Exposing cancer's lethal couriers: Nanochains mark micrometastases for early diagnosis, treatment

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Malignant cells that leave a primary tumor, travel the bloodstream and grow out of control in new locations cause the vast majority of cancer deaths. New nanotechnology developed at Case Western Reserve University detects these metastases in mouse models of breast cancer far earlier than current methods, a step toward earlier, life-saving diagnosis and treatment.

A team of scientists, engineers and students across five disciplines built nanochains that home in on metastases before they've grown into new tissues, and, through magnetic resonance imaging, detect their locations.

Images of the precise location and extent of metastases could be used to guide surgery or ablation, or the same technology used to find the cancer could be used to deliver cancer-killing drugs directly to the cells before a tumor forms, the researchers suggest.

The work is described in this week's online issue of the American Chemical Society journal *ACS Nano*.

"Micrometastases can't be seen with the naked eye, but you have to catch them at this stage – see the exact spots they're located and see them all," said Efstathios Karathanasis, assistant professor of biomedical engineering and radiology, and senior author. "Even if you miss only one, you prolong survival, but one metastasis can still kill."

Karathanasis worked with research associate Pubudu M. Peiris, graduate student Randall Toy; undergraduate students Elizabeth Doolittle, Jenna Pansky, Aaron Abramowski, Morgan Tam, Peter Vicente, Emily Tran, Elliott Hayden and Andrew Camann; medical student Zachary Berman, senior research associate Bernadette O. Erokwu, biomedical engineering professor David Wilson, chemical engineering associate professor Harihara Baskaran; and, from the Case Western Reserve School of Medicine, radiology assistant professor Chris A. Flask and pharmacology associate professor and department vice chair Ruth A. Keri.

Tumor detection technologies fail to uncover cancer cells that have taken hold in new locations because young metastases don't behave the same as established tumors.

After a breast cancer cell enters the bloodstream, it most often stops in the liver, spleen or lungs and begins overexpressing surface molecules called integrins. Integrins act as a glue between the cancer cell and the lining of a blood vessel that feeds the organ.

"We target integrins," Karathanasis said. "Normal blood vessel walls don't present integrins towards the blood site unless cancer cells attach there."

To home in on the cancer marker, the researchers first needed to build a nano device that would drift out of the central flow of the blood stream and to the blood vessel walls. The most common shape of nanoparticles is a sphere, but a sphere tends to go with the flow.

Karathanasis' team tailored nanoparticles to connect one to another much like a stack of Legos. Due to its size and shape, the oblong chain tumbles out of the main current and skirts along vessel walls.

The exterior of the chain has multiple sites designed to bind with integrins. Once one site latches on, others grab hold. Compared to nanospheres, the chains' attachment rate in flow tests was nearly 10-fold higher.

To enable a doctor to see where a relative few cancer cells sit in a sea of healthy cells, the scientists incorporated fluorescent markers and, to make the nanochains more visible in magnetic resonance imaging, four links made of iron oxide.

Next, the team tested the chains in a mouse model of an aggressive form of breast cancer that metastasizes to sites and organs much the same way it does in humans.

From established research, they knew metastases would be present five weeks into the modeling. They injected nanochains into the bloodstream and, within an hour, two imaging techniques - fluorescence molecular tomography and MRI's - showed where traveling cancer cells had established footholds, primarily in the liver, lungs and spleen.

The metastases located using the nanochains ranged from .2 to 2 millimeters across.

Later imaging at high magnification showed that these metastatic cancer cells were found mostly in the blood vessel walls, before they'd had time to grow into organ tissue.

"Once metastatic cells move into the tissue, develop their own microenvironment, and grow into a 1-centimeter lesion, it typically indicates a late stage of metastatic disease which has an unfavorable outcome," Karathanasis said.

According to the American Cancer Society, the 5-year survival rate of

breast cancer patients sharply decreases from 98 percent in cases that catch the disease when it has produced only a localized primary lesion to 23 percent in cases in which distant large metastases have grown.

Now that they've proved the concept works, the team is bringing clinical radiologists on board led by Vikas Gulani, assistant professor of radiology. Their job is to help with a new study, calculating how much new cancer the technology finds and misses.

Provided by Case Western Reserve University