Cyto-Mine®

Interactive brochure

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sphere FLUIDICS

work small, think big.

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Cyto-Mine®

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Cell line development
Antibody discovery

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Find, analyze and isolate your most valuable cells, with ease and speed

Introducing Cyto-Mine®

Cyto-Mine® is our high-throughput, fully-automated, antibody discovery and cell line development platform, incorporating single cell analysis capabilities for industrial-scale discovery and development. Underpinned by Sphere Fluidics' patented microfluidic picodroplet technology, the Cyto-Mine® simplifies and accelerates your cell line development and biopharma discovery workflows.

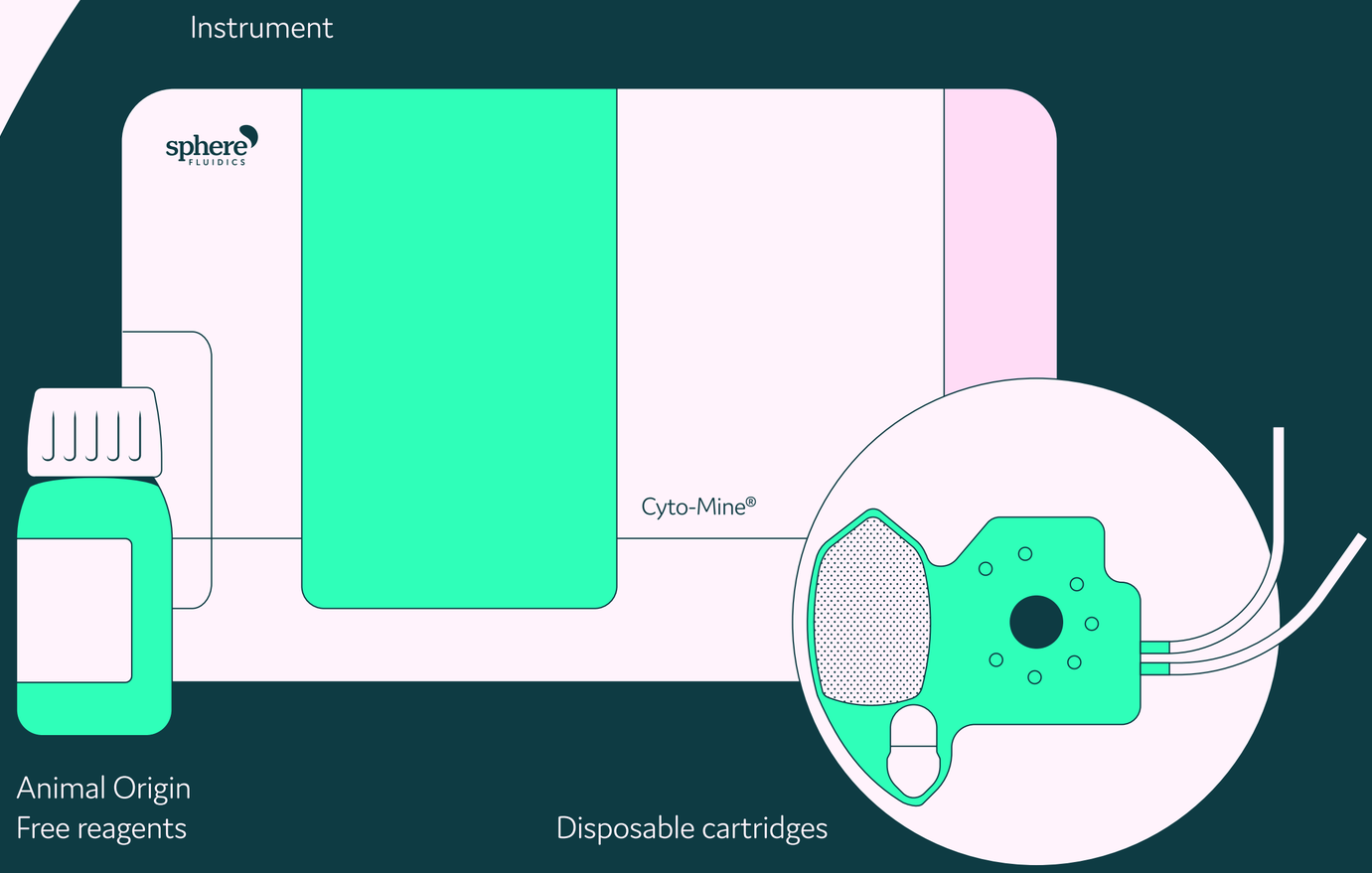
Cyto-Mine® integrates single cell screening, sorting, imaging and dispensing, into a simple-to-use instrument that can be used without any specialist training, so you can start generating data on day one. Each run takes place within a disposable Cyto-Cartridge®, minimizing cross-contamination risks. The simple, "load-and-go" system streamlines your workflows and reduces hands-on time, allowing the analysis of up to 350,000 single cells or 40 million cells (in pools) in 1 day.

Cyto-Mine® supports 21 CFR Part 11 compliance, the entire process utilizes Animal Origin Free (AOF) reagents, and the benchtop system is suitable for use inside Class II biosafety cabinets.

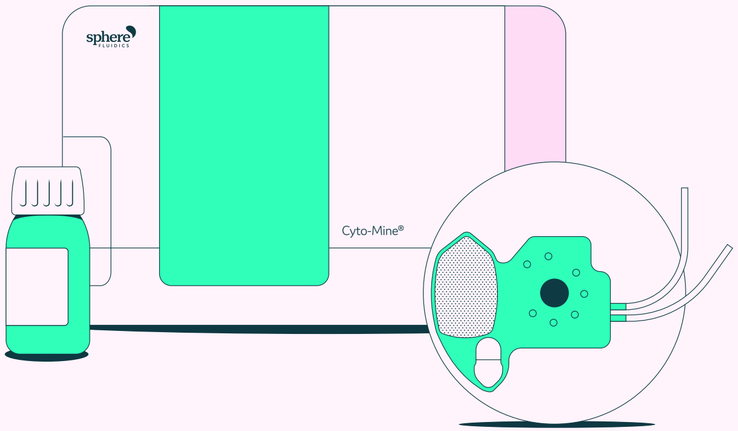
- **Direct measurements of secreted proteins in live cells**
- **Provides visual evidence of monoclonality**
- **Improved cell viability and outgrowth**
- **Analyze up to 350,000 single cells or 40 million cells (in pools) in 1 day.**
- **Single use Cyto-Cartridges® minimize cross-contamination risks**
- **Animal origin free consumables and reagents**

The Cyto-Mine® platform

The Cyto-Mine® Platform consists of the instrument, software, consumables and support.



