

PROVIDING TECHNICAL SOLUTIONS FOR STEM CELLS

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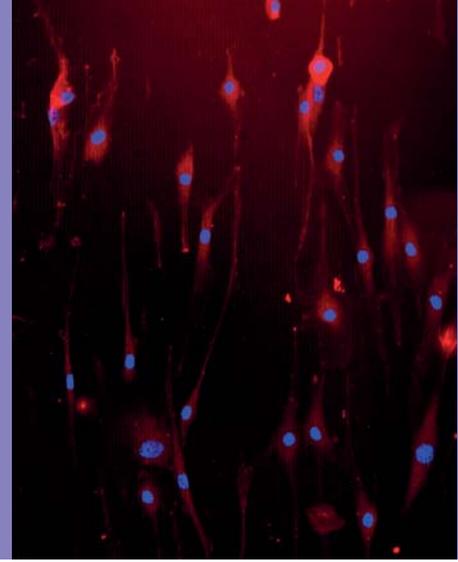
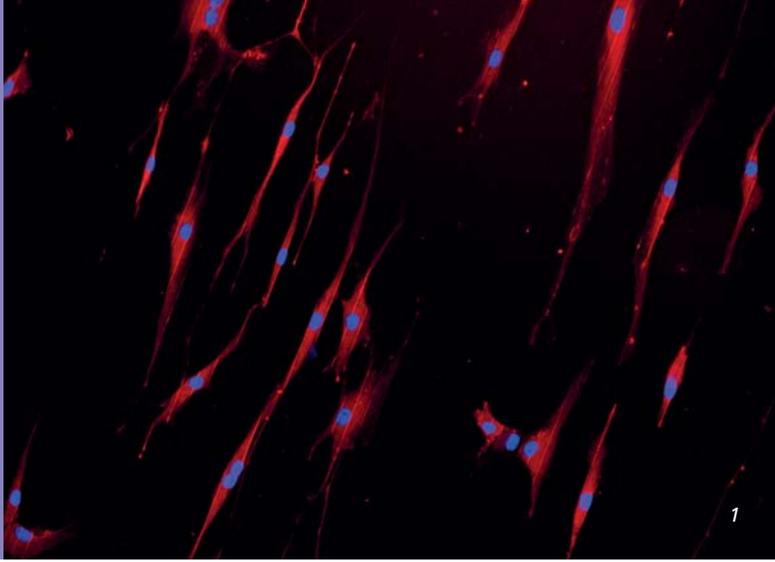
INTRODUCTION

The vision of personalizing treatment and regenerating damaged tissue or organs to cure diseases is the motivating force behind stem cell research. Fraunhofer IPT recognized this development early on and started to develop technical solutions for quality-driven processes which generate cell products for research and clinical applications in a standardized way. In cooperation with researchers from academia and industry, the Fraunhofer IPT has acquired expertise in providing technical systems for quality control, handling and processing stem cells.

At the Fraunhofer IPT, the cells used are mainly human Mesenchymal Stem Cells (MSC), since these can be harvested in abundance directly from tissue removed in standard surgical procedures, grown easily and reliably and handled safely. MSC have also proved to be highly mechanosensitive and are rapidly emerging as clinically-relevant. The scientists from Fraunhofer IPT have considerable experience in isolating stem cells from medical waste, such as fat tissue, foreskin biopsies or cord tissue with a view to adapting manual isolation procedures to develop automated processes in accordance with "Good Manufacturing Practice" (GMP).

About Stem Cells

Stem cells are defined by their ability to divide limitlessly and to differentiate into various kinds of cells. A wide range of cell types are used in research and in clinical applications. MSC are an example of multipotent cells that can be obtained from ethically acceptable sources, such as adult fat tissue and bone marrow. Therefore, they provide enormous potential for both autologous and allogenic, regenerative therapies. Other applications require pluripotent cells, which can form almost any kind of cells or tissue. Induced pluripotent stem cells (iPSC) can be generated by reprogramming adult tissue-derived cells such as fibroblasts in order to conduct disease research or to perform patient-specific drug screening.



