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1 *Cellular states and dynamic processes of fibroblasts with live cell imaging.*

2 *BioImaging system with 3 modules and hardware to investigate processes with different time scales.*

BIOIMAGING SYSTEM – FLEXIBLE AND DYNAMIC EXPERIMENTS BY LIVE CELL IMAGING

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Motivation

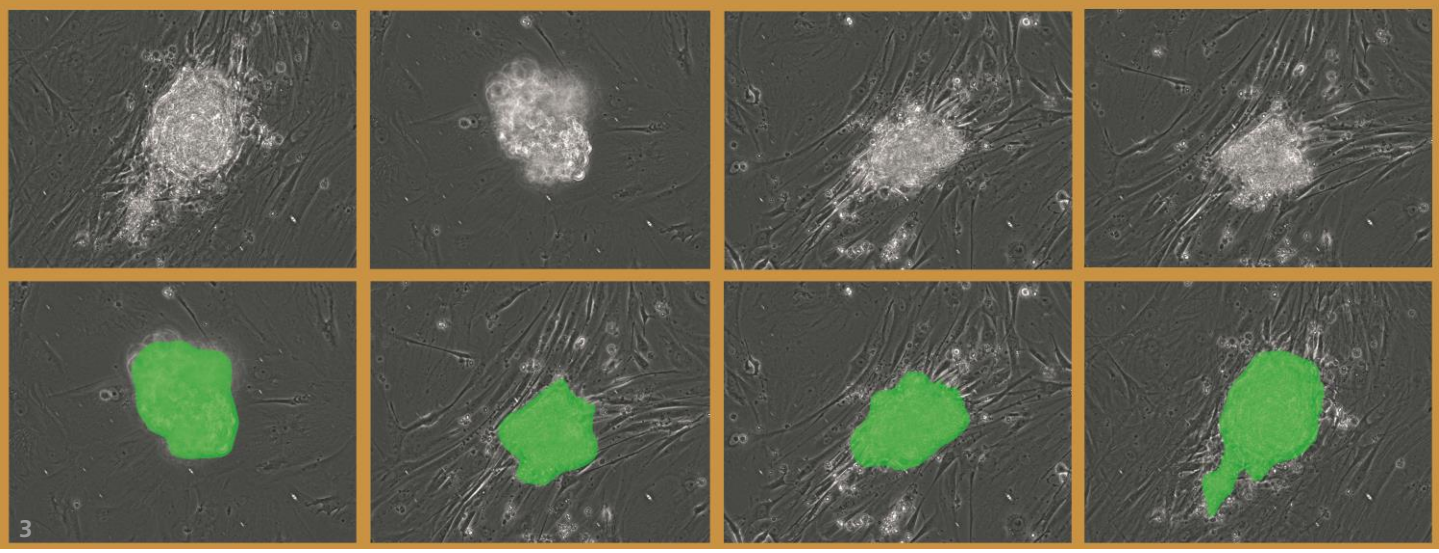
The microscopic long term observation of cellular systems under physiological conditions brings new insights into cellular behaviour. This provides the basis for analysis, and optimisation of processes as well as the development of protocols in regenerative medicine and life sciences. The broad distribution of investigations in fields of research requires a system which is scalable and can realise flexible dynamic experiments. In addition, there is a high interest in the investigation of several thousands single cells for long time in order to detect and analyse rare cellular events.

Approach

The solution to this challenge is a parallelised microscopic system that integrates several automated microscopes in an infrastructure. The biological specimen must be positioned in culture chamber which guarantees optimal physiological conditions in order to realise complex experiments and long term observation in combination with microfluidic hardware. The design with the free scalability and parallelisation offers the feasibility of observation of several thousand single cells in one experiment. With the purpose of performing dynamic experiments in life sciences the development of an unique control is necessary which communicates with microfluidics, microscopes and image analysis and manipulates the experiment by predefined events.

Implementation

At Fraunhofer Institute for Biomedical Engineering a prototype of such a BioImaging system was implemented. In a lab infrastructure 8 automated microscopes (Nikon Biostation IM) are installed in parallel and



can be controlled centrally by one workstation. Microfluidic components for connection of microscopes are available to realise dynamic experiments when required. Supervision of experiments takes place by a special software environment which allows control of microfluidics (i.e . cetoni neMESYS, www.cetoni.de) at the same time and can be integrated in modern lab management system.

Components

The BioImaging system consists of several automated microscopes which allow the investigation of biological short term (seconds) and long term processes (days and weeks). Microscopes allow a fully automated multidimensional observation and investigation of biological specimens: Multipoint observation, time sequences, phase contrast- and multichannel fluorescence microscopy. Cultivation of specimens during experiments is realised under physiological conditions (5% CO_2, 37°C and 95% humidity). For microfluidic connection the IBMT CellCartridge and IBMT FluidicAdapter are available. The innovative IBMT CellCartridge (based on Perma Cryo Technologie ICEBREAKER, www.perma-cryo.com) combines substrate for cryopreservation, automatisation and modern biobanking. The IBMT CellCartridge will permit fully automated experiments in future: information of biological content of substrate as well as control sequences for microscopes, microfluidics and image analysis can be saved on the CellCartridge's physical storage volume.

Advantages of the system

- Parallelisation
- Flexibility
- Controlled physiological conditions
- Realisation of complex experiments
- Automatisation of experiments
- Multidimensional resolved experiments
- Scalability
- Automated image analysis
- Integrable in existing lab infrastructures
- High optical resolution

Examples of application

- Cytotoxicity assays
- Dynamic in-vitro organ simulation
- In-vitro simulation of immune system
- Functionality assays of cellular systems
- Detection and investigation of rare cellular events
- Long term investigation of cellular systems
- Long term investigation of implants
- Investigation of tumour models
- Functionality assays of organ models

Services

- Installation and integration of connected automated microscopes into lab infrastructures
- Integration of devices in modern lab management systems
- Development of fluidic hardware components
- Expert advice to and development of cell based in-vitro-assays
- Expert advice and development of alternatives to in-vivo-tests
- Realisation and analysis of cell based in-vitro-assays

3 *Dynamic investigation of human embryonic stem cell growth and proliferation in co-culture with PMEF (top). Automated detection of colony by image analysis software (bottom).*