The Cyto-Mine® platform



Simplify and accelerate your single-cell workflow

Combine cell isolation, assay, sorting, imaging, and dispensing into an automated workflow on a single, easy-to-use platform, with real-time interactive tracking and proof of monoclonality for each selected cell*.

Screen and Select High Value Clones

Encapsulate single cells in picodroplets to increase your screening capabilities and analyze up to 350,000 single cells or 40 million cells (in pools) in 1 day.

Maintain Cell Viability

Picodroplets protect cells from sheer forces during processing, as well as allowing gas exchange, which together ensure high levels of downstream cell viability and outgrowth. Accelerate the media development process and optimize the growth conditions for your cell line by quickly running multiple cloning experiments.

Assay Secreted Proteins

Cyto-Mine® can accomodate a wide range of FRET-based assays with high sensitivity and specificity. The assay format can be tailored to suit your specific project needs.

Prove Monoclonality

The Cyto-Mine® accurately and reliably selects single target cells and dispenses them into plates. Automatically recorded images of cells in picodroplets are taken as the droplet moves and rotates in the channel.

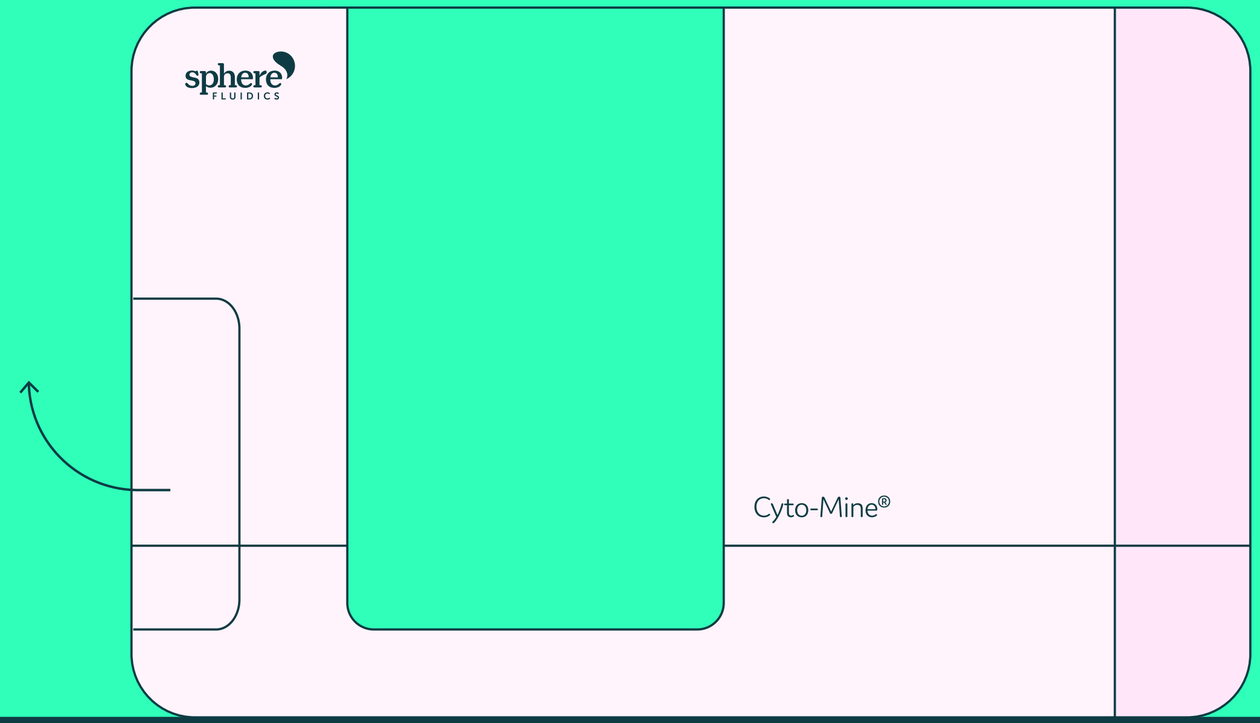
*with >99% confidence

DISCOVER - **interactive page**

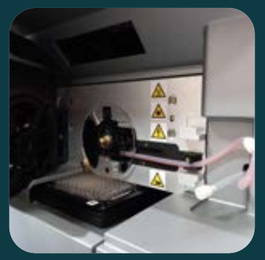
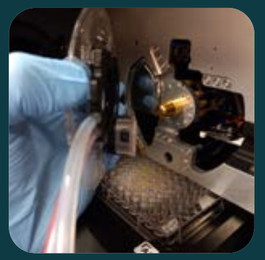
Cyto-Mine® instrument

Loading the Cyto-Mine® cartridge into the instrument is quick and easy.

1. **Open outer door**
2. **Open inner door**
3. **Load Cyto-Cartridge®**







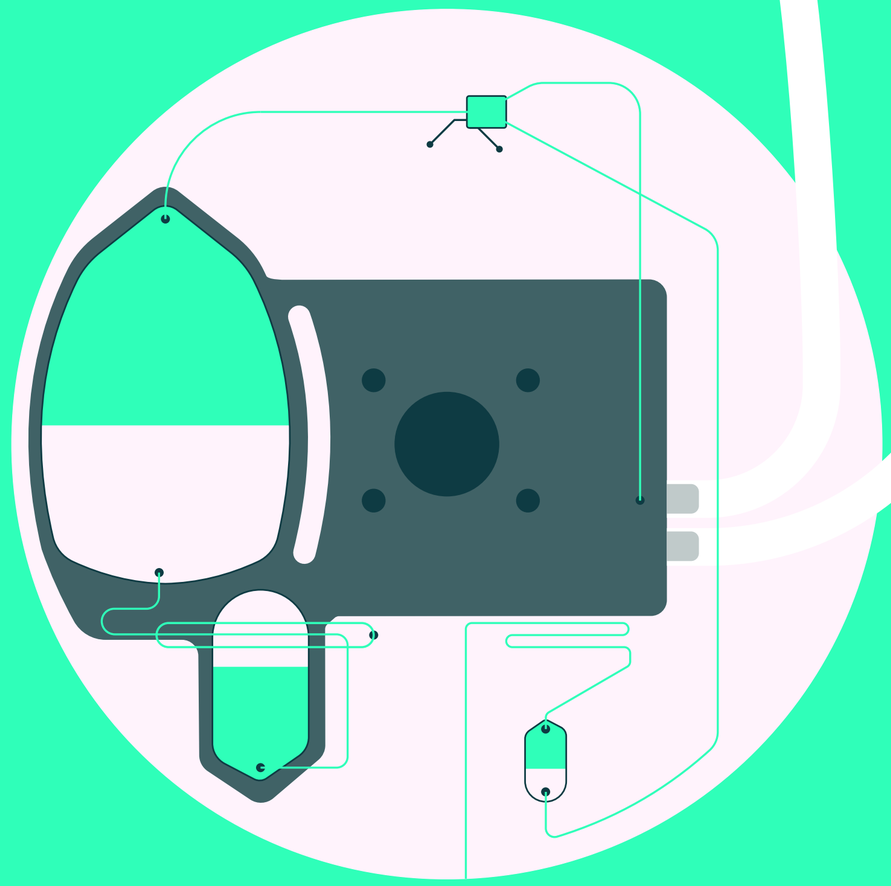
DISCOVER - **interactive page**

Cyto-Cartridge®

The Cyto-Cartridge® is the core of the Cyto-Mine® platform, providing all the necessary microfluidics for implementing picodroplet workflows.

