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CellCultivator

AUTOMATICALLY CULTIVATE, ANALYZE AND SELECT CELLS

CellCultivator at a glance

- Generation of reproducible cell cultures with high throughput
- High-resolution live cell imaging (transmitted light or fluorescence)
- Fast scanning
- Image analysis with trainable pattern recognition (cell confluence, cell counting, etc.)
- Picking of single cell colonies

- Continuous documentation and quality monitoring
- State-dependent system control
- Standard culture vessels

- Customer-specific system layout
- Modular design for the entire system
- Expandable by spectroscopy or holographic analysis

TITLE PAGE *CellCultivator guides the cell cultivation process completely on its own. The system includes a microscope which captures and documents the state of the cultures at each point in the growth process.*

6 *The transfer station provides the user with a complete, sterile user interface for insertion and removal of all materials.*
(image source: Studio Nordbahnhof/ Fraunhofer)

Development partners

Fraunhofer Institute for Manufacturing Engineering and Automation IPA
- Central handling unit
- Liquid handling unit
- Storage incubator
- Transfer station
- Colony picker

Fraunhofer Institute for Physical Measurement Techniques IPM
- Automatic microscope with pattern recognition function
- Picker microscope

Fraunhofer Institute for Applied Information Technology FIT
- Pattern recognition function for automated microscope

Max Planck Institute of Molecular Cell Biology and Genetics MPI-CBG
- Definition of cell structure protocols and specifications
- System testing and commissioning

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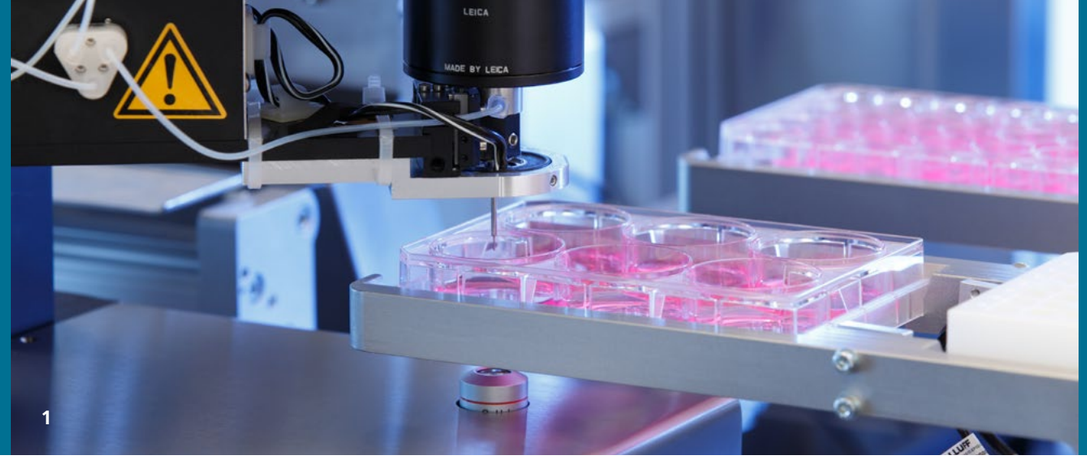

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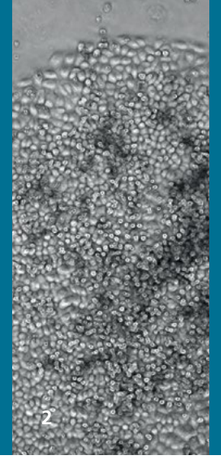

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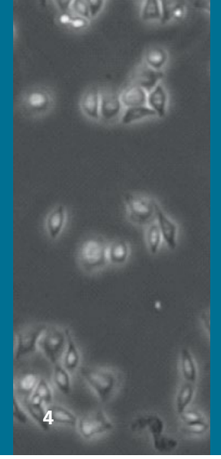

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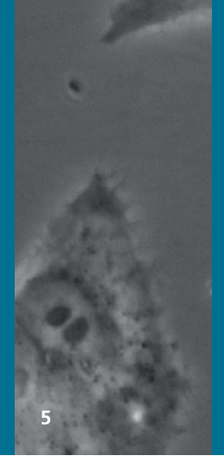

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Working with cell cultures is part of the daily routine in medical and biological research – both in industry and in academia. During cell cultivation and performance of standardized cellular screenings, automated protocols make for greater process efficiency and reproducibility. CellCultivator is a modular, fully automatic system that performs time-consuming laboratory work independently and with high throughput. An automatic microscope, combined with intelligent software, continuously monitors, optimally controls and documents the culture process.

