SINGLE CELL GENOMICS: MARKET TRENDS



Aaron Fisher afisher@broadoak.com

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WHAT IS SINGLE CELL GENOMICS?

Single cell genomics is a developing market that defines the tools and services enabling the analysis of nucleic acid content of individual cells, as opposed to cell populations. Researchers care about this (important) level of analytical nuance because individual cells may look the same, but they express different genes and have different behavior relevant to disease. Understanding heterogeneity in cells has important implications for disease and overall understanding of cellular biology. This level of resolution at significant levels of throughput wasn't available until Fluidigm created its suite of single cell genomics tools.

HISTORY OF THE SINGLE CELL ANALYSIS MARKET

Single cell analysis has historically been performed using a common suite of tools, including micromanipulation, fluorescence-activated cell sorting (FACS), and laser capture microdissection. These tools support large markets, including the flow market and the multi-billion-dollar microscopy and cytology reagent markets.

But there are limits to these tools. For example, conventional methods are limited in their ability to analyze more than ~5 biomarkers at once (although Flow technology continues to become more capable), throughput is an issue, and assessing 'multi-omic' components in a single sample is limited.

SINGLE CELL GENOMICS MARKET TODAY

Today's single cell genomics tools market was developed on droplet-based microfluidic technologies. 10x Genomics' Chromium system is the market-leading instrument leveraging droplet-based microfluids. RNA-seq comprises the largest part of today's market, with a growing base of other analytes like DNA and proteins that are increasingly analyzed in tandem ("multi-omics"). Sequencing remains the largest downstream applied analytical technology. Illumina has been a prime beneficiary of the rise of the single cell market.



FLUIDIGM PIONEERED TODAY'S SINGLE CELL GENOMICS MARKET

At BroadOak, we define the "single cell genomics era" beginning with Fluidigm's IPO in February 2011. Fluidigm pioneered single cell genomics and led the market for five years until the rise of 10x Genomics.



10X GENOMICS BECOMES THE SINGLE CELL GENOMICS MARKET LEADER

In 2016, 10x Genomics launched its Chromium system and quickly became the market leader (see Exhibit A). As of FYE2021, 10x has an installed base of ~3,500 systems globally. 10x took the market by storm solving for the bottleneck of cellular throughput that Fluidigm struggled with. The Chromium increased throughput from hundreds of cells to tens of thousands of cells, and this number continues to grow. With a capital infusion of \$250 mil and rebranding as Standard BioTools, it seems likely that Fluidigm is set on challenging 10x Genomics' market dominance.

THE CUSTOMER BASE IS EXPANDING

While the state of today's market is predominantly academic/research-focused where researchers look to survey entire single-cell transcriptomes and genomes, these tools have a growing Biopharma customer base, primarily in discovery and translational applications. These tools may be used in clinical settings in the intermediate term. Like the genomics market of the 2000's, single cell genomics will move from discovery to diagnostics to therapeutic development.

We are in the early stages of single-cell panels, biomarker discovery, clinical trial endpoints, and analytical assays for cellular medicine. These promising applications will continue to grow.

SINGLE CELL GENOMICS INVESTMENT

In addition to a positive commercial market outlook for the single cell space, the appetite for funding single cell technology companies from venture and growth investors has remained strong (although we will see how this trends in light of unfavorable financial market conditions and deceleration in venture financings overall).



Exhibit B illustrates how single cell companies have attracted more money in larger investments and higher valuations. Investors should follow the development of the market closely. Single cell genomics is leading to biological insights that will eventually lead to new and improved therapies in oncology, immune-oncology, and immunology. Single cell genomics, now approximately a \$1 bil market, has been one of the fastest growing markets in all of life sciences research tools, with an estimated CAGR of 20% (Source: Miguel Edwards, Partner, DeciBio Research). There are several emerging players and many potential applications as this market continues to evolve.



TRENDS WE ARE WATCHING

Trend 1: Competitive Threats to Droplet Microfluidic Technologies

Droplet-based technology, led by 10x Genomics, is promising, but there are still many issues.

