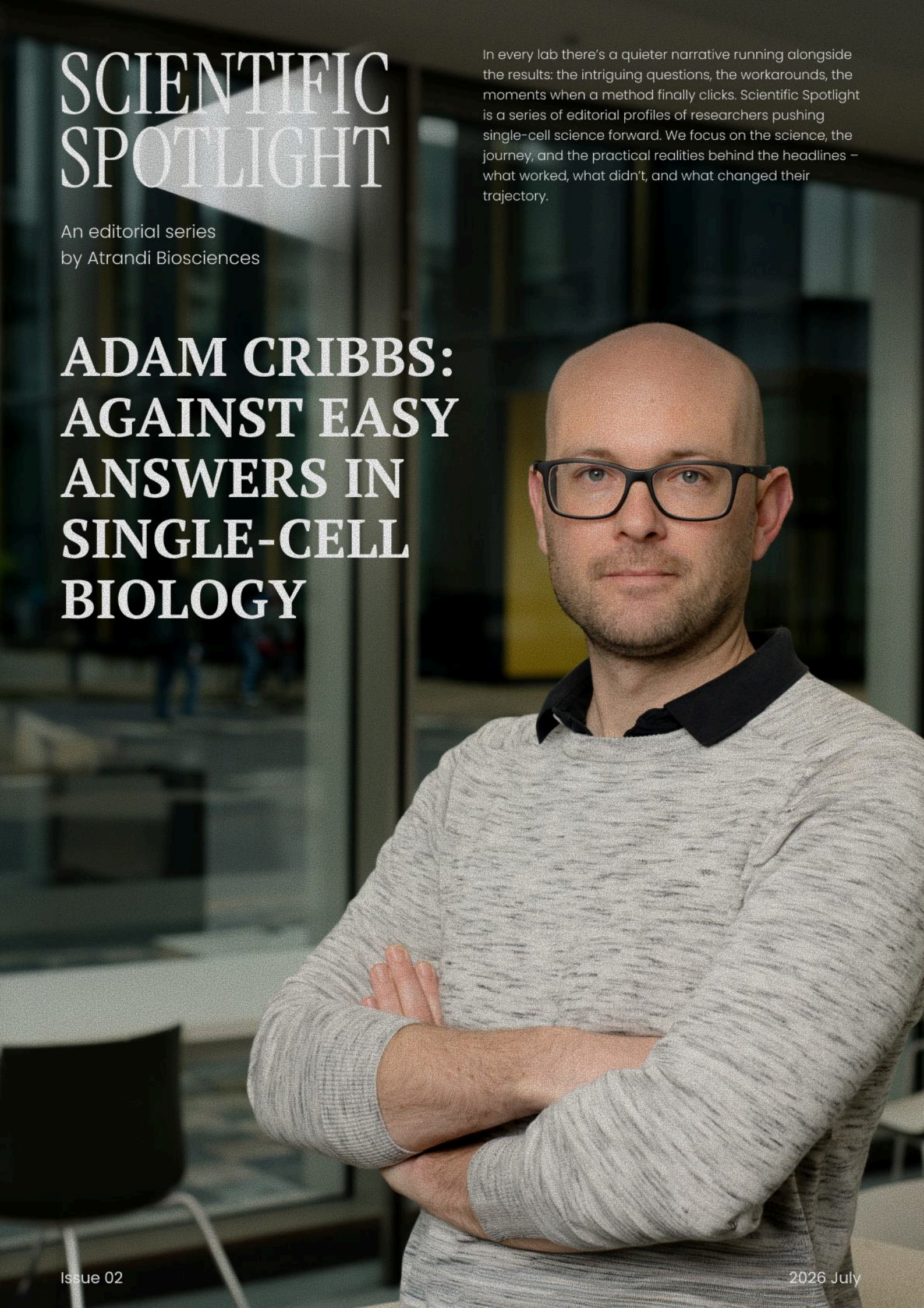
SCIENTIFIC SPOTLIGHT

An editorial series
by Atrandi Biosciences

In every lab there's a quieter narrative running alongside the results: the intriguing questions, the workarounds, the moments when a method finally clicks. Scientific Spotlight is a series of editorial profiles of researchers pushing single-cell science forward. We focus on the science, the journey, and the practical realities behind the headlines – what worked, what didn't, and what changed their trajectory.

