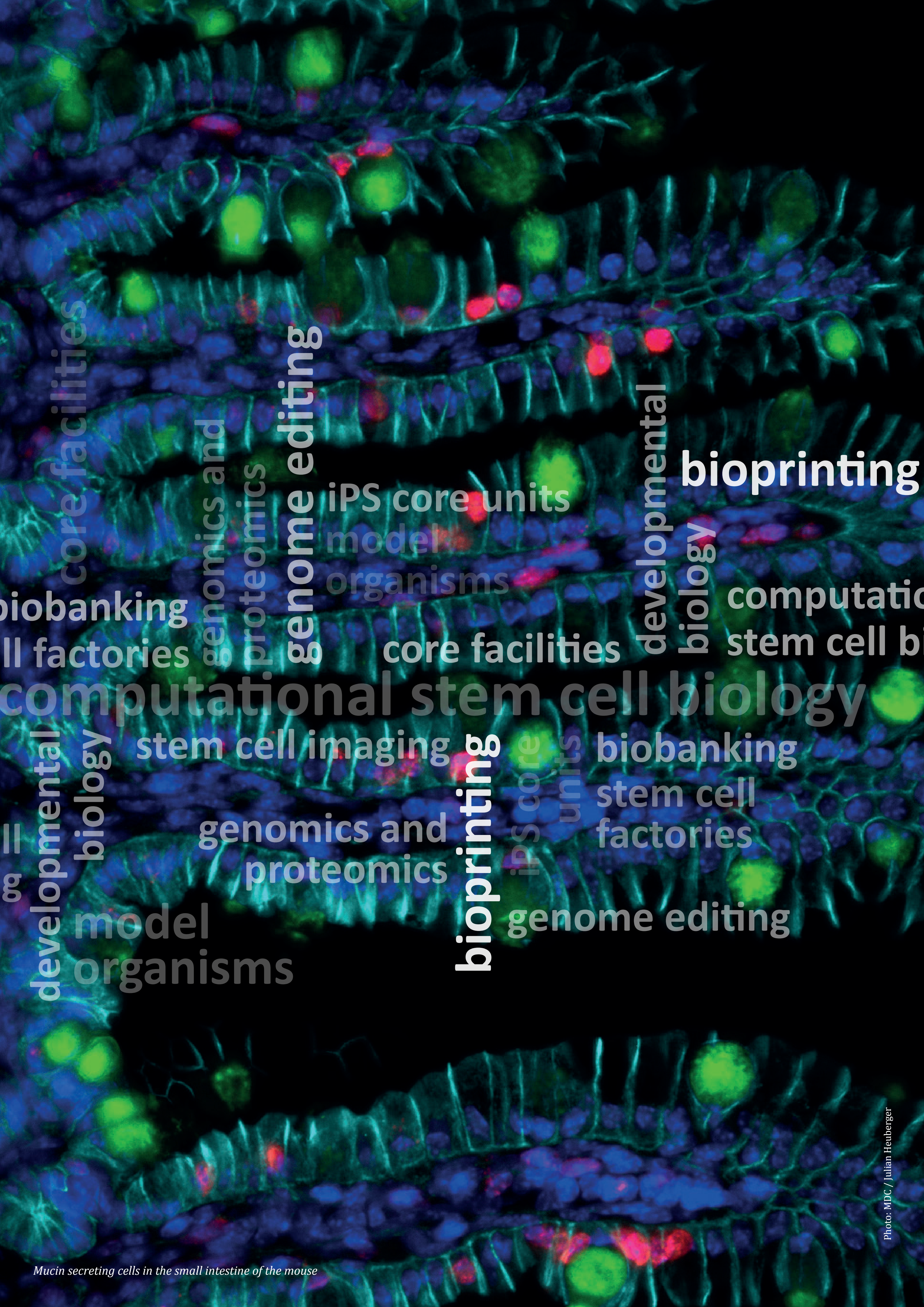



*Mucin secreting cells in the small intestine of the mouse*

Photo: MDC / Julian Heuberger

Bioprinting

# Tissue from the laser printer

*Using living cells to print out tissue in 3D is no longer such a distant dream, thanks to bioprinting. Here in Germany, as elsewhere, engineers are working on production systems that use bio-inkjet printers or laser-based systems. Bioprinting is of interest not only in connection with tissue replacement in clinical applications but also for stem cell research.*

A freshly printed organ, cell layer after cell layer made in the laboratory, still sounds like science fiction. But scientists are convinced that this will be possible in future. Additive manufacturing processes, also known as "3D printing", are becoming ever more sophisticated and less expensive. They have been in use for some time in innovative industries such as solar technology, consumer goods manufacturing, and the automotive sector.