Separately or as a package – modular design to meet customer requirements

The system primarily consists of six modules that can also be used separately from one another:

- robotics for cell cultivation
- liquid handling unit
- automatic microscope with pattern recognition function
- colony picker
- transfer station
- storage incubator

CellCultivator offers plenty of flexibility: Its modular design allows the system to be adapted to existing, customer-specific processes – including individual requirements, such as specific culture vessels or special procedures. Even existing systems can be expanded with individual CellCultivator components.

Continuous monitoring – automatic colony picking

An automatic microscope with intelligent image processing captures and documents the state of the cultures at each point in the process. This allows cultivation processes to be monitored online, automatically controlled and optimized – without the presence of a laboratory employee. Current measured values – such as the cells' degree of confluence, fluorescent properties and morphological characteristics – flow into the system controls. Thus CellCultivator automatically optimizes the processes individually for every culture – up to now a unique function in automated cell cultivation. The high quality of optical imaging and image analysis allows it to recognize and select the relevant structures in the multititer plates (MTPs). The entire colony picking process is done automatically with precision in the micrometer range.

One system – six modules

Central handling unit
The central handling unit consists of a high precision planar table with two running plates which transport the cultures in MTPs (of 6 to 96 wells) to each of the stations. The unit works with positioning precision of 0.25 µm over a surface of 0.8 m x 2 m. Up to six MTPs can be processed in parallel.

Automatic microscope plus self-learning software
The inverse microscope is fully automatic: from transfer of the support plates onto the microscope platform, to focusing and lens change, and activation of light sources, all the way to image capture and processing. In the microscopic unit, standardized cell culture conditions prevail (37° C, up to 90% relative humidity, 5% CO_2 content). Transmitted light and fluorescence images of the cultures are taken both in quick scan mode and at subcellular resolution. Microscopic optics and adapted pattern recognition allow state-dependent processing of the cultures. To recognize the sample of grown cells on the support medium automatically, software is trained through self-learning algorithms. For example, using example areas for the foreground and background, the software can determine confluence automatically with high throughput. The software's ability to learn allows it to adapt to various cell types.

Precise colony picking with integrated imaging
The automatic picking unit consists of a picking arm, including a hollow needle, and a microscope optimized for this task, which can be used with transmitted light in phase contrast. The cell areas to be picked are determined by the optical unit. Their position is transmitted to the picking unit which then transfers the colony into a new cell culture dish (MTP). The picking unit's image recording ensures optimization of the picking position and evaluation of the picking result.

Storage incubator
The incubator contains a barcode reader and stores up to 360 MTPs of various formats. Temperature, humidity and CO_2 are precisely controlled within the incubator. The incubator can be completely sterilized.

Liquid handling unit
A multi-dispenser distributes up to 8 media with dosing precision of up to 3 µl. The system has a set of several needles, so that various pipetting steps can be carried out in parallel.

Transfer station
The transfer station provides the user with a complete, sterile user interface for insertion and removal of all materials. Special attention has been paid to its intuitive handling.

1 *The microscope is fully automatic: from transfer of the culture vessels, to focusing and lens change, all the way to activation of light sources. Scanning with the hardware autofocus provides a fast initial overview. High-resolution optics and additional software autofocus allow a look into the individual cells.* *(image source: Studio Nordbahnhof/ Fraunhofer)*

2–5 *Cell culture images:*
Overview images (1.25x) of a GFP-marked adherent cell colony (2 transmitted light, 3 fluorescence); 4 scans (5x) of adherent HeLa cells (phase contrast);
5 HeLa cells at 40x resolution (phase contrast) *(image source: MPI-CBG)*