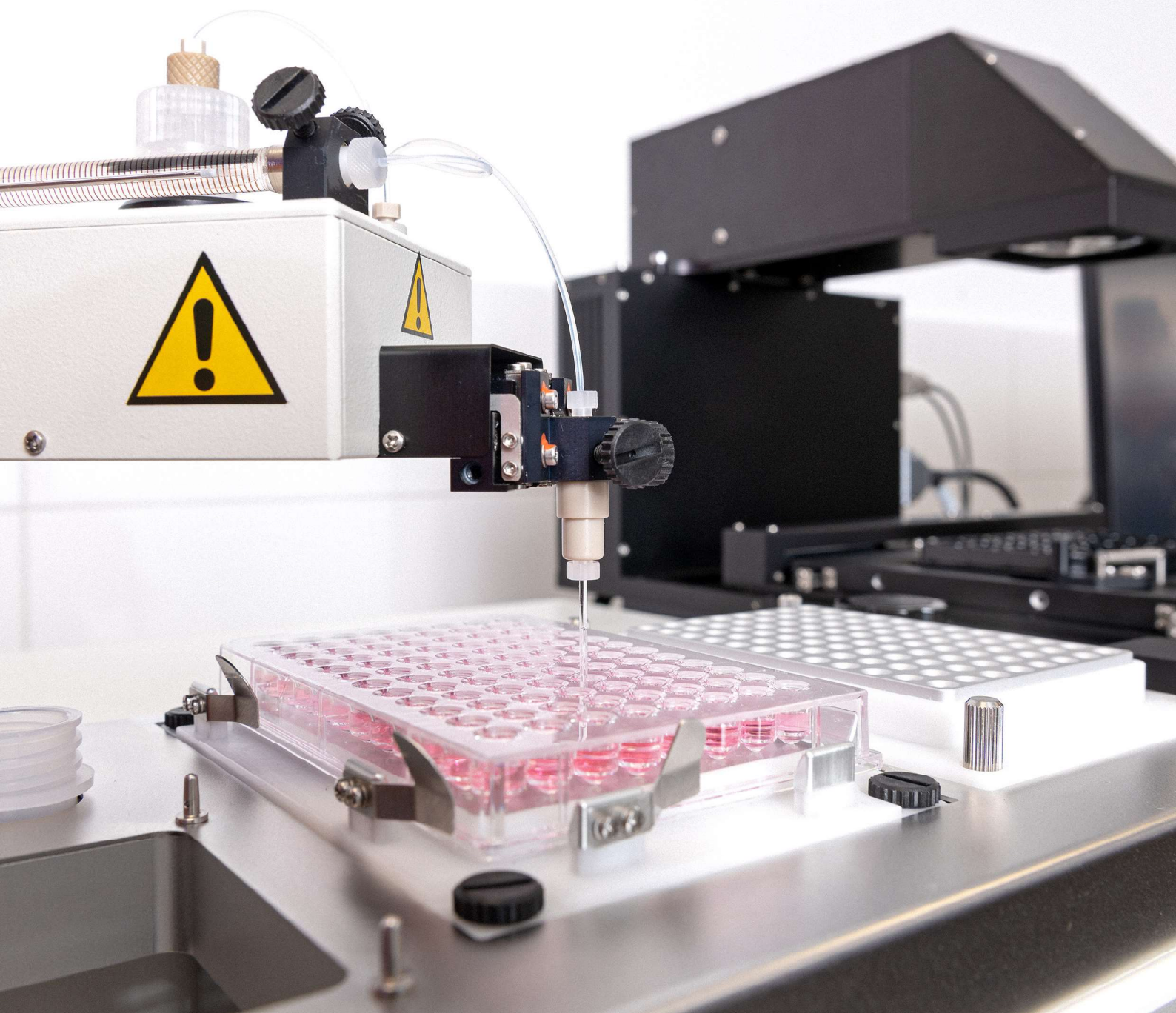




CellCelector Flex

Automated Single Cell
and Colony Picking System

Simplifying Progress

SARTORIUS

Cell Selection and Retrieval

The CellCelector Flex platform is a unique and fully automated cell imaging and picking system developed for the detection, selection and isolation of single cells, clusters, spheroids and organoids, as well as single cell clones and adherent colonies.

The cell picking technique is predicated on a non-invasive mechanical aspiration process where cells of interest can be detected, identified and selected in a fully automated manner, using either label-free size and morphology characteristics, or fluorescence markers.

The entire workflow is fully documented by providing live images before, during and after cell picking, as well as cell tracking data from source to destination to ensure full traceability of the screening and cell recovery process.

Used in a multitude of research areas, such as circulating tumor cell | CTC screening, stem cell research, cell line development and antibody discovery, the CellCelector's unique versatility utilizes three exchangeable picking modules to ensure optimal cell selection and retrieval.

