ApoCell Entering the Commercial Ring In Rare Tumor Cell Diagnostics

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In less than a decade, the Houston-based research services company **ApoCell** has made a name for itself amid the developing life sciences industry in Texas. Based on its rapid revenue increases, ApoCell has been named to the **Inc 5000** list of fastest-growing private US companies for the past three years.

ApoCell has now set a new goal that could be seen as a kind of Holy Grail in molecular diagnostics. By 2016, ApoCell hopes to begin selling benchtop devices that could alert doctors when cancer drugs have stopped working for an individual patient, and might also help reveal which drugs are most likely to restore control of tumor growth.

ApoCell is one of several companies developing instruments that can capture tumor cells circulating in the blood of cancer patients. The number of these cells alone is a valuable clue to the severity of the disease, and the effectiveness of drugs. But in addition, once these rare cells have been isolated from the blood cells by the company's ApoStream device, they can be tested to provide a snapshot of the signature molecular traits of the diseased cells.

Already this kind of molecular analysis, performed on cells from tumor biopsies, can often point to the drugs best tailored to attack particular cancer subtypes. But biopsies can be invasive and painful. The hope is that tumor cells could be routinely extracted instead from patient blood samples with the help of analyzers like ApoCell's. This "liquid biopsy" could be repeated more often than a traditional biopsy, to track a patient's tumor cell population as it evolves and develops resistance to initial drug treatments.

"The testing technologies used in tumor biopsies are applied to rare cells," says ApoCell CEO Darren Davis.

It was ApoCell's clients who, in 2007, sent the company on the hunt for a new way to pluck tumor cells out of the blood, leading to the development of ApoStream, Davis says. The company, which Davis founded in 2004, had quickly become profitable as a

provider of tests such as genetic analysis and cancer biomarker detection for drug developers, he says. ApoCell was also offering a commercial test for blood levels of circulating tumor cells—the **CellSearch** system, marketed by Johnson & Johnson unit **Janssen Diagnostics** of Raritan, NJ. But pharmaceutical companies asked ApoCell to look for another method that would expand the range of information that could be gleaned, beyond the limits of the CellSearch product.

CellSearch delivers a total count of circulating tumor cells, and is FDA-cleared for clinical use in three major cancers—breast cancer, prostate cancer, and colorectal cancer. A rise in the mere numbers of such cells points to a poor prognosis in these cancer types, according to studies using the CellSearch system. A higher blood count of tumor cells indicates that diseased cells are escaping from the original tumor, and may give rise to new tumors at different sites in the body—the process of metastasis. Doctors may decide to start the patient on a new course of treatment, based on the circulating tumor cell count and other monitoring tests.

But ApoCell's clients wanted to capture circulating tumor cells from a wider range of cancers. The CellSearch system uses an antibody that sticks to tumor cells, to selectively "fish" them out from the large population of blood cells. However, the antibody doesn't bind to every type of tumor cell. To extend that reach, the ApoCell device separates out tumor cells using charged electrodes. The tumor cells are pulled toward the electrodes, while blood cells are repelled from them, because of factors that differentiate tumor cells from blood cells. These include cell density and electrical conductivity.

"We're isolating these cells based on biophysical properties," Davis says. ApoCell has an exclusive license to the method, a microfluidic antibody-independent dielectrophoresis process developed at the University of Texas MD Anderson Cancer Center's Laboratory of Diagnostic Microsystems.

The ApoStream device captures tumor cells without regard to their antibody affinities, and also preserves them as intact living cells that can be subjected to an array of different tests. The company began providing its own circulating tumor cell isolation service as an in-house offering to clients in 2010, and ApoStream has been used in a number of clinical trials. For example, San Francisco-based **Nektar Therapeutics** (NASDAQ: **NKTR**) has been using the service to obtain circulating tumor

cells at intervals from participants in a late-stage trial of its experimental breast cancer drug etirinotecan pegol. The captured tumor cells are being tested for biomarkers that might help identify patients who would respond best to treatment with the Nektar drug.

With fine-tuning of the ApoStream settings, the device can isolate circulating tumor cells from other cancer types, including sarcoma and pancreatic cancer, Davis says.

In 2011, ApoCell received its first commercial order for ApoStream devices—a $2.9 million contract from SAIC-Frederick that funded the company to develop a prototype for use by outside researchers contributing to the National Cancer Institute's Pharmacodynamics Program. In June, ApoCell began delivering the first of 12 ApoStream instruments to investigator sites including Leidos Biomedical Research, formerly SAIC-Frederick, which operates the federally funded Frederick National Laboratory for Cancer Research.

ApoCell plans to increase its commercial sales of ApoStream devices in 2014 to investigators who will use the device for research purposes only. No price has yet been set for the benchtop analyzer, which is about the size of a large microwave oven.

But ApoCell has recently announced much more ambitious plans. By 2016, ApoCell hopes to market the device as a clinical tool to guide doctors in their treatment decisions. For this goal, ApoCell got another boost from the National Cancer Institute in November—a $1 million **Small Business Innovation Research (SBIR) grant** to develop ApoStream as a point-of-care tool for use by doctors, hospitals, and clinical labs.

This is a challenging objective, because makers of such diagnostic devices need to prove to regulators and health care payers that the data they generate can make a difference in the choice of treatments or their outcomes. To do this, companies must usually conduct clinical trials. The lack of funds to carry out studies was a big factor in the decision by another company developing a circulating tumor cell diagnostic system, Waltham, MA-based On-Q-ity, to cease operations in April. Janssen Diagnostics (formerly named Veridex) has been collaborating with researchers at Massachusetts General Hospital on the **CTC-iChip**, an antibody-independent device to capture circulating tumor cells. The Janssen unit has not announced a timeline for its commercial development.

As for ApoCell, its new NCI grant will help pay for clinical studies. The company has a head start from the clinical trials it has already supported with the ApoStream technology for clients or research collaborators, Davis says. ApoCell will most likely put non-small cell lung cancer first on its list as a focus of studies to prove the clinical utility of the device, he says. The company has been working with researchers at the University of Texas M.D. Anderson Cancer Center to detect the mutations found in tumor biopsy samples from patients with non-small cell lung cancer, and compare them with mutations found in the circulating tumor cells of the same individuals. The research focused on various mutations of a cell surface protein called EGFR, or epidermal growth factor receptor, which is the target of a group of cancer drugs such as erlotinib (Tarceva).

Through studies like these, researchers can explore some interesting questions that could help physicians to better understand the development of an individual's disease over time, and possibly to direct the choice of drug treatments.

If the mutations found on the primary tumor are the same as those found on the circulating tumor cells, then a mere blood sample could be yield a diagnosis just as effectively as a tissue biopsy under some circumstances. It could suggest, for example, that the primary tumor would be vulnerable to a drug that blocks EGFR.

On the other hand, if the mutations on the primary tumor are different from those found on the circulating tumor cells, the circulating cells could provide a guide to the next course of treatment that will be needed. The circulating tumor cells may have evolved to resist the initial drugs given to control the primary tumor. But they may bear new mutations that would make them vulnerable to another drug, if one already exists to target those mutations.

The circulating tumor cells may also help researchers discover previously unknown cancer mutations that could be exploited as new targets for novel drugs.

"I think that's going to be a huge area of discovery and opportunity," Davis says.