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‘Milestone’ research method measures gene activity across whole mice

New way to analyze frozen tissue slices could reveal bodywide effects of drugs, diseases

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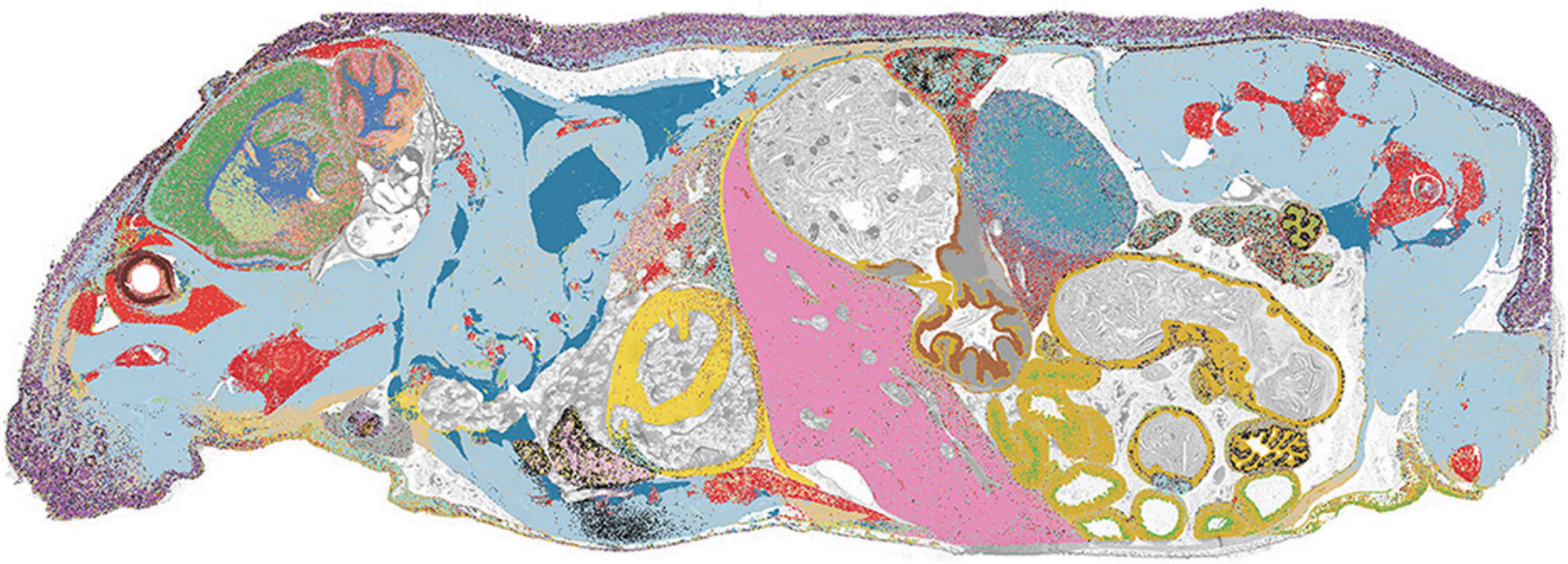


An image created using the new technique shows the cross-section of a whole mouse treated with bacterial toxin, colored by cell type. MARGARETTE CLEVENGER

Now, there may be a better way: a method that measures gene expression across an entire cross-section of an animal at once. The new approach—described today in *Cell*—combines a specialized machine that cuts superthin slices of a mouse's frozen body with molecular techniques to gauge the activity of thousands of genes at specific locations within each slice. The researchers behind the study say the method could offer unique insights into bodywide effects of drugs and diseases, perhaps one day leading to better treatments for people.

"It's a technical milestone," says Jeffrey Moffitt, a microbiologist at Boston Children's Hospital who develops gene activity measures and was not involved in the research. Although the method expands on existing techniques rather than inventing entirely new ones, its scale is unprecedented, he adds. "This is a very beautiful demonstration of a promise that has been floating in the field for a while."

