Third-generation device significantly improves capture of circulating tumor cells

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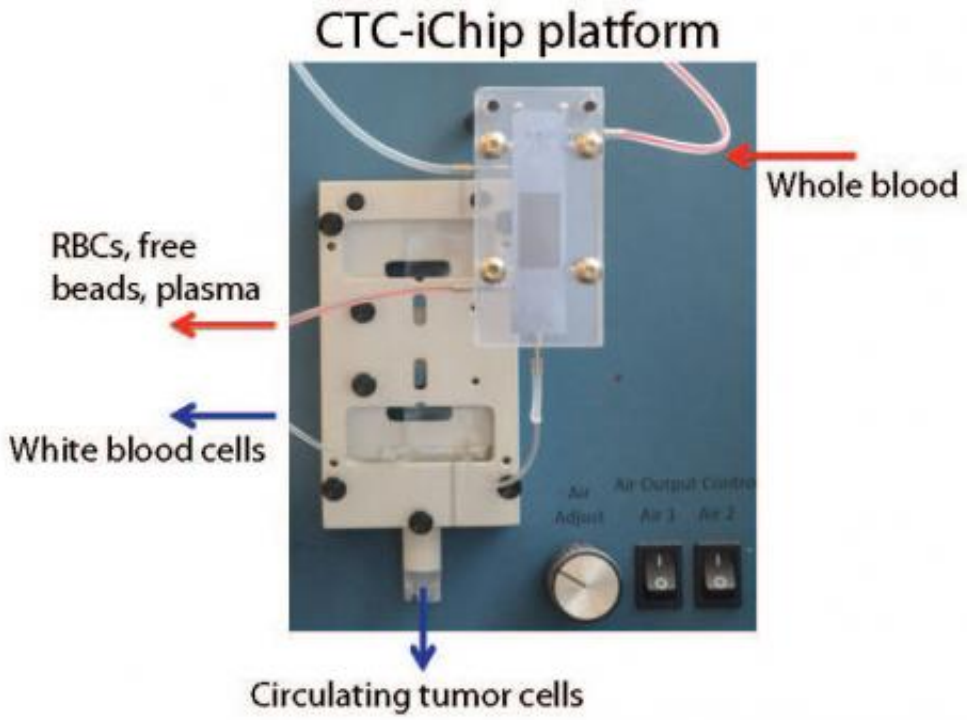

Antigen-independent cell sorting begins by tagging the white cells in a blood sample with magnetic beads. The sample is then passed into the CTC-iChip microfluidic system, which first removes red cells, plasma and free magnetic beads and then sorts out tagged white blood cells, leaving a purified solution of circulating tumor cells. Credit: Emre Ozkumur, Mass. General Hospital Center for Engineering in Medicine

A new system for isolating rare circulating tumor cells (CTCs) – living

solid tumor cells found at low levels in the bloodstream – shows significant improvement over previously developed devices and does not require prior identification of tumor-specific target molecules. Developed at the Massachusetts General Hospital (MGH) Center for Engineering in Medicine and the MGH Cancer Center, the device rapidly delivers a population of unlabeled tumor cells that can be analyzed with both standard clinical diagnostic cytopathology and advanced genetic and molecular technology. The MGH team's report has been published in *Science Translational Medicine*.

"This new technology allows us to follow how cancer cells change through the process of metastasis," says Mehmet Toner, PhD, director of the BioMicroElectroMechanical Systems Resource Center in the MGH Center for Engineering in Medicine, the paper's senior author. "Cancer loses many of its tissue characteristics during metastasis, a process we have not understood well. Now for the first time we have the ability to discover how cancer evolves through analysis of single metastatic cells, which is a big step in the war against cancer."

The new device – called the CTC-iChip – is the third microchip-based device for capturing CTCs developed at the MGH Center for Engineering in Medicine. The first two systems relied on prior knowledge of a tumor-specific surface marker in order to sort CTCs from whole blood and required significant adjustment for each different type of cancer. The systems also required four to five hours to process a single blood sample.

The only U.S. Food & Drug Administration-cleared, commercially available device for capturing and enumerating CTCs – the CELLSEARCH system developed by Veridex, LLC – relies on magnetic nanoparticles that bind to the same epithelial protein used in the MGH -developed microchip-based devices and cannot always find CTCs present at very low numbers. In January 2011 the MGH entered into a

collaborative agreement with Veridex and its affiliate Janssen Research & Development, LLC, to establish a center of excellence in research on CTC technologies.

Combining elements of both approaches – magnetic labeling of target cells and microfluidic sorting – the CTC-iChip works by putting a blood sample through three stages. The first removes from the sample, on the basis of cell size, all blood components except for CTCs and white blood cells. The second step uses a microfluidic process developed at the MGH to align the cells in a single file, allowing for extremely precise and rapid sorting. In the third stage, magnetically labeled target cells – either CTCs tagged via the epithelial marker or white blood cells tagged on known blood-cell antigens – are sorted out. Tagging white blood cells instead of CTCs leaves behind a population of unlabeled and unaltered tumor cells and doesn't rely on the presence of the epithelial marker or other known tumor antigens on the cell surface.

The new system was able to process blood samples at the extremely rapid rate of 10 million cells per second, handling a tube of blood in less than an hour. Both the mode of sorting out tagged CTCs, called tumor-antigen-dependent, and the technique that depletes white blood cells, called tumor-antigen-independent, recovered more than 80 percent of tumor cells from different types of cancer that had been added to blood samples. Comparison of the antigen-dependent-mode CTC-iChip with existing commercial technology for processing blood samples from patients with prostate, breast, pancreatic, colorectal and lung cancer showed the CTC-iChip to be more sensitive at detecting low levels of CTCs.

In the antigen-independent mode, the CTC-iChip successfully identified CTCs from several types of cancers that had lost or never had the epithelial marker, including triple-negative breast cancer and melanoma. CTCs isolated through this mode were put through standard

cytopathological analysis, which revealed structural similarities to the original tumor, and detailed molecular genotyping of CTCs from a single patient found significant differences in gene expression patterns among individual CTCs.

"We're only beginning to identify potential applications of the ability to analyze how tumors mutate as they spread, but this should help improve our understanding of the fundamental genetic principles of metastasis," says Toner, the Benedict Professor of Surgery at Harvard Medical School (HMS). "We hope to develop this technology to the point where it could be used for early diagnosis, which is the 'Holy Grail' that all of us working on CTC technology have been striving for."

Ravi Kapur, PhD, of the Center for Engineering in Medicine, leader of the innovation team within the MGH Circulating Tumor Cell Center, says, "The CTC-iChip provides a first-in-class device for high-efficiency, high-speed tumor cell sorting from a clinically relevant blood volume. The chip is designed for mass manufacturing, and simple automation for clinical translation." The team is working with collaborators at Veridex and Janssen to refine the system for commercial development.

Study co-author Daniel Haber, MD, PhD, director of the MGH Cancer Center and Isselbacher/Schwartz Professor of Oncology at HMS, adds, "The study of cancer metastasis has been limited by the inability to quickly and reliably isolate tumor cells in transit in the blood. This new approach is likely to be a game changer in the field."

Provided by Massachusetts General Hospital

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