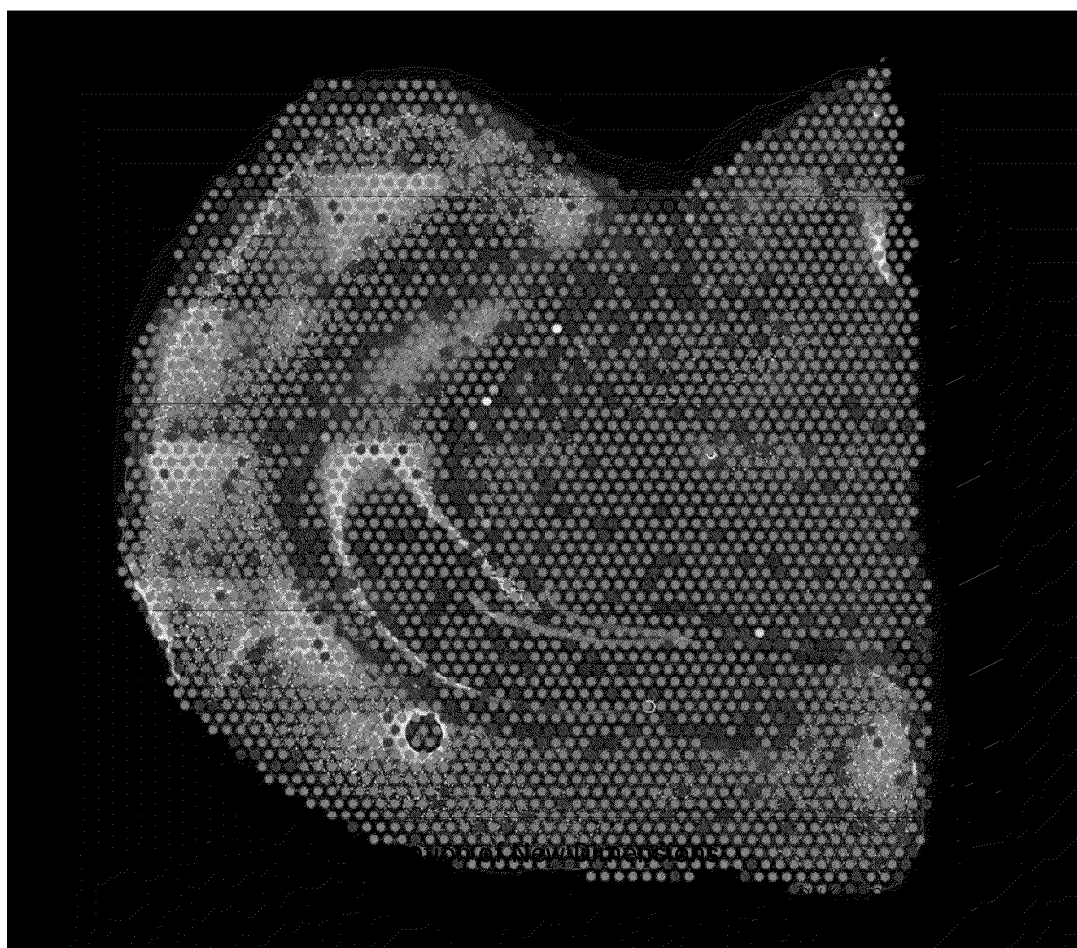




(https://www.genengnews.com/wp-content/uploads/2020/03/GenomeMap-AGBT_10xGenomics-scaled-e1585670045996.jpg)

At Left. Combining whole transcriptome analysis with morphological context, spatial transcriptomics allows researchers to uncover the “where” for every “what,” according to 10X Genomics. Here, a section of mouse brain, visualized using the company’s spatial transcriptomics platform, the Visium Gene Expression Solution, shows immunofluorescence staining of glial cells (GFAP: magenta). Overlaid spots represent GFAP mRNA selected from whole transcriptome data from the Visium Solution. [10x Genomics]

A casual observer might have failed to see past the merriment—the sun and sand, the food and drink, the singing and dancing. But make no mistake, despite occurring in a resort atmosphere, the most recent Advances in Genome Biology and Technology (AGBT) meeting was mostly business.