The disposable cartridge is designed to be easy-to-use, ensuring zero cross-contamination between runs and maintaining the integrity and quality of your cells for each experiment.

Cyto-Cartridges® are manufactured from fully biocompatible materials under our ISO 9001 quality management system, in a clean environment.



1. Sample
2. Droplet generator
3. Incubation chamber
4. Sorting junction
5. Dispensing nozzle

CLEAR

Powerful picodroplet

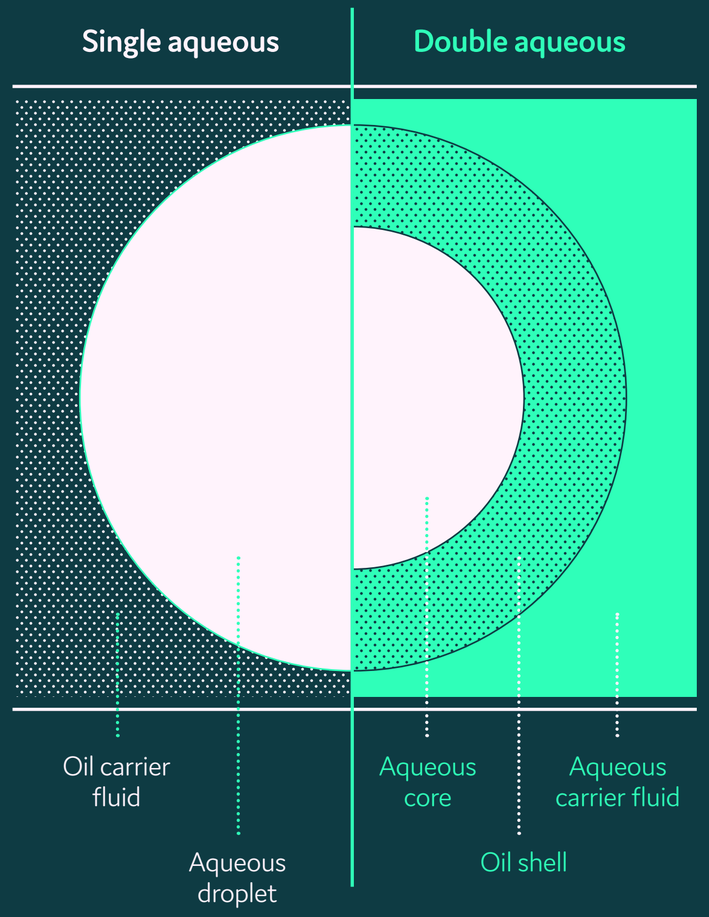
At the heart of our platforms are picodroplets, tiny droplets of aqueous fluid that can contain media and reagents, and encapsulate individual cells or groups of cells. Generated using Cyto-Surf® our proprietary range of surfactants which maintain stability and allows gas exchange, they maintain high cell viability for several days, acting as ultra-miniaturized reaction vessels in which to conduct bioassays on living cells.

Picodroplets are tiny, highly uniform 450µL droplets. Their small size facilitates their rapid generation and manipulation, and allows the use of only very small quantities of reagents for assays.

They can be either:

- **Single aqueous – aqueous droplets in an oil carrier fluid***
- **Double aqueous – droplets with an aqueous core surrounded by an oil shell in an aqueous carrier fluid**

The chemistry of the emulsions is carefully designed to give stable, biocompatible droplets with minimal leakage of molecules from within the droplet, even for small molecules such as metabolites.

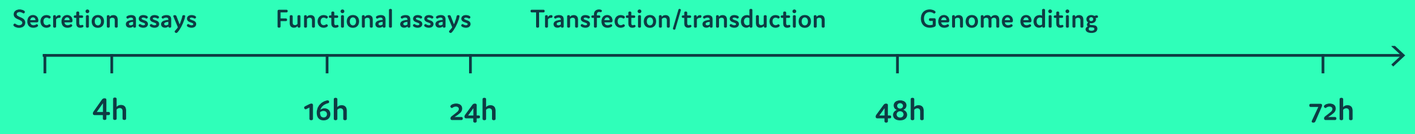


*The Cyto-Mine® generates single aqueous picodroplets

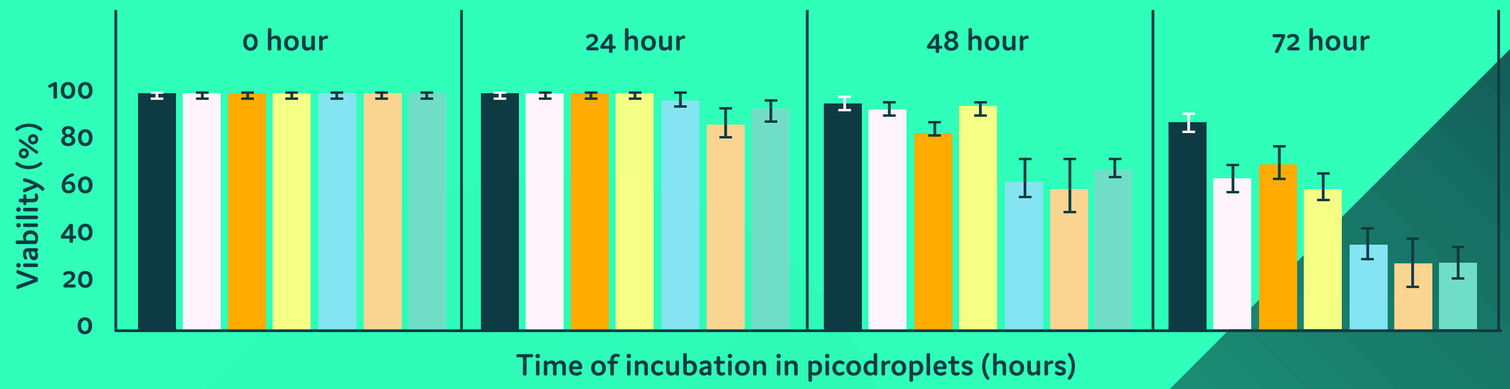
Cell viability

Picodroplets allow gas exchange, maintaining cell viability and enabling assay workflows for several days.

