Case study

Application of Cyto-Mine® in Cell Line Development at FUJIFILM Biotechnologies



FUJIFILM Biotechnologies

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Scientists at FUJIFILM Biotechnologies have transformed their cell line development processes through the incorporation of Cyto-Mine®, the next-generation single cell analysis system developed by Sphere Bio. The new processes are streamlined, compared with previous workflows, and productivity has been enhanced. Projects are now able to swiftly transition from the initial transfection phase through to development of highly productive cell lines, within approximately 10 weeks.

Cell line development: critical objectives and challenges

Specialist contract development and manufacturing organizations (CDMOs) offer technical expertise and capacity in cell line and process development to optimize production of biological medicines for biotherapeutic manufacturers. In this commercially competitive field, CDMOs are under increasing pressure to deliver robust and productive stable cell lines within shortened timeframes, to drive faster transfer of therapeutic molecules into clinical development. This must be achieved while maintaining excellence concerning biological product quality.

Emerging biotherapeutics have begun to focus on novel antibody fragments and bispecific antibodies, which are more challenging to produce in stable cell line expression systems at high enough titers for commercial drug development programs and large-scale manufacture, compared with standard monoclonal antibody molecules. Technologies that provide better predictive screening capabilities and higher throughputs than those traditionally used in cell line development laboratories have been sought to meet the growing urgency and demand for unique biotherapeutic molecules. Conventional manual screening techniques, such as colony picking and limiting dilution cloning, are time-consuming, laborious and restricted concerning the number of cells that can be processed or analyzed within a given period.

Industry regulators, such as the Food and Drug Administration (FDA), require evidence of monoclonality regarding cell lines used in the production of biological medicines. Manufacturers must prove that each cell line is derived from a single parent cell in order to avoid costly delays to market authorization and clinical trial programs. Traditional approaches do not allow visualization of individual cells upon initial seeding, making demonstration of monoclonality difficult or impossible in certain cases.

Cyto-Mine® in practice: improving efficiency and ensuring quality

Cyto-Mine® is a single cell analysis platform that enables individual cells to be encapsulated within picolitre-sized aqueous droplets in a biocompatible carrier oil (picodroplets). FUJIFILM Biotechnologies has harnessed this technology to develop a single-step cloning process, which removes bottlenecks in the cell development process and improves both accuracy and efficiency.

Time-consuming and low-throughput conventional screening techniques (e.g. colony picking and limiting dilution cloning) do not allow individual cells to be visualized and monoclonality can be difficult to demonstrate using these methods.

Dr Fay Saunders,
FUJIFILM Biotechnologies



Each picodroplet provides a controlled, defined and adjustable environment that maintains cell viability (**Figure 1**). Single cells may be screened with speed and precision and secreted proteins are trapped within the picodroplets, making them easily accessible for characterization.

Multiple procedures and assays within the cell line development pathway are miniaturized and integrated within Cyto-Mine®, allowing tasks that would previously have taken weeks to complete to be undertaken within one day. Approximately 200,000 individual cells can be screened in a matter of hours using this approach, compared with around 10,000 cells with manual analysis techniques.

Quality and quantity of molecular product are enhanced as screening is now conducted at an early stage so that only cells expressing the protein of interest, and the best-performing cells within this pool, are taken forward in the development process. Workflows have been significantly shortened, from around 25 weeks to approximately 10 weeks (**Figure 2**), Importantly, single cells may be visualized using Cyto-Mine® and accurate monoclonality data can be provided to support regulatory submissions.

