New technologies aim to take cancer out of circulation

BOSTON — A plashet of blood slowly leaks out from atop the microfluidics chip in Daniel Haber's lab here at the Massachusetts General Hospital (MGH) Cancer Center. "That's not supposed to happen," murmurs technician Jenna Lord, as she carefully pipettes the fluid into a Falcon tube.

The blood, taken from a man with elevated levels of prostate-specific antigen who is suspected of having cancer, is being pushed through eight tiny channels, each coated with cancer-specific antibodies to capture any circulating tumor cells (CTCs). Four years ago, Haber and his MGH colleague Mehmet Toner first reported the effectiveness of such a microfluidics-based contraption for isolating CTCs, which are approximately one out of every billion cells in the blood (*Nature* **450**, 1235–1239, 2007). And last year, they refined their invention to create a platform that can be manufactured on a commercial scale with improved cell capture rates (*Proc. Natl. Acad. Sci. USA* **107**, 18392–18397, 2010).

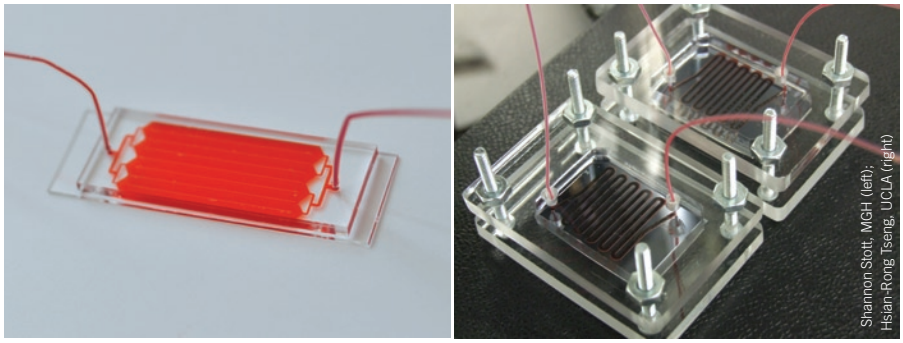
"Now, you can draw a blood sample and say, 'aha, this is the molecular status of my tumor, and this is how it has or has not been changed by the drugs I've been given,'" Haber says.

Haber and Toner's technology has garnered immense attention—and investment. In January, New Jersey–based Johnson & Johnson, the world's largest medical devices and diagnostics company, announced a five-year, $30 million deal with the MGH team to build the next-generation assay: a 'liquid biopsy' test for early cancer detection that would be as easy to use as a home pregnancy test.

Clearly, the researchers aren't there yet, as the mishap with the leaky blood shows. But with dozens of competing devices under development in labs around the world, the MGH team—and its pharma backers—are facing pretty stiff competition to deliver a diagnostic cancer test.

"We poked the sleeping bear," Toner says. "It has suddenly created a frenzy."

Currently, the only CTC device approved by the US Food and Drug Administration for tracking cancer progression is a technology called CellSearch. Manufactured by the Johnson & Johnson subsidiary Veridex, CellSearch, like the MGH team's device, captures CTCs on the basis of their affinity to antibodies against a protein called epithelial cell adhesion molecule (EpCAM), which is found on tumor cells but not on blood cells. Using CellSearch, researchers have shown that the number of CTCs is a good predictor of survival and disease progression in people with metastatic breast, colon and prostate cancers.



Chips off the old block: The MGH (left) and UCLA (right) microfluidic CTC detectors.

But "the problem with the current platform is that the cell yields are very low, and they're not consistent," says Shivaani Kummar, a clinician at the US National Cancer Institute in Bethesda, Maryland. Moreover, "what the CellSearch system definitely doesn't do now is tell a physician what treatment to give," says the technology's inventor Leon Terstappen from the University of Twente in the Netherlands.

Tech transfer

Steven Soper, a bioengineer at Louisiana State University in Baton Rouge, is also working on a microfluidics device based on EpCAM binding. But unlike the MGH chip, the antibodies in Soper's device can be easily detached, allowing researchers to collect cells intact for further study. "Now, we actually have the opportunity to collect those cells and do molecular profiling," says Soper, who reported his device last month in *Analytical Chemistry* (doi:10.1021/ac103172y, 2011).

This month, Hsian-Rong Tseng, a chemist at the University of California–Los Angeles, reported another microfluidics design that relies on EpCAM-coated nanofibers that bind like Velcro to the unusually high number of microvilli on the surface of tumor cells (*Angew. Chem.*. doi:10.1002/ange.2010005853, 2011). "Because our surface is much stickier," says Tseng, "we can operate in a much faster blood flow through the device and also have a shorter channel length," which makes the chip smaller and cheaper to manufacture than competing designs.

Meanwhile, at Stanford University in Palo Alto, California, a team led by surgeon Stefanie Jeffrey has created a technology called the MagSweeper. The device, now licensed to and further developed by sequencing giant Illumina, consists of a magnetic rod that sweeps through blood to capture CTCs. In collaboration with Microsoft, biophysicist Peter Kuhn of the Scripps Research Institute in La Jolla, California, is working on a staining and imaging approach for identifying CTCs without relying on any given specific surface marker such as EpCAM. And in December, Chwee Teck Lim from the National University of Singapore's Mechanobiology Institute reported another chip that separates CTCs on the basis of their physical qualities; they are generally larger and stiffer than blood cells (*Biosens. Bioelectron.* **15**, 1701–1705, 2010)

"It's really exciting because the number of technologies is really exploding," says Howard Scher, an oncologist at Sloan-Kettering Memorial Cancer Center in New York. "But at the end of the day there has to be focused development on the specific decision the test is going to inform."

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