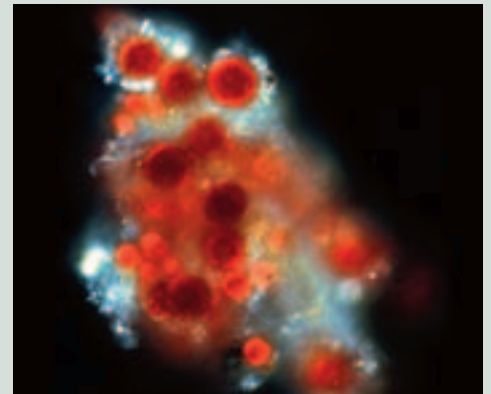
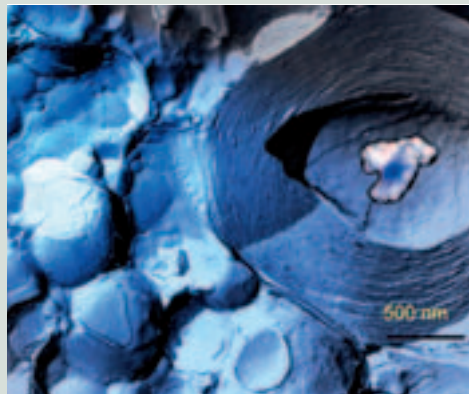
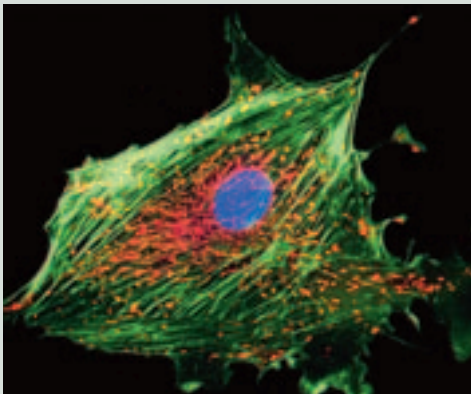




Fraunhofer Institut
Biomedizinische
Technik

Performance and Results Annual Report



Fraunhofer Institute
for Biomedical Engineering IBMT

Annual Report

Editorial



Institute director Prof. Dr. Günter Rolf Fuhr.

In superficial hindsight the results and successes at an institute like the IBMT, with a history of two decades, appear as evenly dispersed, almost continuous achievements. A closer look over the years reveals that most of the successes can be traced back to usually unspectacular decisions made some time ago. However, in retrospect it is often possible to determine exactly which discussion and sometimes even which statement was seminal for a very fruitful development that over the years proved scientifically and economically profitable for the institute. This poses the question of whether such decisions can be reached in a more targeted manner, a question I would like to return to at the end of this editorial.

One of these sustainable decisions was taking on research projects with a focus on cell biology in the traditional field of medical and technical ultrasound. In fact, the department for "Ultrasound", led by Dr. Robert Lemor since May 2006, has now grown to a size of nearly forty personnel and is thus one of the largest ultrasound development units in Europe. The department has extended its research and development area from medical imaging far into cell biology fields such as high resolution ultrasonic microscopy and technical applications such as underwater sonar. This development essentially stems from strategic decisions and investments made some four to five years ago. Last year, the department developed an ultrasonic microscope that is not only combined with a laser scanning microscope but also allows time-lapse recordings of cell cultures over several days at a resolution of about one micrometer, and moreover, is easy to use. An advantage of ultrasonic microscopy is the high-resolution visualization of mechanical characteristics of cells in vitro even in total darkness and on optically non-transparent surfaces. In

comparison to the rapid development of laser scanning microscopy over the last decades the possibilities of ultrasonic microscopy are not nearly exhausted yet.