ADAM CRIBBS: AGAINST EASY ANSWERS IN SINGLE-CELL BIOLOGY



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THE SCIENTIST WHO WORKS ON THINGS THAT ANNOY HIM: ADAM CRIBBS ON COMPLEXITY, HARD TISSUES, AND WHY BIOLOGY NEVER BEHAVES

Few institutions have a longer history of sitting with hard questions than the University of Oxford. Across its colleges and research institutes, it has produced more Nobel laureates than most countries, and a long tradition of scientists who chose the problem over the path of least resistance. Adam Cribbs, Associate Professor of Computational Genomics and group leader at the Botnar Research Centre, fits that tradition quite perfectly, though he might describe it rather more plainly. "I only work on things that really annoy me," he says laughing. "Things that I think need to be solved."

In practice, that means spending over a decade working on some of the most technically demanding and scientifically underexplored corners of single-cell genomics – hard and complex tissues that don't yield easily to standard methods, long-read sequencing applied at single-cell resolution before the technology was ready, and musculoskeletal diseases that the field, as Adam puts it, simply hasn't funded enough. It also means building a group that deliberately sits at the intersection of wet lab, computational biology, and machine learning, because, in his view, that intersection is where science actually moves.

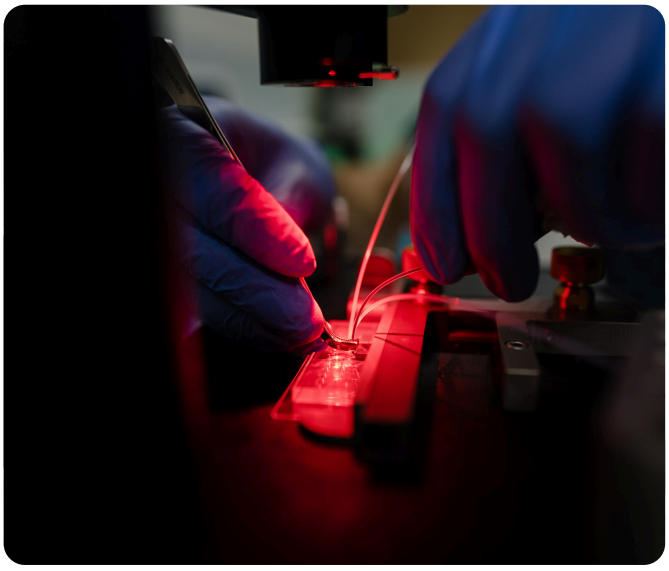
STARTING FROM CURIOSITY

Adam's scientific formation was quantitative before it was biological. He came to his PhD in molecular immunology at the Kennedy Institute of Rheumatology at Oxford with a mathematical orientation and left with a conviction he has carried since – a direct view of what happens when basic science translates into medicine.

The Kennedy Institute was known for the development of anti-TNF therapy. A story that began with fundamental work on TNF biology as a key mediator in inflammatory processes, moved through antibody development and clinical trials, and ended with patients who had been crippled by rheumatoid arthritis running up and down stairs after three weeks on the drug. Adam was there as that story was becoming widely used in the clinic, close enough to see what basic science could do.

"I've always been trying to emulate the ability to either identify a mechanism that could lead to novel therapeutics or at least have research that has a much wider global impact," he says.

But the route from curiosity to impact, Adam has come to understand, is rarely straight. Early in his career, he was drawn to clean, reductionist systems, the kind where you perturb something at the bulk level and observe a clear outcome. Over time, that idealism gave way to something more honest about what biology actually is.



> *"Biology rarely behaves in neat averages," Adam says. "What we call a mechanism is often a population-level summary of the underlying heterogeneous behaviours of the cell. You're not going to get clean, neat biology."*

The shift from the idealism of clean mechanisms to the reality of cellular heterogeneity, is what eventually led Adam to single-cell sequencing – the right tool for the question he had been trying to answer.

THE PROBLEM WITH AVERAGES

Adam has a specific frustration with how the field has historically interpreted bulk sequencing data. "When a gene appears to go up in a tissue sample, that observation could mean several things," Adam explains. "The gene is genuinely more transcriptionally active, or a cell type that wasn't previously there has moved into the tissue… or both, or neither, in the way the interpretation assumes. Bulk measurements average across all of those possibilities without distinguishing between them."

Single-cell sequencing changes that. Instead of an average, you get a distribution – a view of the individual behaviours that the average was obscuring. And for tissues where heterogeneity is not a complication but the central biological question, that distinction matters enormously.