The timeline represents the typical time required for the different applications



The graph shows cell viability after incubation in picodroplets



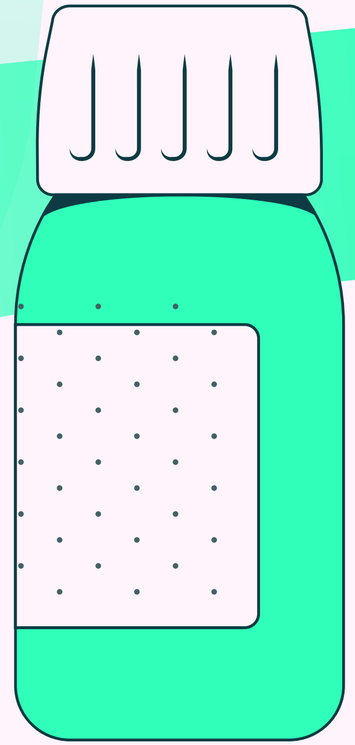
Cyto-Surf®

Cyto-Surf® A and B are the droplet forming reagents required for the Cyto-Mine® platform, manufactured in-house to the highest quality standards.

Cyto-Surf® A provides the oil phase of the aqueous-in-oil picodroplet system, allowing reliable and precise picodroplet dispensing.

Cyto-Surf® B provides the surfactant necessary to produce long-term stable aqueous droplets with the oil phase. It provides the optimum conditions for cell viability.

- **Fully optimized for Cyto-Mine®**
- **Ensure reliable and robust instrument operation**
- **Fully biocompatible**
- **Animal origin free**
- **Manufactured under our ISO9001 quality management system**



Bioassays

Identifying the most valuable cells requires a robust, reliable assay workflow. The ability to select the best cells early in the workflow, saves time, reagents and labor costs. Picodroplets act as ultra-miniaturized reaction vessels containing media, reagents and cells, allowing high throughput assays of single cells whilst maintaining cell viability.

Flexible Assay Design

Cyto-Mine® enables miniaturized fluorescence-based assays of target proteins, with high sensitivity and specificity. We provide off-the-shelf assay kits but also work with customers to adapt and optimize their own assays for use on the Cyto-Mine®.

Single Cell Assays

Use picodroplets to encapsulate single cells, reagents and media, and screen up to 350,000 cells/day using miniaturized reaction volumes that reduce reagent costs.

Types of assay

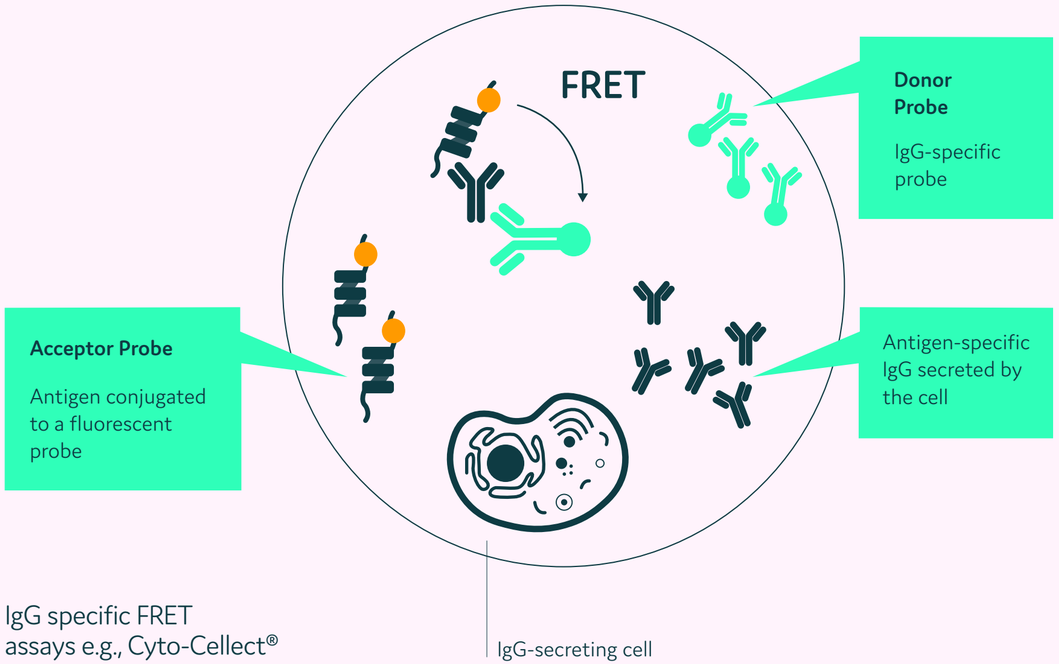
There are three key types of assays for Cell Line Development and Antibody Discovery

HUMAN IgG SPECIFIC FRET ASSAYS E.G., CYTO-CELLECT®

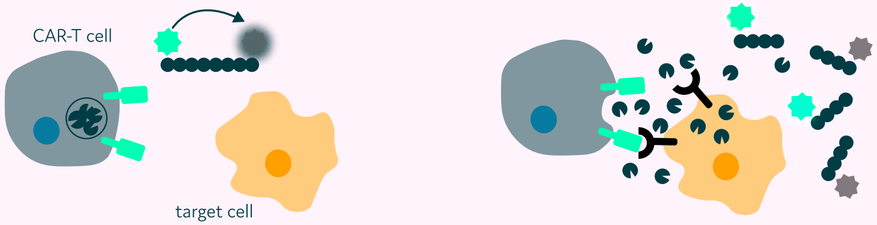
An example of a FRET assay is the Cyto-Cellect® Human IgGκ Detection Kit. This sensitive, easy-to-use, animal origin-free kit is designed to detect the kappa light chain of secreted IgG molecules and can be used to select cells based on their productivity. The kit functions effectively in conjunction with the Cyto-Mine® Single Cell Analysis Platform, which detects whole human IgG molecules with kappa light chains secreted from cells encapsulated within picodroplets. The fluorescent probes immediately bind to the IgG upon its secretion, facilitating the rapid assessment of single-cell productivity. This capability allows for the identification and selection of the most productive cells.

Each kit includes 5 vials, each containing the donor-acceptor pair of Human IgGκ Detection probes. The kit is compatible with CHO cell culture media and workflow-ready, so you can get up and running with minimum effort.

