Researchers develop a new way to study how breast cancer spreads

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In a breakthrough study appearing in advance online publication of *Nature Methods*, researchers at Albert Einstein College of Medicine of Yeshiva University describe for the first time a method of viewing individual breast cancer cells for several days at a time. The study, by scientists in Einstein's Gruss Lipper Biophotonics Center, provides detail on how cancer cells invade surrounding tissue and reach blood vessels. These movements are the first steps of the potentially deadly stage of cancer known as metastasis.

The new method of viewing cancer cells over several days in their natural environment is considered significant because prior methods of study only allowed cells to be viewed clearly for several hours at one time. Having a longer and clearer window into how cancer cells move during the early stages of metastasis may help scientists develop more effective cancer therapies. For 2007, the American Cancer Society reported that a woman with metastatic breast cancer had an average survival rate of two years.

Using intravital imaging, the researchers developed a "photoswitch" to mark cancer cells of their choosing within a tumor and observe how these tumor cells in mice move in their surrounding tissue. The technique allowed researchers to see individually labeled tumor cells move in real time and in living mice.

"One focus of our laboratories has been developing methods to see what cancer cells are doing when followed over time in the most realistic

setting," explained Jeffrey Segall, Ph.D., professor of anatomy and structural biology. "Mapping the fate of tumor cells in different regions of a tumor was not possible before the development of the photoswitching technology," explained John Condeelis, Ph.D., co-chair and professor of anatomy and structural biology and co-director of the Gruss Lipper Biophotonics Center.

The new method involves the placement of a frame containing a small glass window onto the breast tumor of a mouse formed from cancerous cells that have a specific tag. Through the glass, individual breast tumor cells are targeted with a laser that 'marks' the cancer cells red. By viewing the cells through the window using a microscope, researchers can follow the cells as they spread. The mouse can move around and live normally with the glass plate and then be anesthetized briefly for observance under the microscope. The marked cancer cells are followed over a period of days until they lose their brightness.

Using this technique, investigators found that breast cancer cells closer to blood vessels were more aggressive and directed in their invasiveness than cancer cells farther from blood vessels. The cancer cells near blood vessels also appeared in the lung indicating that they are disseminated throughout the body.

As co-lead author, Bojana Gligorijevic Ph.D., explained, "Our work showed how important the microenvironment of a tumor is to the behavior of a cancer cell and the metastatic outcome of the tumor itself. We can now look at the early steps of metastasis in high resolution and specific regions of the tumor."

This finding marks the first time a direct link was shown between the presence of blood vessels and the invasive ability of a cancer cell, which strengthens the growing theory that blood supply is crucial to effective metastasis. It also suggests that many cancer therapies currently in

development, which are directed at cutting off blood supply to tumors, may be on the right track.

The research was conducted by Dmitriy Kedrin, Bojana Gligorijevic, Ph.D. and team leader Jacco van Rheenen, Ph.D. under the direction of Drs. Segall and Condeelis. Vladislav Verkhusha, Ph.D., associate professor of anatomy and structural biology, and Jeffrey Wyckoff, M.F.A., B.S., senior associate of anatomy and structural biology, both members of the Biophotonics Center, contributed novel photo-switching protein, and expertise in intravital imaging, respectively. This study required this broad multidisciplinary team and the resources of the Center to make the technical leap needed to achieve this new result. The Center has been supported by the generous contributions of Evelyn Lipper.

Each year, cancer kills 553,000 people in the U.S. Most cancer deaths are caused by complications from metastasis, the spread of cancer cells to distant tissues and organs through the blood, rather than from the primary tumor itself. This research provides a powerful tool for studying cancer metastasis and is part of a growing body of Einstein cancer research that sheds light on how cancer spreads.

The study has been chosen for highlight at the 48th Annual Meeting of The American Society of Cell Biology in San Francisco on December 15, 2008 to be presented by Dr. Gligorijevic.

Source: Albert Einstein College of Medicine