STEM CELL DIFFERENTIATION ON STRUCTURED SURFACES

Stem cells used to study diseases or to perform drug screening are usually differentiated into specific cells or tissues. At the Fraunhofer IPT, scientists have developed novel solutions in order to facilitate large scale differentiation of stem cells. By cultivating the cells on selected biomaterials with specific topographies, optimal conditions are provided for directed differentiation of human stem cells into selected cell types.

MSC preferentially differentiate into specific lineage directions, depending on their home tissue. We have demonstrated that it is possible to pre-differentiate MSC from selected tissue sources into skeletal muscle cells, neuronal-like cells and endothelial cells by their adhesion to different structured micro and nanosurfaces. Surfaces with different structures have therefore, been selected and produced, using a range of engineering technologies developed at the Fraunhofer IPT.

Both nano and microscale topographies are important for the mechanotransductive induction of stem cells. Well defined and highly accurate micro- and nanostructures in 2.5- and 3-D can be produced using 2-photon polymerization. Other techniques, such as laser structuring and diamond milling, can be used to generate microstructures for the stimulation of specific mechanosensitive receptors on cell surfaces and to guide the cell body to form a required morphology. The topographies can then be molded into biomaterials with a specific stiffness to mimic the natural microenvironment.

When selecting a biomaterial for cultivation and differentiation of stem cells, it has to be taken into account that stem cell fate is co-determined by inherent substrate stiffness. We have considerable experience in the use of both natural and synthetic biomaterials. Synthetic materials have many advantages since they are not degradable and apply a constant mechanical force to the cells that can be adjusted precisely via material stiffness. In the case of the synthetic PDMS, the biomaterial can also be molded easily. Native biomaterials like collagen, on the other hand, exhibit inherent nanostructures that can be recognized by the cells. We have developed a method of embossing biogels sustainably in order to exploit this beneficial property. Stem cells can thus be stimulated on the native topographically modified matrix substrates.

We offer:

- Solutions for pre-differentiation of stem cells into a variety of different lineage directions using microstructured surfaces
- Producing metal and plastic micro- and nanostructures for biological applications using laser ablation, micro-milling and 2-photon polymerization
- Micro- and nanostructuring of complex 3D shapes

1 Adipose-derived stem cells growing on a structured surface for pre-differentiation into neuronal cells



AUTOMATION SOLUTIONS FOR STEM CELL CULTURE

Manual stem cell processing and cultivation is a labor intensive and time-consuming process. Effort and the risk of human error are minimized by automating handling and quality control. This also allows for complex processes to be performed reliably and reproducibly, thus generating high quality cell products in a standardized process.

In order to provide automated solutions tailored to the customer, scientists at the Fraunhofer IPT closely collaborate with biologists and engineers. Our services range from concept design to the modular construction of fully automated cell production platforms with integrated quality control devices. The innovative aspect of the concept, however, lies in the user-friendly operating software. Intelligent scheduling algorithms and metrology-based process decisions support quality-driven cell generation. This is complemented by a data tracking concept that ensures full process transparency in line with manufacturing guidelines and standards.

