Anti-cancer Agent Stops Metastasis in its Tracks

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The following news release issued by Cornell University's Weill Cornell Medical College describes research conducted, in part, at the U.S. Department of Energy's Brookhaven National Laboratory. At Brookhaven's National Synchrotron Light Source, scientists from Cornell and BNL used powerful beams of x-rays to take molecular "snapshots" of an anti-cancer agent in action. For more information about Brookhaven's role in this research, contact Kendra Snyder at 631-344-8191 or ksnyder@bnl.gov.

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Weill Cornell Medical College Team Shows That Macroketone Can Prevent Cancer Spread, Describes How It Works

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NEW YORK — Like microscopic inchworms, cancer cells slink away from tumors to travel and settle elsewhere in the body. Now, researchers at Weill Cornell Medical College report in today's online edition of the journal *Nature* that new anti-cancer agents break down the looping gait these cells use to migrate, stopping them in their tracks.

Mice implanted with cancer cells and treated with the small molecule macroketone lived a full life without any cancer spread, compared with control animals, which all died of metastasis. When macroketone was given a week after cancer cells were introduced, it still blocked greater than 80 percent of cancer metastasis in mice.

These findings provide a very encouraging direction for development of a new class of anti-cancer agents, the first to specifically stop cancer metastasis, says the study's lead investigator, Dr. Xin-Yun Huang, a professor in the Department of Physiology and Biophysics at Weill Cornell Medical College.

"More than 90 percent of cancer patients die because their cancer has spread, so we desperately need a way to stop this metastasis," Dr. Huang says. "This study offers a paradigm shift in thinking and, potentially, a new direction in treatment."

Dr. Huang and his research team have been working on macroketone since 2003. Their work started after researchers in Japan isolated a natural substance, dubbed migrastatin, secreted by Streptomyces bacteria, that is the basis of many antibiotic drugs. The Japanese researchers noted that migrastatin had a weak inhibitory effect

on tumor cell migration.

Dr. Huang and collaborators at the Memorial Sloan-Kettering Cancer Center then proceeded to build analogues of migrastatin — synthetic and molecularly simpler versions.

“After a lot of modifications, we made several versions that were a thousand-fold more potent than the original,” Dr. Huang says.

In 2005, they published a study showing that several of the new versions, including macroketone, stopped cancer cell metastasis in laboratory animals, but they didn’t know how the agent worked.

In the current study, the researchers revealed the mechanism. They found that macroketone targets an actin cytoskeletal protein known as fascin that is critical to cell movement. In order for a cancer cell to leave a primary tumor, fascin bundles actin filaments together like a thick finger. The front edge of this finger creeps forward and pulls along the rear of the cell. Cells crawl away in the same way that an inchworm moves.

Macroketone latches on to individual fascin, preventing the actin fibers from adhering to each other and forming the pushing leading edge, Dr. Huang says. Because individual actin fibers are too soft when they are not bundled together, the cell cannot move. The new animal experiments detailed in the study confirmed the power of macroketone. The agent did not stop the cancer cells implanted into the animals from forming tumors or from growing, but it completely prevented tumor cells from spreading, compared with control animals, he says. Even when macroketone was given after tumors formed, most cancer spread was blocked.

“This suggests to us that an agent like macroketone could be used to both prevent cancer spread and to treat it as well,” Dr. Huang says. “Of course, because it has no effect on the growth of a primary tumor, such a drug would have to be combined with other anti-cancer therapies acting on tumor cell growth.”

Also pleasing was the finding that the mice suffered few side effects from the treatment, according to Dr. Huang. “The beauty of this approach is that fascin is over-expressed in metastatic tumor cells but is only expressed at a very low level in normal epithelial cells, so a treatment that attacks fascin will have comparatively little effect on normal cells — unlike traditional chemotherapy which attacks all dividing cells,” he says.

Dr. Huang and his colleagues reported another key finding in the same Nature paper — on x-ray crystal structures of fascin and of the complex of fascin and macroketone. They demonstrated how macroketone blocks the activity of fascin. The images showed precisely how macroketone snugly nestles into a pocket of fascin affecting the way it regulates actin filament bundling.

“The molecular snapshots provide an approach for rational drug design of other molecules inhibiting the function of fascin, the therapeutic target,” says Dr. Huang.

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Co-researchers include Dr. Lin Chen, Dr. Shengyu Yang and Dr. J. Jillian Zhang — all of Weill Cornell Medical College, and Dr. Jean Jakoncic, from Brookhaven National Laboratory. The authors declare no competing financial interests.

Weill Cornell Medical College, Cornell University's medical school located in New York City, is committed to excellence in research, teaching, patient care and the advancement of the art and science of medicine, locally, nationally and globally. Physicians and scientists of Weill Cornell Medical College are engaged in cutting-edge research from bench to bedside, aimed at unlocking mysteries of the human body in health and sickness and toward developing new treatments and prevention strategies. In its commitment to global health and education, Weill Cornell has a strong presence in places such as Qatar, Tanzania, Haiti, Brazil, Austria and Turkey. Through the historic Weill Cornell Medical College in Qatar, the Medical College is the first in the U.S. to offer its M.D. degree overseas. Weill Cornell is the birthplace of many medical advances — including the development of the Pap test for cervical cancer, the synthesis of penicillin, the first successful embryo-biopsy pregnancy and birth in the U.S., the first clinical trial of gene therapy for Parkinson's disease, and most recently, the world's first successful use of deep brain stimulation to treat a minimally conscious brain-injured patient. Weill Cornell Medical College is affiliated with NewYork-Presbyterian Hospital, where its faculty provides comprehensive patient care at NewYork-Presbyterian Hospital/Weill Cornell Medical Center. The Medical College is also affiliated with the Methodist Hospital in Houston, making Weill Cornell one of only two medical colleges in the country affiliated with two U.S.News & World Report Honor Roll hospitals. For more information, visit www.med.cornell.edu [3].

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