Picking Modules

- Single cell picking module
- Adherent colony picking module
- Semi-solid media picking module

Deck Tray for Destination Plates and Buffers

- Temperature control for destination plates (4 °C - 40 °C)

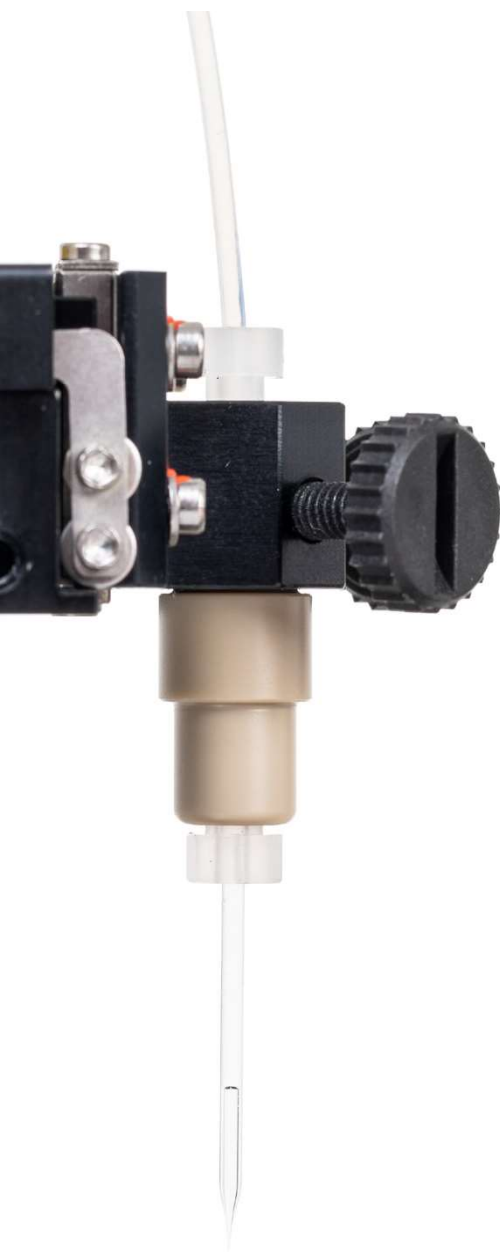
Inverted Microscope with CCD Camera

- Objectives ×2 to ×40
- Bright field (BF)
- Phase contrast (PhC)
- Fluorescence with 6 excitation channels and up to 14 colors

Motorized High-Precision X|Y-Stage with Autofocus

- For source plates





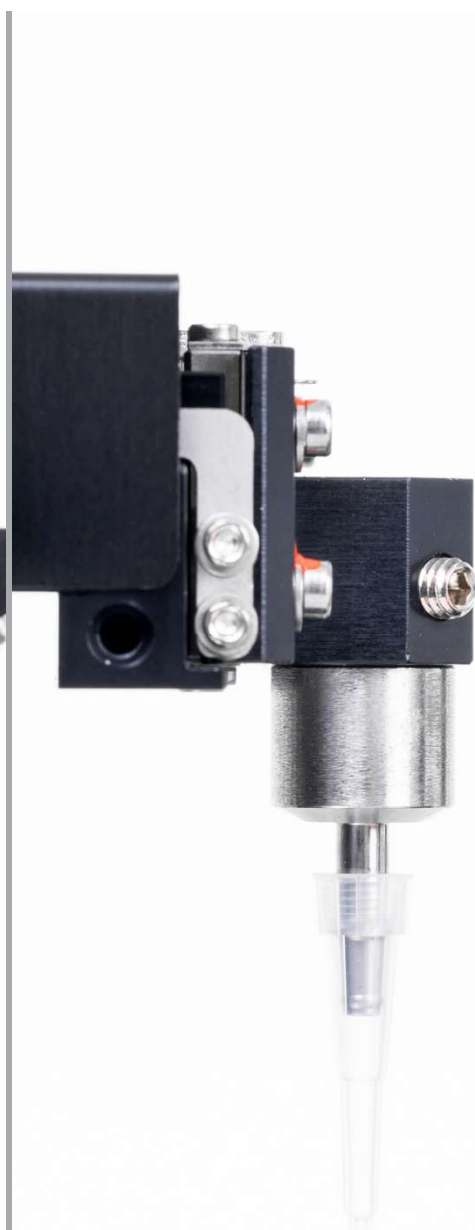
Single Cell Picking Module

The single cell picking module uses liquid buffered, single-use glass capillaries for a gentle, high-precision, low-volume aspiration of cells and liquids. This module is ideal for the isolation of individual cells and multi-cellular objects from nanowell arrays and mixed cultures in liquid or semi-solid media.



Adherent Colony Picking Module

The scrape module utilizes reusable and autoclavable stainless steel ScrapeTips, allowing for contamination-free adherent colony picking. This module is suited for the clonal picking of adherent stem cell colonies in liquid media, such as iPSC, mESC, hES and hASC, both from feeder cells and feeder-free cultures, or any other adherent colony, spheroid, or tissue applications.