Another decision made some two years ago has considerably influenced and enriched the scientific and economic profile, as well as the scope of the IBMT in the period covered by this report: It was the decision to join programs in developing countries, especially those concerning the fight against HIV and AIDS. What can an Institute of the Fraunhofer-Gesellschaft achieve in this wide field of global activities? Much, as it turns out, since the IBMT possesses a portfolio of technologies, device development strategies and experience in setting up and coordinating networks, which are urgently needed in public health programs to combat epidemics such as AIDS, tuberculosis, hepatitis and malaria. The Bill & Melinda Gates Foundation, whose founding capital was recently increased by US\$ 31 billion by Warren Buffett, put out a call worldwide at the beginning of 2005 for submission of projects to combat AIDS, investigate HIV and develop vaccines. On the basis of its established cryotechnology, the IBMT proposed the installation of a "Central HIV Cryo-Depository" linked to a global network for the use of these samples in HIV research, in close cooperation with the World Health Organization (WHO) and seven scientific partners in Europe and the USA – and was successful. Out of a broad field of competitors this research initiative was granted a US\$ 7.5 million budget, and since August 2006 is coordinated by the Fraunhofer IBMT in

St. Ingbert/Sulzbach. It is the first project of the Gates Foundation to be headed by German scientists. Dr. Hagen von Briesen, virologist and leader of the project at the IBMT, has taken on the challenging task of globally coordinating virus registration and deposition. The Federal State of Saarland and the Fraunhofer-Gesellschaft are supporting the project with research funding, so that the large-scale project has access to a sum of over ten million over its three-year duration. You can find further details about this in the present annual report.

However, not only a consolidated project portfolio, but also knowledge transfer brings scientists and customers together. In 2006, the first international workshop on laser medicine took place in St. Ingbert/Sulzbach. The topic "Advanced Multiphoton and Fluorescence Lifetime Imaging Techniques" attracted scientists and developers from the most diverse application areas of femtosecond lasers to exchange experiences. Although planned as a test, this initiative also turned out to be a success. Prof. Dr. Karsten König, head of the department of "Microsystems and Laser Medicine" summarizes the results on page 30. A second workshop followed in 2007, building upon the experience gained from the first one.

A central, and currently the largest research project at the IBMT is "Cell-PROM", an integrated EU project within the 6th Framework Program. After having started in 2004, 27 European partners assembled in May 2006 and April 2007 for an "assessment meeting" important for the continuation of the project. The approach to encouraging cell differentiation by artificial biological surfaces and developing novel technologies for the in vitro cultivation of stem cells has paid off. The results and progress in the project headed by physicist Daniel Schmitt were evaluated extremely positively on every aspect in the assessment report. Particular praise was given to the innovative device concept with magnetic microcarriers upon which cells grow, and the professional project management with a number of tools meeting special requirements, such as "White Papers" to follow-up the current state of the art in this multidisciplinary research area, "Key Experiments" to verify unproven hypotheses and a highly illustrated work plan updated monthly. Over the next years, two automated differentiation devices for animal and human stem cells will be produced – prototypes for a new generation of cell handling systems that will create the basis for novel approaches in regenerative medicine and tissue engineering.

The development of gentle cell handling systems for stem cell research and applications is another example of an early decision with profound consequences. In 2003, the IBMT was the first Fraunhofer Institute to initiate a broad development of stem cell manipulation and characterization systems. This initially comprised the professional cultivation of adult and embryonic stem cells and, what is very likely to be fundamental for their later clinical use, low temperature storage with high survival rates. In cooperation

with the group of Dr. Charli Kruse at the University of Lübeck and the departments of "Cryobiophysics and Cryotechnology" and "Cellular Biotechnology and Biochips" led by Prof. Dr. Heiko Zimmermann and Dr. Claus Duschl, respectively, complementary groups were set up at the IBMT locations in Lübeck, St. Ingbert and Berlin. The development of novel, more gentle and higher-yield isolation processes allowed the harvesting and establishment of an extensive stem cell collection, which apart from mouse, rat and human stem cells, also contains exotic and so far uncharacterized stem cell isolates from fish, birds and mammals. The demand and orders for stem cell samples from academia and industry are validating the concept. Currently, nine stem cell projects with external funding and further pilot projects financed by the Institute's own funds are being pursued at the IBMT.

An additional novelty has to be reported: In summer 2006 the IBMT was the first Fraunhofer Institute to be granted approval for importing human embryonic stem cells within the context of two EU projects. One project aims at improving the cryopreservation efficiency of human and adult stem cells; the other project focuses on developing novel non-invasive measuring methods for monitoring osteogenic differentiation. Both projects efficiently reflect the strategy of the IBMT, i.e. developing both instruments and processes.

