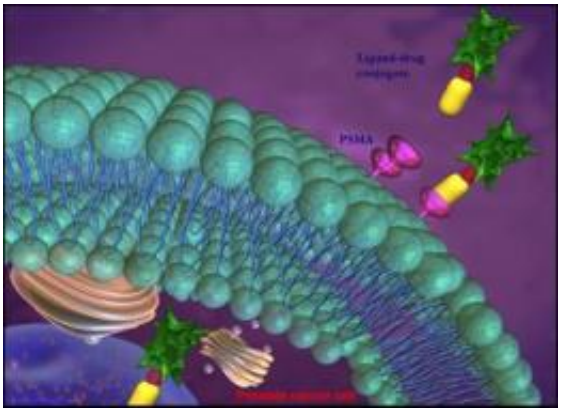
Researchers create prostate cancer 'homing device' for drug delivery

July 6 2009



This image depicts transporter molecules carrying therapeutic drugs to PSMA targets on a prostate cancer cell. A Purdue research team designed a molecule that finds and penetrates prostate cancer cells and can transport drugs or imaging agents into the cell. Credit: Image courtesy of Low laboratory

A new prostate cancer "homing device" could improve detection and allow for the first targeted treatment of the disease.

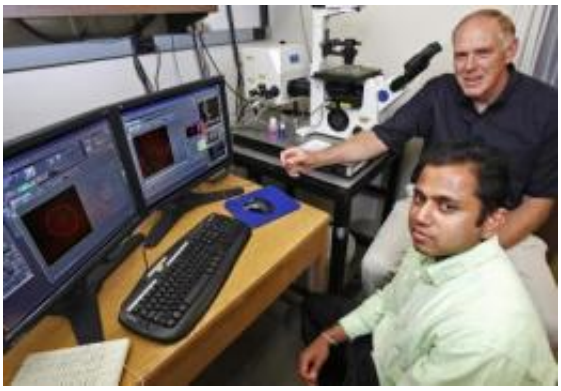
A team of Purdue University researchers has synthesized a molecule that finds and penetrates prostate cancer cells and has created imaging agents and therapeutic drugs that can link to the molecule and be carried with it as cargo.

A radioimaging application used for body scans is expected to enter

clinical trials this fall, and an optical imaging application used to measure prostate cancer cells in blood samples is already in clinical trials.

Philip Low, the Ralph C. Corley Distinguished Professor of Biochemistry who led the team, said a targeted treatment could be much more effective in treating cancer and would greatly reduce the harmful side effects associated with current treatments.

"Currently none of the drugs available to treat prostate cancer are targeted, which means they go everywhere in the body as opposed to only the tumor, and so are quite toxic for the patient," said Low, who is a member of the Purdue Cancer Center. "By being able to target only the cancer cells, we could eliminate toxic side effects of treatments. In addition, the ability to target only the cancer cells can greatly improve imaging of the cancer to diagnose the disease, determine if it has spread or is responding to treatment."



Philip Low, the Ralph C. Corley Distinguished Professor of Biochemistry at Purdue, and graduate student Sumith Kularatne, in foreground, examine the uptake of an imaging agent in prostate cancer cells. Low led a research team that designed a molecule to find and penetrate prostate cancer cells and has created imaging agents and therapeutic drugs that can link to the molecule and be carried with it as cargo. Credit: Purdue University photo/Andrew Hancock

Prostate cancer is the most common cancer, other than skin cancers, and is the second leading cause of cancer death in American men, according to the American Cancer Society. It is estimated that about 192,280 new cases will be diagnosed and 27,360 men will die of prostate cancer in the United States this year.

The molecule Low's team created attaches to prostate-specific membrane antigen, or PSMA, a protein that is found on the membrane of more than 90 percent of all prostate cancers. It also is found on the blood vessels of most solid tumors and could provide a way to cut off the tumor blood supply, Low said.

"A lot of new drugs are being designed to destroy the vasculature of solid tumors, and, if they could be linked to this new targeting molecule, we could have a two-pronged attack for prostate cancer," he said. "We could not only kill the prostate cancer cells directly, we could also destroy the vasculature that feeds the tumors."

There also is potential for the targeting molecule to be used to attack the vasculature of solid tumors of other types of cancers, Low said.

Two papers detailing the work of the Purdue team were published in the June 1 issue of *Molecular Pharmaceutics*. Endocyte Inc. funded the work.

The team's animal study data shows an ability to eliminate human prostate cancer cells in mice with no evidence of collateral toxicity in normal tissue.

Sumith Kularatne, a graduate student in Purdue's chemistry department and first author of both papers, compared the targeting molecule to a

homing device.

"The molecule acts like a homing device for prostate cancer," he said. "PSMA, which is found only on prostate cancer cells and tumor blood vessels, acts as the homing signal that the molecule targets. The molecule and its cargo go only to cancerous tissue, leaving healthy tissue unharmed."

Once the molecule reaches the PSMA protein, it binds to it. The molecule is designed with a specific shape that fits with the protein like a key to a lock, Kularatne said. The molecule and its cargo are then carried inside the cell with the protein as it goes through its normal cycle.

In 1995 Low developed a similar method to infiltrate cancer cells by attaching treatments to the vitamin folate, which many cancers rapidly consume. This method provided a "Trojan Horse" entry of large treatment molecules that otherwise would not be able to enter cancer cells.

Low was inspired to find a similar way to target prostate cancer, which does not have the same appetite for folate, he said.

A clinical trial of the radioimaging application is expected to begin at the Indiana University Medical Center in the fall through a collaboration between the Purdue Cancer Center and the Indiana University Cancer Center with additional support from Endocyte Inc.

A radioimaging agent linked to the targeting molecule will be injected into prostate cancer patients and pictures will be taken using a special camera that detects radioactivity. The pictures show where the cancer is present to help doctors determine if it has metastasized, or spread, to any other areas of the body. It also will help doctors decide on the best

course of treatment, Low said.

There is currently only one radioimaging agent for prostate cancer approved by the Food and Drug Administration.

"The current imaging capabilities available for prostate cancer are very poor," Low said. "The existing imaging agent is limited because of its large size, which is difficult to get into a solid tumor. Also it seeks out a target located inside the cancer cell and is only able to mark injured cells that are falling apart as opposed to actively growing cancer cells."

The targeting molecule and radioimaging agent combination designed by Low's group is more than 150 times smaller than the existing agent and has much easier penetration through a solid tumor to reach all of the cells inside, he said. It also has the advantage of targeting an area of PSMA exposed on the outside of cancer cells.

Already in clinical trials is an optical imaging application that involves attaching a fluorescent dye to the targeting molecule and mixing it with a patient's blood sample. Circulating prostate cancer cells in the sample fluoresce and are easily measured to help in diagnosing patients with prostate cancer. Researchers also are investigating whether this could be used to evaluate a patient's response to therapy, Low said.

Low's research group modeled the targeting molecule after a naturally occurring molecule that strongly binds to PSMA, called DUPA. Several alterations were necessary to create a molecule that fit the needs of a homing device and delivery vehicle, Kularatne said. The team created an area on the molecule that would link to various imaging or therapeutic agents to bring them along as cargo and created a spacer that would stretch the molecule so that its cargo would not keep it from properly fitting into the binding site. The spacer also was designed to improve binding of the targeting molecule to PSMA.

Source: Purdue University (news : web)