Putting Tumors to the Blood Test

Melding advances in nanotechnology and microfluidics, devices for detecting circulating tumor cells and other cancer biomarkers move into clinical testing

“In a tube of blood there are about 100 billion cells, and to find rare cells you need to process every cell in an identical manner,” says Mehmet Toner, PhD, a professor at Harvard Medical School and director of the Center for BioMicro-ElectroMechanical Systems at Massachusetts General Hospital (MGH) in Boston. “If it takes you 1 second per cell, that will be 3,700-plus years. So you need to do the processing in a massively parallel way.”

Toner and his associates have done just that, building extraordinarily sensitive systems that integrate advanced bioengineering, nanotechnology, and microfluidics techniques to capture circulating tumor cells (CTC), which spill into blood from solid tumors and act as harbingers or agents of potential metastasis.

Their plastic microfluidic chip, slightly smaller than a business card, works by immunoaffinity capture: It takes whole-blood samples and collects the one-in-a-billion CTCs via antibodies that recognize tumor cells, which coat tiny channels through which the blood flows in extremely well-controlled patterns. “You’re pushing whole blood through channels that are no more than 20 to 40 microns wide at very fast flow rates,” says Toner. “It’s like putting a garden hose through a microfluidic chip.”

Preliminary clinical studies have shown that the device can capture CTCs from pancreas, breast, lung, and other tumors. “In about one third of patients with localized prostate cancer, you can see CTCs before surgery, and then after surgery they’re gone,” says Daniel Haber, MD, co-primary investigator on the project, director of the MGH Cancer Center, and a professor at Harvard Medical School. This raises the prospect, in some cancers, of finding CTCs before they can leave the bloodstream and metastasize, he says.

Early testing also produced a surprise that added fuel to the discussion of how these rare cells might function in metastasis: multi-cell CTC clusters are found in 5% to 8% of patients with prostate cancer.

**BETTER LIQUID BIOPSIES**

The MGH system, which has moved into clinical testing at several major cancer centers, is one among many microfluidic systems now being engineered to greatly broaden the sensitivity and scope of “liquid biopsies” in cancer research, detection, monitoring, and treatment.

Sanjiv Sam Gambhir, MD, PhD, director of Stanford University’s Center for Nanotechnology...
Excellence and Translation in Stanford, CA, and colleagues are working on a number of such platforms and projects. One initiative in the lab of Shan Wang, PhD, is creating tunable magnetic nanoparticles that can be sensed and sorted out after they attach to numerous different types of proteins (related to cancer or other conditions) in blood or other fluids. Reported in Nature Nanotechnology in April 2011, the basic approach, using giant magnetoresistive (GMR) biosensors, is “similar to that in a hard disk drive but developed to detect very low levels of specific proteins present in blood,” Gambhir says.

Several other nanotechnology-based platforms are being engineered in the labs of James Heath, PhD, of Caltech, in Pasadena, CA, and his partners to simultaneously measure high numbers of different types of proteins. As described in May 2011 in Nature Medicine, one system was used to examine single-cell secretions in blood from patients with melanoma undergoing immunotherapy treatment. It was successful in identifying a dozen effector molecules secreted from tumor antigen-specific cytotoxic T lymphocytes that were responding to the melanoma tumors.

With strong interest from physicians, and the relative ease of acquiring blood samples from patients, “we have often been able to go from concept to clinical testing in less than a year,” notes Heath. “In this paper, we reported both the technology and its first clinical application.”

It’s much earlier days for other detection concepts, among them a prototype system created at the University of Missouri, Columbia, to find combinations of microRNAs that may predict lung cancers. In this approach, reported in September 2011 in Nature Nanotechnology, RNA concentrate extracted from blood plasma goes through a protein-based “nanopore” device, which employs a form of nanoscale filtering found in certain next-generation DNA sequencing systems. Because microRNAs are extremely rare and only 18 to 22 nucleotides long, it’s difficult to find and quantify them via polymerase chain reaction, notes Michael Wang, MD, PhD, assistant professor at the University of Missouri and co-lead developer. “One advantage of the nanopore approach is specificity,” says Wang. “With a nanopore system, we can detect microRNAs at a single-molecule level.”

**CHANGING CHECKUPS?**

“Many different types of brains and intellectual know-how must go into these devices to make it happen in actual clinical use,” comments MGH’s Toner. “We needed expertise in blood biology, rheology, non-Newtonian fluids, tumor cells, surface chemistry, microfabrication, genetics, industrial practice, FDA [U.S. Food and Drug Administration] regulation, and other disciplines. And development of any of these technologies needs to be done working very closely with real blood and patients. That’s a much more complex problem than modeling it in tumor cell lines.”

“I would not be surprised if 10 or 20 years from now, this becomes part of the annual checkup,” Toner speculates. “The vision is that the measurement is done from the same blood that you use to do other measurements.”

“Any time you change what you measure by orders of magnitude, big things happen,” says Chad Mirkin, director of the International Institute for Nanotechnology at Northwestern University in Evanston, IL, whose lab’s many inventions include systems that have vastly improved the precision of prostate-specific antigen detection. “Advances in measurement happen first on the research side, then they are translated into diagnostics that are used in medicine. The impact in cancer will be enormous.” – Eric Bender

*Cancer Discovery; published OnlineFirst January 12, 2012; doi:10.1158/2159-8290.CD-ND2012-003*