Spatial mapping and quantification of mRNA transcripts using Resolve Biosciences' Molecular Cartography™ technology. The image shows expression of transcripts in the mouse brain. Note the layered structure of the cortex, which is captured using a few marker genes.

Spatial multiomics – the next Big Thing?

TRANSLATING SCIENCE When it comes to development, molecular biology is at a crossroads. Especially in medical molecular biology, failed molecule-centered approaches are far more numerous than success stories, although they have attracted much greater attention and thus shaped mindsets surrounding the sector. The field is in flux, but looks set to change some fundamental paradigms.

Some scientists focus on a holistic view of ecosystems. For example they look at the entire interplay of organisms that makes up what we call 'biodiversity'. Many more researchers, however, dive into labs in an attempt to fathom the nature of individual pieces of the puzzle by examining ever-smaller units. In an extreme form, this can lead to a narrow, winnowing simplification. Looking only at the interaction between for instance two macromolecules like proteins ignores the world in which they exist, which is influenced by countless factors – among them neighbouring pathways, other metabolic processes, organ-typical relationships, how organs are embedded in the overall biological system, evolutionary comparisons with close biological relatives, and the distinction between male and female, just to name a few. Higher levels of complexity remain hidden or are simply ignored. Consciously or unconsciously, researchers are often forced by reasons of experimental accessibility or economic expediency to try to make quick discoveries.

In medical molecular biology in particular, molecule-centered approaches fail far more often than they succeed. That fact alone creates a self-reinforcing spiral, and has shaped mindsets in the field to simplify rather than complexify. It encourages researchers to seek to achieve insights into successful intervention in human biological systems in clever ways that often turn out to be useless or even dangerous. But as a rule, there are no simple answers even to seemingly simple disorders. Deaths or severe side reactions within early trials with interferons, tumour necrosis factor, and some interleukins or their antagonists have shown that.

> "Spatial biology is to know which biological events are happening where. It provides that spatial context to the underlying molecular machinery."
> Nachiket Kashikar, ESBC

The lesson we need to learn from them is that in our efforts to better understand individual organs and/or systems – whether it's the immune system, nervous system, or metabolic systems – we need to recognize that molecular interactions also involve the interaction of different cells inside and outside an organ. Interestingly, every once in a while, new cell types or even new organlike subcompartments in the human body are identified, even today. That leaves room for discoveries, but also plenty of space to misinterpret what we do know. In recent years, studies on the immune system have seen the most progress here, extending to the relatively new ability to genetically modify T cells. That allows us to now control them to some extent from the outside, amplifying a patient's normal response many times over. CAR-T technology has just celebrated its 10th anniversary.

Single-cell tech coming of age

In other words, this is still very young technology. If you compare developments to what happened within the first decade of the invention of the automobile, for example, you can see it's still very early days. In order to be successful with CAR-T and upstream research, technologies and investigation methods had to be developed that could recognise, sort and analyse individual cells. The door to the broad field of 'single-cell' technologies has therefore only been open a little longer than it took the first CAR-T cell therapy to reach the clinic. In the last two decades, the aims there have been to accomplish the separation of the cell mixtures technologically on the one hand, and on the other to carry out the analysis of the cells and their sorting – according to the markers – in such a way that these cells would still be 'usable' afterwards. Here, to become the standard of gene and cell therapy, the FACS devices developed even earlier, as well as loading with magnetic beads, had to undergo an update on clinical usability in a needle-to-needle strategy.

This all happened in just a few years, with great success, as evidenced by the current enormous number of clinical studies in cell therapy. According to recent data (Q3/2021), 1,129 industry-sponsored and 1,132 academic cell-therapy studies are currently underway, while a total of 216 studies are already in Phase III (Alliance for Regenerative Medicine; GlobalData, Statista). They make it clear how great the need for single-cell analysis is in these clinical trials alone. It's a market that is strongly influenced by US-based companies.

Beyond single cells

Moving beyond that are innovations like those from market leader 10x Genomics. Leaders there think its droplet separator should be available in every cell biology laboratory, and would like to see the technique grow as common as real-time PCR is today. And the technology throws out other options for the market leader. 10x offers a wide range of other applications in its device environment to meet a range of volume research demands.

Cell analysis is constantly expanding as a field. In addition to the focus on RNA sequencing, more and more researchers are also interested in protein analysis, which is seeing a lot of strong promotion. 10x Genomics and other companies in the area are now trying not to get boxed into the corner of single-cell examination. They're aware it could turn into a dead end, and are now trying to see not just the trees, but the whole forest. In other words, as discussed above, not to get so bogged down in macromolecular dynamics that you forget it's about the whole tissue, the whole organ, and preferably the whole organism. Like others, 10x now wants to occupy the area known as 'spatial omics'.

Named "Technology of the Year" by Nature back in 2020, the field is extremely dynamic at the moment. Some companies are being snapped up, others are going public, small ones are joining forces with peers. All are jockeying for the best possible position, seeking to grab a share of the market as they accelerate the greater spread of related technologies – especially when it comes to equipment in research institutes. Bigger fish are still watching from the sidelines.

Watching and waiting

Both Thermo Fisher and Qiagen, for example, have expressed interest in the area, but are holding back. That's at least partially because the market for spatial omics, though growing, has not yet exploded. According to Research And Markets, its growth rate in the years 2021-2028 is projected at about 10%, up to US$484m. That ballparks its current value at about US$250m – not yet an order of magnitude that makes big lab companies sit up and pay attention. But it's more than enough to draw existing companies from the single-cell sector that – like new entrants – want to leave a clear footprint in the spatial omics sector.