But how well can biological materials be printed? Bioprinting is the branch of research in which tissue engineers seek to construct biological structures through printing. The applications are many and varied and either involve printing cells directly onto surfaces or manufacturing scaffolds and biomaterials onto which cells can be seeded.

## The right printing technique

There are three main ways of printing cells directly. One is the inkjet technique, which works like a commercial inkjet printer. A mix of cells and a hydrogel – the "bio-ink" – is dispensed through a fine nozzle in the form of minute droplets. Another widely used process uses an extrusion technique: the material is gradually built up as a continuous bead, as though from a tube. The third method involves a laser-based process. It is a 3D laser printing technique of this sort that physicist Lothar Koch and his team have developed. Koch heads the Biofabrication Group at the Laser Zentrum Hannover (LZH). "We have taken a technique that has been used for some time in the production of solar cells and transferred it to living cells," he explains.

The laser-based printer used in Hanover works by mixing the cells with a viscous hydrogel, which is applied in a layer beneath a glass slide. Between the glass slide and the biomaterial is another layer that can absorb the energy of a laser beam. When the laser is focused on this absorbing layer, it vaporizes explosively in the form of a bubble. The expansion gives the biomaterial a sudden impetus, accelerating it precisely onto a surface.

## Cells survive unharmed

This may sound like a turbulent process, but it is completely harmless for the cells: "No matter what cell type they are, the cells are not affected at all by the process; the survival rate is 99 percent," says Koch. The genetic material also remains intact and cell behavior is completely normal. The results are significantly better than with other bioprinting processes. "In addition, the laser process enables us to work with high cell densities and viscous gels and also at a high resolution," continues Koch. This means that cells can be printed in the density at which they actually occur in tissues.

With all bioprinting techniques there is still a need for considerable research into the optimum bio-ink mixture.

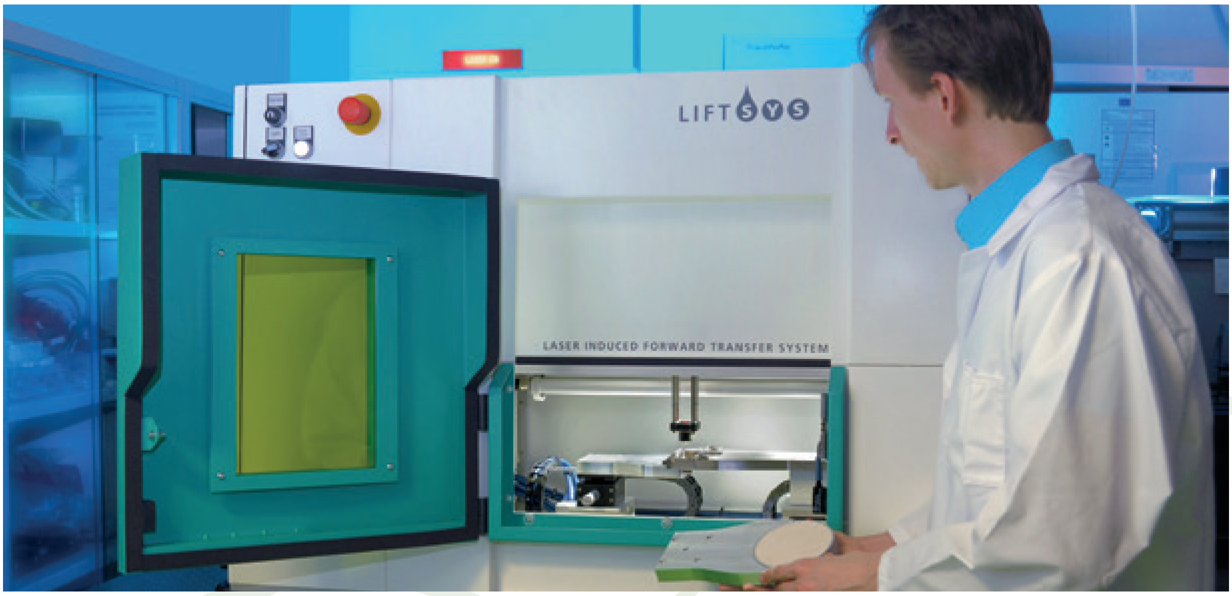
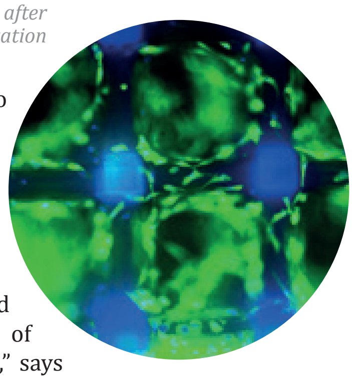



Photo: Fraunhofer ILT, Aachen

*LIFTSYS-facility (laser induced forward transfer system) of the Fraunhofer ILT for the selective transfer of biogenic material*

