From the University of Mississippi Medical Center Division of Public Affairs

EXISTING LEUKEMIA DRUG BRINGS NEW HOPE FOR FIGHTING AGGRESSIVE BREAST CANCER

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Photos and raw video can be found here.

The full scientific article can be found here.

JACKSON, Miss. – A drug used to treat leukemia patients shows promise in fighting triple-negative breast cancer, a particularly aggressive subtype often affecting African-American women, researchers at the University of Mississippi Medical Center Cancer Institute said.

Scientists found roughly half of more than 800 triple-negative tumor samples they tested exhibited a key protein in the cells' nuclei. Further experiments proved the drug imatinib mesylate targets that protein and stops the growth process.

"By identifying a biomarker and oncogene found in about half of all triple-negative cases, we were able to successfully target and kill tumor cells in that subset of triple-negative samples," said Dr. Wael M. ElShamy, UMMC associate professor of biochemistry and Cancer Institute researcher.

"The next step is to organize a phase one clinical trial, where we would test this drug in a small number of women with this cancer subtype in addition to their regular treatment. We hope to be able to start in that process shortly."

PLOS (Public Library of Science) ONE, an online peer-reviewed journal, published ElShamy and his team's findings in April.

Triple-negative breast cancer, most often diagnosed in African-American women, is notorious for spreading, following initial treatment, to the brain, lungs or liver.

Triple negative refers to a sub-type of cancer whose cells lack three kinds of receptors on their cell surfaces. Conventional cancer drugs target those receptors, but they're ineffective for triple-negative patients.

If the drug imatinib passes clinical trials, it would be a new targeted therapy for triple-negative breast cancer.

Targeted therapies seek and destroy cancer cells, leaving healthy ones unharmed. While every targeted therapy can have side effects, they usually are not as bad as those associated with systemic or chemotherapy drugs.

ElShamy, who heads the UMMC Cancer Institute's Molecular Cancer Therapeutics Program, spent more than a decade searching for a match of a target protein in triple-negative breast cancer and a drug that would lock onto it.

"Breast cancer kills 40,000 women a year in the United States," he said. "This subtype of breast cancer, triple-negative, is overrepresented in Mississippi's population of African-American women and kills many young women."

According to the Mississippi Cancer Registry, at least 307 Mississippi women were diagnosed with TBNC in 2011. Testing was not completed on tumor samples from about 100 other women.

Imatinib already has Food and Drug Administration approval for use in humans so it could be OK'd for market quicker than would a new drug, ElShamy said. Oncologists currently prescribe imatinib for children and adults with certain types of leukemia.

Dr. Srinivasan Vijayakumar, professor and chair of radiation oncology and director of the Cancer Institute, called the results another step toward helping more Mississippians survive cancer.

"This work directly links our researchers and physicians in efforts to halt the toll cancer takes on Mississippi," he said.

ElShamy, the Dr. Lawrence and Mrs. Bo Hing Chan Tseu American Cancer Society Research Scholar, pursued this research with a $720,000 grant from the ACS funded by Dr. Lawrence Tseu, a Hawaiian dentist, and his late wife, Mrs. Bo Hing Chan Tseu.

In the search to identify a target in triple-negative breast cancer, ElShamy and his team found that the cancer gene geminin is overexpressed in about half of the 800-plus tumor samples they analyzed.

Like a car's tires spinning too fast and causing the driver to lose control, overexpression of geminin promotes uncontrolled cell division and tumor growth.

Looking further upstream, they identified the protein c-Abl as a culprit helping geminin's tumor-promoting role. Curiously, c-Abl itself was overexpressed in 90 percent of the samples, sometimes in the cells' nuclei, sometimes in the surrounding cytoplasm. However, c-Abl was overexpressed in the nuclei of only the 400 or so geminin-overexpressing samples.

What they'd found, in general terms is called a biomarker. Biomarkers – such as genes and their product proteins – act as flags to help identify all kinds of specimens and diseases, including subtypes of cancers.

The finding means doctors can check for geminin and nuclear c-Abl overexpression to further categorize the cancer sub-type in women with triple-negative breast cancer. Armed with the new biomarker, doctors will know a treatment is more likely to work in women who have it and unlikely to help those who don't.

"That will bring the cost way down and will bring the anguish way down," ElShamy said. "If you stratify patients by who will respond and who will not respond before you start them on trial, you can save patients that agony of wondering if this drug will work."

While no one can guarantee one drug will work, he said, the research indicates chances are favorable.

ElShamy and his team knew the leukemia drug imatinib targets c-Abl. In further experiments with live triple-negative cells, they found imatinib essentially cuts a link in the chemical-reaction chain that would allow geminin to overexpress inside the cell nucleus.

No geminin overexpression means no cell division. No cell division means no tumor growth.
Better still, they found shearing that link actually sends many of the cell into apoptosis, or programmed cell death.

In studies with mice the drug destroyed more than 80 percent of each triple-negative tumor that was positive for the biomarker.

ElShamy said if the laboratory findings and statistics for the biomarker hold true in patients, imatinib could halt tumor growth in large number of women with triple-negative breast cancer.

Dr. Barbara Craft, UMMC associate professor of medicine and a medical oncologist, said about 30 percent of UMMC's breast cancer patient population is triple negative.

"We also have a large African American population that typically is not well represented in clinical trials nationwide," she said.

ElShamy said the best thing about his lab's findings is the therapy is targeted.

"And it's individualized," ElShamy said. "Currently there are no good targeted therapies for triple-negative breast cancer."

Craft agreed.

"The only option now is chemotherapy," she said. "This is a targeted drug with fewer side effects. If this works, it will really help our patients."

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