Creatv MicroTech Aims to Detect Patient Immune Cells for Cancer Drug Response Prediction

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NEW YORK – Liquid biopsy firm Creatv MicroTech is developing a diagnostic platform that measures the amount and size of specific circulating stromal cells called cancer-associated macrophage-like cells (CAMLs) to identify traces of cancer in a patient's bloodstream.

The Potomac, Maryland-based company initially plans to commercialize the method, called LifeTracDx, to predict immunotherapy response in stage II to III non-small cell lung cancer (NSCLC) cancer patients.

CAMLs are phagocytotic myeloid cells that are part a patient's immunological response to active malignancies such as cancer and can engulf cells containing cancer proteins and DNA.

Founded in 2000 by President and CEO Cha-Mei Tang, Creatv initially began developing diagnostic assays for a variety of diseases, including environmental detection of Escherichia coli and Alzheimer's disease. Creatv also built microfabrication devices, such as terahertz waveguides.

Starting in 2010, the firm started developing precision microfilters using photolithography, branded as "CellSieve," to capture circulating tumor cells (CTCs) in a patient's bloodstream. However, the team noticed that CellSieve also collected additional cell types besides CTCs.

As part of a collaboration with oncologists at the University of Maryland, Creatv began distinguishing the different types of cells captured on the CellSieve microfilters in blood samples from an initial cohort of breast cancer patients.

"We began identifying very large and polynucleated cells in CellSieve," Tang said. "It took us a while, but we found that these cells were macrophages, and that they had not been studied by anyone in the CTC field."

Tang's team saw that in cancer patients with aggressive tumors about 10 percent of the macrophage cells were in the process of engulfing tumor cells. Creatv therefore began developing a method to detect the CAMLs, believing they could be a sensitive and specific blood-based biomarker for patients with solid cancers.

To begin the LifeTracDx process, Creatv collects about 7.5-ml sample of a patient's blood and performs a prefixation step in one of its CellSieve tubes. The firm filtrates the sample through its CellSieve microfilter, followed by a series of fixation and permeabilization steps on the captured cells.

Creatv then stains the cells on the filter with antibodies using a fluorescent dye to identify specific cell-based markers (CD45 and CD14). After mounting the filter on a glass slide, a technician then examines the cells under a microscope to distinguish CAMLs from apoptotic CTCs and measures their size.

While the sample processing time requires a little under two hours, Tang said that the time required for actual CAML detection depends on the number of visible cells that the technician needs to measure. However, she pointed out that CAMLs can be easily spotted because of their size and can help determine the patient's prognosis.

"If you have a CAML that is larger than 50 microns, the patient is not doing well and will [likely] have a shorter progression and shorter overall survival," Tang said. She highlighted that the firm has so far successfully spotted CAMLs in 21 distinct cancer types.

Massimo Cristofanilli, a medical professor in the medicine and surgical oncology department at Northwestern University Feinberg School of Medicine, noted that CAMLs had been linked to tumor progression before immunotherapy existed as a method for treating cancer.

"[Researchers have focused] on circulating tumor DNA and the cancer [tumor], but we've not thought about other cells that correspond to what we've seen in the tumor microenvironment," Cristofanilli noted.

Along with Tang, Cristofanilli and his colleagues successfully isolated and identified CAMLs as potential biomarkers of solid tumors in different stages in a study published in 2014. While Cristofanilli's team partnered with Creatv in the study, he said that he does not have any financial ties to the firm.

Initially looking into the prognostic value of the new cells, Cristofanilli's team speculated that the detection of CAMLs could inform about the presence of cancer — before CTC detection — by indicating the activation of innate immunity. Detecting CAMLs in late-stage cancer would mean that a patient's innate immunity is preparing or responding to the presence and development of tumors.

ASCO studies

At the virtual 2020 American Society of Clinical Oncology meeting last month, Creatv demonstrated LifeTracDx's ability to identify CAMLs in several cancer types.

Using the firm's CellSieve microfilters to isolate CAMLS from whole blood, Tang and her colleaguescollected blood samples from 308 stage I to IV cancer patients, 76 healthy controls, as well as non-malignant categories such as benign breast masses, liver cirrhosis, and lupus. Cancer types included lung, pancreatic, prostate, esophageal, renal cell carcinoma, hepatocellular, neuroblastoma, and melanoma.

The researchers identified CAMLs in 79 percent of stage I, 89 percent of stage II, 88 percent of stage III, and 95 percent of stage IV cancers. They also found CAMLs in 21 percent of benign samples while failing to find any of the cells in the healthy controls.