Adam's immunology background gives him a particular lens on this. He was always skeptical of the tendency to call every slightly different cell phenotype a new cell type. "I bet you haven't discovered a new cell type," he says, with the directness of someone who has sat through many such presentations. "You've just found a slightly different phenotype, and because it has a particular receptor combination,

someone decided it deserved a new name."
What single-cell sequencing makes visible, in his view, is not a collection of discrete boxes but a continuum. Cells move through states. They carry memory of prior states. They respond to context in ways that are fundamentally graded, not binary. Understanding that continuum, and establish the computational models that can represent it faithfully, is what his group is built around.

THE TISSUES NO ONE WANTED TO WORK ON

When single-cell sequencing began to take off, the field moved quickly toward the easiest targets: blood, bone marrow, PBMCs. These are already single-cell suspensions. You take a blood draw, run it through the machine, and get data. The methods are well established, the cell types are well characterised, and the datasets accumulate fast.
Adam watched this happen and noticed what was left out. His tissues of interest, musculoskeletal: bone, cartilage, synovium, skeletal muscle, are dense, fibrous, and extraordinarily difficult to dissociate without losing the cells you want to study the most. Every tissue requires its own optimised extraction protocol. And if you don't optimise carefully enough, the first cells that drop out are immune cells, which means you're back to profiling the immune component of a tissue rather than the tissue itself.
"We just haven't funded, as a science, enough harder tissues to work on," Adam says. "We have primarily gone for the really easy hits."
His group, in collaboration with Prof Sarah Snellings group, decided to go the other way. For years, they worked on building reproducible, robust isolation protocols for musculoskeletal tissues. The key, it turned out, was working at the nuclei level rather than the whole cell. COVID, counterintuitively, helped. When tissue collection stopped, the group had time to focus entirely on method development and get the protocols right before the work resumed. Those protocols are now open source, published on protocols.io, and have been adopted by musculoskeletal groups around the world.
Adam is also the biological coordinator for the Musculoskeletal system of the Human Cell Atlas. For a long time, he notes, the only Chan Zuckerberg-funded musculoskeletal map in the entire project. That distinction reflects both how underserved the area has been and how much ground his group has covered in it.

LONG READS AND THE ISOFORM QUESTION

Alongside the tissue challenge, Adam had been watching another technology mature for years before most of the field was ready to take it seriously – long-read sequencing.
He had access to one of the first Oxford Nanopore devices (around 2014) when the reads were short, the error rate was high, and the consensus was that it wasn't ready. Adam disagreed with the consensus, or rather, he disagreed with the

conclusion people drew from it. “I know technology takes time to figure out,” he says. “You can develop something 90% of the way, but it’s actually the 10% of the assay that really gets you to where it’s functional.” He was waiting for the technology to reach that threshold.

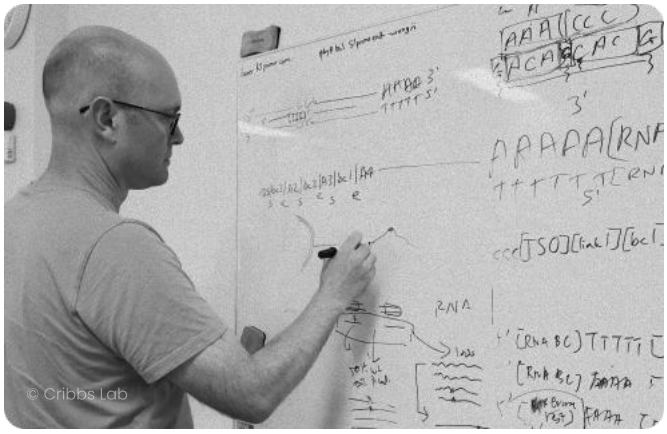
The reason he was waiting is specific. Standard short-read single-cell sequencing, particularly droplet-based methods, captures the five-prime or three-prime end of a transcript. That is enough to quantify gene expression, but it is not enough to resolve which transcript isoform is actually expressed in a given cell. A question that matters enormously in complex diseases where the same gene can produce proteins with very different functions depending on how it is spliced.

Long-read sequencing solves that by reading the mRNA end to end. Adam’s group has now published work applying Oxford Nanopore and PacBio technologies at single-cell resolution and is building reference atlases from a long-read perspective to map isoform diversity across immune cells and musculoskeletal tissues. The spin-out company, Entelo Bio, he has founded works in part from this foundation, aiming to take insights about splicing complexity in musculoskeletal diseases toward therapeutic applications.

