Further Expansion Into Liquid Biopsy Space Eyed by Precision for Medicine With Recent Acquisition'

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NEW YORK (360Dx) – With its recent buy of ApoCell and its circulating tumor cell enrichment technology, Precision for Medicine aims to continue its expansion into the liquid biopsy market.

Precision acquired ApoCell, along with the Apostream circulating tumor cell enrichment instrument, which leverages dielectrophoretic field-flow fractionation to separate cells, in October, and it now plans to offer the system as a diagnostic device for oncologists in the clinical space.

According to Precision, the acquisition allows it to expand its suite of specialty laboratory and biomarker informatic services, which it said includes cell-based assays and immune monitoring technologies.

Precision Senior VP and former ApoCell CEO and President Darren Davis said the firm purchased Houston-based ApoCell because it had developed novel technology, including those based on immunohistochemistry and immunofluorescence imaging. While ApoStream strictly uses body fluid samples including blood, urine, and cerebral spinal fluid, ApoCell also offers tissue sample-based services.

Davis noted that ApoCell sought to expand its capabilities to a larger market and highlighted that the acquisition allows ApoCell to offer a "full suite of CRO and lab services on a global scale."

Before being acquired by Precision for Medicine, ApoCell had raised about $4 million in separate grants and contracts to build out its CTC detection platform.

Originally spun out as part of a collaboration between the University of Texas MD Anderson Cancer Center with the National Cancer Institute in 2004, ApoCell began developing the ApoStream technology in 2010 to detect levels of CTC cells in cancer patients. Since then, it has gone through three iterations as a working instrument, each time with design and hardware improvements.

Davis explained that ApoCell decided on prostate cancer as its initial condition because the firm was searching for cell types that expressed high levels of cytokeratin, an epithelial-based marker expressed in multiple cancers including prostate cancer as well as colorectal cancer and breast cancer.

Davis explained that the ApoStream technology works by evaluating the differences in cellular dielectric charge between normal cells and abnormal cells. Because cancer cells have a very distinct charge difference compared to normal cells, ApoCell's researchers developed a microfluidic chamber with alternating current to separate the two different types of cells.

According to Davis, ApoStream starts by preparing a whole-blood sample and pumping it into a microfluidic chamber. The system generates a small kilohertz charge using an electric field to separate the cancer cells from the normal cells. The cancer cells gravitate toward the bottom floor of the channel, while the leukocytes are repelled toward the center of the channel.

As the cancer cells migrate along the bottom of the chamber, they fall into a collection port. The normal leukocytes pass the cancer cell collection port and land in a second port, where researchers can characterize them via flow cytometry and other methods. Meanwhile, the cancer cell collection port aggregates the cancer cells in a tube, where researchers can process them downstream for protein expression via image analysis, sequencing, FISH, and other methods.

According to Davis, the ApoStream platform can isolate and detects rare cells from 8 milliliters of a blood sample in about 30 minutes.

Phase III pharmaceutical study

As part of an ongoing Phase III clinical study, Davis and his team at ApoCell and Precision have partnered with Tracon Pharmaceuticals to use ApoStream to evaluate the utility of different drugs for angiosarcoma. The group presented the initial results in a poster presented at the Connective Tissue Oncology Society in Rome in November.

The researchers began the study by drawing 8 milliliters of blood from 190 patients with angiosarcoma prior to either treatment with pazopanib, or pazopanib and TRC105. They then performed CTC enrichment using ApoStream. After six weeks of treatment, the researchers repeated the process and compared the results before and after therapy.

"We were looking for [cells with] the therapeutic target CD015/endoglin glycoprotein, [which is] expressed on the tumor cell's surface," Davis explained. "[By] [u]sing it as a liquid biopsy marker to monitor the patients … we can look for the number of cells that express CD105 and see how it's changing with drug treatment."

Davis noted that researchers counted CTCs that expressed endoglin using nuclear staining and immunofluorescence. In addition, the team has so far identified 51 patients, or about 63 percent of patients in the study, that have enrolled with enough time for researchers to process their samples before and after treatment.

The study authors considered a CTC increase or decrease to be significant if the change was at "least twofold and by at least 1 cell per milliliter" from the onset. In the same vein, researchers charted changes for cases of a CTC rise or drop "by at least tenfold and by at least 1 cell per milliliter from baseline" in order to measure the drugs' potential efficacy.

While the group does not have information regarding the clinical response profile, Davis highlighted that his team found patients with lower levels of angiosarcoma cells after the combined drug treatment. He therefore believes that for "this specific cell type, these patients would have better response profiles than patients with increased or no change."