Small market, but set to grow

Some companies – like 10x Genomics – are acting from a position of strength. The California-based firm maintained a torrid growth pace in Q4/2021, with revenue jumping 64% year-over-year to US$490m. In Europe, its team has expanded from eight staff to over 100 within a few years. The entire company now has well over 1,000 employees and went public in 2019 based solely on its highly specialised expertise and offerings in the single-cell space. Originally priced to bring in US$100m, the IPO far exceeded expectations at US$390m. But the price for its stock has since fallen back to that entry level, and the company obviously is looking out for new development steps to help rekindle imaginations on the trading floor. At least in theory, the acquisition and integration of Swedish-based firms Cartana and Spatial Transcriptomics has turned 10x Genomics into a spatial-omics company in a single bound.

With over US$2bn in revenues, science instrument maker Bruker is pursuing a similar strategy of acquisition. It recently bought Acuity Spatial Genomics and Canopy Biosciences, both small-

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? How do you view the hype in spatial multiomics?

! *The life sciences have after all long since become a data science. And all the new bioinformatic algorithms and artificial intelligence only work with large reference datasets of excellent quality and uniformity. The real horizon lies somewhere else. The use of single-cell information is for clinical decisions in diagnostics – for patient stratification, for target identification and for completely rethought "clinical trials of the future". The Holy Grail is a "Foundation Medicine for Single Cell" - the next step after Personalized Medicine, and one level down to a "Medicine of the Single Cell". And of course, Spatial Genomics will also contribute to this at some point. But today's race lies first and foremost in the smart translation of existing single cell data into clinical decisions. And it is precisely driven by this idea that platform company Singleron has just acquired our single cell clinical data company, Proteona. Because as I said: algorithms and AI only work with large reference datasets of excellent quality and uniformity.*

Picture: Singleron Biotechnologies

The first European Spatial Biology Center threw open its doors in Ghent, and was officially opened by Flemish Minister-President Jan Jambon (middle) at the Gasthuisberg campus in Leuven during a ribbon-cutting ceremony in early May.

er companies, but ones with a focus on the multiplex processes that are key to overcoming the next challenge facing the spatial omics community – the high-throughput process. Nanostring Technologies, Fluidigm (now renamed Standard BioTools Inc.) and Akoya are also ranked among the top five in relevant rankings of listed companies in the emerging field, but they still have quite humble sales figures.

Small companies adapting fast

In the private sector, company rankings in the spatial-omics segment can also be based on the amount of capital they've raised. By that metric, the top five would include Ultivue, RareCyte, Lunaphore Technologies, Vizgen and Nukleai. According to a listing published by Genetic Engineering & Biotechnology News, Ultivue and RareCyte could raise triple-digit million amounts, the other companies mid-double-digit sums.

But Europe, though only represented in these rankings by a few companies like Lunaphore and acquired small start-ups, does not want to give up without a fight. Companies like Germany's Resolve Bioscience, which was founded by ex-Qiagen employees, may not be listed in top-notch rankings so far, but have managed to build their own community of followers and supporters, like the European Spatial Biology Center (ESBC), which was newly founded this May. It's preparing to follow suit in the Flemish city of Leuven (Belgium), as Nachiket Kashikar, Managing Director and Co-Founder of ESBC N.V., announced at the German Biotechnology Days in Hamburg (second from left in photo above). Located not far from the VIB, KU Leuven and expert Martin Guilliaums, and in the neighbourhood of European scientific research elites such as Nikolaus Rajewsky (Berlin), the Friedmann Laboratory in Paris and others, the ESBC sees itself as a service and research institution to provide biological insights to its customers through the analysis of "big spatialomics data".

Europeans enter the arena

To further expand the market for applications in spatial multiomics technologies, the companies will have to encourage a new base of customers and researchers to use the devices and technology. As always, some are moving fast and adopting early. But the movement is gaining momentum with the publication of spectacular scientific results such as new insights into the hepatocellular environment in a study from the Guilliaums lab (*Spatial proteogenomics reveals distinct and evolutionarily conserved hepatic macrophage niches*, Cell, January 2022). Other areas where groundbreaking work is happening include SARS-CoV-2 pathology with COVID-19 tissue atlases, global projects like the Human Brain Atlas, usage of spatial omics in cancer biology revealing the interaction in checkpoint inhibition, and many other high-impact publications that have come in the last three years alone. The field is ripe for use in applications in the world outside the lab and renowned scientific institutions.

The next move might be into diagnostic labs. Some early adopters appear to be trying to figure out how to implement the new technology to streamline analytics – and of course to find customers willing to pay for such new diagnostic tools. Kashikar also sees the market for the applications as much more visionary and larger than today's market research: "By taking into consideration spatialomics as a suite of technologies that provide spatial analyses of DNA, RNA, metabolites, proteins, etc., and by looking at a combined market space in basic sciences, pharma companies (from discovery to clinical trials), and even agricultural sciences, I expect an annual market potential in 2025 of about US$12-14bn," he said in his presentation in Hamburg. When asked, Kashikar only briefly acknowledged the fact that the diagnostics sector would have to make great strides, and that the burning pace of new discoveries of relevant cell activities, which had previously been overlooked, also have to be quickly translated in clinical development pipelines.

It's still far from clear which companies will end up on top in a field where new startups continue to pop up like mushrooms. Will there even be a single dominant platform? Uniform quality in datasets will be essential for the new bioinformatic algorithms and AI that will have to power the sector.

So there are still some hurdles, but as the field sorts itself out, takes a deep breath and raises money to bundle the challenges of a truly holistic viewpoint, we should soon see more and more integration of many molecular and cellular interactions into an overall picture of disease events. ■

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Picture: ESBC Leuven; www.esbc.science