- **Easy to use FRET-based assay**
- **Sensitive and robust**
- **Miniaturized reaction volumes lower reagents costs**
- **Animal origin free**



Viability assays
e.g., Granzyme
B Assay



VIABILITY ASSAYS E.G., GRANZYME B ASSAY

Commercially available assays can be adapted for use on the Cyto-Mine® platform. In this example, a Granzyme B viability assay (SensoLyte® Granzyme B Activity Assay Kit, Anaspec, Fremont, CA) was adapted to picodroplet technology to produce a high-throughput, rapid, and robust workflow. Single CAR-T cells were screened using the assay, and levels of cell-mediated toxicity were determined.

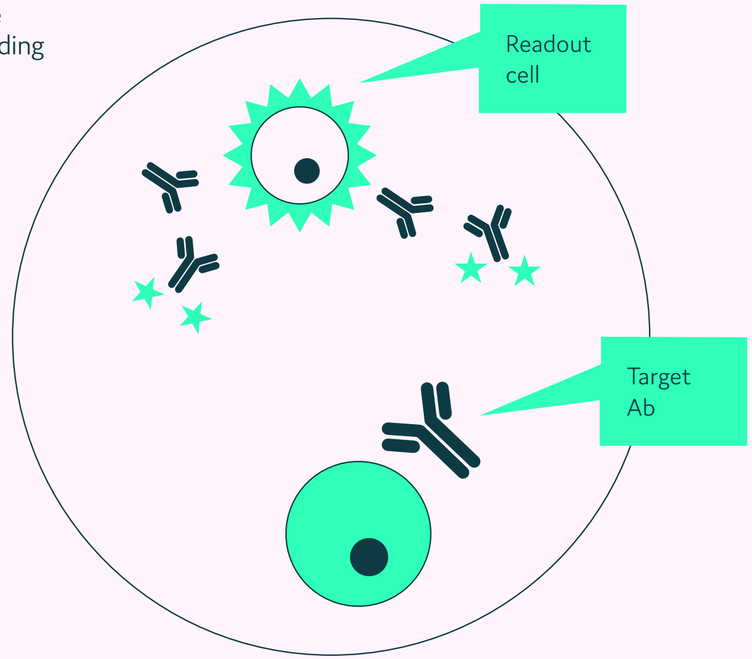
The assay is based on the cleavage of a Granzyme B substrate peptide, labelled with a 5-FAM fluorophore and a QXL®-520 fluorophore quencher. In the intact, uncleaved, state no fluorescence is emitted upon excitation of the fluorophore - due to the quenching effect of the nearby QXL®-520 molecule. In the presence of Granzyme B the peptide substrate is cleaved, releasing the quenching molecule, and resulting in a fluorescent signal.

CELL-SURFACE ANTIGEN BINDING ASSAYS

For this assay antibody-secreting cells are encapsulated together with antigen-expressing cells and detection antibodies. Upon secretion, the primary antibody is recognized by the detection antibody and also binds the antigen on the surface of the cell.

The binding of the antibody complex to the cell surface in the translocation of some of the detection antibody from homogenously dispersed appearance into cell-surface labelling. This is detected as an increase in green fluorescence using the Cyto-Mine®.

Cell-Surface
Antigen Binding



Application

Cell line development

Applications such as therapeutic antibody production or gene therapy require the development of robust, stable cell lines, that produce high quantities of target protein and can be easily scaled up to manufacture proteins commercially. Regulatory bodies (e.g., FDA, HMRA) require proof of monoclonality to ensure consistent protein production.

Large numbers of cells must be screened to find the highest producing cells, and cell viability must be maintained for subsequent large-scale manufacturing.

Continued over

Application Cell line development

Traditional methods of selecting single cells for CLD have significant limitations:

- **Fluorescence-activated cell sorting (FACS) is a high throughput screening and sorting method based on selecting cells based on their surface protein expression levels. Cell sorting is useful for finding high producing cells, but during sorting, cells are subjected to high shearing forces, which can damage them and lead to difficulties with downstream cell viability.**
- **Limiting dilution cloning involves diluting cells to a low concentration, plating them out, and waiting for them to proliferate. Limiting dilution cloning is a gentle method but is time consuming, low-throughput, labor intense, requires large amounts of reagents, and is prone to contamination. The Cyto-Mine® workflow eliminates the need for two rounds of limiting dilution cloning, saving a minimum of 2-3 months.**

Compared with traditional methods, the Cyto-Mine® platform provides automated and cost-effective high-throughput screening, with gentle processing and reduced contamination risks. Cell isolation, sorting based on productivity and clonality assurance are miniaturized and integrated within the Cyto-Mine® eliminating the need for two rounds of limiting dilution cloning. This allows productivity screening earlier in the process, and saves time, costs, and resources required to demonstrate monoclonality.

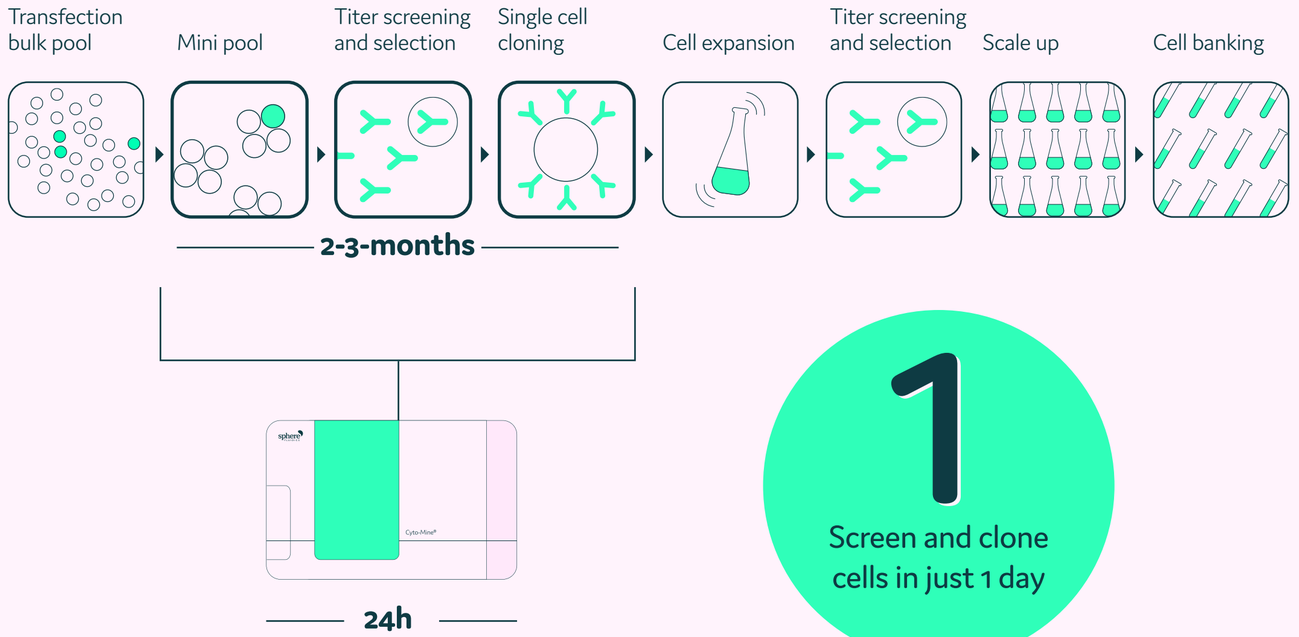
Continued over

Application Cell line development

The Cyto-Mine® can screen approximately 350,000 individual cells in a single day using this robust one-step cloning strategy. Cyto-Mine® supports 21 CFR part 11, regulation issued by the FDA.

