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SciLifeLab, Broad Institute Researchers Go High Definition With Spatial Transcriptomics

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NEW YORK – A team led by researchers at the Broad Institute and the Science for Life Laboratory in Sweden has refined a method providing both gene expression and positional information in tissues, achieving sub-cellular resolution.

The so-called "high-definition spatial transcriptomics" (HDST) method offers two data types simultaneously. By placing an RNA capture array on top of a pathology slide, it records gene expression and where in the tissue it occurs, which can be analyzed together. Initially developed by researchers at SciLifeLab using microarray slides, the updated method uses Illumina's barcoded bead array technology instead.

A study describing the method, which also involved Illumina's senior VP and CTO Mostafa Ronaghi, was published earlier this week in *Nature Methods*.

The high-def version increases resolution by up to two orders of magnitude, achieving a resolution of 2 microns — a millionth of a meter and less than the size of an average human cell — up from 100 micron resolution with microarrays.

"Increased resolution is indeed a driving force in the field of spatial transcriptomics," Joakim Lundeberg, the study's senior author and a professor at SciLifeLab, said in an email. "The study showed for the first time that one can reach sub-cellular resolution."

But there's a tradeoff with sensitivity, Lundeberg said. John McPherson, deputy director of the University of California Davis Comprehensive Cancer Center who has worked with NanoString on GeoMx, its spatial profiling technology, agreed. "The data are a little sparse," he said, which may be due to the capacity of the beads used. "This is a good screening tool to see what you might be interested in looking at. If you want to look quantitatively at cell microenvironments, you'll want to go to a more targeted approach."

These aspects matter as researchers in academia and at genomics tools companies try to improve upon a raft of spatial genomics methods that have come out in the last few years.

"Digital spatial profiling is going to be really important," said McPherson, who was not involved with the study. "This will go into the bucket of methods and some will adopt it because it looks quite easy to use" and appears to be less expensive than some of the other options.

Lundeberg and his team first described a spatial transcriptomics method in 2015. Other techniques have since joined the hot field. Researchers at the Broad Institute, for example, described a method called Slide-seq, which also uses tissue slides and Illumina bead technology. Seattle-based NanoString Technologies has developed GeoMx, a method that can tag proteins as well as RNAs with barcodes *in situ*.

Soon, these will be joined by another offshoot of the original spatial transcriptomics method: 10x Genomics' Visium Spatial Gene Expression Solution. This product will be based on technology the

Pleasanton, California-based single-cell analysis firm obtained when it acquired Spatial Transcriptomics, a company founded by Lundeberg and several other SciLifeLab researchers.

But HDST will differ from both Visium and Slide-seq, Lundeberg said. "The basic principles are the same for Visium and HDST — a barcoded surface onto which you place tissue sections to capture messenger RNA. The difference is the way you make the barcoded surface — Visium uses a glass surface and HDST uses small beads to place the barcoded probes onto," he said. The barcodes are dispersed randomly across the tissue and their positions are decoded using software, which was also provided by Illumina. Visium will provide 55 micron resolution, Lundeberg added.

10x Genomics did not immediately respond to request for comment.

Compared to HDST, Slide-seq, which uses a similar type of barcoded beads, although made by ChemGenes, not Illumina, "provides 25× lower resolution than HDST and has a higher rate of measurements confounded by signals from multiple cells," the authors wrote said, adding that it also "does not include histology".

"We're excited that spatial transcriptomics technologies are garnering so much interest right now," Fei Chen, a fellow at the Broad Institute who helped develop Slide-seq, said in an email. " He added that Slide-seq's resolution "hits the sweet spot of cellular features within tissues without compromising on capture efficiency."

HDST's increased resolution comes with a cost, namely lower sensitivity in terms of measuring gene expression. In their paper, the researchers wrote that only roughly half the expression profiles generated by HDST were "confidently assigned to a single cell type." This kind of cell segmentation "needs additional work," Lundeberg said.

"This sort of sensitivity will be enough that you'll be able to identify cell types, likely, but won't get quantification if you want to look at signaling pathways," McPherson explained.

The method has also only been tested on frozen samples, and not formalin-fixed, paraffin-embedded (FFPE) ones. McPherson said he believes these methods will eventually be used in the clinic, which would require that they be validated using FFPE samples. "All diagnostic samples go into formalin," he said. "It's what's available now and what's going to be available in the future."

Whether or not HDST will be commercialized is unclear. Lundeberg said the work was begun before the 10x Genomics acquisition. Several of the authors have either obtained or applied for patents related to the technology described in the new paper. "HDST is part of the patent 'family'" acquired by 10x, Lundeberg said, and the original patents covered "a multitude of different barcoded surfaces." But he added that he has "no knowledge of how the patent portfolio is managed." What effect the use of Illumina's beads would have on the commercialization path is also unclear.

For what it's worth, Lundeberg said 10x's Visium reagents "actually appear to substantially increase the sensitivity." This indicates there's still room for improvement, he said, "which is very exciting given the wide implications of coupling histology directly to transcriptome measurements *in situ*."

"The next step for any high-resolution array is to increase sensitivity, to capture more of the transcriptome" Lundeberg said. "Now we need to crank [it] up."

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