Current stem cell research projects at the Fraunhofer IBMT

Adult stem cells:

1.	EU IP CellPROM	Mesenchymal stem cells Pancreatic stem cells Hematopoietic stem cells
2.	BMBF project	Mesenchymal stem cells
3.	Project Schleswig-Holstein	Pancreatic stem cells
4.	Cryoprojects (industry)	All adult stem cells
5.	EU CCS	Breast cancer stem cells



Embryonic stem cells:

6.	Project Saarland	Mouse embryonic stem cells
7.	BMBF EU CCS	Cardiomyocytes and chicken embryonic stem cells



Human embryonic stem cells:

8.	EU STREP 2005	NIH cell lines, isolated before 1.1.2002
9.	EU CryoP 2006	



Within the context of DFG-funded research in polar regions, with the objective of establishing an algae collection of low temperature-tolerant, so-called psychrophilic unicellular organisms from both hemispheres, the first Antarctic exploration was carried out between January and March 2006, following eight previous expeditions to the Arctic. Dr. Thomas Leya led this expedition to King George Island in cooperation with the University of Innsbruck, and transferred more than 70 Antarctic algae strains in stable laboratory cultures. The "CCCr_{yo}" collection now comprises more than 300 cryopreserved and living strains and is therefore one of the largest collections of extremophilic algae worldwide. Apart from questions concerning taxonomy and low temperature tolerance, the algae collection is of economical

importance due to the secondary metabolites such as asthaxanthin, fatty acids and cold-adapted enzymes and membrane transporters. As a result of an Arctic expedition in 2000/2001, a stretch of land in the Raudfjorden on Spitsbergen was named by the Norwegian Geographic Naming Committee following the suggestion of IBMT scientists (see page 27).

Finally, I would like to mention the new IBMT building in Potsdam-Golm (Brandenburg) whose architecture fits harmoniously into the collection of existing institutes. Constructed as planned in about two years, and equipped with state-of-the-art fittings,

this building has been available to the departments of "Molecular Bioanalytics and Bioelectronics" and "Cellular Biotechnology and Biochips" since October 2006. Locations at the Humboldt University in Berlin and the German Institute for Nutrition Research in Nuthetal were vacated and the rooms returned to the host institutions with modern laboratory equipment. We are grateful for their hospitality and look back on fertile cooperation, which we will continue in the future through joint projects.

To a great extent the functional aspects of the new building were defined by the personnel and include a number of special features that we believe could be exemplary for other new institute buildings in the biotechnology sector. The IBMT is now well equipped, with its parent institute in St. Ingbert and its branch in Potsdam-

Golm, and more than able to effectively meet all the requirements of a Fraunhofer Institute in the field of life sciences.

Altogether, these were very successful years for the IBMT. Analyzing the reasons for success leads back to the initial question: Can one catalyze such developments in a more targeted manner? The answer is: yes and no. Yes, because every successful project enriches our experience and gives confidence for tackling new tasks. As a consequence of such accumulated experience, predictions become more reliable. The expertise of the Institute and interactions between the research groups are enhanced. The atmosphere of a scientific institution particularly depends on its tradition and history, i.e. projects pursued in the past. On the other hand, the answer is also "no", because, as in business, a successful project in science cannot be repeated by merely copying a previously successful strategy. The interrelations are too complex. Some luck in solving a task and a fortuitous international situation play just as important a role as the good idea itself. It is still risky to believe that a particular research approach will be successful. Initiating a number of well-prepared projects in parallel and carefully analyzing their development is more a recipe for success. Which project will eventually prevail remains uncertain. Precisely this aspect is what makes research and development work at a Fraunhofer Institute so interesting and satisfying for all, from the student to the director.

I wish to thank all our customers and partners for their confidence in the work of our Institute. We appreciate your visits and your commissions. As a technology developer and traditional institute for medical engineering, the IBMT aims to solve your problems with all its workgroups and departments headed by renowned staff. Discover for yourself our range of competent services in this annual report and find your best contact partner. My personal thanks are directed to the staff at all IBMT locations. You have not only worked successfully on all projects despite difficult relocations and additional problems, but were even able to expand the Institute's scientific profile. Therefore, well-prepared we look into the future, which will certainly be one of medical technology as well as molecular and cellular biotechnology.



Prof. Dr. Günter R. Fuhr
(Director of the IBMT)

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The Institute in Profile



Parent institute in St. Ingbert.