- **Rapid identification and isolation of high-producing cells of interest**
- **Screen 350,000 individual cells/day, or tens of millions of cells in pools per day, to find your best target**
- **Measure secreted proteins**
- **Accurate single cell dispensing – select and dispense directly into wells**
- **Visual proof of monoclonality**

TRADITIONAL VS CYTO-MINE® WORKFLOWS



The Cyto-Mine® platform has been specifically designed to ensure monoclonality by using picodroplets which encapsulate single cells. Additionally, it can interrogate many cells at once, significantly streamlining the cell line development process and reducing timelines by up to 2-3 months.

CASE STUDY

Cell line development at FUJIFILM Diosynth Biotechnologies

FUJIFILM Diosynth Biotechnologies is a leading provider of cell culture services for biologics, advancing and delivering life changing therapies by offering complete solutions for cell line development, process development, late phase activities, and clinical and commercial manufacturing of a wide variety of biopharmaceuticals.

Contract Development and Manufacturing Organizations (CDMOs) such as FUJIFILM Diosynth Biotechnologies are under increasing pressure to quickly deliver robust and productive stable cell lines for emerging biotherapeutics while maintaining excellent product quality and providing evidence of monoclonality.

Adopting the Cyto-Mine® transformed the cell line development process for the team. Projects now transition from an initial transfection phase through to the development of highly productive cell lines within approximately 10 weeks, even for challenging biotherapeutics. Scientists now spend less time on laborious manual procedures, completing more projects within a given timeframe and visually demonstrating monoclonality using the Cyto-Mine®.

Motivated by the increases in efficiency within the cell line and process development teams, FUJIFILM Diosynth Biotechnologies is now exploring further applications for their Cyto-Mine® technology platform.

> *"We have integrated the Cyto-Mine® into our cell line development workflow which has allowed us to shorten our timeline without compromising on the quality of the cell lines that we generate. The ability to image the picodroplets prior to dispensing into a 96-well plate together with a 'heat-map' of the 96-well plate is a feature that we find very useful."*
>
> *Dr Alison Young | FujiFilm Diosynth Biotechnologies*

Read more

WORKFLOW **interactive page**

Cell line development workflow

FUJIFILM Diosynth biotechnologies

Show all | Clear

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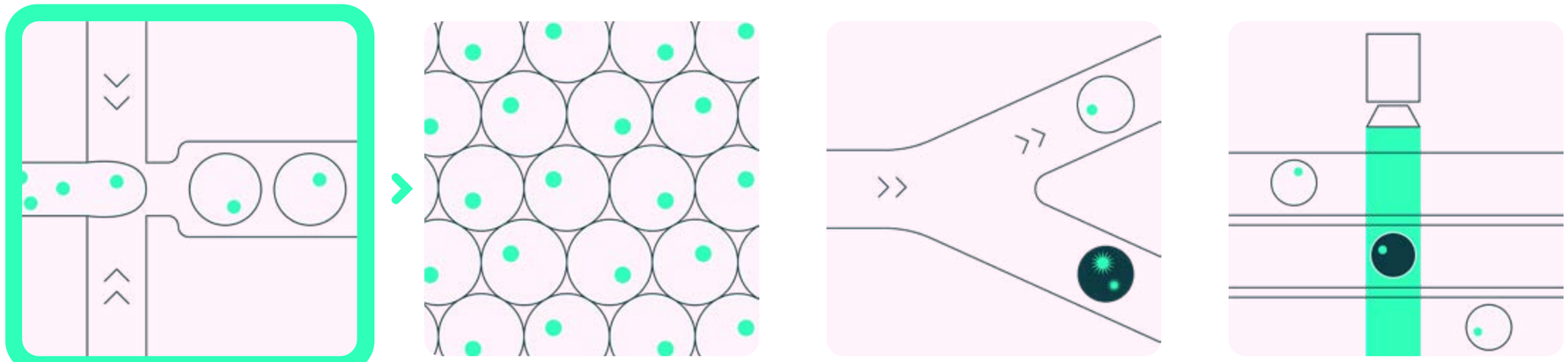


ENCAPSULATION
Into picodroplets

Application

Antibody discovery

Cyto-Mine® provides a high-throughput, fully integrated workflow for the interrogation of large antibody repertoires, accelerating the discovery of antigen-specific monoclonal antibodies.

Up to 40 million cells per day can be encapsulated in picodroplets, assayed, isolated and dispensed into 96- or 384-well microtiter plates for downstream analysis. Cells are encapsulated within picodroplets to protect them from shearing forces, and maintain viability. Sensitive single-cell antibody expression assays can be performed within picodroplets.

Traditionally, mouse B cells are immortalized through hybridoma fusion. However, the production of hybridoma fusions is time consuming, expensive and inefficient. B cells rapidly die off in culture and many do not survive the fusion process, meaning that a rare B cell of interest may be lost during the hybridoma generation process. The gentle Cyto-Mine® workflow allows direct selection of B cells, removing the need for hybridoma production.