The meeting, which took place last February in Marco Island, FL, marked a significant anniversary (officially the 20th, but technically the 21st). The robust conference program featured presentations by the pioneers of genomics, luminaries such as Richard Wilson, PhD, Francis Collins, MD, PhD, Barbara Wold, PhD, Leroy Hood, MD, PhD, George Church, PhD, Rick Myers, PhD, and Marco Marra, PhD, while showcasing the current work of up-and-coming researchers.



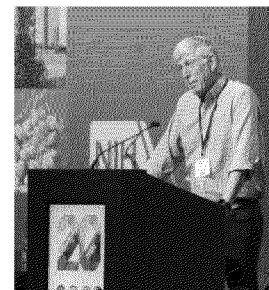
Barbara Wold, PhD, professor at the California Institute of Technology and a pioneer in the field of genomics, has led many development efforts, including the one that produced the large-scale chromatin immunoprecipitation assay known as ChIPSeq. [AGBT]

The sharing of insights was lively and intense. One of the genomics pioneers, Wold, emphasized another kind of sharing, the sharing of data. A culture of data sharing, she insisted, represents a hard-won achievement, and it contributes, she continued, to genomic science as much as inspiration, grit, and funding.

Focusing largely on technology, AGBT meetings have often served as the place to introduce big developments. For example, over the years, AGBT meetings have highlighted the launches of next-generation sequencing stars such as Complete Genomics, Pacific Biosciences, Ion Torrent, and Oxford Nanopore. This year's meeting did not disappoint. From the much anticipated "\$100 genome" to the launch of multiple spatial transcriptomics platforms, conversation from the pools to the beach cabanas was buzzing with news

of a field that shows no signs of slowing down.

The AGBT meeting, then, was mainly about the work of genomic science's movers and shakers, notwithstanding the spectacle, one evening, of scientists moving and shaking to an oceanfront performance of "Love Shack" by the B-52s. Given the venue, the song's refrain, the "bang bang bang on the door," seemed less about the urge to party, and more about the determination to propel genomic science forward.



Francis S. Collins, MD, PhD, director of the National Institutes of Health, is a physician-geneticist noted for his landmark discoveries of disease genes and his leadership of the international Human Genome Project. At the annual Advances in Genome Biology and Technology meeting, his plenary session included this quote: "Two decades of breathtaking progress in genomics—but the best is yet to come." [AGBT]

Exploring the transcriptome-space continuum

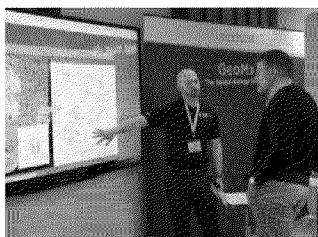
At this year's AGBT meeting, the biggest stir was caused by spatial transcriptomics, a technique to visualize gene expression in the context of a tissue. The technique allows researchers to perform transcriptomics while retaining the positional information for the cells. That is, the cells are allowed to occupy intact tissue sections instead of being obliged to contribute to homogenized biopsies.

Spatial transcriptomics is "at the nexus of pathology, molecular biology, computational biology, cell biology, and genomics" noted Alex Swarbrick, PhD, principal research fellow at the Garvan Institute in Sydney, Australia. He told *GEN* that spatial transcriptomics could be used to answer broad research questions as well as "directed" translational questions. Regardless of the application, Swarbrick asserted, spatial transcriptomics could almost always "bring a unique perspective."

Last year, 10x Genomics took a deep dive into this field when it acquired Spatial Transcriptomics, a Swedish company that developed the technology that supports 10x Genomics' spatial transcriptomics platform, the Visium Spatial Gene Expression Solution. Two other spatial transcriptomics platforms were announced at the AGBT meeting. The first, from NanoString, is the GeoMX digital spatial profiler, and the second, from Readcoor, is the RC2 multi-omic spatial solution.

The launch of 10x Genomics' Chromium, about four years ago, expanded the utility of single-cell genomics by moving the technology into the hands of researchers. The company is looking to the Visium to do the same with spatial transcriptomics. Visium is basically a slide and reagent kit that is

readily adoptable within existing lab infrastructure.