Semi Solid Media Picking Module

The semi-solid media picking module uses disposable plastic PrecisionTips to prevent cross-contamination and offer minimal routine maintenance. This module is ideal for the picking of clones, colonies, spheroids, large organoids and other 3D objects from semi-solid media such as methylcellulose or Matrigel®.

CellCelector Workflow

An intuitive and easy-to-use graphical user interface guides the operator through every step of the experiment. Each step provides access to only those features and data required for each respective step. Accordingly, all options unrelated to the current experiment step are hidden from the operator, thus reducing complexity.

In addition, different user levels allow easy access to the software without intensive training for new operators, while offering advanced features, open access to all parameters, calibrations and customization capabilities for power users. This enables simple day-to-day use as well as performing sophisticated and complex experiments.

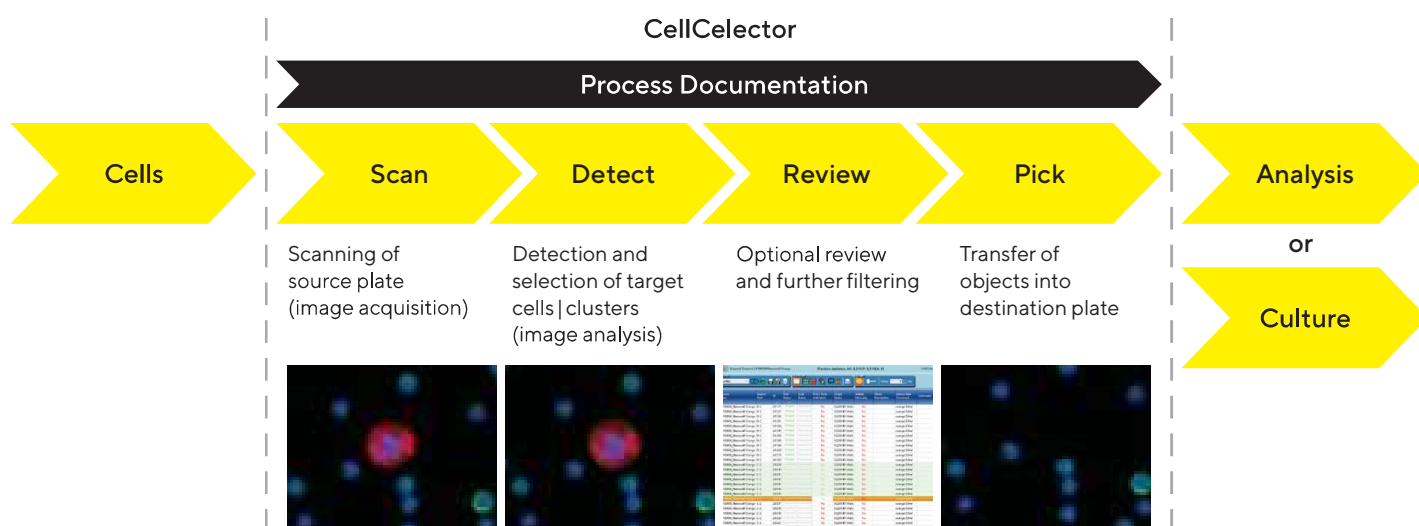


Figure 1:

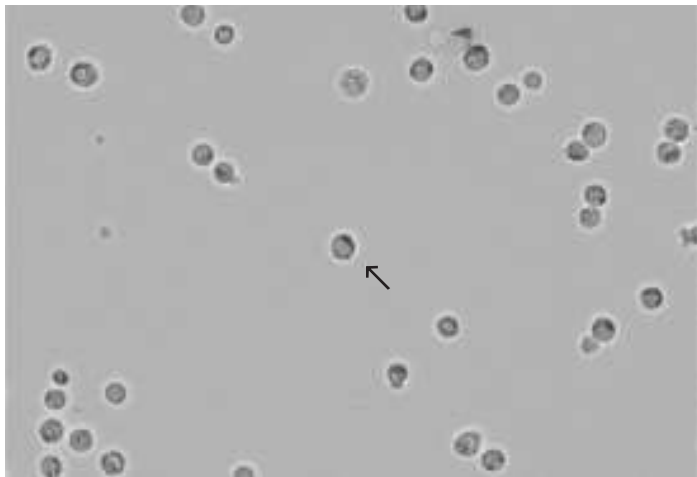
The CellCelector Flex offers a simple, streamlined workflow to ensure optimal cell transfer efficiency. Starting with cells in suspension or any adherent or tissue applications, the CellCelector Flex acquires source images and selects target cells for picking, before further analysis or additional cell culture.