- Cost has been a key inhibitor of market adoption, particularly for researchers with lower sample volumes looking to perform single cell analysis in-house
- Higher volume labs demand ever-increasing cellular throughput
- The market requires more flexibility

10x Genomics has created a market of its own, and an evolving base of tools are commercializing to simplify problems in workflows across sample types created to use the Chromium system (and next generations of the instrument).

Several new companies built on instrument-free technology platforms could disrupt 10x Genomics' market dominance, including Honeycomb Bio, Fluent Biosciences (droplet free technology), Parse Biosciences (combinatorial indexing technology), and Scale Biosciences (combinatorial indexing technology).

10x Genomics will likely dominate the single cell market in the near-to-intermediate term.

There is room in the market for instrument-free technologies, but entrants may struggle to attract research customers that have already committed to 10x Genomics' system. These customers may find it costly to switch from workflows built around and standardized for the Chromium.



Trend 2: Multi-Omics

'Multi-Omics' is trending in the research tools market. In the context of single cell high-throughput sample prep instrumentation, we are seeing interest in certain target analytes being analyzed together on single platforms:

- Analysis of gene expression and cell surface proteins simultaneously in single cells (see: Bio-Rad/Illumina, BD, and 10x platforms)
- Analysis of copy number, single nucleotide variants, and cell surface proteins in single cells (see: Mission Bio)

Platforms for other analytes will continue to be developed, for example, in epigenetics, characterizing chromatin accessibility across the genome in single cells. We expect many of the players in the single cell market will continue to develop products enabling multi-analyte assessment at the single cell level as a source of product differentiation. Multi-omics creates added complexity on the backend of the workflow: what does all of this new data and information mean? While informatics is often overlooked as an opportunity in the research tools market, particularly in academic environments that have historically resisted paying for these solutions, we expect the complexity of data integration and making sense of multi-omic datasets will remain а bottleneck in need of continued innovation.



Trend 3: Spatial Biology

Spatial Biology refers to assessing the context of the 'spatial' microenvironment in tissue organization (how cell types in a piece of tissue are responding to changes in environment). Spatial techniques enable researchers to go further than just relying on quantitating proteins or evaluating gene expression data to also understand the spatial context in tissue biology. New spatial technologies are building on legacy insitu hybridization (ISH) technologies and will continue to move towards single cell resolution. There is a compelling amount of venture money, demand in industry (biomarker discovery) and in basic research markets. and developing technology platforms to suggest this market has a strong outlook.

Today's spatial biology technologies complement single cell methods. The top two industry players are NanoString GeoMx platform) (the and 10x Genomics (the Visium platform). While the GeoMx platform enables multianalyte assessment (RNA and proteins), the Visium platform has been focused on spatial gene expression (RNA). Spatial platforms are gaining significant interest and traction in oncology where researchers seek to use these technologies to further interrogate the tumor microenvironment.



Trend 4: Clinical Applications of Single Cell

The timeframe for single cell molecular applications to penetrate the clinic is a subject of debate. Even today, bulk next generation sequencing ("NGS") hangs at the gates of the clinic primarily as lab-("LDTs"). developed tests As the preferred downstream analytical method of single cell genomics tools is NGS technology, expect single cell we technologies to follow the timeline of NGS. As most new forays into the clinic, we expect to see single cell genomic techniques enter first as LDTs.

All current molecular assays in the clinic are bulk-based and thus lack sensitivity to see smaller clonal changes. There also remains growing interest in isolation and detection of circulating tumor cells ("CTCs"), arguably one of the nearestterm applications of single cell in the clinic. Single cell genomics is most promising in oncology, immuneoncology, and immunology. It's also important to note that the rise of new cell-and-gene-therapy-based drug modalities (like CAR-T, for example) will likely drive adoption of single cell techniques for characterization. (Source: Miguel Edwards, Partner, DeciBio Research)

Single cell adoption is expedited by the drug development industry's growing interest. The next phase of market adoption of single cell is likely to be driven by therapeutic developers, not academic research, who are looking to single cell in discovery and translational research applications.



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DISCLOSURE

BroadOak has active investments in Honeycomb Biotechnologies, S2 Genomics, and SeqWell – each of which are active participants in the single cell genomics market.