Contrast agent puts new light on diagnosing breast cancer

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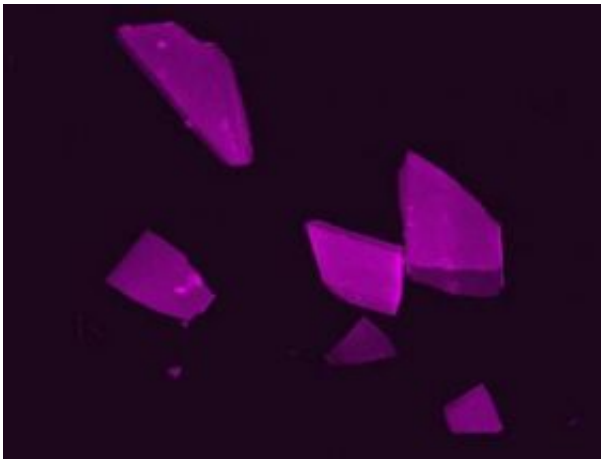

Hydroxyapatite crystals (pseudo-colored in purple), like those found in human breast cancer, are detected with high sensitivity using an optical contrast reagent and invisible near-infrared fluorescent light. Photo courtesy of Dr. John Frangioni

Harvard Medical School researchers are working on a new, simpler way to distinguish malignant tumors from non-cancerous masses when screening for breast cancer.

Scientists in the laboratory of Dr. John Frangioni, M.D., Ph.D., associate professor of medicine and radiology at Harvard Medical School, have developed a contrast agent that selectively targets and highlights malignant micro-calcifications in the breast, while ignoring similar

micro-calcifications found in benign breast conditions.

Details of the new technique were described today at the 233rd national meeting of the American Chemical society, the world's largest scientific society, by Harvard's Kumar R. Bhushan, Ph.D., who led the chemistry group that participated in the research.

When used with a non-invasive imaging method that relies on harmless light instead of X-rays, the contrast agent could help doctors diagnose disease within minutes and determine where biopsies are needed.

"Because this agent is highly selective in targeting the product of malignant tumors, this approach may prove most useful for monitoring women who have dense breast tissue, or those who are at a higher-than-average risk for developing a malignant breast tumor," Frangioni says.

For screening applications, the new technique most likely would be used to supplement, not replace, mammography, according to Frangioni. But the two methods used together, he says, may potentially catch more cancers than mammography alone.

Mammography is still considered the "gold standard" for early detection of breast cancer, but the method often gives false positives, requiring additional screenings and painful biopsies for patients. In addition, studies show that traditional mammograms may miss 10 percent to 20 percent of breast cancers, especially if the tumor is buried in dense tissue.

About half of women under 50 and a third of older women have naturally dense breast tissue, making it harder to distinguish between healthy tissue and questionable masses in mammograms, Frangioni says.

The new agent works by binding to micro-calcifications produced in

breast cancers. Though scientists can't explain exactly why these calcifications occur, studies show that the calcifications in malignant breast tumors contain a higher proportion of a particular calcium salt called hydroxyapatite. In benign tumors, the predominant calcium salt is calcium oxalate.

"By homing in on hydroxyapatite, we can target these malignant cells with a high degree of specificity, and that has the potential to improve the patient's outcome," Frangioni says.

The contrast agents are designed using a combination of bisphosphonate, a type of drug used to strengthen bone, with a near-infrared fluorophore. When used with optical tomography, an imaging method that transmits near-infrared light through the body, doctors can reconstruct a three-dimensional image of tissues deep inside the breast, highlighting areas where malignant tumors appear.

The agent also may be used during surgery to pinpoint the location of hydroxyapatite, and therefore the breast cancer cells themselves, Frangioni notes.

His group began working to develop agents to target hydroxyapatite six years ago, but efforts were stalled by the inability to manufacture large quantities of the agent.

"It was a chemical catch–22," he says. "Bisphosphonates are insoluble in anything but water, but to prepare large quantities of the substance for our studies, we need to perform the reaction in the absence of water."

Last year, Frangioni's chemistry group, led by Bhushan, went back to the drawing board and devised a scheme that allowed them to synthesize the agents sans water. Once the compound was completely assembled, the researchers found a way to then make it water soluble.

Recent studies by the lab proved that the new agent works well in large animals approaching the size of humans, and that it can be used to guide surgeons performing procedures near growing bone.

Future studies will focus on translating the new compound to the clinic for human testing. It will likely be a few years before the compound is ready for use in human trials, according to Frangioni.

Source: American Chemical Society