The standard experiment workflow of the system is separated in up to five steps:

- **Scanning** of source vessels in brightfield, phase contrast and/or fluorescence to acquire and store images
- **Analysis** of acquired images and detection of cells or colonies of interest according to user-defined criteria
- **Review, Classification and Ranking** of the analysis results by the operator
- **Picking** of the detected single cells and colonies
- **Documentation and export** of the results (images, numeric data)

Before Picking



After Picking

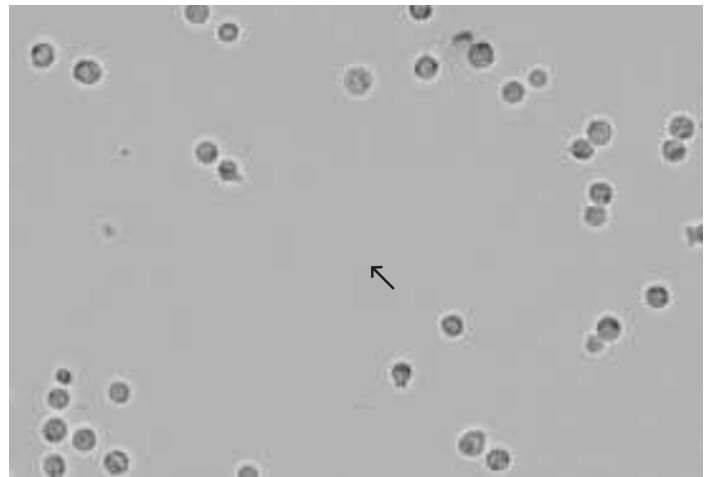


Figure 2:

Example of automatically acquired before and after picking images during single cell picking (bright field, $\times 10$, PC3 cell line)



Key Workflow Steps

Scanning

The microscope and camera are completely controlled by the CellSelector software, with customizable imaging configurations containing all imaging parameters, easily interchangeable with a simple click. Depending on application requirements, scans can either be conducted in brightfield, phase contrast or across 6 fluorescence channels (up to 14 color). Each scan runs according to predefined settings to guarantee a successful recognition and detection of cells and cell colonies.

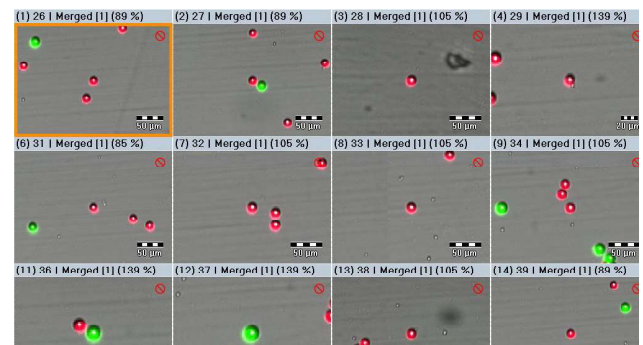
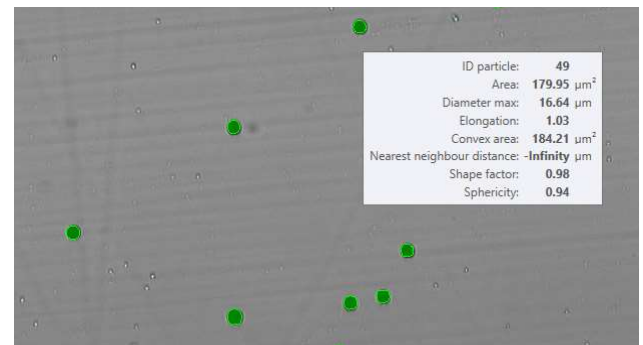
Analysis and Detection

Each scan is automatically analyzed to detect the target cells of interest according to pre-defined user parameters such as grey values, fluorescence intensities and a wide range of morphological measurements. A preview mode allows for the simple examination of each measurement and the quality of the current analysis settings.

Review and Selection

Analysis results are listed as detected objects with their corresponding parameter values, and can be revised by applying additional numerical filters, setting gates, ranking target cells or reviewing the images of detected cells in an image gallery.

The detected target cells can be visualized in various modes, for example as a gallery of all scanned channels for the detected cells or as an overview gallery, which allows for a fast visual confirmation of the picking list.



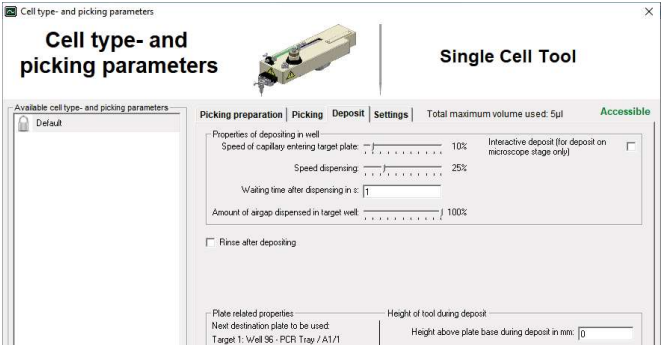
Picking

The CellSelector software gives the operator access to a wide range of picking parameters which can be individually adjusted to optimize picking results. The system not only allows objects to be picked from standard cell culture dishes or plates, but also from membranes, filters or microscope slides.

