread to distant organs. The research team was surprised to discover that the PSES imaging system developed was able to accurately detect bony metastasis of prostate cancer that grew in the leg of a mouse while two traditional imaging methods were unable to detect the metastasis.

The researchers tested the performance capacity of the PSES bioluminescent imaging system in mice that had prostate tumor cells implanted in their right knee to establish bony metastasis. After allowing six weeks for the tumor to grow, the PSES imaging reporter vector was injected into the tumor-implanted mice to search for the metastasis. Four days after the injection, the signal from the reporter gene could be clearly seen, correctly identifying the prostate cancer metastasis in the right tibia bone in nine out of nine animals. Concurrent use of PET scans were unable to distinguish between the tumor-bearing right knee and the uninvolved left knee.

The tumor growth rate in this bone metastasis model is not uniform, ranging from no spread to large tumor lesions in the bone marrow cavity. The PSES imaging system correctly identified two out of nine animals in which the tumor did not grow. These results give researchers confidence that the PSES imaging system is functioning correctly in being able to seek out prostate cancer bone metastases in a specific and sensitive manner, Wu said.

"Taken together, this study demonstrated that the promising utility of a potent, androgen-independent and prostate cancer-specific expression system in directing gene-based molecular imaging in castration resistant prostate cancer, even in the context of androgen deprivation therapy," the study states.

Prostate cancer is the most common cancer for males in America and its spread to other organs is the major cause of mortality. This year alone, more than 217,000 American men will be diagnosed with the malignancy. Of those, more than 32,000 will die from their disease.

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