genomeweb

AiGene Aims to Remodel Clinical Trials With ctDNA Tech for On-Treatment Response Monitoring

Apr 14, 2023 | Molika Ashford

Premium

NEW YORK – Working quietly behind the scenes for the last few years, cancer detection firm AiGene recently published a preprint commentary describing the future it sees for its epigenetic ctDNA platform in changing the way clinical trials are performed for cancer immunotherapies and potentially other drugs.

The company's approach mirrors many others in the growing blood-based testing, or liquid biopsy, field, targeting epigenetic signatures in cell-free DNA that indicate the presence of tumor DNA fragments circulating in the blood.

But unlike current sequencing-based strategies, the company's technology exploits differences in the way methylated tumor DNA interacts with solvents compared to normal DNA, as well as changes in its binding affinity, to create electrochemical or colorimetric one-step assays for the detection of cancer.

Floyd Taub, the company's CEO, first learned about the technology, developed by investigators at the University of Queensland in Australia, in a 2018 publication in *Nature Communications*, which led to "great discussions, a visit to Australia, and a decision to start the company in 2019."

A former NIH pathologist, Taub has been a part of a variety of startups over the years, including proteomics cancer screening firm OTraces and nucleic acid-based cervical cancer screening pioneer Digene.

In the 2018 paper, the Australian innovators of AiGene's platform describe their investigation of a consequence of cancer-induced genome-wide epigenetic reprogramming that they said had been overlooked to date: that the key physicochemical properties of purified genomic DNA are fundamentally different between normal and epigenetically reprogrammed cancer genomes.

Specifically, the group found that genomic DNA derived from normal cells shows greater tendency toward aggregation in aqueous solutions than genomic DNA derived from cancer cells. These different solvation properties in turn significantly influence normal and cancer-derived DNA's affinity toward bare metal surfaces, such as gold.

Most of the study was devoted to exhaustively characterizing these affinity differences in terms of overall methylation level and patterning across the genome. The authors concluded that in addition to solvation properties, binding is indeed modulated by different affinity of methylcytosines and cytosines, and by their clustered or dispersed patterning across the genome.

Developing a label-free, naked-eye electrochemical prototype, the team tested their method on a cohort of over 200 human samples (from cell lines, tissue, and plasma) representing various cancer

types.

Initially, in tissue samples, the platform was able to distinguish cancer from controls with high positive and negative predictive value. When the team applied it to cell-free DNA from blood samples, accuracy remained high with a PPV of 91 percent and a NPV of about 70 percent.

In a poster shared at the 2022 American Association for Cancer Research annual meeting, AiGene and collaborators at the University of Colorado added new data describing a revised and optimized binding methodology, which they said more than doubled the rate of cfDNA binding.

According to the authors, cancer samples not distinguishable from normal with their previous method now showed statistically significant detection. There was also a "dramatically increased ability to separate cancer from normal DNA."

The investigators were also able to show that changes in binding reflect a correlation between the electrode response and patients' cancer burden, illustrating that the technology could be used not just to detect cancer at a single timepoint but also to track its growth or recession.

The AACR work featured just a handful of patient samples, but Taub said the company is working on expanding to larger and larger studies. The first is a set of about 24 samples that will be analyzed in a "blinded, pseudo-prospective manner."

Beyond that, AiGene is collaborating with other institutions on prospective collection, though he declined to name these partners. Finally, the firm has IRB approval to directly collect specimens and anticipates recruiting about 100 patients for its studies this year. "As the test is so easy, we are open to additional collaborations," Taub added.

Taub said that the company's vision at this point is not to compete with companies applying epigenetic distinguishers to early cancer detection or screening, but rather as an on-treatment biomarker test, which could serve as a tool for improving precision oncology clinical trials.

In the company's recent preprint, authored by Taub and University of Colorado professor Dexiang Gao, Taub makes the case for what he sees as a prime target for AiGene's technology — enabling what the two dub the SMARTer clinical trial design (Sequential Multiple Assignment Randomized Trial to Enhance Registration), which they estimate could reduce required study sizes by 80 percent by allowing early therapy switching.

Unlike a traditional companion diagnostic, in this scenario AiGene assays would serve as an "optimizing diagnostic" that determines early during treatment if a patient should remain on the novel regimen being trialed or be switched to standard of care.

Based on modeling, Taub and Gao reported that this could allow approval of drugs that would not be able to cut it in a standard head-to-head trial.

Using immunotherapy as an example, the two argued that while traditional trials can show superiority or inferiority of an immunotherapy compared to standard of care, they do not address the "critical medical question of whether a patient's path should begin with IO to deliver the best long-term outcome."

"In some situations, IO may have a greater chance of curing, but [standard of care] may, on average, create as many or more responses, creating a dilemma for patients, physicians, and third-party payors. The modeling of SMARTer design presented herein, shows that even when IO has no greater benefit than SOC, if it is used first and patients transferred to SOC based on [an optimizing test], the total benefit may be better," the authors wrote.

Taub said that although this is an untested strategy it isn't unprecedented. Just as pretreatment biomarkers drive sequencing of drugs in trials and in clinical practice, so would an "optimizing test."

If shown in the trial to be necessary for the drug's success, such a test could be codified into the therapy's label the same way a companion diagnostic currently is.

AiGene isn't alone in hypothesizing about on-treatment monitoring value for ctDNA-based tools.

Established clinical assays like Natera's Signatera have been shown to be able to monitor response and predict immunotherapy outcomes when applied in an on-treatment setting.

Authors from Stanford and Memorial Sloan Kettering also published a study in 2020 that showed that adding an early on-treatment measurement of circulating tumor DNA improved prediction over a multimodal pretreatment testing strategy used on its own.

They proposed a similar trial strategy in which all patients might be treated with immunotherapy upfront for one cycle with subsequent cycles personalized based on on-treatment testing. But, they wrote that establishing such a paradigm would be a "sizable undertaking."

Taub said AiGene has "soft-circled" enough funds to support the studies it has planned for this year. But, "to set up CLIA service, larger validation trials, and marketing, we will seek strategic investment from partners and/or venture funding."

One of the advantages highlighted by the platform's Australian inventors is that AiGene's direct detection approach doesn't require the extensive sample preparation of sequencing-based approaches for epigenetic DNA profiling.

Taub said that the firm is hoping that the associated cost savings, and the additional cost savings implied by the company's recent SMARTer trial modeling exploration, may draw the eye of pharma collaborators.

Filed Under Liquid Biopsy | Cancer | Molecular Diagnostics | circulating tumor DNA | methylation | epigenetics | Immunotherapy | Companion Diagnostics | North America | University of Queensland | Editor's Pick