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- New institute building in Potsdam-Golm
- Competencies and applications
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- Scientific events and awards
- Nanobiotechnology as a future research area



St. Ingbert



Sulzbach



Eurocryo Saar, microsystem-based cell bank in the Saarland



Nuthetal (until October 2006)



Humboldt University Berlin (until October 2006)



New building Potsdam-Golm (since October 11, 2006)



Lübeck



Shenzhen, China

Objectives



Founding director of the Fraunhofer IBMT, Prof. Dr. Klaus Gersonde (1987-2001).

The Fraunhofer Institute for Biomedical Engineering (IBMT) is one of the five life science institutes of the Fraunhofer-Gesellschaft and primarily focuses on technology development. Since its foundation in 1987, the Fraunhofer IBMT is a partner with industry for solving tasks in the areas of biomedical and medical engineering, laser medicine, biotechnology, health telematics, environment technology, laboratory development, cryotechnology, material testing technology, home, air conditioning and security technologies, as well as industrial process automation and in-line/on-line process surveillance, particularly for the food, chemical and pharmaceutical industries. The institute supports “living” technology transfer in medicine and biotechnology and in various branches of production industry and knowledge-intensive services. Core competencies are: non- and minimal-invasiveness, miniaturization, linking technical microsystems to biological microsystems (biohybrid systems, molecular bioanalytics, neuroprosthetics), molecular and cellular biotechnology, nano(bio)technology, cryo(bio)technology, biocompatibility, ultrasound technology, sensor manufacturing processes, magnetic resonance, telemetric data and energy transfer, multilocal sensors linked by communication technology and telematic systems. Central application areas are medical diagnostics, therapy and therapy monitoring as well as analogous issues in the industrial sector. Important new focus areas are methods and technologies for industrial implementation of innovations from molecular and cellular biotechnology and cryotechnology for storing viable samples at low temperatures, as well as isolating, cultivating and differentiating stem cells for regenerative medicine. The Fraunhofer IBMT has been working in stem cell research for three years and was the only institute of the Fraunhofer-Gesellschaft to be granted

approval (No. 18 and 19) by the Robert Koch Institute to import human embryonic stem cells. Technology transfer from basic research is achieved along the innovation chain of scientific and technical consulting, feasibility studies, prototype development, field tests and manufacturing processes. If needed, IBMT spin-offs take on system manufacturing as contract services, ensuring as rapid as possible implementation and maturation of our customers’ wishes into marketable products. Additional operation areas are advising venture capital (VC) companies, preparing studies and reports and assisting start-up companies. The IBMT is located in four regions (Saarland, Brandenburg, Schleswig-Holstein, Shenzhen [China]), and there it contributes to the overlying tasks of re-directing regional structures towards a global orientation and to creating new regional employment potential.

Short portrait

By founding the precursor of the Institute for Biomedical Engineering in 1987, the Fraunhofer-Gesellschaft's goal was to promote natural sciences and engineering research, modern technology and technology transfer within clinical research in the Saarland in cooperation with the University Hospital in Homburg/Saar. The original institute is located at St. Ingbert (Saarland) and since April 1, 2001, directed by Prof. Dr. Günter Rolf Fuhr, who was simultaneously appointed professor of Biotechnology and Medical Engineering at the Medical Faculty of the University of Saarland. His predecessor, Prof. Dr. Klaus Gersonde, was appointed in 1987 to the newly established chair of Medical Engineering at the University of Saarland, meaning that at the same time as being co-director of the Fraunhofer Institute for Non-destructive Test Procedures (IZFP), he took over leadership of the precursor of the IBMT, i.e. the main department of Medical Engineering in St. Ingbert. On the basis of its continuous development, this department was converted into an autonomous Fraunhofer Institute for Biomedical Engineering in 1992. Consequently, pursuing the tried and tested technology transfer strategy, the IBMT branch in Sulzbach/Saar was founded in 1994, where the workgroup for sensor manufacturing started working.

The Institute is financed by contract research and development commissioned by public and private (industrial) customers and the close connection between medical engineering, biotechnology and microsystems technology ensures it an outstanding position in Europe. Since 1997, the IBMT houses the European Center of Competence

for Biomedical Microdevices (MEDICS) located in Sulzbach/Saar. On October 1, 1998, the IBMT presence in China started with its branch in Shenzhen/Guangdong (FTECS) going into operation. It was headed by Prof. Dr. Nai-Teng Yu (the Hong Kong University of Science and Technology, HKUST) and promotes contacts to regional governments and industry in China as a further part of the IBMT network. In 2000, activities in China were complemented by the Fraunhofer IBMT Technology Center in Xiamen (FTECX).