Kit Fuhrman, PhD, the GeoMx Digital Spatial Profiler product manager at Nanostring, delivers a presentation at the company's suite at the annual meeting of Advances in Genome Biology and Technology. Here, he explains the nuts and bolts of the GeoMX platform. From dawn to dusk, the Nanostring team answered scientists' questions and explained how researchers are currently using the platform in their research. [AGBT]

By contrast, Nanostring's GeoMX is big, robust, and powerful—and expensive (roughly \$300k). It provides an incredibly dense and complex array of information with an easy-to-use interface.

Both protein and RNA expression can be obtained on slides that present fresh tissue or formalin-fixed, paraffin-embedded (FFPE) tissue. The researcher can evaluate two distinct areas, for example, comparing the tissue of a tumor with the stroma or microenvironment surrounding it. Alternatively, the researcher can pinpoint an area, enclosing just a few cells within a circle.

The antibodies that bind the tissue have photo-cleavable oligonucleotide tags (or barcodes) that are attached by a UV light-sensitive linker. When the UV light hits the sample, the tags released from the bound antibodies, and the oligos are moved onto a microtiter plate where they can be analyzed by sequencing. The barcode design with sequencing readout “will open up the imagination of every

scientist,” assert Brad Gray, president and CEO of Nanostring.

Readcoor was founded by Richard Terry, who is now the company's CEO and CTO. Previously, he had spent several years in George Church's lab at Harvard Medical School. Then he developed Readcoor's technology while working at the Wyss Institute.

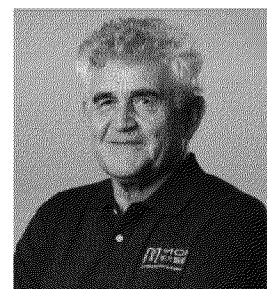
Although Readcoor's launch was signposted all over the conference center, information about the company's RC2 platform was hard to find. Terry told *GEN* that Readcoor is “different than other companies” and has “a new approach.” The RC2 is powered by proprietary FISSEQ (fluorescent in situ sequencing) technology, but other details have yet to be revealed. However, the company has divulged that the RC2 has been designed to provide higher resolution than other spatial transcriptomics platforms—down to a single cell.

The proliferation of platforms, which is bound to continue, suggests that spatial transcriptomics has arrived. Spatial analysis of tissue is “already revealing new biology across many research disciplines like cancer biology, neuroscience, and infectious disease,” notes Gray. He adds that in the next 5 to 10 years, we will be able to create visual constructs of how cells are organized in organs, and that these constructs will provide new insights into how organs function and respond to stimuli.

Chasing the \$100 Genome

At the AGBT conference, the last presentation—a coveted speaking slot—promised to be a blockbuster. Its title: “First \$100 genome sequencing enabled by new extreme throughput DNBSAQ platform.” Its speaker: Radoje (Rade) Drmanac, PhD, CSO of MGI (a subsidiary of China's genomics powerhouse BGI) and a co-founder of Complete Genomics.

Drmanac presented details of two MGI products: the DNBSAQ Tx sequencing platform and the CoolMPS sequencing chemistry. He also announced that MGI's sequencing platforms will be made available in the



United States for the first time in April 2020.

*Radoje (Rade) Drmanac, PhD,
CSO of MGI*

The DNBSeg Tx can boast of several improvements over its predecessors. These improvements, Drmanac asserts are “not about going from bad to good.” Rather they are “about going from excellent to extremely excellent.” MGI reports on average one error in 170 kilobases of sequenced DNA. According to Drmanac, users are usually happy with about one error in one thousand.

With a surface that is five times larger and a doubling of the number of spots that can capture DNA, the DNBSeg Tx can sequence up to 700 genomes on a single run—a capacity that is an order of magnitude larger than any sequencer on the market today. Also notable is the new fluidics system designed to handle the big arrays in the DNBSeg Tx. Rather than a flow cell, where the solutions wash over the samples, a robot dips a large panel through a series of solutions, conserving reagents and cutting cost.

CoolMPS (MPS stands for massively parallel sequencing) is the first nucleobase-specific antibody-based sequencing chemistry. Drmanac told *GEN* that MGI wanted to avoid the DNA “scars” that can accumulate with traditional sequencing methods that use dye-labeled reversibly terminated nucleotides (RTs) and affect the accuracy of subsequent reads.