Documentation

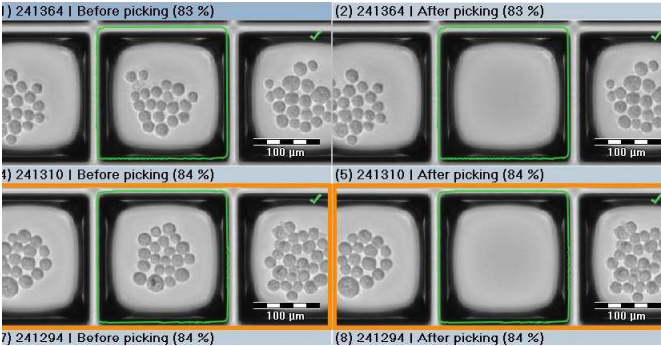
The entire workflow – from imaging to picking – is fully documented and compliant to GLP and GMP standards. The software automatically saves microscopic high-quality images immediately before and after each pick allowing for a subsequent review of picking results, both in brightfield and |or any fluorescent channel.

Each detected |picked object can be identified by its unique ID and tracked through the complete process, from source to destination well, and all numeric data including all user defined detection parameters, as well as the images, can be exported quickly and easily for documentation, archiving or importing into an LIM system.



[Import] 200415 [Particle statistics: All: 31,94]

Source Plate	Source Well	ID	Pick Status	Scan Status	Export Images	Destination Plate	Destination Well	Status Description	Origin Name	Source Well Comment	Comment
1	200415	D-1	39714	Picked	Unscanned	Yes	Left	A-2		10x BF	
2	200415	D-1	39713	Picked	Unscanned	Yes	Left	A-2		10x BF	
3	200415	D-1	39712	Picked	Unscanned	Yes	Left	A-2		10x BF	
4	200415	D-1	39711	Picked	Unscanned	Yes	Left	A-2		10x BF	
5	200415	D-1	39710	Picked	Unscanned	Yes	Left	A-2		10x BF	
6	200415	D-1	39709	Picked	Unscanned	Yes	Left	A-2		10x BF	
7	200415	D-1	39708	Picked	Unscanned	Yes	Left	A-2		10x BF	
8	200415	D-1	39706	Picked	Unscanned	Yes	Left	A-1		10x BF	
9	200415	D-1	39705	Picked	Unscanned	Yes	Left	A-1		10x BF	
10	200415	D-1	39704	Picked	Unscanned	Yes	Left	A-1		10x BF	
11	200415	D-1	39703	Picked	Unscanned	Yes	Left	A-1		10x BF	
12	200415	D-1	39702	Picked	Unscanned	Yes	Left	A-1		10x BF	
13	200415	D-1	39701	Picked	Unscanned	Yes	Left	A-1		10x BF	
14	200415	D-1	39700	Picked	Unscanned	Yes	Left	A-1		10x BF	
15	200415	D-1	39699	Unpicked	Unscanned	No				10x Cy5	
16	200415	D-1	39698	Unpicked	Unscanned	No				10x Cy5	



CellCelector Housing

Working with live cells invariably requires sterile work conditions and a continuous, regulated physiological environment. The Incubator Flowbox provides a unique combination of:

- A HEPA filtered, vertical laminar airflow
- Precise control of temperature, humidity and CO₂ levels
- Smart air speed and exhaust control even when access doors are opened
- High energy UV-C lamps for surface sterilization
- Optimal cell viability in source and destination plates
- User-friendly control panels
- Easy access to instruments without losing the controlled environment

Three Different Housing Options are Available, Depending on Specific Research Requirements



Incubator FlowBox

- User protection
- Sterility
- Temperature, CO₂ and humidity control



Customized Biosafety Cabinet

- User protection
- Sterility
- Provided by Sartorius or customer biosafety cabinet