He acknowledged that the study is ongoing and that the team will perform an interim analysis in Q1 2019 to select a path to pursue and how many additional patients the team will need to enroll. "If the interim analysis shows that over 50 percent of patients are responding, then [the researchers] wouldn't have to continue testing, and we could get the drug through the [US Food and Drug Administration] to get it to patients, which is the best hope for patient care," Davis explained.

After completing the study, Precision plans to continue using the ApoStream technology as a service offering for outside customers in its Houston laboratory. According to Davis, the

firm will also incorporate ApoStream in Phase I and Phase II trials done with pharmaceutical partners.

While the study applied the ApoCell instrument as a prognostic, Davis highlighted the instrument's ability to detect CTCs in patients as early as stage II cancers.

"We've made advances in the last five years showing that we can isolate different cancer cells from blood," Davis said. "There are hundreds of thousands of clone cancer cells, which we've learned [about] using the ApoStream technology and then performing downstream assays like NGS and FISH, which [are] good way[s] to look at chromatin alterations."

Since developing the dielectric tool, Davis noted that ApoCell has received several patents regarding the ApoStream technology, which have now become part of Precision's wider portfolio.

While Precision is currently using the ApoStream technology for research-use-only purposes, Davis noted that the firm is putting plans together to eventually pursue 510(k) approval from the FDA to establish the tool as a Class 1 medical device for noninvasive use.

"The claim is that we can use the technology to generate cancer material with a blood source," Davis explained. "Whatever you do with it after that, such as using FISH or DNA detection, sequencing, that would be an analytical endpoint that would need to be validated, as well."

After receiving approval, Precision will continue working with biopharmaceutical partners to further build the ApoStream technology as a companion diagnostic tool.

While Precision has not begun selling the instrument, Davis said that the firm determined that customers would pay between $1,000-$1,500 to capture CTCs and run sequencing panels for target oncogenes per liquid sample.

In addition to cancer diagnostics, Davis believes that researchers and clinicians could use the ApoStream technology to detect the presence of fetal cells, bacterial and viral disease, and sepsis. He also envisions its use in regenerative medicine and drug manufacturing, or "any field interested in targeted particle separation technology."

As Precision for Medicine pushes to commercialize the ApoStream technology, it will enter a bustling field of companies with their own cell-sorting platforms for CTC collection and detection. Groups like Angle and Vortex Biosciences offer their own microfluidic systems to enrich cancer cells. Angle's Parsortix system examines cell size and compressibility using a disposable cassette to capture and harvest CTCs from blood.

"[The] Parsortix system is based on a combination of cell size and compressibility (not size alone), [as] circulating tumor cells are significantly larger and less compressible than blood cells," Angle CEO Andrew Noland explained in an email. As with the ApoStream technology, "the harvested cells are alive and can be analyzed with a wide range of downstream analysis techniques."

Similarly, Vortex Bio's VTX-1 platform uses a microfluidic chip to capture CTCs by applying "micro-scale vortices" based on a cell's physical properties.

While noting that systems like Parsortix uses effective characteristics of cancer cells, Davis argued that the system's dependence on size and compressibility limits the tool's ability to capture a "wide range of various types of CTCs."

In contrast, Davis believes that ApoStream's ability to use charge differences — caused by different cellular proteins, the cell membrane's rigidity, the DNA density, and chromatin-to-cytoplasmic ratio — can deliver a variety of CTCs often missed by other fluidic systems using limited cellular characteristics. He noted that his team has also performed research studies comparing the ApoStream technology to other size-, antibody-, and microfluidic-based technologies.

Davis believes that nothing exists "in the market currently to capture cells [and microparticles] based on the charge difference from a fluidic specimen." By profiling cells, he envisions researchers developing better drug-target therapeutics and diagnostic assays.

According to Davis, Precision is working with some of the largest biopharmaceutical companies and biotech firms in the space. In addition to Tracon, Davis noted the firm has also partnered with Rexahn Pharmaceuticals to use the ApoStream technology for undisclosed purposes. Between the pharmaceutical partners and the NCI, the team has developed around 20 instruments to examine circulating tumor cells in different cancer types.

Davis said that Precision will continue improving the CTC isolation technology through internal research and development efforts that include hardware, mechanical, and software use.

Since Precision is not an instrument company, Davis noted that the group is currently seeking diagnostic or commercialization partners to help translate the technology into a diagnostic instrument. While Precision has begun ongoing discussions with several firms, which Davis declined to disclose, he said they have not formalized any agreements at this time.