Spatial Transcriptomics, a Stockholm-based startup. Their technique predates Slide-seq but employs a common principle, in which users overlay the tissue under investigation onto a slide arrayed with barcoded RNA-capture probes. The RNA transcripts are captured from the specimen, sequenced, and assigned to a location on the slide based on their associated barcode. “It’s an unbiased platform that will give you full coverage of the polyadenylated transcriptome,” says Mikkelsen. He notes that the platform slots easily into histopathology workflows, as it can profile any fresh-frozen tissue specimen within a week using only a slide preparation kit and an Illumina sequencer. However, the current version of the platform is also limited in spatial resolution, with array features spanning 100 micrometers—considerably larger than most cells.

ReadCoor has developed a different sequencing-based approach, which delivers expression mapping at subcellular resolution. This method also works with formalin-fixed, paraffin-embedded tissue samples—a mainstay of the pathology world that is currently incompatible with Slide-seq or 10x’s platform.

ReadCoor’s fluorescence in situ sequencing (FISSEQ) technology—first developed in the Harvard lab of George Church—enables direct molecular analysis within the sample itself, but with the advantages of sequencing-based analysis. “It gives us the ability to lock molecules in place in their native three-dimensional tissue environment and then read those molecules out with next-gen sequencing reads,” says Richard Terry, the company’s chief technology officer and cofounder. ReadCoor has already developed a first-generation platform for core facilities, which researchers at Harvard’s Wyss Institute for Biologically Inspired Engineering are using to perform functional connectomic mapping of the mouse brain in a collaboration funded by the US Intelligence Advanced Research Projects Agency. A benchtop system is also in the works. “We have not publicly released a sale date, but we are looking at beta sites now,” says Terry.

For users who want to detect large numbers of unique transcripts but not always at single-cell or subcellular resolution, there is the GeoMx instrument, launched commercially in April by Seattle-based NanoString. It first labels slides using hybridization with oligonucleotide probes coupled to unique barcodes via a photocleavable linker. These linkers are cleaved at specific sites in the tissue with light targeted by an array of controllable micro-mirrors within the instrument, and the released barcodes are then harvested from each region of interest with a

microfluidic system for further analysis. “You can adjust these micro-mirrors from a region spanning one-tenth of a cell up to a region with hundreds of thousands of cells,” says Joseph Beechem, senior vice president of R&D. These barcodes can either be quantified with the company’s nCounter platform, for experiments targeting a hundred or so unique RNAs, or subjected to high-throughput sequencing for whole-transcriptome analysis. In a presentation at AGBT, the company demonstrated 1,600-plex gene expression profiling in formalin-fixed, paraffin-embedded tumor specimens.

Although it can visualize gene expression within individual cells, GeoMx cannot deliver such resolution across an entire tissue sample. However, pathologists or researchers working in the translational space can still resolve many important questions at the multicellular level. “If I put a tumor slice in the microscope, the mirrors can automatically reconfigure to look at just the tumor or just the tumor microenvironment,” says Beechem. CEO Brad Gray notes that many early-access users have been particularly interested in analyzing tumor samples at the multicellular level for biomarker studies in immuno-oncology. Their workshop at AGBT featured talks from clinicians Peter Nelson of the Fred Hutchinson Cancer Research Center, Seattle, and John McPherson of the UC Davis Comprehensive Cancer Center, Davis, California, highlighting the platforms ability to spatially resolve RNA and protein biomarkers in prostate cancer and melanoma, respectively.

Itzkovitz believes these technologies could transform our understanding of disease. “Many pathologies have a spatial axis to them—think about microbes attacking the gut, or cancer,” he says. “If we can spatially map the different functions of these different cell types, then we’ll be able to understand the vulnerabilities of these tissues much better.” Even richer insights should be possible by layering data from more ‘omes’, and many of these platforms might be adapted to other targets. For example, GeoMx is already compatible with tagged antibodies as well as oligonucleotides, to allow protein and RNA expression analysis in parallel. ReadCoor, meanwhile, aims to extend the FISSEQ principle to detect virtually any biomolecule. “We’re working on proving out our ability to look at DNA, RNA, proteins and therapeutic molecules in situ, all with a single readout based on next-gen sequencing reads,” says Terry. □

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China’s bispecific bet

Nanjing, China-based pharma NJCTTQ will pay up to \$4 billion as part of a deal to boost its R&D in antibody therapies for oncology. Abpro, located in Woburn, Massachusetts, will receive \$60 million up front and up to \$4 billion in milestones and royalties to generate dual-targeting T-cell engager antibodies using its antibody engineering platform. NJCTTQ (Nanjing Chiatai Tianqing) is an R&D center for parent company Chiatai Tianqing. The deal is one of the largest US–China immuno-oncology tie-ups to date. NJCTTQ will take advantage Abpro’s DiversImmune platform, which uses novel immunization methods (using purified proteins, engineered cells, virus-like particles and DNA) and co-stimulation strategies to generate antibodies with custom-targeted antigens. These antibodies can then be engineered into bivalent, trivalent or tetravalent bispecific formats using Abpro’s MultiMab platform. Bispecific antibodies promote T-cell engagement by binding simultaneously to tumor-specific antigen on a cancer cell and to an antigen (usually CD3) on a cytotoxic T cell. This engagement causes the T cell to kill the tumor cell. Tumor cell targets in the deal were not disclosed. A small number of bispecific antibodies are already in clinical trials in China, including Blnceyto (blinatumomab, Amgen), which received US FDA accelerated approval in 2018. Chinese companies are investing heavily in US biotech (*Nat. Biotechnol.* **36**, 8–9, 2018) to gain access to cutting-edge science. This is fueled by China’s changing drug landscape, including major regulatory reforms and government-led initiatives to increase the number of home-grown biopharma products. Oncology is a particular focus of China’s biotech buzz, as the country needs new treatments for its many patients with advanced or metastatic tumors.

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“[The Human Genome Project] is like sending a man to the moon. When you think about it, sending a man to the moon is easy—it’s getting him back that’s difficult. So I think we now need to get the human genome to return to work.”
Sydney Brenner, 2000. Brenner died on 5 April 2019. (@Kevin Davies, Twitter, 6 March 2019)