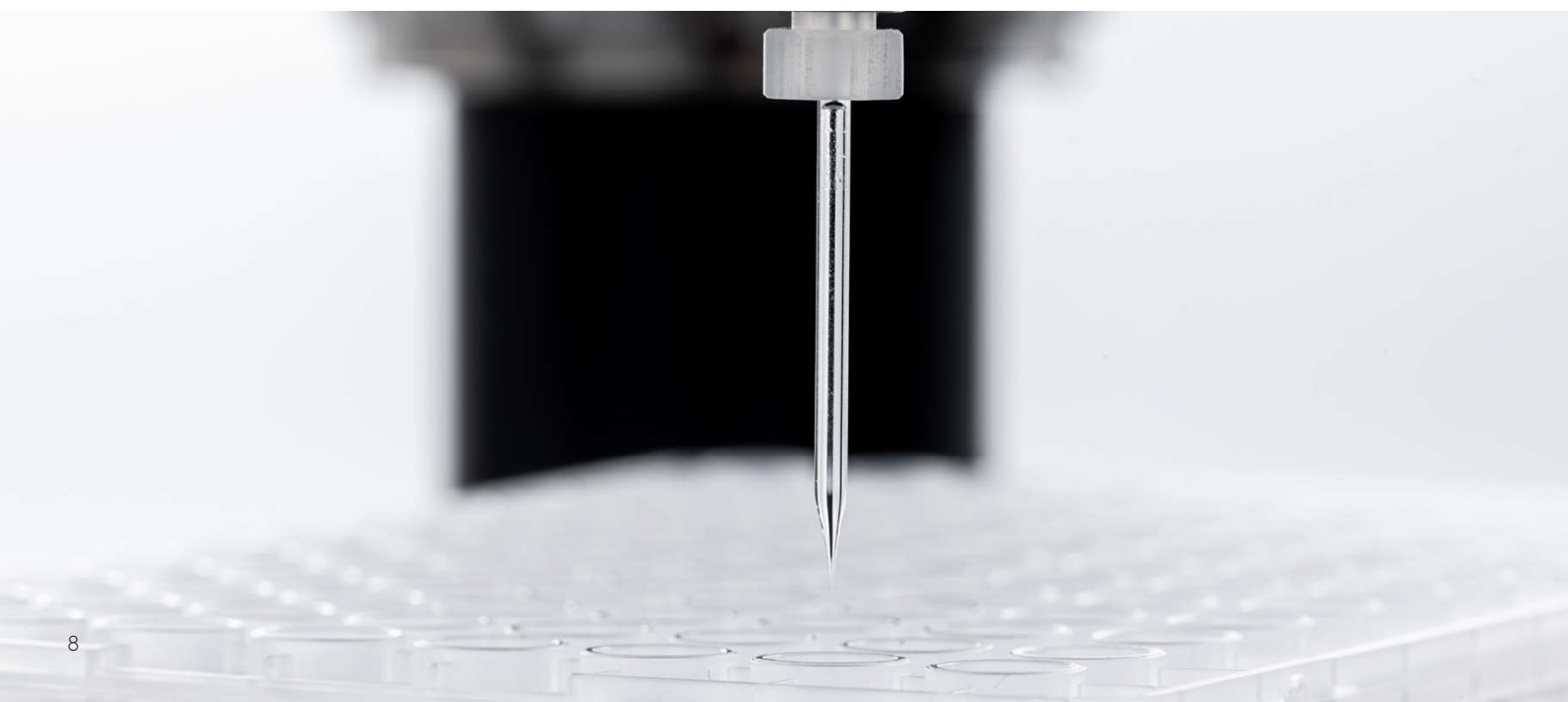


CellCelector Flex PCR Hood

- User protection

Figure 3:

Different CellCelector housing options are available, from the CellCelector Flowbox, to customized biosafety cabinets and PCR hoods.



Nanowell Arrays for Single Cell Isolation, Screening and Cloning

Innovative CellSelector nanowell plates are available for single-cell screening, isolation and cell cloning workflows within various clinical, research and bioprocessing applications. Nanowell arrays are available in various formats – from 2 well chamber slides to 6 and 24 well plates – and feature from 100,000 to several millions of nanowells per plate or slide, at nanowell volumes from several nanoliter down to a few picoliter.

CellSelector nanowell plates are ideal for high-throughput single cell cloning and screening, single cell cloning after gene editing, the isolation of sets of defined cell numbers for reference samples, and spheroid formation, imaging and screening

