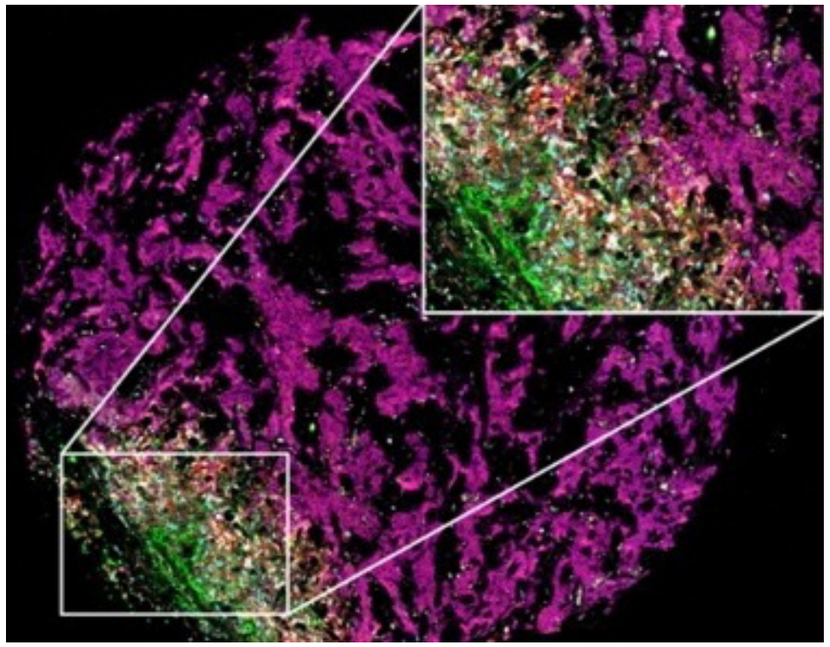
ADVERTISEMENT FEATURE

SPATIAL BIOLOGY BRINGS A NEW DIMENSION TO PRECISION MEDICINE

Understanding where cells are, who they interact with, and how they organize white tissues is uncovering disease at the systems level – opening new therapeutic possibilities.



Multiplex imaging reveals a spatially organised tumour microenvironment in Merkel-cell polyornavirus-associated cancer, shaping anti-tumour immunity. Credit: Garry Nolan

Scientists have an increasingly detailed lens on how cells organize and interact within their native tissue environment. This hidden architecture is revealing how cells work together to shape healthy tissue function, and how even subtle disruptions to this complex ecosystem can influence disease development, progression and response to treatment. Garry Nolan, professor of pathology at Stanford University School of Medicine, California, has spent his career at the forefront of this field, developing many of the tools used to uncover these functional networks, with the goal of translating spatial insight into a predictive framework for precision medicine.

What first drew you to spatial multiomics?

The work in my laboratory had long been focused on single-cell multiomics, such as proteins, phosphor-proteomics, and RNA. While profiling individual cells can generate incredibly rich datasets, it was not always clear how that information translated into what was happening in the tissue itself. When you looked at a tumour biopsy, for example, you could see immune cells beginning to organize into structured clusters resembling lymph nodes, now recognized as tertiary lymphoid structures. These spatial arrangements carry important clues about the tumour-immune interface, but little attention had been paid to how cells were interacting with each other within the tumour microenvironment. Those insights were sitting in biopsies, waiting to be discovered.

How is spatial multiomics shaping precision medicine?

Biopsies are a long-established standard across cancer, immunology, and inflammatory disease. The next step is moving from two-dimensional tissue sections to three-dimensional spatial analysis – and the early work in 3D multiomics is extraordinary and being investigated by many other labs now.
That shift will change how we think about the fundamental unit of biology. Rather than individual cells, the focus will move to transient assemblies — what I call metacells — where a biological function only exists because those cells are within a few cell-distances of one another. This is especially relevant with dynamic systems like the immune system and cancer. Once that can be captured mathematically, you can begin to model the system dynamically: remove a component, change a variable, ask how to destabilize a 'bad' stable state. That's where completely novel therapies will come from. Not from targeting a single enzyme or protein, but from understanding and intervening in the system as a whole.

Have any key moments in your lab driven spatial innovations?

In 2012, shortly after my laboratory had co-developed an advanced single-cell mass cytometry technique, a soon-to-be postdoc came running into my office and suggested we could adapt it to image tissue directly – and that led to a new method for mapping multiple proteins within intact tissue sections1. Later, another postdoc asked whether the same principle could be achieved using fluorescence alone, without the mass spectrometer. That idea evolved into a technique that allows researchers to visualize and map up to 60 or more proteins simultaneously within a tissue sample, while preserving the exact spatial location and context of each cell2.

These high-dimensional spatial imaging approaches generate vast datasets that demand entirely new computational approaches to interpret. About two years ago, a scientist in my lab began experimenting with large language models. It quickly became clear that these systems could help transform data into meaning — connecting experimental results with the vast body of knowledge already published in the scientific literature. My group has since developed AI agents that contextualize raw biological data, integrate insights from multiple disciplines and present results in intuitive, visual ways – all within minutes.

What are the biggest technical challenges facing spatial biology?

A key challenge is integrating RNA and protein measurements simultaneously at sufficient resolution. Proteins carry rich spatial information, often acting as molecular zip codes that reveal exactly where immune cells are located and who their neighbours are. RNA-based methods currently lack the resolution and dynamic range of protein-level readouts.

What makes this kind of research possible?

My work has always been highly multidisciplinary — bringing together chemists, mass spectrometry experts, computational scientists and immunologists. I see myself less as an immunologist than as someone who builds technologies for immunology.
I have always stolen my inventions from the future, by which I mean science fiction. It opens your mind to possibilities that conventional thinking has not yet entertained. Once you can picture what could be, you can begin to reverse engineer it: find the right experts, put them in a room together, get them excited about the idea, and then let the collaboration take over.

How do you hope this field will impact patients?

Cancer is an existential moment. If you have ever had it, you know. You wake up, and everything is ordinary, until you remember. I've lived that moment many times personally, as I carry a mutation that predisposes me to several cancers. I've also lost friends to the disease. That is what drives this work — making cancer something people never have to think about.

REFERENCES

1. Keren, L. et al. MIBI-TOF: A multiplexed imaging platform relates cellular phenotypes and tissue structure. Sci. Adv. https://doi.org/10.1126/sciadv.aax5851 (2019).

2. Black, S. et al. CODEX multiplexed tissue imaging with DNA-conjugated antibodies. Nature Protoc. 16, 3802-3835 (2021).