On April 1, 2001, when the previous director retired, leadership of the Fraunhofer IBMT passed on to Professor Fuhr. A biophysicist, Günter Rolf Fuhr joined the Fraunhofer-Gesellschaft and the University of Saarland from the Humboldt University Berlin (Chair of Membrane Physiology since 1993, and in parallel representing the Chair of Experimental Biophysics since 2000). Like his predecessor, he is a member of the Medical Faculty and at the same time elected member of the Faculty of Physics and Mechatronics, as well as member of the Center for Bioinformatics and elected member of the Humboldt University Berlin. Professor Fuhr received his PhD in 1981 on the subject of photo-morphogenesis in higher plants, and in 1985 he qualified as a professor in biophysics. In 1999, he founded a Center for Biophysics and Bioinformatics at the Humboldt University Berlin, where he was the first executive director until his departure on April 1, 2001.

The IBMT is a member of the association of 80 Fraunhofer establishments, of which 58 are Fraunhofer Institutes. In 2006, the IBMT comprised a staff of 134 scientific and 60 technical and administrative personnel as well as 29 student assistants and 57 project students. The IBMT is connected to the University of Potsdam through Prof. Dr.

Frank Bier, head of the department for Molecular Bioanalytics & Bioelectronics (Chair of Applied Bioelectronics and Biochip Technology). A chair of Biomedical Engineering links the IBMT to the "Hochschule für Technik und Wirtschaft" (HTW) (College for Engineering, Industry and Commerce) of Saarland. The Chair of Microsensors with Assembly and Packaging Technology, held by Prof. Dr. Karsten König, links the IBMT to the Faculty of Physics and Mechatronics of the University of Saarland. Moreover, the IBMT hosted 10 guest scientists and a junior professorship in conjunction with the University of Saarland.

The institute is subdivided into eight departments corresponding to its research areas: Microsystems/Laser Medicine, Ultrasound, Biohybrid Systems, Cryobiophysics & Cryotechnology, Telematics/Tele-Medicine, Molecular Bioanalytics & Bioelectronics, Cellular Biotechnology & Biochips and the Fraunhofer IBMT Technology Center Shenzhen (China). The departments are run as separate profit and cost centers. Besides the departments, there are independent workgroups that are on their way to developing into autonomous departments. Since September 2001, the IBMT is the founding member of the Fraunhofer Life Sciences Association.

Organization and contact partners

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Links to universities and colleges:

Chair of Biotechnology and Medical Engineering
 Clinical Medicine (Medical Faculty)
 Elected member of the Natural and Technical Science Faculties II and III
 University of Saarland and
 Elected member of the Faculty of Mathematics and Natural Sciences I
 of the Humboldt University Berlin
 Prof. Dr. Günter R. Fuhr

Chair of Microsensors with Assembly and Packaging Technology
 Faculty of Physics and Mechatronics
 (Faculty of Science and Technology II)
 University of Saarland
 Prof. Dr. Karsten König

Junior Professorship of Cryobiophysics and Cellular Bioinformatics
 Faculty of Chemistry, Pharmacy, Biological Substances and Materials Sciences
 (Faculty of Science and Technology III)
 University of Saarland
 Prof. Dr. Heiko Zimmermann

Chair of Applied Bioelectronics and Biochip Technology
 Institute for Biochemistry and Biology
 Faculty of Mathematics and Natural Sciences
 University Potsdam
 Prof. Dr. Frank F. Bier

Chair (Master's program) of Biomedical Engineering
 Electrical Engineering
 College for Engineering, Industry and Commerce of Saarland (HTW)
 Prof. Dr. Klaus-Peter Hoffmann

Central work topics



Dr. Jianbo Gao.