Continued over

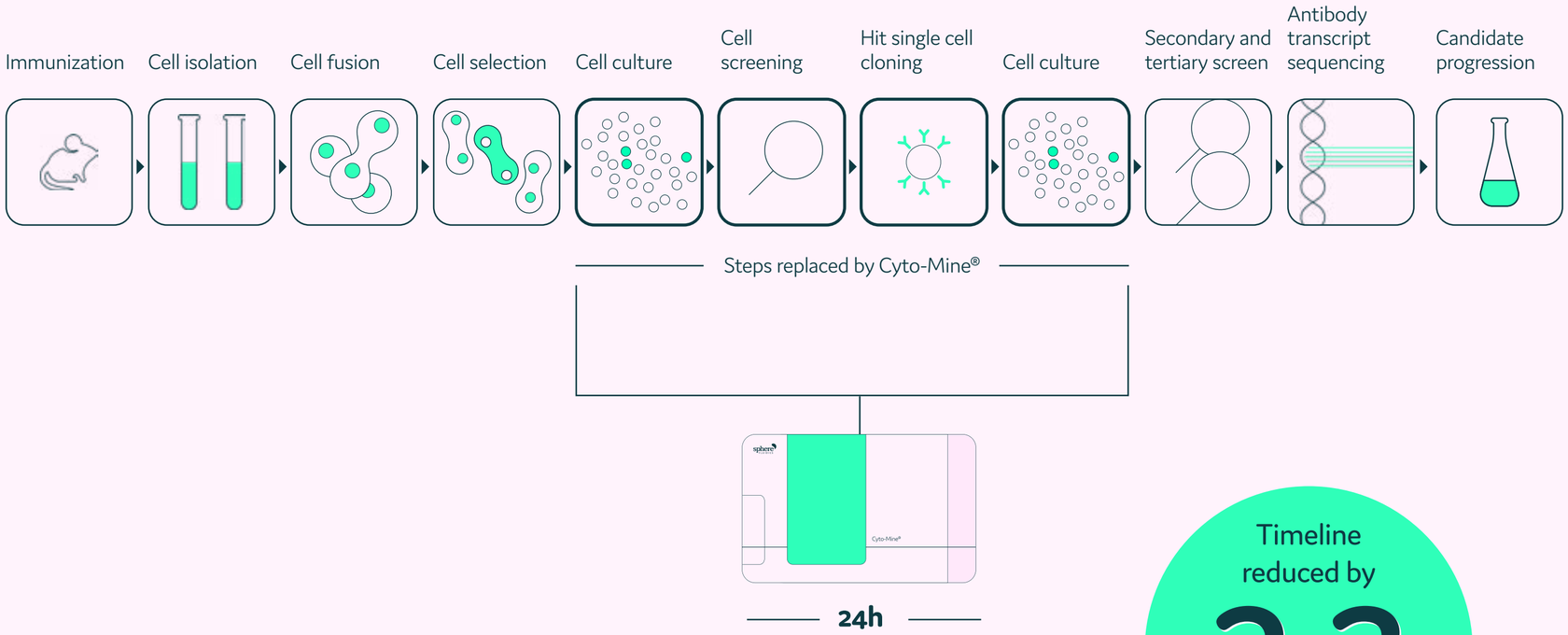
Application Antibody discovery

The Cyto-Mine® workflow also removes the need for rounds of limited dilution cloning to ensure monoclonality because picodroplets containing a single cell can be selected visually. Removing this cloning step not only saves time, but also reduces the risk of contamination or damage due to the cells during handling.

Whether you are screening hybridomas or primary B cells, the gentle Cyto-Mine® workflow offers:

- **Fully integrated workflow**
- **Sensitive single cell assays to assess antibody expression**
- **Single cells directly dispensed into microwell plates**
- **Rapidly screen large populations of B cells or hybridomas**

TRADITIONAL VS CYTO-MINE® WORKFLOW



Timeline reduced by **2-3** Months

APPLICATION NOTE

A high-throughput method for identifying and isolating rare cells secreting antigen-specific antibodies

Highly efficacious immunoglobulin-based drugs have been developed using antibody-producing B cells of the mammalian immune system. However, finding rare, high producing cells for large-scale production has always been challenging.

A key feature of Cyto-Mine® is its ability to analyze the secreted immunoglobulins from millions of cells for antigen specificity while maintaining cell viability. The gentle treatment of cells throughout the process means that, if required, B cell populations can be analyzed directly without the need for hybridoma production.

This application note demonstrates how Cyto-Mine® can:

- **Accurately identify and isolate 'hit' cells, using an antigen specific assay, from a large cell population**
- **Quantify varying concentrations of antigen-specific antibodies**
- **Significantly shorten the Antibody Discovery workflow using a high-throughput, fully integrated instrument**

Cyto-Mine® is the first fully integrated platform designed specifically for biopharma that screens millions of cells for secreted immunoglobulins, identifies and sorts the antigen-specific candidates, and then gently dispenses them into 96- or 384-well microtiter plates.

The antibody discovery workflow can be used to identify and isolate cells directly from B cells or hybridoma populations.

Read more

*This work was partly funded by the UK Government Advanced Manufacturing Supply Chain Initiative (AMSCI) as part of the BioStreamline Project which exists to develop new approaches for the more efficient development and manufacture of next generation biologics

WORKFLOW **interactive page**

Antibody discovery workflow

Show all | Clear

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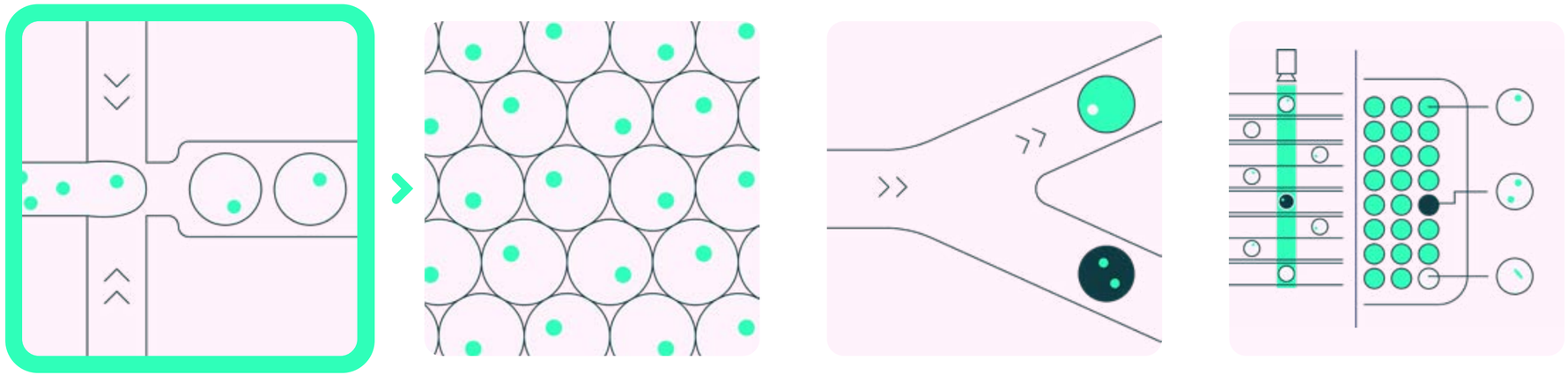


ENCAPSULATION
Into picodroplets

CASE STUDY

Revolutionizing Biologics Discovery: The Impact of Cyto-Mine® at KU Leuven

Focused on providing solutions for improved management of diseases, PharmAbs is an innovation, incubation and valorization platform at KU Leuven that bridges the gap between cutting-edge academic research and practical industry/clinical implementation. PharmAbs' primary objective is to cultivate a pipeline of groundbreaking antibody-based diagnostic and therapeutic solutions emerging from pioneering academic research.