Cyto-Mine® is designed using integrated user-friendly software, that requires minimal specialist training to understand and implement effectively. Overall efficiency and productivity in the cell line and process development team at FUJIFILM Biotechnologies has been enhanced through the application of Cyto-Mine®. Scientists spend less time conducting laborious manual procedures and are able to complete a greater number of projects within a given timeframe. This allows

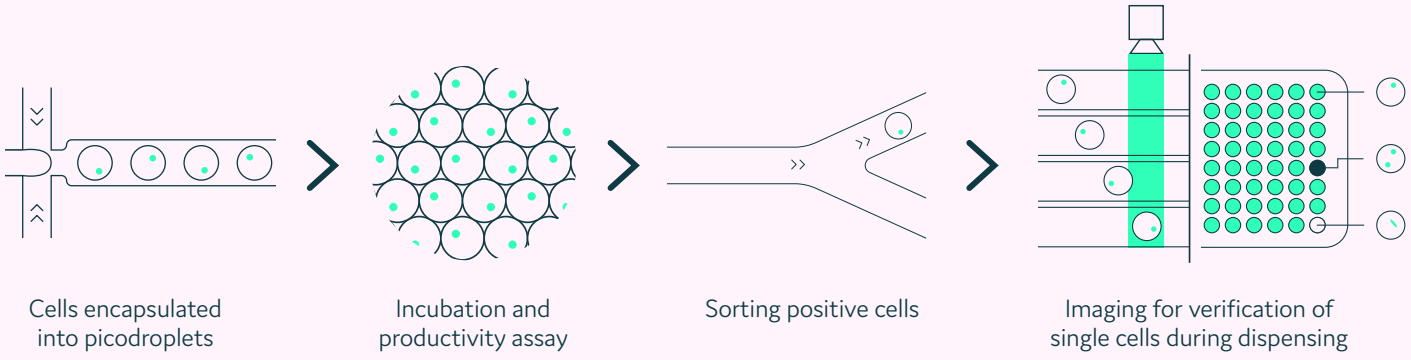


Figure 1. Integration of productivity assay screening, sorting, isolation and verification using a fully automated picodroplet microfluidic process.

them to apply their specialist skills and expertise to other important aspects of their work. Motivated by the possibilities for Cyto-Mine® in enhancing or refining other features of their research, scientists at FUJIFILM Biotechnologies are now exploring further applications for this technology platform.



Figure 2. Example timeline highlighting the streamlining of workflows using mammalian cell line engineering technologies in combination with single-cell picodroplet innovations.

Our workflows are considerably more efficient as cellular screening is conducted early in the process, allowing the best-performing cells (expressing the protein of interest) to be selected and taken forward for development.