The Fraunhofer IBMT sees itself as a technology developer and focuses on technological issues such as linking technical microsystems to biological components such as cells and tissues; molecular and cellular biotechnology with medical objectives; nano(bio)technology; biocompatibility testing; cryobiotechnology; biochip development; laser medicine; microsystems technology (microsensor, microactuating and signal processing); ultrasound; sensor manufacturing technology; multi-local sensor connected by communication technology; health telematics; telemetric data and energy transfer; magnetic resonance; imaging and spectroscopy. The required basic knowledge is gathered in a project-related manner and then converted through contract development into products and production lines in cooperation with industry. The scope of its activities ranges from basic technological analyses to the development of components and systems and construction of demonstration units for industrial operations. Not only medical technology and biotechnology companies, but also other areas such as the polymer and ceramic industry, manufacturers of semiconductors, environmental technology, hydraulics industry, food industry, house and air conditioning technologies, process and process surveillance technologies, production and automation technologies and material testing technologies find competent advice and problem-specific solutions at the IBMT. Successful improvements and innovations are based on feasibility studies, prototype development, the creation of small-scale production lines and permanent sensor manufacturing lines. With an area covering more than 3 800 square meters, the neighboring industry park Sulzbach-Neuweiler is a thriving development site for flexible manufacturing setups of sensors and cryoequipment, enabling small and medium-sized companies to produce ultrasound and microsensors at competitive costs. Regional and nationwide

customers are supported by the IBMT to become competitive on the European market.

Another important future field of interest has developed since 1994 by reinforced activities in the area of medical telematics. Novel approaches to individual healthcare of patients by telemedical services are being realized, for example in the two promising telematics projects "Stroke Aftercare Saar" ("Home Care" area) and "Patient Accompanying Documentation – PaDok" (physician-physician and physician-hospital networking).

In the context of ongoing globalization of the IBMT's activities, of special note is the successful founding of the Chinese IBMT branch, the Fraunhofer IBMT Technology Center in Shenzhen/Guangdong (FTeCS) in 1999. After a short interruption, research efforts will be resumed on a larger scale in 2007. The long-term IBMT collaborator Dr. Jianbo Gao will take on coordination of activities in China. The main focus of the FTeCS R&D services is supporting the automation and operation of surveillance technologies of many different industrial sectors by implementing microsystems, microsensors, microactuators and signal processing routines. Initial customers come from industries involved in medical technologies, processing polymers and refining chemicals. Apart from these specific tasks, the FTeCS is a contact point for R&D customers who want to capitalize on the expertise of the whole Fraunhofer-Gesellschaft. FTeCS therefore represents the Fraunhofer-Gesellschaft in China. Another essen-

tial task is supporting German companies in China with installing and optimizing sensor production processes and production lines and introducing biotechnology.

The Fraunhofer IBMT Technology Center Hialeah (FTeCH), continuously developed since its foundation in 1996, left the IBMT in 2004 to become an autonomous institution under the patronage of the City of Hialeah. This IBMT spin-off on the American continent is the successful conclusion to many years of shaping an international profile. During the course of the year 2006, IBMT's long-term experience in the USA resulted in acquiring a large-scale project funded by the Bill & Melinda Gates Foundation.

In November 1998, the workgroup Molecular Bioanalytics was founded as a new IBMT branch in Potsdam-Rehbrücke. Playing a major role in the choice of this location was its vicinity to the Institute for Biochemistry of the University of Potsdam, where biosensors have been successfully developed up to market standards for years, and also the fast-growing biotechnology market in the Berlin-Brandenburg region. The goal of the new workgroup was the development of on-site analysis systems for cost-effective diagnostics and therapy monitoring and environment surveillance, e.g. point-of-care analyses for immediate medical diagnostics, sampling of contaminated soil or systematic monitoring during the manufacture of biotechnological products. In the year 2000, this workgroup evolved into the department of Molecular Bioanalytics & Bioelectronics and was integrated, together with the newly adopted (in 2001) workgroup of Medical Biotechnology & Biochips at the Center of Biophysics & Bioinformatics at the Humboldt University Berlin, into the Fraunhofer-Gesellschaft workgroup Medical Biotechnology (AMBT). In the year of the present report, a new building was completed

as an IBMT member institute in Potsdam-Golm to accommodate these previously decentralized workgroups. The first spade of earth was dug on August 30, 2004, the topping-out ceremony took place on June 22, 2005, and staff moved in and started work mid-October 2006. The R&D scopes of both departments complement each other almost ideally to form a competence cluster for biochip systems and nanobiotechnology.