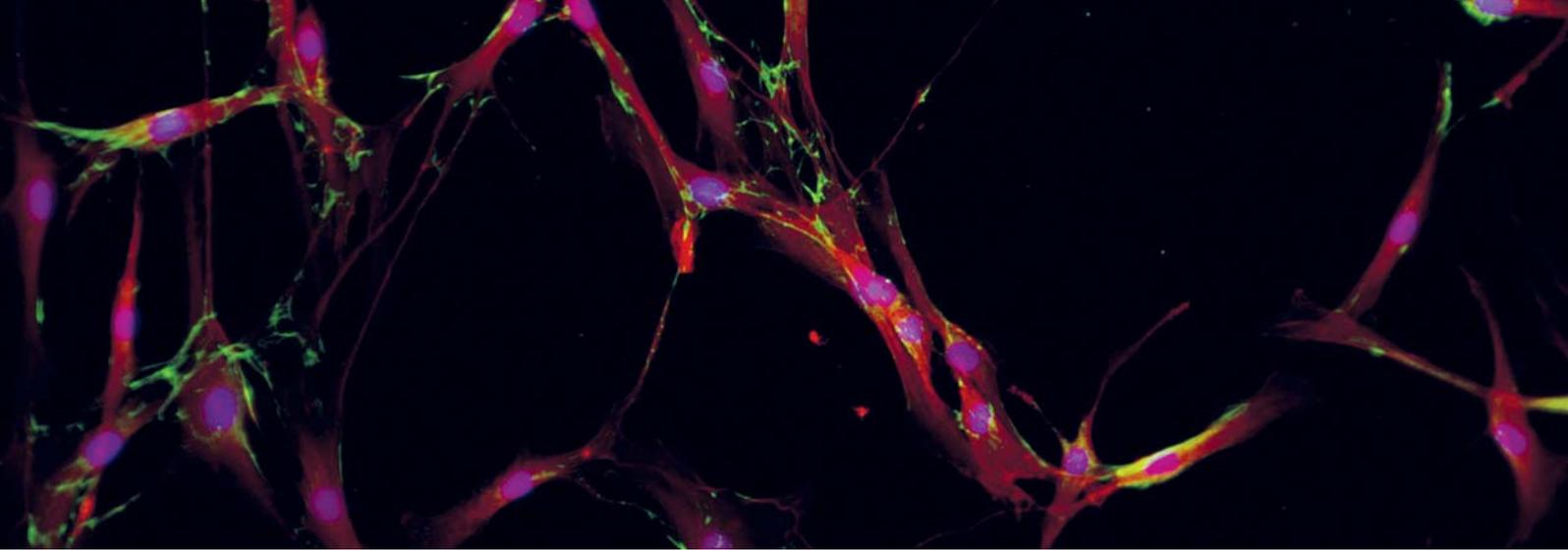
When implementing automation concepts, customers benefit from our know-how and expertise in the field of production technology. In the publically funded project 'StemCellFactory', the Fraunhofer IPT developed and realized an automated platform for the generation of induced pluripotent stem cells (iPSC) with support from WZL of the RWTH Aachen. Within the StemCellFactory, human fibroblasts are reprogrammed and the generated iPSC are subsequently picked and propagated in multiwell plates.

In a different project, a platform for expansion of adipose-derived MSC was developed at the Fraunhofer IPT. On top of this, we participate in a project funded by the European Union, in which MSC from bone marrow are propagated in a production platform according to GMP guidelines. The stem cell production process also involves automated generation of MSC for cell therapy in bioreactors.

We offer:

- Concept design of automated platforms for production of cell products
- Realization of modular production plants for standardized production of cell products
- Automation of laboratory processes for cultivating cells on our in-house automated platform

2 Inside view of the StemCell-Factory, an automated platform for the generation of induced pluripotent stem cells (iPSC)



STEM CELL AND TISSUE IMAGING

Visual inspection is the most common form of quality control in cell culture. In order to ensure highest standards of quality for the generation of stem cell products, engineers at the Fraunhofer IPT have developed innovative solutions for automated imaging and assessment of cell cultures.

A high-speed scanning method for phase-contrast and fluorescence microscopy, which allows for microtiter plate scanning at unprecedented speed, has been developed. The novel solution overcomes the conventional “stop-and-go” mode by imaging a continuously moving object. During the scan, the object is kept in focus by a hardware-based autofocus system developed in-house. The solution can be integrated within the majority of commercially available microscopes and considerably reduces the time required for cell observation.

The microscopic images can be used to assess cell culture status and growth behavior. In manual processes, culture evaluation is usually affected by the operator. So the engineers at the Fraunhofer IPT developed image processing algorithms that automatically and reliably determine the confluence of the cell cultures based on microscopic images. Using this technique, cell culture assessment becomes reproducible and can easily be automated.

In addition to two-dimensional cultures, research is increasingly focusing on tissues and organoids for studies and screening. In response to this, we offer innovative solutions enabling 3-D cell cultures to be imaged. We use light sheet and full-field optical coherence microscopy to visualize both fluorescence and structural information in organoids or tissues.

We offer

- Fast imaging solutions for two- and three-dimensional cellcultures
- Image-based tools for automated and standardized quality-control (e.g. confluence measurements)

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