

New technology advances cancer detection through blood testing

By Darren Davis, PhD

More than 1.5 million people are diagnosed with cancer annually in the U.S., and nearly 570,000 die as a result of the disease, according to estimates from the American Cancer Society.¹ The National Institutes of Health estimates overall costs of cancer in 2010 at \$263.8 billion, of which \$102.8 billion is for direct medical costs.¹ This is due, in part, to the fact that cancer is a highly individualized disease, and today's treatments are mostly "one-size-fits-all". Improvement of treatment outcomes for patients with solid tissue tumors depends on the drug's ability to effect the genetic mutations and other factors responsible for tumor growth. Currently, mutational analysis requires painful tissue biopsy, which is invasive, expensive, and impractical to perform repeatedly. However, delivery on the promise of personalized medicine to treat cancer requires access to the patient's tumor(s) or tumor cells. The diagnosis of cancer is often confirmed by a surgical biopsy of the primary tumor but continued access to the tumor is often not

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feasible, such as in liver, lung, brain and pancreatic cancers.

Given the aggressive and transformative properties of cancer, the characteristics of the tumor will likely change during disease progression and the information obtained at the time of the original tissue biopsy may become irrelevant over time. Furthermore, as tumors develop, tumor cells shed from the primary location and begin circulating in the bloodstream. Metastasis is the result of dissemination of tumor cells into the bloodstream and is the most deadly phase of cancer. The ability to isolate and characterize these rare circulating tumor cells (CTCs) may provide critical insights into the primary tumor, the process of metastasis, and disease progression. Moreover, performing molecular analysis on CTCs offers an attractive approach for genotyping patient-specific tumors and mutations and guiding treatment decisions.



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Technological advances

It has been known for more than half a century that cancer cells are present in the blood of individuals afflicted with cancer, but only in the last decade has the field of isolating cancer cells from blood made significant technological advancements sufficient to enable clinical applications. Thus far, only one technology is FDA cleared for use in only three tumor types: prostate, breast and colorectal cancers.²⁻⁴ This technology, along with several others, is antibody-dependent, meaning that the detection and capture of the CTCs depends on antigen expression on the surface of cancer cells of epithelial origin (e.g. EpCAM).

One limitation of this pioneering technology is that it is useful only in cancers of epithelial origin, leaving highly aggressive cancers such as liver, pancreatic, and melanoma unaddressed. Additional CTC shortfalls of the antibody-dependent technologies are detection in only a small proportion of patients and low CTC yields, preventing post-recovery molecular analysis. This is attributed to the metastatic phenotype of the CTC; more specifically, the cell surface markers required for detection are often low or lost following the epithelial mesenchymal transition—the process by which a cell becomes metastatic. Because the current antibody-dependent technology detects only CTCs that express EpCAM (epithelial cellular adhesion molecule), the field of CTC enrichment has been underserved, leaving CTCs with no-or-low EpCAM expression (like those involved in metastatic dissemination) undetected and

unstudied. This limitation underscores the need for improved CTC isolation and recovery.

A new, next-generation antibody-independent technology has recently been developed which relies on continuous field-flow assisted dielectrophoresis (DEP) to isolate and recover CTCs from the blood of cancer patients.⁵ It has already proved successful in detecting and isolating a wider range of cancers in greater cell quantities, and research prototypes of the technology are now being used in a variety of Phase I, Phase II, and Phase III clinical studies. The isolation of rare cells from blood using DEP field-flow assist is based on the differences in dielectric properties between blood cells (lymphocytes, monocytes, and granulocytes) and solid tissue-derived cancer cells. The technology is truly revolutionary in the capture of CTCs for several reasons. First, it permits the isolation of cancer cells from all types, including lung, prostate, melanoma, breast, pancreatic, liver, glioblastoma, and other rare forms. Second, the higher CTC isolation and capture capability provides greater opportunities for downstream analysis of the cancer cells, which has significant implications for treatment selection and assessing effectiveness. Third, the DEP technology captures the cancer cells in a viable state, allowing for additional biological testing.

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Clinical applications

In a recent study, the new DEP technology was first to reliably isolate and recover CTCs from patients with hepatocellular carcinoma (HCC), one of the most common forms of liver cancer.⁶ CTCs were recovered in all HCC cancer patients in the study, capturing hundreds of CTCs in some cases. This is the first time that this quantity of CTCs has been isolated from liver cancer patients. Based on these findings, researchers believe that the highly sensitive DEP technology could detect liver cancer in patients earlier. Early detection is significant because HCC diagnosis is typically made at an advanced stage of the disease, when the cancer is especially aggressive and survival probability is low. If the disease is detected at an early stage, when patients are still candidates for targeted therapies, organ transplantation, or other surgery, then the survival rate could increase substantially.

Future applications for this technology that are currently being explored include utilizing CTC counts and characteristics to monitor the effectiveness of a particular treatment. Because the technology is effective in isolating all cancer types, even rare ones, it has the potential to be used as a noninvasive screening tool, enabling earlier detection of cancers.

Looking beyond current clinical trial research, this new CTC isolation technology has the potential to be used for a wide variety of applications including the study of the biology of micro metastatic development of solid tumors, the identification of new genes responsible for invasion and metastasis, and the early detection of CTCs and disseminated tumor cells.

In this era of genetic and molecular information, access to the tumor cells is essential. CTCs coupled with molecular analysis are fast becoming an accepted supplement or alternative to biopsy samples to aid drug therapy decisions. CTCs hold the key to understanding the biology of metastasis and provide a means to noninvasively measure the evolution of tumor genotypes during

treatment and disease progression. There is a need for qualification and validation of CTC tests and a need to establish correlations with clinical outcomes. Continued development and commercialization of blood tests to recover CTCs will facilitate implementation of personalized medicine and enable improved clinical outcomes for millions of cancer patients. □

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