Together with the State President of Saarland, Peter Müller, the Fraunhofer-Gesellschaft under the presidency of Professor Hans-Jörg Bullinger opened the cryoresearch bank EuroCryo Saar in Sulzbach/Saar on September 9, 2003. Including the Center for Cryobiotechnology and Cryobiophysics, this became the second technology platform to be implemented by the IBMT that specifically addresses future demands from biotechnology and medicine. The European cryoresearch bank is intended to support and store valuable and unique cell collections (bioresources) from many different branches of life sciences and to develop and demonstrate modern automated technologies. The storage of viable cell suspensions not only allows propagation at any later point in time, but also retrospective sample analyses. This means that decades from now, genes, macromolecules, diseases, pathogens and contaminations can be identified for which neither knowledge nor methods exist today. Setting up a cell bank thus represents the most extensive and complete documentation of biological sample properties. Cryostorage tanks with a net volume of up to

1 400 liters each will be installed in an area of more than 1 200 square meters. Apart from fulfilling its research tasks, the cryoresearch bank is also meant to be a demonstration bank for new technologies, particularly for industrial users and public bodies.

In 2004 the external Fraunhofer IBMT workgroup "Cell Differentiation & Cell Technology" was founded at the University of Lübeck, which primarily focuses on the medical use of adult stem cells. Via this cooperation with the University of Lübeck, the IBMT embarked on stem cell research with the aim of supporting regenerative medicine and tissue engineering. The workgroup is headed by Associate Professor Dr. Charli Kruse and moved into new rooms in the multi-functional center at the University of Lübeck campus on November 8, 2004. Over the last two years the workgroup succeeded in establishing a considerable number of stem cell isolates and cell clones, which represent research resources belonging to the IBMT. In September 2006 the rented laboratory area was expanded due to the excellent results.

New institute building in Potsdam-Golm

Building handed over to the IBMT in Golm



View of the new building from the south-east with the container docking station (by the black wall).



Mr. Wagner (Fraunhofer-Gesellschaft, Department C3) hands over the building to Professor Bier.

After a construction period of two years, the new building for the Fraunhofer IBMT Branch in Potsdam-Golm was officially handed over on October 11, 2006, by R. Bartl and B. Wagner (Fraunhofer-Gesellschaft, Construction Department) in a short ceremony during the last on-site construction consultation. The three-storey building with its characteristic façade now accommodates the departments of Molecular Bioanalytics & Bioelectronics and Cellular Biotechnology & Biochips in an area of nearly 4 000 m².

The meandering shape of the façade gives the square building a dynamic and open appearance. Only at a second glance does one realize that the windows are at different heights, which gives an individual character to each room. The main entry is on the north side. A path through the pine tree grove leading towards the bridge creates a second connection to the Fraunhofer IAP. In addition to the 12 pine trees on the north side, an oak was planted in front of the main entry and a row of sweet gum trees on the south side. The L-shaped pond at the north-west corner takes on the shape of the terrace floored with oak boards. Materials and colors are borrowed from the natural surroundings of Golm and Potsdam, especially from the buildings of Schinkel and Persius.

The architects hammeskrause (Stuttgart) continued the strictly rectangular shape of the building in the interior with a tripartite structure of laboratories on the south side and offices on the north side. The central area also houses laboratories, including

dark room laboratories, utility rooms and the library. The length of the parallel corridors running east to west is accentuated by the lights that were installed lengthwise. This design is dissected by the many possible ways to pass across the corridors. This is not only achieved by transecting corridors, but mostly indirectly, e.g. by several directly connected laboratories that are accessible from both the north and south corridors. The glass insets in the doors and a number of glass walls not only allow a visitor to observe work in the laboratory without disturbing the personnel, but also let in light even to the central laboratories (e.g. cell culture cluster and production room) making the rooms appear light and spacious.

The library, the foyer with the free-hanging staircase connecting all three floors and the technical area form vertical axes across the building.

The laboratories, designed by the architect Mr. Hammes, include the latest highly functional fittings and are furnished with the most up to date technology and equipment. The planning took into account working procedures where several laboratories can combine into a cluster, e.g. the cell culture laboratory, the open-plan laboratories on the ground floor and the cryolaboratories on the second floor. The state-of-the-art research building meets the challenges of molecular medicine and biotechnology. The institute focuses on research and development in molecular diagnostics, lab-on-chip device development as well as nanobiotechnology and preliminary steps towards regenerative medicine. Examples of developed applications are systems for the gentle handling of cells and their targeted manipulation on surfaces that can be used within regenerative medicine for checkups, early diagnosis and optimization of therapies.