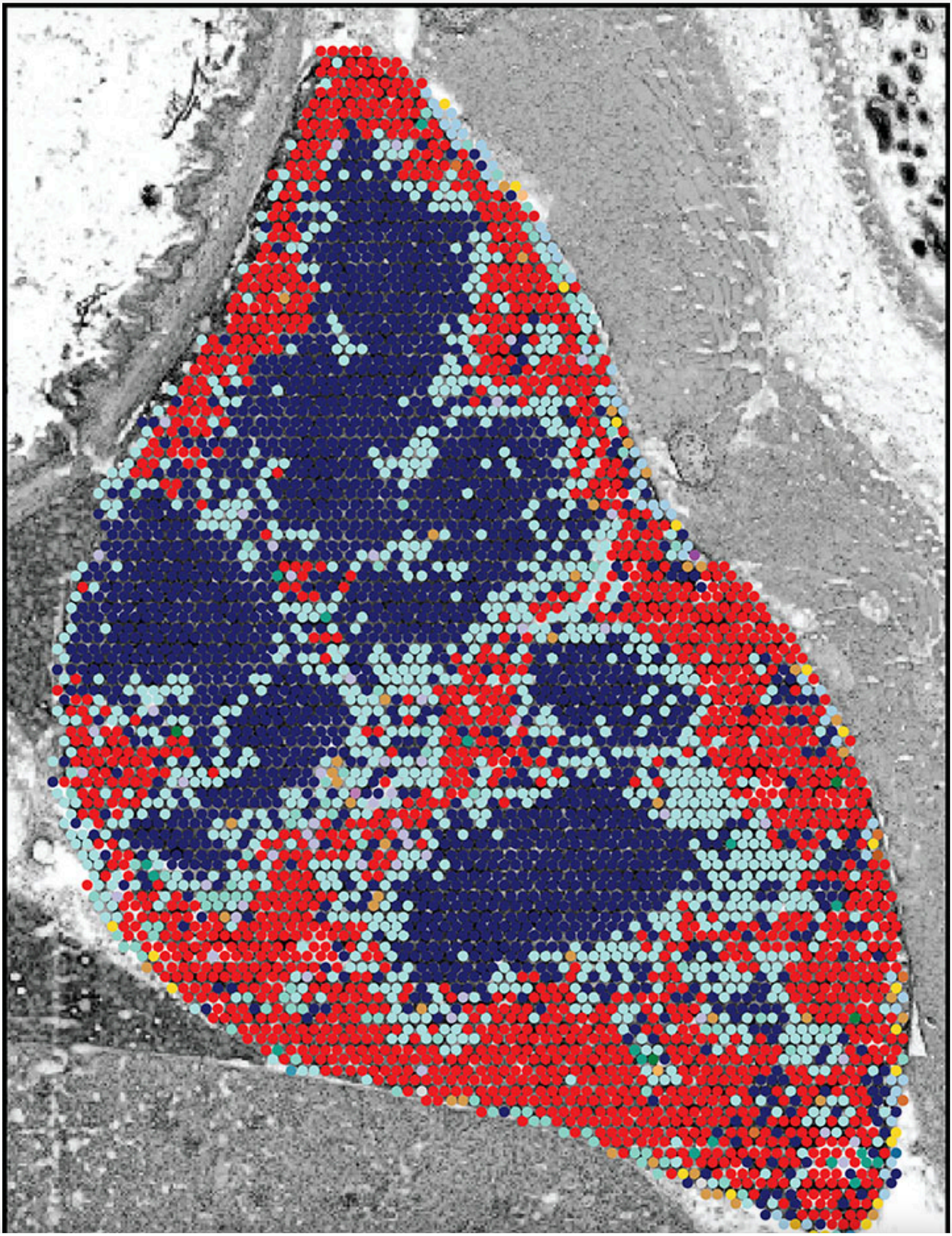
Over the past decade, researchers have developed various methods to measure the expression of multiple genes at specific locations in an organ or tissue. One, known as sequencing-based spatial transcriptomics, involves dotting a glass slide with tiny spots that contain fragments of nucleic acids called probes, each of which has a specific molecular tag based on its location on the slide. A thin piece of organic tissue—ideally just one cell thick—is laid on top of the slide. Protein-coding RNA molecules transcribed from active genes in the tissue stick to the probes below, effectively stamping each transcript with location information. When researchers remove and put these transcripts through a sequencing machine, they can use this stamp to deduce where each came from, and so determine gene expression at each location.

