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Spatial Genomics Field Sees Growing Interest

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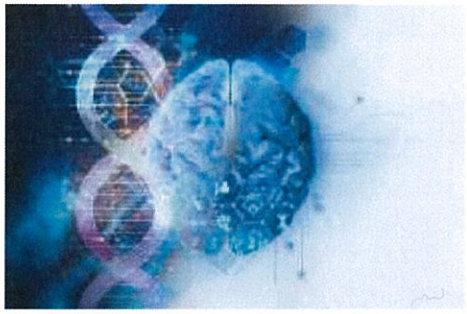

SAN FRANCISCO (GenomeWeb) – Over the past month, a number of research groups have described technologies for analyzing gene expression within a spatial context, highlighting a growing interest in the nascent field of spatial genomics.

Last month, for example, research groups from the California Institute of Technology and the Broad Institute described new spatial gene expression methods in publications in *Nature Letters* and *Science*, respectively, while a team led by the New York Genome Center described how a technology previously developed by the Science for Life Laboratory in Sweden could be used to identify where in the brain genes are being expressed during the progression of amyotrophic lateral sclerosis (ALS).

The Caltech team's technology involves combining advances in fluorescent *in situ* hybridization with microscopy, while the Broad Institute's approach harnesses the barcoded bead strategy used in Drop-seq to encode spatial information with barcodes.

These studies add to a growing list of companies entering the spatial genomics space, including NanoString Technologies and 10x Genomics, as well as startups such as BioSpyder and Cartana. NanoString launched its Digital Spatial Biology platform GeoMx last month, while 10x is developing a product based on technology it acquired from Swedish startup Spatial Transcriptomics.

"It's extremely exciting times," said Joakim Lundeberg, a professor at the Science for Life Laboratory in Sweden and a visiting professor of bioengineering at Stanford University. He was part of the team that described the use of the Spatial Transcriptomics technology to map gene expression during the progression of amyotrophic lateral sclerosis in a publication in *Science*.

Lundeberg said that his group's paper demonstrates the value of the spatial technologies. "ALS is a terrible disease and understanding spatial context really helps," he said. For example, whether an astrocyte is

involved in the disease is dependent on where in the tissue it is located. "Being able to see where the astrocytes are makes the science so much richer," he said.

Lundeberg added that the *Nature Letters* and *Science* papers by the Caltech and Broad Institute groups "represent the evolution of spatial technologies."

There has been a "revolution in the last couple of years for single-cell technologies," said Fei Chen, a senior author of the *Science* study and fellow at the Broad Institute. "But those cells are dissociated from the tissue context." The next logical step is to try and figure out where those cells are in the tissue.

The Broad Institute's method, called Slide-seq, makes use of the same barcoded beads that are used in the Drop-seq method, said Evan Macosko, a principal investigator at the Broad and one of the developers of Drop-seq.

The researchers then pack these DNA-barcoded beads onto a rubber-coated glass coverslip, which they call a puck.

Chen said they then digitize the pucks, or bead arrays, using an old SOLiD sequencing system, a sequencing-by-ligation platform that is no longer being sold but was marketed by Life Technologies before it was acquired by Thermo Fisher Scientific. Chen said that the team had previously reverse-engineered the system to work with the lab's microscope for *in situ* sequencing technologies developed by George Church's lab, adding that , the method is not dependent on the SOLiD technology.

Next, they placed a tissue section over the puck, where mRNA from the tissue would be released and captured by the beads for sequencing.

Because the slide had first been imaged and digitized, the location of the beads was known, which enabled the researchers to get the spatial information for the mRNA molecules.

In the *Science* study, they first tested the technique on a mouse brain tissue section, demonstrating that it was consistent with known locations of specific cell types.

Chen said that the team plans to continue to develop the method and will explore options for making it available to the broader scientific community.

The researchers have applied for a patent on the method and Macosko said they are looking at a few options for commercializing it, including licensing the technology to companies with expertise in array manufacturing.

Macosko said the technology would have a number of applications, including in oncology to better understand tumor structure and heterogeneity. Another interesting application would be in genomic pathology to "relate gene expression to specific lesions or regions that are important for a specific pathology," he said, for instance, to study amyloid plaques and their relationship to Alzheimer's disease at the genomic level.

"There's recognition that these spatial relationships are key for so many tissue types," Macosko said. "And I think we'll see a lot of exciting innovations."

Long Cai, professor of biology and biological engineering at Caltech and senior author of the *Nature Letters* study, agreed that "there is now a lot of interest in the industry."

Cai said that the spatial technology developed in his lab built on his group's previous work to use microscopy to look at RNA directly in cells. In 2014, the group described a technique known as sequential

fluorescence *in situ* hybridization in *Nature Methods* where the researchers used hybridization to target transcripts with FISH probes labeled with a fluorophore.

In the recent study, Cai's team scaled up the method to be able to image mRNAs from 10,000 genes in single cells by expanding the four-color fluorophore method described in the 2014 paper to 60 so-called pseudocolors, which were created from different combinations of three fluorophores.

Next, they divided up the analysis to target just 500 genes at a time in one image, rather than trying to include all 10,000 genes in one image, which was too crowded and made it hard to distinguish each gene.

As part of the method, primary probes are first hybridized to each gene in the cells, followed by four rounds of barcoding. In each pseudocolor hybridization round, only about 500 genes are labeled, so that the image is not too dense. At the end, the images are "stitched together to generate a super-resolved image," Cai explained.

The researchers have filed for a patent on the pseudcolor encoding method, but Cai declined to discuss any potential plans for commercialization.

"It's a fantastic research tool to dissect the intracellular architecture," Lundeberg said of the seqFISH+ method.

The seqFISH+ technology would also be complementary to technologies like the Broad's Slide-seq or the Spatial Transcriptomics technology, since they could be used for different purposes and may appeal to different types of users. The Caltech seqFISH+ method requires the use of microscopy and working with large images, so would likely be more appealing to pathologists or cell biologists who have more expertise working with those tools. In addition, Lundeberg said, the method is not really a discovery tool. "You're using a set of probes to investigate the corresponding genes," he said, "so you need to know what you're looking for."

On the other hand, Lundeberg said, the Slide-seq technology is based on capturing mRNA at the poly-A tail and then "sequencing to deconvolute that information," and similar to the Spatial Transcriptomics technology, could be used for discovery.

Lundeberg said the growing interest in the field coincides with the growth of single-cell sequencing. "It's a logical evolution," he said, from bulk sequencing to sequencing at single-cell resolution to wanting spatial resolution for that single-cell data. "People now have vast amounts of single-cell sequencing data and are realizing that we don't have a clue where it's coming from," he said. "So now it's time to get those single-cell clusters into a spatial context."

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