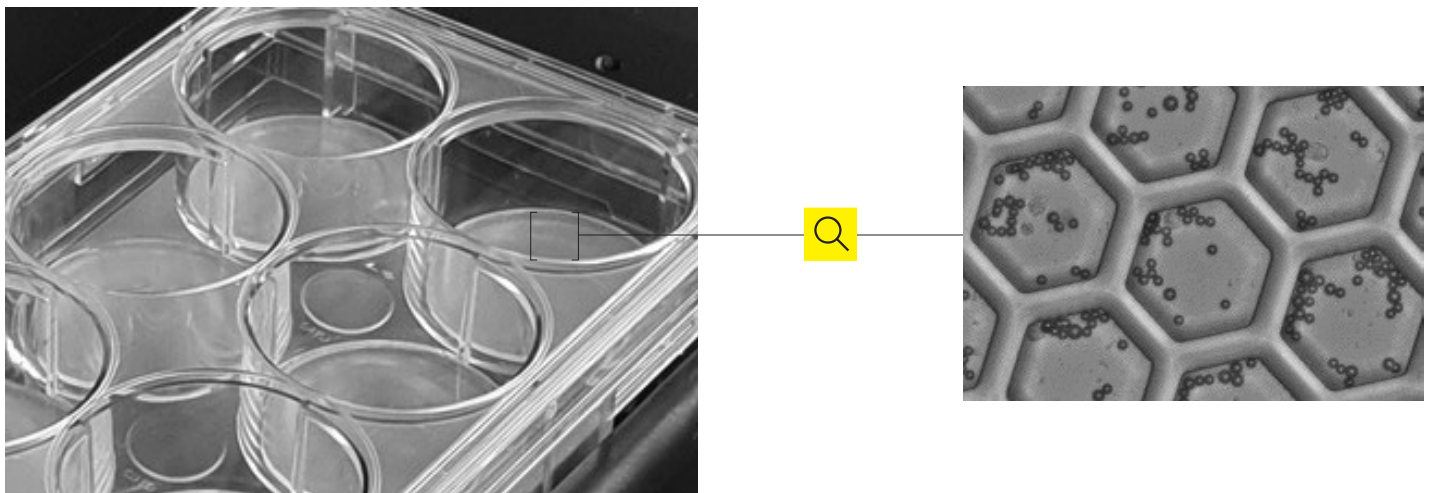
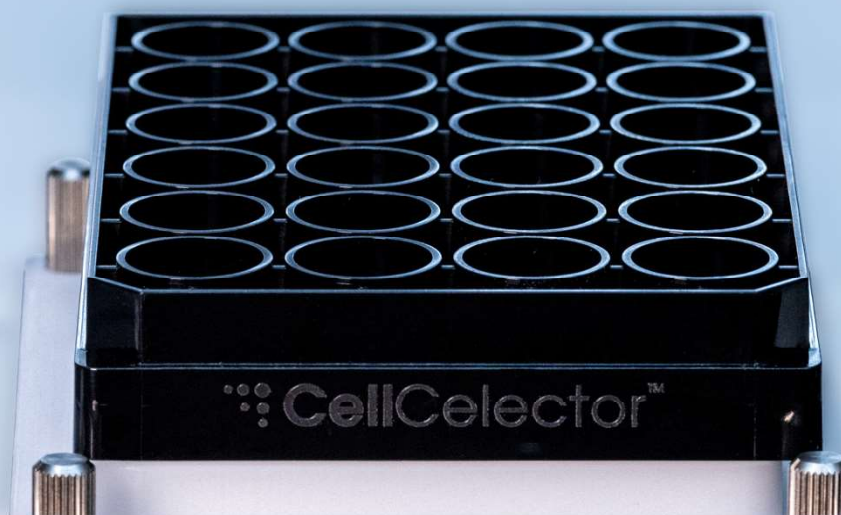


Figure 4:

CellSelector nanowell plates feature thousands of 200 μm square shape nanowells allowing for the parallel cloning of hundreds or thousands of clones. An ultra-low attachment (ULA) surface prevents cells from adhering to the surface and therefore allows 3D spheroid formation and a 100% efficient automated single cell or clone transfer from the nanowells to regular cell culture plates for expansion or analysis.



Key CellCelector Features – At a Glance

Extremely Versatile

- Adherent cells, cells in suspension or in semi-solid medium
- Single cells, clusters, spheroids or colonies
- Primary cells or cell lines
- Living or fixed cells

Flexible

- Brightfield, phase contrast and fluorescence imaging
- Automated, semi-automated or manual cell selection for picking
- Standard or custom source and destination vessels like microplates, dishes, slides, filters, chips, PCR plates| tubes
- Upgradability, customized solutions and integration into a large platform

Reliable

- Accuracy of picking > 95% of selected specific sub-populations
- Automatic re-location of moving objects
- Possible re-picking of failed picking events
- Software automatically detects successful picking

Gentle

- No influence on characteristic properties of cells
- Isolation of pure intact cells ready for molecular characterization or cell culture
- High cell integrity and outgrowth rates after picking
(including up to 95% and more viability in single cell cloning applications)

Fast

- Short experiment hands-on time
- 20 to 30 seconds per pick

Upstream | Downstream Compatible

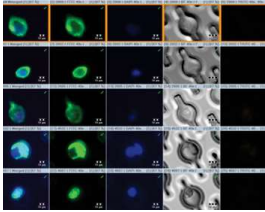
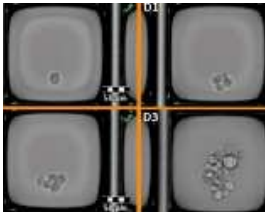
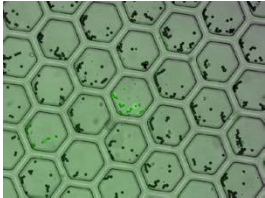
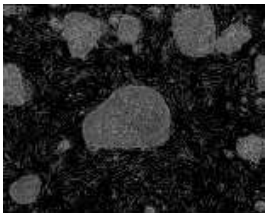
- No complex sample preparation and no expensive consumables required
- Compatible with several upstream enrichment technologies (immunomagnetic enrichment, sized based separation etc.)
- Low aspiration, dispensing and buffer volumes (down to ~10 nl)
- Single cell PCR, NGS, RNA-Seq, cell cloning, titer analysis, upscaling etc.