To adapt the approach for an entire lab mouse, University of Chicago biologist Nicolas Chevrier and colleagues used a special piece of slicing equipment, called a cryomacrotome, to cut sections of entire, frozen, 6-week-old mice. They also tweaked existing spatial transcriptomic techniques to work better for larger samples, and developed computational tools to help analyze the data.

For each 2-centimeter-by-6-centimeter whole-body cross section, the team relied on about 600,000 spots to cover some 5 million cells, Chevrier says. "It's a lot of information in one slice."

The researchers demonstrated the technique's potential by measuring bodywide changes in gene expression in response to an injected bacterial toxin that causes inflammation. More than 5000 genes across 37 tissue subregions and 16 organ types either increased or decreased their activity in the toxin-treated mice, they found.

The results are compelling, says Rong Fan, a biomedical engineer at Yale University who has co-founded companies that measure gene activity and was not involved with the work. They demonstrate "exactly what this platform uniquely enables—capturing coordinated, whole-body–wide responses across multiple organs and cell types in a single experiment."



Chevrier says the method could reveal how various organs respond to a particular medicine, and so aid development of new treatments. “What happens when you inject a drug that’s supposed to target the liver, but maybe does something elsewhere that we never measured before?” he says. “Now you can ask what happens across [the whole body].” The same could be done for any disease or genetic mutation, helping researchers understand the causes, and possible therapies, for particular conditions.

It’s a “smart” approach, says Detlev Arendt, an evolutionary biologist and zoologist who uses spatial transcriptomics at the European Molecular Biology Laboratory. The method seems effective at identifying specific cell types on the basis of RNA data, he notes. Extending the method to different species so gene activity can be compared could help groups like his study the evolution of tissues and organs, Arendt adds.

Like other sequencing-based approaches, the new approach can’t determine gene expression at the single-cell level, as each spot captures RNAs from a handful of cells at once.

And Moffitt, who co-founded a company that develops imaging-based spatial transcriptomics, adds that not all RNAs are captured by the spots, meaning the technique could miss some rare transcripts—potentially underestimating gene expression changes associated with a particular treatment.

Still, it’s an exciting demonstration of what can be achieved, Moffitt says. “I think we will see more and more papers that work at this type of scale—and then we’re going to have a ton of biological discovery that comes from that.”

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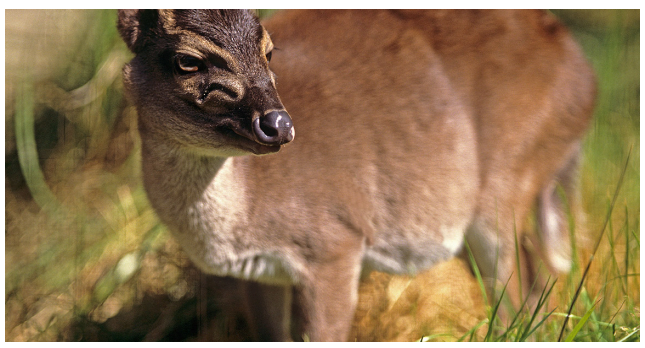

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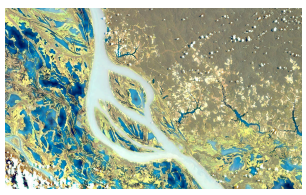

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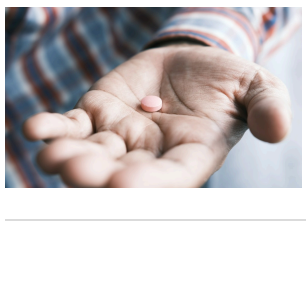

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