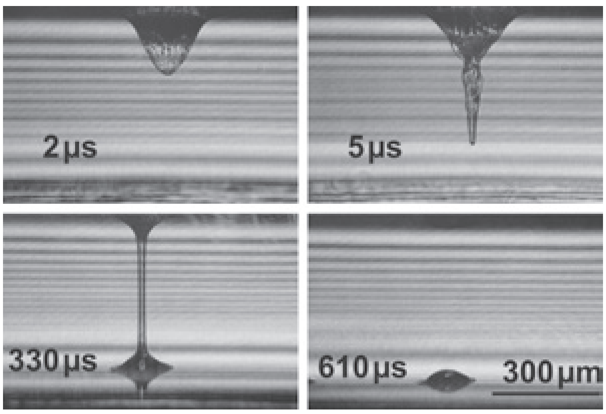
*New cells on a scaffold after two-photon-polymerization*



A powerful, laser-based method for printing biomolecules and cells has also been developed by the team of Dominik Riester and Martin Wehner from the Fraunhofer Institute for Laser Technology (ILT) in Aachen. Prior to transfer, each cell can be analyzed microscopically. The so called system LIFTSYS is therefore designed to target individual cells and print them with high yet gentle precision in high rates on surfaces. This allows in-vivo-structures to be replicated in the laboratory. Thus, fibroblasts and endothelial cells have already been arranged in predetermined patterns with LIFTSYS.

For example, a team headed by Kirsten Borchers at the Fraunhofer Institute for Interfacial Engineering and Biotechnology (IGB) in Stuttgart is working on inks based on natural substances such as gelatin. This has enabled them to print cartilage replacement tissue with their inkjet printers.

However, there is still a long way to go before complete organs can be engineered in the laboratory: so far, the laser printing specialists in Hanover have produced only relatively simple fragments of skin tissue and "band aids" from heart muscle cells. Such tissue fragments could someday be used for test purposes in the pharmaceutical and cosmetics industries. In the past, attempts to engineer more complex organs have failed because they have been unable to replicate a functioning blood vessel system.




*Stroboscopic recording of the hydrogel beam/- Jets*

"Printing a heart would take several hours. Then a vascular system would have to be immediately capable of supplying the printed heart muscle," says Koch. In collaboration with biomedical experts in the REBIRTH Cluster of Excellence ("From REgenerative BIology to Reconstructive THerapy"), the researchers have also experimented with adult and induced pluripotent stem cells (iPS cells).

### Stem cell niche products

Another laser-based technique is 3D two-photon polymerization: in the hands of the researchers this has proved particularly useful for generating scaffolds for tissue engineering. "With this we can produce structures with a resolution of less than 100 nanometers," says Koch. That will enable scientists to fine-tune the structuring of pores in biomaterials and replicate particular microenvironments of stem cells, known as niches, in order to observe and influence their behavior.

A group of bioprinting specialists led by Michael Gelinsky at the Centre for Translational Bone, Joint and Soft Tissue Research at TU Dresden is investigating how such printed niches could improve the cultivation of adult stem cells.

Bioprinted cell products thus have great potential. And there is no lack of ideas: in a talk at the 2$^{nd}$ GSCN annual conference in Heidelberg, Boris Chichkov of the Laser Zentrum Hannover explained that the number of cells that can be printed and the size of the printed products is theoretically unlimited. "With our technology it would take two hours and 47 minutes to print a complete person in 3D," he grinned.

*Text: Philipp Graf*

Photos: Laser Zentrum Hannover / Lothar Koch

## The REBIRTH Cluster of Excellence

**From Regenerative Biology to Reconstructive Therapy**

REBIRTH has, under the nationwide Excellence Initiative, been funded as a cluster of excellence since 2006. The aim of the internationally renowned centre for regenerative medicine is to develop innovative therapies for the heart, liver, lungs and blood, and to translate these into clinical use. This involves collaboration – in Hannover and at participating partner institutions – between physicians, physicists, chemists, biologists, engineers, legal professionals and ethicists, the main research priorities being stem cell biology, the reprogramming of cells for cell therapy, disease models and tissue engineering.

**Participating Partners:**

- Hannover Medical School
- Leibniz University of Hannover
- Hannover Laser Centre
- University of Veterinary Medicine Hannover, Foundation
- Helmholtz Centre for Infection Research Braunschweig
- Max Planck Institute for Molecular Biomedicine, Münster
- Institute of Farm Animal Genetics, Friedrich Loeffler Institute, Mariensee
- Fraunhofer Institute of Toxicology and Experimental Medicine, Hannover

**REBIRTH Cluster of Excellence**
Hannover Medical School
Carl-Neuberg-Straße 1, 30625 Hannover
**www.rebirth-hannover.de**