New Technologies Aim To Find Cancer in the Blood

Like colonists sailing in search of a land where they can settle and prosper, rogue cancer cells ride the bloodstream in search of new tissues where they can take root.

Although not all the wanderers will form their own metastatic dominions, oncologists are beginning to exploit these cells as a form of bloodstream biopsy that might signal a problem more quickly than waiting for the disease to show up on scans. And other researchers are developing new ways to find and characterize these rare cells—maybe just a few thousand in one person—called circulating tumor cells (CTCs). This information might help researchers begin to understand metastatic cancers.

“The thing I find really exciting about CTCs is that they likely represent the state of your cancer right now,” said Jeff Smerage, M.D., Ph.D., of the University of Michigan in Ann Arbor. “It’s like having access to tumor tissue that you might not be able to get to.”

CTCs break off from solid cancers and spread to other areas of the body, but how they do it isn’t yet understood. Luckily, they don’t look like every other blood cell. Researchers can distinguish them from standard blood cells because CTCs originate as epithelial cells and therefore have proteins on their surfaces that blood cells do not.

“Those cells have no business being in the bloodstream,” Jorge Nieva, M.D., of the Scripps Research Institute in La Jolla, Calif.

The best known CTC detection method so far, known as CellSearch from Immunicon, identifies cancer cells in the blood by using antibodies directed against an epithelial cell protein called EpCAM. The antibodies are attached to a bit of iron. The rogue cells become coated in antibodies and can be pulled out of blood with a magnet.

Using this test, Daniel Hayes, M.D., of the University of Michigan Comprehensive Cancer Center reported in 2004 that women with breast cancer who had high levels of CTCs in their blood did not remain disease free as long as women with low levels (see News, Vol. 96, No. 14, p. 1055, July 21, 2004). Hayes and his colleagues followed up this research by counting the number of CTCs in blood samples from women with metastatic breast cancer every 3–5 weeks after the start of therapy. The overall survival of patients who consistently harbored fewer than five CTCs in their blood was a relatively long 18.5 months. Women who had five CTCs or more coursing through their veins at various time points had much shorter median survival times, ranging from 1.3 to 3.6 months. If the women had elevated numbers of cells 2–4 weeks after the start of treatment, “they’re probably on the wrong therapy,” Hayes said, whose study was published in Clinical Cancer Research.

To test this idea, Hayes, Smerage, and researchers at five other sites are planning a randomized trial this fall to examine whether changing the treatment of women who continue to have high numbers of CTCs after therapy will affect their survival or time to progression. Some women will get a different therapy if their CTCs do not drop, whereas others will stay with the standard treatment.

“A biomarker [for metastases] that can be followed in the blood is urgently needed,” said Klaus Pantel, M.D., Ph.D., of the University Medical Center Hamburg–Eppendorf in Germany. “All the protein serum markers [currently used for prognosis] don’t work. If patients have those markers, they already have metastases.”

Not everyone is convinced that finding CTCs with magnets is the way to go. Some researchers think that immunomagnetic separation methods might miss some CTCs or damage them. Richard Bruce, Ph.D., of Xerox’s Palo Alto Research Center in California suspects that magnetic methods that rely only on EpCAM might undercount CTCs, because the amount of EpCAM on cell surfaces varies greatly. Some cells might not collect enough iron to be pulled in by the magnet.

“The fundamental problem is that we’d like to be able to look at every single cell,” Bruce said.

Nieva and others at Scripps are working with Bruce to develop a way to search accurately and quickly for CTCs among 60 million white blood cells—the number found in a typical blood sample. To do this, they’ve come up with a gadget that is part microscope, part laser printer, and part fiber optic cable. They spread out 1 or 2 mL of white blood cells on a 100-cm² slide. They then add a fluorescent antibody to cytokeratin, a protein found inside epithelial cells but not blood cells. A laser printer–like scanner examines the slide in 80 minutes, marking the location of any fluorescent spot.

Cellular pathologists later look at the marked spots to investigate whether the fluorescence is due to a CTC or “garbage” such as aggregated fluorescent antibodies. But their work is not done there. Not all CTCs can start a new cancerous growth, and Scripps researcher Peter Kuhn wants to make CTCs reveal whether they have a future. He hopes to test each cell for a variety of protein markers to investigate which ones will be prone to metastasize and which ones are probably on their way to death.

“They should tell us where they came from, where they want to go, and what are the chances they will get there,” he said.

In initial tests, Nieva and his colleagues found CTCs in the blood of 14 women with breast cancer by using this technology, which they call FAST (fiber-optic array scanning technology) cytometer. They also found no CTCs in the blood of 10 healthy donors, they
reported in *Biosensors and Bioelectronics* in February.

To determine whether they can find more CTCs than current technologies can, Bruce plans to measure CTCs in a variety of patients and cancer types. They also plan to further characterize the CTCs. For example, they want to try to determine whether the CTCs are from the original tumor or from a previous metastatic growth.

Technologies that capture enemy CTCs for further interrogation might prove useful in the war on cancer, said molecular biologist Avraham Rasooly, Ph.D., the National Cancer Institute officer who oversees Nieva and colleagues’ funding from NCI.

“The war on cancer was declared 40 years ago and cancer is still here,” he said. “FAST is a promising start for cancer diagnostics.”

—Mary Beckman

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