Overall, Tang's team saw that LifeTracDx had a clinical sensitivity of 87 percent and specificity of 100 percent for the entire cancer patient cohort.

In a second ASCO poster, Creatv demonstrated the results of a two-year, single-blind study using LifeTracDx on lung cancer patients undergoing immunotherapy.

In a cohort of 104 stage II/III or locally recurrent disease NSCLC patients, Tang's team collected blood samples at baseline, directly after conformal radiation therapy, and after a round of anti-PLD-1 or anti-PD-1 therapy including durvalumab (AstraZeneca's Imfinzi) and pembrolizumab (Merck's Keytruda). The team then measured CAML size at each timepoint to evaluate progression-free survival and overall survival.

Overall, the researchers identified CAMLs in 87 percent of samples, with CAML size serving as an early predictor of progression-free and overall survival, independent of other variables.

Clinical potential

Because of the ASCO studies' results, Tang argued that LifeTracDx could be used for a broad spectrum of cancer-based diagnostic applications, including immunotherapy, prognosis, purified tumor DNA for sequencing, minimal residual disease, and early detection of cancer recurrence.

In addition to academic collaborations, Creatv has received an undisclosed amount of funding from the US Department of Defense (DoD) and the National Institutes of Health for a series of cancer-based studies using the LifeTracDx platform.

In the first trial, Creatv is working with the DoD to detect CAMLs in blood samples from 1,000 lung cancer patients with indeterminate nodules undergoing low dosecomputed tomography screening. The firm believes LifeTracDx may help narrow down the number of patients that actually have lung cancer and avoid costly tissue biopsies.

In the second trial, Creatv is working with the NIH to screen for breast cancer in 1,000 patients following a mammogram. Tang highlighted that her team had initially performed a double-blind trial with 41 patients that yielded promising results and spurred the larger study on using the technology to minimize the need for invasive biopsies. Creatv has also teamed up with the NIH in a separate trial to analyze blood samples from 250 prostate cancer patients over time to determine if they had progressed from nonaggressive to aggressive cancer.

In addition to the government trials, Creatv is implementing LifeTracDx in more than 20 clinical trials — from basic research to drug development — with biopharmaceutical firm such as BriaCell, where it is aiding in development of cancer vaccines. Creatv has also partnered with CytoDyn in two clinical trials using the firm's drug that targets the CCR5 cancer gene.

Technical limitations

Tang acknowledged that one of LifeTracDx's major issues is that the overall process, from sample collection to analyzing slides, is manual and requires a longer time than she would like to produce diagnostic results.

"If we want this process to be used to look at thousands of cells, we need to automate [and] speed it up," Tang said. "We [also] need microscope imaging software to read the slide and report how many CAMLs are there."

Creatv has thus recently launched a $20 million funding round to expedite and automate the LifeTracDx workflow. The firm will also use the funding to apply for US Food and Drug Administration approval as part of its plan to commercialize LifeTracDx for predicting immunotherapy treatment response for stage III NSCLC patients.

Pointing out that no commercial precedent exists for LifeTracDx given its unique molecular biomarker, Tang said her team has hired Paraxel, a contract research organization, to help prepare its plans for FDA submission.

Tang noted that Creatv has currently filed three patents with the US Patent and Trademark Office and 11 international patents related to CellSieve microfilters and a "spectrum of diagnostics."

Creatv is also revamping its current lab in Monmouth Junction, New Jersey to qualify for CLIA approval and CAP accreditation. Once the firm achieves this, Tang envisions launching LifeTracDx as a clinical service out of the lab, where the team would receive lung cancer samples and provide diagnostic results to clinicians within a day of sample arrival. In addition, she highlighted that the updated lab would allow Creatv to participate in Phase III drug development trials.

"For the CLIA lab, we initially will focus on early detection of cancer recurrence and providing services to drug companies for FDA clinical trials," Tang said. "We will expand the type of test in the CLIA lab as we proceed."

Creatv expects to publish a paper within the next month that compares the detection of CAMLs, cell-free DNA, and tissue biopsy as markers for detecting cancer in 73 NSCLC stage I-IV patients using next-generation sequencing.

While pointing out that the assay does not test for a specific organ, Cristofanilli noted that the test's results could help guide a clinician to perform a CT scan or other imaging studies to analyze patients who are in an inoperative state. He argued that the test could be great for detecting early-stage pancreatic cancer, highlighting that cancer field lacks a blood-based test to diagnose the disease.

"It's definitely a new concept and a different biomarker than we're used to, so we, along with physicians and pathologists, need to think about cancer in a different way, especially since we're using immunotherapies in cancer," Cristofanilli said.