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Cyto-Mine: an integrated, automated antibody-research platform with CRISPR–Cas9 potential

Providing ultra-high-throughput screening of single cell assays and antibody-producing cells as well as the ability to sort them, Cyto-Mine is ready for use.

Sphere Fluidics has now successfully manufactured and shipped its brand new Cyto-Mine single-cell analysis and monoclonality-assurance platform (**Fig. 1**). The technology integrates and automates the processing, analysis, dispensing and imaging of single cells that produce high levels of antibodies, freeing researchers from the inefficient assemblage of technologies used today.

The Sphere Fluidics team designed Cyto-Mine to revolutionize how researchers improve existing cell lines and identify cells that produce therapeutic antibodies.

Before Cyto-Mine, researchers struggled to quickly screen large numbers of cells, select the rare cells that produce antibodies, and dispense single-cell 'hits' into the wells of a microtiter plate. Clone pickers, fluorescence-activated cell sorting, and the limiting dilution approach were the tools of choice, but all of them have weaknesses. Some approaches take several weeks or more per run. Others require trained staff and deliver inferior cell outgrowth. None provides an efficient end-to-end solution.

Cyto-Mine does provide such a solution. The platform enables ultra-high-throughput screening, single-cell assays, and the rapid sorting and dispensing of cells into individual wells of a microtiter plate. Cyto-Mine is the only platform that does individual cell encapsulation, rapid and sensitive assays, and gentle screening of millions of cells to assess antibody specificity and production. This enables researchers to funnel a huge population of cells, test each one individually, select the most promising prospects, and ensure improved chances of recovering viable cells.

Figure 1. The Cyto-Mine single-cell analysis system.

Multi-use platform

The Sphere Fluidics platform has three main uses. Antibody-discovery biopharma researchers can use it to identify rare antibody-producing cells. Teams in cell-line development can identify and isolate single-cell clones with high expression. Uniquely, the machine also provides monoclonality assurance via integrated imaging of cells during dispensing. Monoclonality assurance is a legal requirement for approval of all biopharmaceuticals by the world's leading regulatory agencies.

The system has also been designed to satisfy cell-line development requirements for all components to be certified as animal-origin free. Miniaturization in its proprietary assay format (i.e., the microfluidic Cyto-Cartridge) also means the system has a minimized environmental impact owing to dramatically reduced plasticware usage and assay reagent consumables costs. The system has a modern user-friendly software interface and is easily connected to popular laboratory automation systems.

Cyto-Mine is the first system to provide a totally integrated solution for biopharmaceutical discovery and development. Two important outcomes of the Sphere Fluidics picodroplet encapsulation and processing workflow are (1) the ability to rapidly measure antibody output from individual cells (antibodies are secreted and accumulated in the picodroplet during incubation) and (2) 'protection' of each cell by the picodroplet environment, which makes cell viability rates very high and cell outgrowth of single-cell clones in microtiter plates demonstrably and reproducibly better than that achieved with other cell-sorting platforms.

The speed at which Cyto-Mine handles these tasks has attracted immense interest. Two leading biopharma companies, both of which collaborated with Sphere Fluidics to shape the design of early versions of the instrument, will now receive the mass-manufactured final product. Other companies that have tested Cyto-Mine at Sphere Fluidics' laboratories are also now buying the platform.

Integrating precision genome editing

Sphere Fluidics' collaborators and in-house scientists have assessed how Cyto-Mine's integrated single-cell processing capabilities can be used for other applications. This, when aligned with forecasts of where drug discovery is heading, has prompted a surge in interest in using Cyto-Mine for precision genome editing with technologies such as CRISPR–Cas9. Genome editing offers the potential to create new therapies and advanced cell-line models for pharmaceutical discovery and production.

The combination of Cyto-Mine and CRISPR–Cas9 should enable researchers to perform high-throughput genome editing at the single-cell level in a fully automated device. Researchers will take, for example, a batch of several thousand single cells, transfect a genome editing library member, and process the cells. This process will be repeated with multiple different batches of cells and library members.

After incubation, the device will perform single-cell phenotypic screening, dispensing and retrieval. Via miniaturization and automation, Cyto-Mine will dramatically reduce consumable and labor costs and increase throughput. The potential for interfacing with other devices, such as sequencers, is also being investigated.

Sphere Fluidics has recently secured a major £1 million Innovate UK grant to apply its core technology to genome editing and is also developing corporate partnerships in this area. This is set to lead to further innovative advances to help researchers working with CRISPR–Cas9, cell–cell interactions, and CAR T cell therapeutics.

Such work is a testament to Sphere Fluidics' commitment to expanding the use of the Cyto-Mine technology. Having developed a platform that makes biopharmaceutical discovery and development more efficient, Sphere Fluidics is now adapting that platform's use for precision cell engineering and the development of personalized cell therapies, and considering its application in medical diagnostics.

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