UC Santa Cruz Spinout ClaretBio Pursues NGS Sample Prep Market With Focus on cfDNA, FFPE

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NEW YORK – Claret Bioscience is seeking to improve sample preparation for next-generation sequencing and cell-free DNA analysis.

Recently, the firm won a $224,396 Small Business Innovation Research award from the National Human Genome Research Institute to develop a method for combined DNA and RNA sequencing from the same sample.

The award is the third for the spinout from Richard Green's lab at the University of California, Santa Cruz. The firm also won two other SBIR grants, worth about $250,000 each, from the National Cancer Institute to develop a single-stranded library preparation protocol for cell-free DNA and to study degradation of cell-free DNA.

ClaretBio's product line currently consists of Srsly, pronounced "seriously," a single-stranded approach to DNA library prep, and Xactly, a method for analyzing DNA overhangs, including their length and sequence. The firm is also in the process of launching its ForShear kit, an enzymatic DNA shearing method that the firm claims works well in samples with degraded DNA, such as formalin-fixed, paraffin-embedded samples.

"Single-stranded" for Srsly is a bit of a misnomer, as it's not just for single-stranded DNA, according to CEO and Cofounder Kelly Harkins, a former postdoc at UCSC. "In fact, it's a single-stranded approach" that also works with double-stranded DNA, she said.

The Srsly kit already has a fan in Jordan Cheng, a graduate student at the University of California, Los Angeles, who used it to verify a method to purify ultra-short, single-stranded, cell-free DNA from plasma samples.

By now, he has run it approximately 200 times, he said. "When you do it enough times, it becomes very straightforward. It's easy to use, and I like how there's a one-hour break in the beginning." Total library prep time is about three to four hours, depending on the sample, and the second part of the protocol can even be done hours later. "Having the option to continue the next day and know it is stable is a relief and a good attribute to have in the kit," Cheng said.

ClaretBio's origins lie in analyzing ancient DNA. Harkins was working in the human paleogenomics lab at UCSC, looking at pathogen DNA in archeological remains. A grant fortuitously required her to reach out to another department, leading her to collaborate with Green. "We started looking at cell-free DNA," she said, "with a theory that if a DNA fragment was damaged at the terminus, it would preclude that molecule from getting integrated into a [sequencing] library." To solve this, they came up with a way to sequence molecules that had end damage, which evolved into Xactly.

Harkins and Green formed ClaretBio in 2016, with seed funding from Edenroc Sciences, an investment firm that has also funded another sample prep spinout from Green's lab, Dovetail Genomics, now called Cantata Bio. The firm has grown to 11 employees and is hiring more. It has also acquired licenses to IP from UC Santa Cruz, including patents for the tech behind Xactly and pending patents for Srsly's tech.

Xactly analyzes whether a DNA fragment has a 5' or 3' single-stranded overhang, how long it is, and what its sequence is. Whether there is clinical utility in that information remains to be seen. "We have lots of hints there are signals in the overhangs," Harkins said, but the firm needs a collaboration to "really go after that question."

For now, ClaretBio's major focus is its Srsly library prep kit. "We provide the best data for the worst samples," Harkins said. "The truth is, it's a prep that works well for all sample types, but it really shines with highly degraded samples."

Srsly's approach can retain single-stranded as well as nicked DNA. "Our value-add is, we capture all these fragment types," said Varsha Rao, ClaretBio's director of clinical affairs and strategic partnerships. The method takes denatured DNA fragments and ligates custom Illumina (for now) adapters, with clean-up and index-PCR steps following.

Srsly can also be used to do RNA-seq library preparation. "You don't have to do any additional second-strand synthesis or DNA tailing, you get directional libraries right away," Rao said. Another application customers have used it for is quality control of synthetic oligos, identifying how many truncated fragments might be in a delivered sample.

In terms of ClaretBio's business, "we have seen year-over-year growth even through the pandemic," Harkins said, but she declined to disclose revenues for specific products or overall revenues. ClaretBio sells to "between 50 and 500" customers, she added.

In addition to cfDNA and ancient DNA, the firm is targeting sequencing DNA from formalin-fixed, paraffin-embedded samples with ForShear.

But the main application customers are using Srsly for is cell-free DNA sequencing, Rao said. While there are other methods for preparing sequencing libraries of longer pieces of cfDNA, there's not much competition in single-stranded fragments. Swift Biosciences, now part of Danaher subsidiary IDT, makes a commercially available single-stranded DNA library prep kit, but otherwise, the option is limited to lab-developed methods.

Cheng, who works in David Wong's lab at UCLA, is looking to analyze cfDNA fragments in plasma and other biofluids for their clinical relevance. "We just hope that it allows you to differentiate between different stages of cancer," he said. The kit was crucial to the study, which was published earlier this month in iScience. "Half of it couldn't have been done without any single-stranded library prep kit," he said.

His lab didn't want to go with a homebrew method and wanted to use unique molecular identifiers (UMIs), something Srsly could do and that Swift's kit had not yet been validated to do. ClaretBio's kit "just worked, so we didn't even compare them," Cheng said.

One struggle was that collaborators outside the US didn't have access to the ClaretBio kit. But he said the company was responsive to their needs and would even send additional reagents if the lab didn't get enough reactions out of the kits because they pipetted too much.

The company's product names and other marketing also appealed to him. "It's very millennial," Cheng said. "It resonates with the people going into the sciences now."

Grad students like Cheng could be the PIs of the future in the burgeoning field of "fragmentomics," as Harkins called it, referring to the study of *in vivo* processes that cause DNA to degrade. "That's a field that sees the benefits of this single-stranded approach," she said.

Sequencing these fragments could provide information on cell of origin, the manner of cell death, or on genome organization — especially when DNA pieces are stuck to other molecules, such as histones.

"All those features are a reflection of fragmentation," Harkins said. "It adds a new layer of data to the stock-standard sequence variant analysis."

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