“MGI has taken a really out-of-the-box approach to drive the per genome cost down for a large project—eliminating fluidics and instead dipping huge slides in reagents” noted Keith Robison, PhD, a leading genomics blogger and authority on next-generation sequencing platforms. The new platform, he says, is “unlikely to influence the pattern of sequencer design,” but it’s “a clever way to minimize the waste of expensive reagents.”

“It’s not unthinkable that a \$10 genome may be a useful genome,” Drmanac suggested. There is “no theoretical limitation.” He ended his talk on an optimistic note: “At future AGBTs, we’ll hopefully present even crazier innovations and breakthroughs.”

Searching for rare variants is becoming more common

“Launching at AGBT is a big deal for us because this is where the technical leaders in the field come,” noted Jesse Salk, MD, PhD, CEO of TwinStrand Biosciences. “We want to put our nickel down [physician-speak for ‘stand our ground’] and say that our product is ready to go and ready to be widely used.”



Jesse Salk, MD, PhD, CEO of TwinStrand Biosciences, presented duplex sequencing technology data to attendees of the annual meeting of Advances in Genome Biology and Technology. The information generated—mutation frequencies, simple mutation spectra, and trinucleotide mutation spectra—can be used together to detect,

TwinStrand has developed duplex sequencing technology to improve sequencing accuracy, making it possible to find low-frequency variants at a level of detection that has not been achievable before. At AGBT, Salk spoke about two of the primary applications where their product could be useful, the first of which is cancer—more specifically, the detection of minimal residual disease in acute myeloid leukemia (AML) patients. The hope is to be able to assess how well treatment works or if cancer remains after treatment. This information could spare patients additional, unnecessary treatments and allow drug companies to run smaller, safer, faster clinical trials.

quantify, and characterize induced DNA mutagenesis. [AGBT]

Why did the company start in this area? Salk, who maintains a part-time position as an oncologist at a University of Washington–affiliated VA hospital, explained to *GEN*, “This is the area where I live.” He added that he wants to focus on something that would bring an immediate benefit by addressing this particular unmet need, which is one that he sees on a daily basis. He said, “It’s not just nice, it’s necessary.”

Besides cancer applications, TwinStrand’s duplex sequencing could be used in almost any application where detection of rare variants is useful. The technology, Salk suggested, could detect the impact of environmental factors on DNA mutagenesis and recognize patterns of mutations that result from smoking, aflatoxin, aristolochic acid, urethane, etc. This work could be important in areas of research such as forensics, NASA’s studies on cosmic radiation, or CRISPR-mediated effects of off-target mutagenesis.

Salk noted that interest has been expressed for applications that he would never have known were important to people. He said that “every few weeks, something new comes up,” and that he has a hard time not getting distracted because there are so many new, cool things the company could do.

PacBio embraces being single

Last year at AGBT, Jonas Korlach, PhD, the CSO of Pacific Biosciences (PacBio) could not speak about much of anything. At that time, PacBio was stuck in the middle of a prolonged process (beginning in November 2018) of merging with Illumina. But, with the deal abandoned earlier this year, *GEN* asked Korlach, “What is next for PacBio?”

Korlach’s answer had a strong, singular message: PacBio is firing on all cylinders. Its HiFi sequencing technology—which offers reads that are long and accurate—is better than ever.

“We feel really good about where we are going,” declared Korlach. “A year ago, it wasn’t clear what the future would be.” Korlach explained that people stayed on the task at hand—to launch the Sequel II—which turned out to be PacBio’s most successful launch ever. Now the gurus of long-read sequencing have a place to stand and can turn toward the future.

When asked about the continuous lowering cost of sequencing, Korlach told *GEN* that “there are limitations to the cheap genomes.” A cheap genome, he asserted, isn’t really a genome. It’s an “SNP table” or a series of reads that is mapped to the reference genome. Those are useful, he conceded, but he insisted that when it comes to wanting a high-quality human reference assembly, long stretches are important. This is where he sees PacBio’s HiFi continuous long reads playing a key part. They are not as long as those some other long-read technologies can produce, notably nanopore sequencing, but they are more accurate. “To do good functional biology,” Korlach concluded, “you need a good genome.”

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Got it!