Dr Fay Saunders, FUJIFILM Biotechnologies



High-throughput cell line development and biotherapeutic production

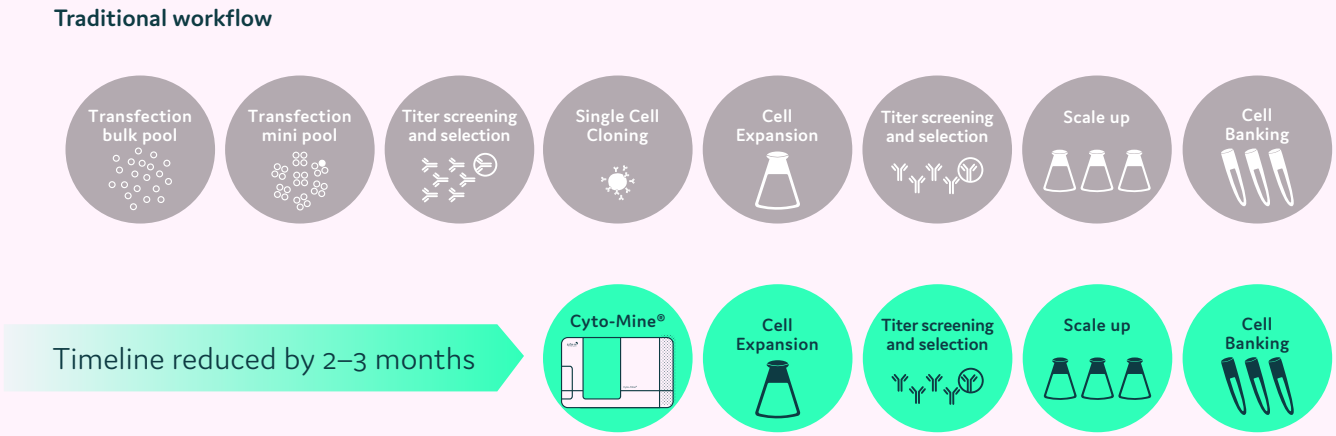
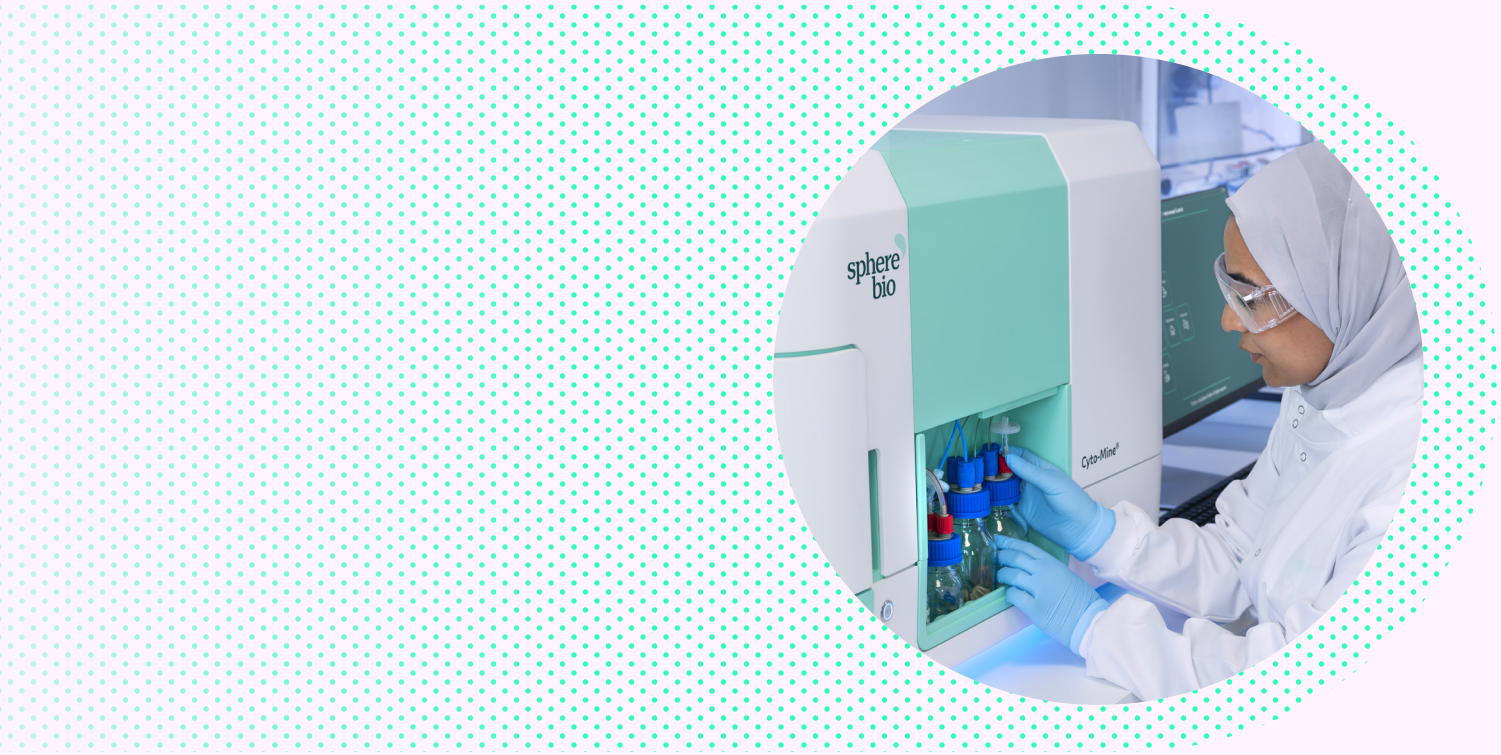


Figure 3. Accelerated cell line development workflow using Cyto-Mine®



The benefits of picodroplet technology

- **Streamlined** and simplified processes
- Miniaturization and integration of **multiple** processes/pathways
- **Accurate** screening of **large** cellular populations (200,000 individual cells)
- **Shortened** timelines/workflows
- Assured **monoclonality**
- Increased **efficiency**
- **Automated** processing and greater freedom from manual tasks

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