In this context, they collaborate closely with the Biosensors group at KU Leuven, committed to advancing bio-molecular detection concepts and miniaturized analysis systems, tailored for various life science applications. Their recent endeavors, within the realm of microfluidics for single-cell omics, have gained momentum through extensive collaborations with fellow research groups and industry partners.

To deepen the exploration of antibody repertoires and foster the development of potent monoclonal antibodies, PharmAbs and the Biosensors group joined forces to create the MabMine® platform. This platform includes different approaches for the identificationg and isolation of individual B cells of interest, followed by antibody sequencing and characterization. Initially utilizing fluorescenceactivated cell sorting (FACS) and internally developed continuous microfluidic techniques, the team successfully isolated antigen-specific single memory B cells, e.g. for the discovery of highly potent SARS-CoV-2 neutralizing mAbs.

Recognizing the need to broaden capabilities and enhance the efficiency of antibody-secreting cell screening, the collaborative team seamlessly integrated Cyto-Mine® into their workflow.

The system has proven highly successful in discerning secreting hybridoma cells from nonsecretors.

Currently, the team is exploring Cyto-Mine's potential for sorting secreting primary cells from various sources, including human donors, immunized mice, and camelids. The success of Cyto-Mine® in the screening process has opened doors to exciting possibilities. The team at PharmAbs and the Biosensors group have ambitious plans to leverage Cyto-Mine® for functional antibody screenings. This involves the immediate selection of single B cells based on functional characteristics, such as agonist-receptor blocking.

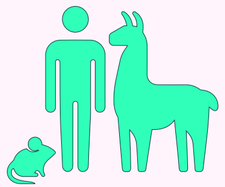
Looking ahead, Cyto-Mine® is set to play a pivotal role in cell line development. The team aims to explore its capabilities in stable cell line generationand screening of display libraries, showcasing the versatility of this revolutionary system.

*This work was partly funded by the UK Government Advanced Manufacturing Supply Chain Initiative (AMSCI) as part of the BioStreamline Project which exists to develop new approaches for the more efficient development and manufacture of next generation biologics

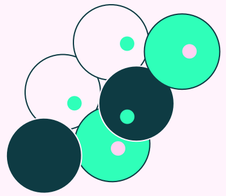
WORKFLOW

Cyto-Mine® is integrated with the MabMine® platform

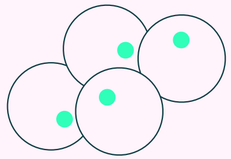
BLOOD / ORGAN COLLECTION



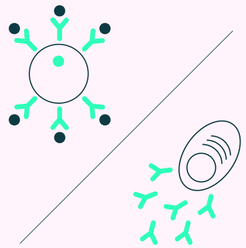
PBMC ISOLATION



B CELL ENRICHMENT

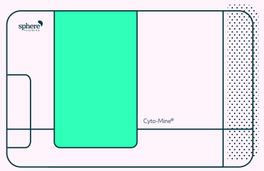


STAINING OF (AG-SPECIFIC) IMMUNE CELL-TYPES



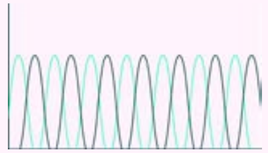
PharmAbs and the Biosensors group's updated workflow integrating Cyto-Mine®, with their proprietary MabMine® platform has enabled them to efficiently distinguish secreting hybridoma cells from non-secretors.

KU LEUVEN



Cyto-Mine®

SINGLE CELL SORTING



SEQUENCING

IN VITRO PRODUCTION

COMPANY OVERVIEW

About us

Based in Cambridge UK, one of the world's best known science and technology hubs, Sphere Fluidics has evolved since it's Cambridge University spin-out days to become leading experts in picodroplet microfluidic technology.

Sphere Fluidics instruments and consumables enable users to find, analyse and isolate the most valuable cells with ease and speed. Backed by 138 patents, 14 trademarks and substantial FTO (freedom to operate), the portfolio includes:

- **Cyto-Mine®, an automated industrial platform capable of screening up to 40 million cells in a matter of hours – compared with 10,000 typically achieved using multi-step manual techniques.**
- **Pico-Mine®, a semi-automated research platform compatible with third party products. Much like the Cyto-Mine® in terms of benefits offered, but available with up to 4 lasers and a pick and mix choice of components; making the platform highly flexible for a variety of applications.**

The strength of Sphere Fluidics core technology and it's development has led to over 70 international innovation awards, ISO certification, and GLP & AOF compliance for customer assurance.

Sphere Fluidics teams are made up of experts with many years of technical, scientific, manufacturing and industry expertise. Along with our global distributors, they work closely with customers to ensure instruments keep delivering the significant time and cost savings, the customers' expect. As well as providing absolute assurance of monoclonality, quality and reliability as stipulated by regulatory authorities such as the FDA.

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IN PARTNERSHIP

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HOW WE CAN HELP

Whether you're developing a functional assay, your targets are soluble molecules or membrane-bound, we have the experience and capability to develop what you need.

The Cyto-Mine® transforms cell line development and antibody discovery operations by streamlining and automating your tasks with unmatched efficiency. This high-throughput solution is designed to suit a broad spectrum of workflows, enhancing both straightforward and complex experimental setups. Choose Cyto-Mine® to elevate your workflows, ensuring a seamless integration of technology and innovation for superior outcomes.

Next steps:

1. Our team will have an in-depth discussion with you to fully understand your unique needs
2. We'll then work to develop a suitable workflow to achieve your goals
3. Steps and timelines will be mutually agreed for the development and delivery of components and a functional platform.

Contact our team today:

Contact us

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Ordering

Product name and description	Product code
Cyto-Mine®, single cell analysis and monoclonality assurance system	S003
Cyto-Cellect®, Human IgGκ Detection Kit	C310
Cyto-Cellect®PLUS, Human IgGκ and IgGλ Detection Kit	C311
Cyto-Mine® Consumables Kit, includes, Cyto-Cartridge®, Pack of 5, Cyto-Surf® A, 250ml bottle and Cyto-Surf® B, 250ml bottle	C301
Cyto-Cartridge®, Pack of 5	C302
Cyto-Surf® A, 250ml bottle	C303
Cyto-Surf® B, 250ml bottle	C304
Cyto-Surf® A, 250ml bottle and Cyto-Surf® B, 250ml bottle	C305

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