TwinStrand Biosciences Explores Error Reduction Sequencing Tech in Various Applications

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NEW YORK – TwinStrand Biosciences has been validating its error-reducing duplex sequencing technology in multiple collaborations while exploring new applications and a potential new financing round to support its growth.

Following a $16 million Series A financing round a year ago, the Seattle-based University of Washington spinout launched its first commercial kits for research use last February, for minimal residual disease detection in acute myeloid leukemia and identifying carcinogens through genetic toxicology assays.

In November, the company also non-exclusively licensed its technology to Roche's Foundation Medicine, which has since incorporated the duplex sequencing technology into its tumor profiling assays.

The firm has grown to more than 40 employees and expects to double in size by the end of this year, according to Jesse Salk, TwinStrand's cofounder, CEO, and CSO. "The amount of demand we've been seeing is going up exponentially, and it's outstripping our infrastructure," he said, adding that he is in early discussions with investors about a "substantially larger" financing round than the previous one to fuel the firm's growth.

TwinStrand's technology, which is compatible with any Illumina platform, enables highly accurate sequencing. It does so by analyzing both strands of a DNA molecule independently and comparing their sequences to eliminate errors. By reducing this background noise, it allows researchers to detect extremely rare mutations.

Since the commercial launch of its technology last year, the firm has been working on validating it in various research studies in partnership with academic groups and pharmaceutical companies, Salk said, and is in the midst of branching out into new application areas.

In cancer, the company started with AML because "there is a lot of drug development and targeted therapy in that space," said Salk, who is a practicing oncologist. He noted that the technology could also be applied to other types of cancer, and that it "can get sensitivities multiple orders of magnitude higher than other technologies out there."

For AML MRD detection, the firm uses two approaches: a predefined 29-gene panel with targets that are frequently mutated in AML patients, and a patient-specific assay that is more complex but also more sensitive. For the latter, it first sequences a patient's cancer genome and then designs a custom assay that covers a select number of mutations. "We don't expect this is going to be standard of care immediately, but we're confident that over the next one to two years, this will become routine, and we can do it better than anybody else," Salk said.

He acknowledged that several other companies have taken a similar approach to MRD testing – for example, Natera also sequences a patient's tumor first and then designs a customized assay for its Signatera test – but he said that these firms have significantly lower sequencing accuracy, so they cannot get to the same level of sensitivity for mutation detection.

However, the firm has yet to show that its technology helps improve outcomes. "Like with everything, the proof is in the pudding, and it's always really important not just to have a powerful, analytical, well-performing technology, but the value is in connecting it with clinical outcomes," Salk said. "Those studies are harder but absolutely essential and that's a big part of what we're doing now."

Last month at the American Society of Hematology virtual meeting, the firm presented results from a collaboration with researchers at the Fred Hutchinson Cancer Research Center and the University of California, San Francisco, on MRD detection in pediatric AML. Using patient-specific hybrid capture panels that targeted between 53 and 200 variants per patient, they demonstrated "the significantly higher sensitivity we can achieve by interrogating many sites," Salk said.

TwinStrand has also been working on a pilot study with researchers at the National Institutes of Health, Southwest Oncology Group (SWOG), and Fred Hutchinson that involves about 100 AML patients, he said, and plans to participate in prospective clinical trials with two unnamed pharmaceutical companies that will include "hundreds to thousands" of AML patients, recruited over several years.

In addition to detecting minimal residual disease, the company has been able to gather data on clonal heterogeneity in response to therapy. "In some patients, it's very uniform, in other patients, it's very heterogeneous," Salk said. "Different parts of the clonal subsets of leukemia seem to respond differently to therapy, and we suspect this will have predictive or prognostic value, which we're investigating in a follow-up dataset."

In another collaboration, with researchers at Penn State University, TwinStrand researchers have shown that they can detect cancer drug resistance mutations "months in advance," he said.

Jerry Radich, a medical oncologist at the Fred Hutchinson Cancer Research Center and a professor at UW, has been collaborating with TwinStrand for several years on sensitive mutation detection in AML. More recently, he has been working with the firm to compare its technology with conventional ways for residual disease detection in leukemia, in particular flow cytometry. As part of an upcoming project to develop new techniques for MRD detection, spearheaded by the Foundation for the National Institutes of Health (FNIH) and funded by several pharmaceutical companies, he also hopes to compare TwinStrand's approach to other technologies.

The main advantage of duplex sequencing is that it is several orders of magnitude more sensitive than other technologies, he said, though it is unclear how much sensitivity is actually needed.

Radich, who is a member of TwinStrand's scientific advisory board, said he sees MRD detection as the most promising application for the company's technology. "The limitation with all of the sequencing platforms is just speed," he said, though they keep getting faster and the speed of the assay is "not terribly important" for MRD testing.

He also likes the company's general approach. "They're not just a technical company," he said. "They are doing a lot of really basic science, which I think is an advantage in the long run."

In the genotoxicity area, TwinStrand has been collaborating for a while with researchers at Millipore Sigma/BioReliance's Toxicology Testing Services, and published a paper with that group and Amgen investigators in the *Proceedings of the National Academy of Sciences* last month. The study demonstrated the ability of duplex sequencing to detect mutations induced by three carcinogens in mice, looking at five types of tissues.

Genotoxicity testing is "something that no other sequencing company has approached as a market," Salk said, and sequencing could help streamline such testing significantly. "At the current time, it takes multiple years to go through the safety testing for mutagenesis and carcinogenesis, and our initial data suggested that that could be accelerated to weeks, potentially," he said. This year, TwinStrand expects to see additional labs offer sequencing-based genotoxicity testing as a service, he added.

Besides animal testing, duplex sequencing could be used to detect exposure to environmental mutagens in humans, which he said has not been possible before.

TwinStrand is also looking into novel applications of duplex sequencing, specifically in cell and gene therapy to look for off-target effects of gene editing and to track therapeutic cells – such as CAR-T cells – inside the body. The plan is to launch kits for these applications later this year.

"The challenge with CAR-T cells, for example, is that the number of cells that are infused is relatively low and the abundance of them after infusion … is quite low and drops quickly as the cells go off to work fighting cancer as they're supposed to," Salk explained. "And being able to detect on the order of one in a million [cells] is essential for having the resolution to understand where these cells are going, and how they behave, over a timeline of months."

Besides developing new applications for its technology, TwinStrand also plans to license it to others for certain uses, like it did with Foundation Medicine. "That particular application area of broad general oncology [testing] is something that we are not ourselves pursuing as a diagnostic service, that's Foundation's business," he said. "We anticipate continuing to work with Foundation and others, to expand the relationship to other fields that we are not commercializing directly ourselves."