ON MACHINE LEARNING AND WHAT THE MODELS ARE ACTUALLY FOR

Adam is careful about the word “AI”. He uses it reluctantly, preferring “machine learning”, as “AI” has become synonymous with large language models in most peoples minds. He is quick to distinguish between what the term now means in public discourse and the much broader toolbox his group actually employs.

That toolbox includes graph neural networks for modelling gene regulatory relationships, causal models for distinguishing genuine regulatory drivers from correlation, and fine-tuned



foundation models, where the data exists to support them. In musculoskeletal biology, that last condition is rarely met. Foundation models are trained on scale, and the field has generated a fraction of the data that exists for, say, the immune system. Applying them naively in bone cancer, where data is genuinely scarce, produces general answers rather than specific ones.

The deeper point Adam is making is about what the models are actually for. Generating a single-cell dataset and annotating the cell types is not, in his view, the end of a paper. It should be the beginning, or the middle – a step toward identifying novel biology that can be functionally validated.

“Gone are the days of just generating a single-cell dataset and saying, hey, this is it, look at all these genes I’ve curated,” he says. “It should be leading to some novel biology that you can validate functionally. That’s how I see single-cell sequencing being used now.”

The same logic applies to complexity. Capturing cellular heterogeneity is not the goal, it is the prerequisite for building models that can actually predict drug response, identify control nodes within gene regulatory networks, and say something about the causal mechanisms driving disease.

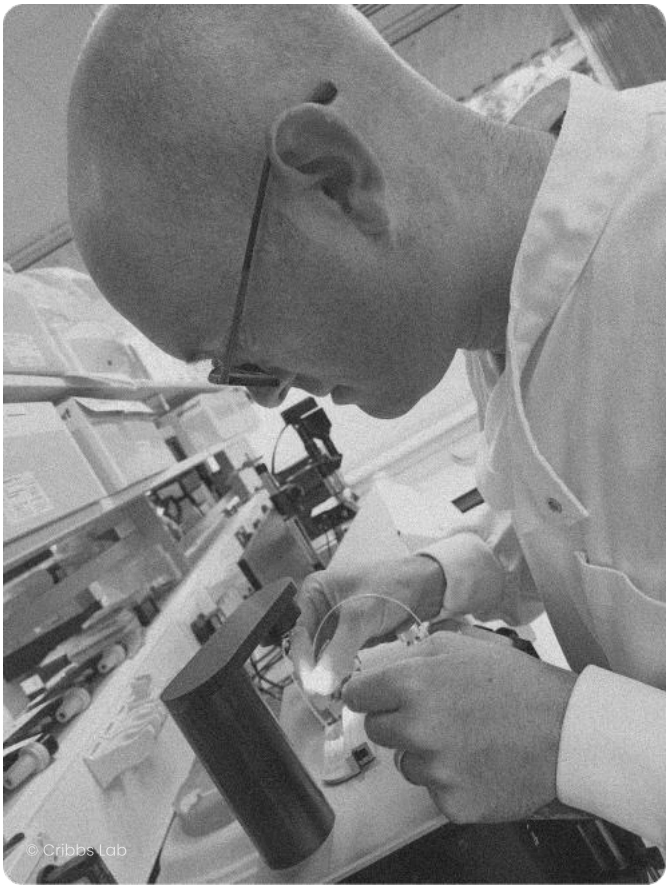
> *“Oversimplify the model, and you learn general biology. Capture the complexity, and you start to learn something specific enough to act on,” Adam states.*