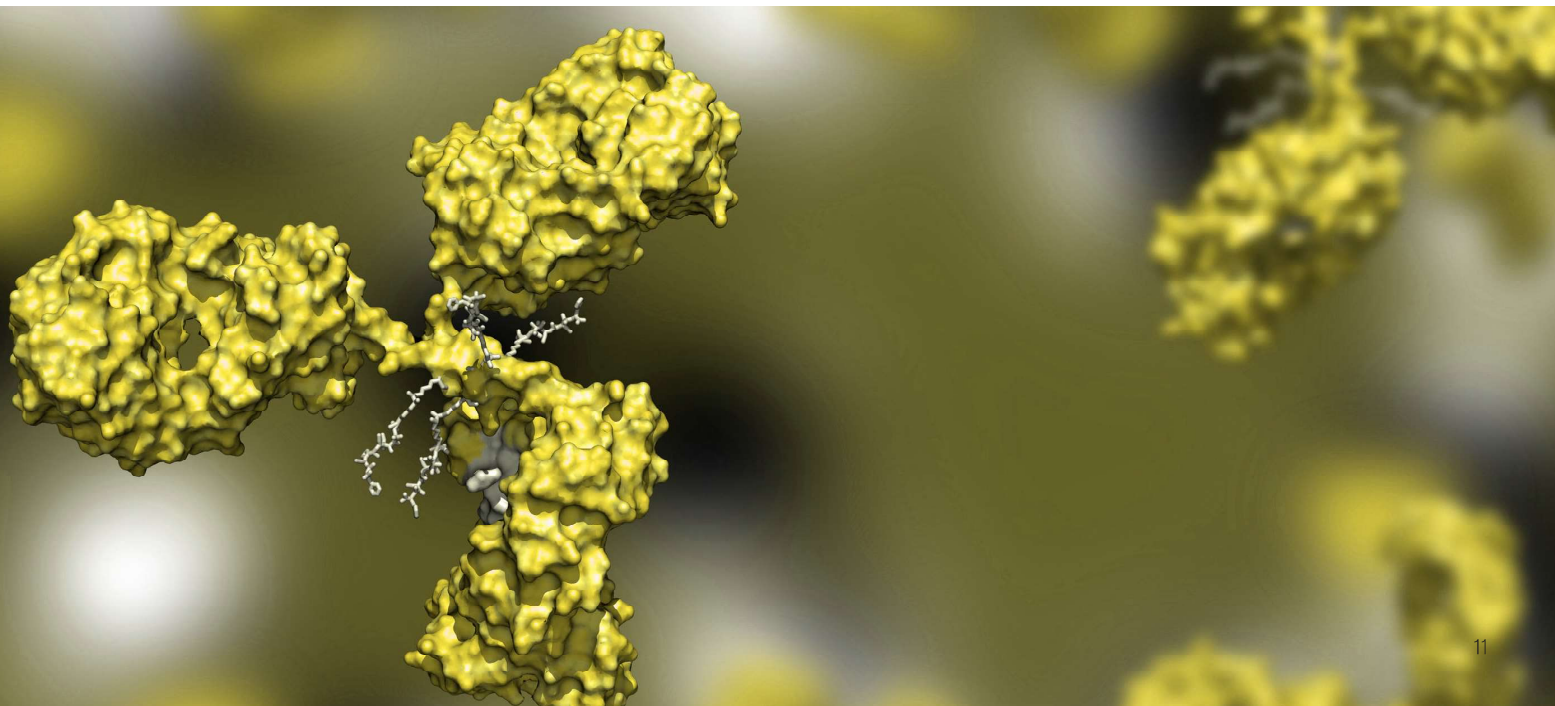
Documented

- Complete work flow documentation compliant to GLP and GMP standards
- Quality control by using live-tracking and high-quality real-time images taken before and after each picking event
- Unique ID for each detected | picked object, tracking from source to destination well
- Easy export of all imaging and numeric data



Key CellCelector Applications – At a Glance

Validated Applications	
Single Cell Isolation	 ▪ Rare single cell isolation ▪ CTC isolation and analysis ▪ Fetal cells cbNIPT ▪ Sperm cell isolation ▪ Protoplasts plant cells ▪ Single cell heterogeneity ▪ CRISPR single cell cloning
Cell Line Development	 ▪ Single cell cloning for CLD ▪ Mini-pool creation and selection ▪ Colony picking from semi-solid media
Antibody Discovery	 ▪ Single cell plasma B-cell screening ▪ Nanowell-based hybridoma screening ▪ Screening and picking of hybridoma colonies from semi-solid media ▪ Hybridoma subcloning ▪ Bead-based assays
Stem Cells	 ▪ iPS single cell cloning ▪ Clonal stem cell colony picking ▪ Hematopoietic stem cell colony picking ▪ Spheroid isolation



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