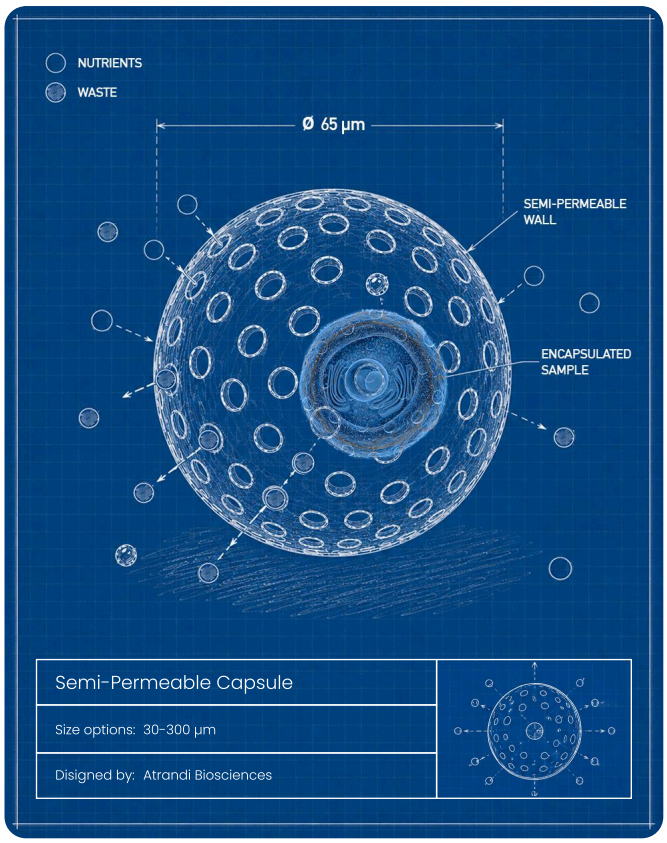
WHERE SEMI-PERMEABLE CAPSULES ENTER THE PICTURE

Adam's group decided to try Semi-Permeable Capsule (SPC) technology for a very specific problem – the need to capture both DNA-level and RNA-level information from the same single cell simultaneously.

Standard bead-based single-cell methods are powerful but chemically constrained – the bead format limits what reactions can be run and in what sequence. SPCs, with their size-selective hydrogel walls that retain cells and nucleic acids while allowing reagents to pass freely in and out, open up chemistry that bead-based approaches simply cannot accommodate. For a group building workflows around multimodal outputs, that flexibility is not a minor convenience – it changes which questions are addressable.

The specific application Adam's group is working toward is the simultaneous capture of translocations at the DNA level alongside RNA expression.





In musculoskeletal cancers, translocations are clinically meaningful - they stratify patients into high, medium, and low risk. Though, linking that genotypic information directly to the transcriptional phenotype of individual cells has not been possible with existing methods. Tying a specific translocation to a specific change in gene expression, and to the heterogeneity visible within a solid tumour, would be a significant step toward understanding which biological mechanisms are actually driving disease in individual patients.

"We can't get that with current techniques," Adam says. The SPC-based workflow is the route he sees toward it.

HIS OWN MEASURE

There is a quality to how Adam talks about his own trajectory that is worth noting. He has moved fields multiple times, crossed disciplinary boundaries deliberately, chosen problems that were unfashionable, and built a group that doesn't sit neatly in any one bucket.

None of that happens without a clear sense of your own direction.

> *"I stopped comparing myself to other people," he says simply. "I compare myself to my future self. I have my idea of where I need to be, and I don't get distracted from that."*

It is, he acknowledges, a data-oriented way of thinking about progress: less about what other people think, more about whether the data he is generating is good and whether it is moving toward something meaningful. That focus on the work itself, rather than on its reception, is what allows him to stay with problems before the field has fully caught up to them.

The three-month rule he mentions – if you're not happy for three months, move on. Sounds simple, but it has meant that his career has followed the science rather than the path.

He has been in academia, built a biotech, worked across immunology,computational genomics, and musculoskeletal biology, and landed, in his own words, "in the area I've always wanted to be in."

THE IMPACT THAT LASTS LONGEST

When the conversation turns to impact – where science should go, what it should achieve, Adam's answer moves between scales.

At the largest scale, it is therapeutic. The Kennedy Institute experience left him with a lasting conviction that basic research should be traceable, however long the arc, to something a patient can benefit from. Entelo Bio is one expression of that conviction.

But the impact he returns to with the most warmth is more local. Training PhD students. Watching them go into the world and hearing, through the network, that they are doing well.

"Knowledge transfer is probably one of the longest-lasting impacts you can have as a scientist," he says.

That instinct, to build things that others can use and carry forward, runs through everything Adam describes. The open-source tissue protocols adopted by labs around the world, the computational frameworks developed to be shared rather than held, the group designed to function at intersections rather than in silos. The science is serious and technically demanding. The orientation is generative.

It is the kind of science that takes time. Adam knows that. He has been waiting for technologies to mature, for the field to catch up to questions he started asking a decade ago. He does not seem particularly impatient about it.

"Life is a journey, not just a destination," Adam says, nodding to the cup on his desk. "I'm not always bothered about the output. It's about solving those hard problems and going on the roller coaster."