View from the north.



North-west side.

Eight docking sites for special container laboratories are located on the east side of the building. Through flexible customer contracts, containment level 3 or GMP laboratories can be connected here for complete media supply and monitoring by the in-house technology. This offers the advantage of rapid expansion of laboratory capacity, avoiding reconstruction costs and in addition being able to hand back their own laboratory to the customer after successful installation and test production.



Cell culture laboratory 1.S 048/49.



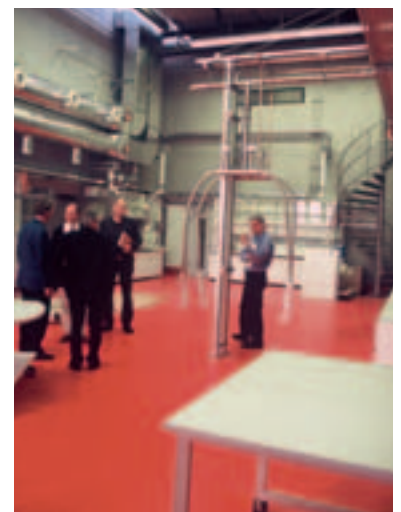
Genetic engineering laboratory 1.S 042.

Twenty years of laboratory experience of the Fraunhofer IBMT went into the design, arrangement and the technical control systems of the building. More than in any other institute of the Fraunhofer-Gesellschaft, emphasis was put on flexibility, economical efficiency and at the same time a pleasant atmosphere. The institute building can be seen as an example for future biotechnology institutions, despite the fact that construction costs per square meter were considerably lower than for university buildings.

The philosophy of the institute is to avoid long distances between office and laboratory bench and to promote personal exchange between the scientists. The library, equipped with wood-



Foyer staircase.



Technical area.



Multi-functional laboratory O.S 029.

Media station in laboratory O.S 033.

Library with gallery.

en fittings, can be entered from two floors and not only serves as the main gathering point for scientists, but can also be used for small-audience talks or seminars.

The library can also be used by personnel from the neighboring institutes of the science park Golm, the Fraunhofer IAP, the Max Planck Institutes and the institutes of the Potsdam University. The close vicinity to the institutes, which will be reached even more rapidly after completion of the railway line tunnel to the University of Potsdam in autumn 2007, promotes scientific exchange and cooperation between projects. In addition, the adjacent GO:IN Technology Center finished at almost the same time and, affording space for companies and spin-offs, will provide yet more opportunities for cooperation.

The new address is:

Fraunhofer Institute for Biomedical Engineering (IBMT)
Branch Potsdam-Golm
Am Mühlenberg 13
14476 Potsdam
Germany

Contact

Dr. Stephanie Schwarz
Telephone: +49 (0) 331/58187-101
Fax: +49 (0) 331/58187-199
stephanie.schwarz@ibmt.fraunhofer.de

The new building in Potsdam-Golm unites the IBMT departments in Potsdam-Nuthetal (Molecular Bioanalytics & Bioelectronics) and in Berlin (Cellular Biotechnology & Biochips at the Humboldt University Berlin) after six years of working separately.

The main scientific focus of the new daughter institute is molecular and cellular biotechnology, and in particular: biosensors and bioanalytics, biochip technology (development of on-site analysis systems for cost-effective diagnosis and therapy control and for monitoring the environment, as well as the development of production technologies for manufacturing biochips and DNA chip development), nanobiotechnology with surface-based animal and human cell cultures, cell conservation techniques and cell sorting, cell manipulation in suspension, lab-on-chip for customer-specific cell characterization and separation tasks, microfluidics simulation, development of dynamic, chip-based immunoassays, special microscope developments, prototype pro-

duction of microstructures using Excimer laser and the cultivation of cryophilic freshwater microalgae (snow algae) in a culture collection CCCryo/extremozyme research.

Architects and Planners

Architect and construction monitoring: hammeskrause, Stuttgart; weight-bearing construction planning: Weiske + Partner, Stuttgart; landscaping: Büro Eurich, Wendlingen; ground analysis: Ingenieurbüro Maschke, Michendorf; surveying: Büro Misewitz-Kaden, Teltow; structural engineering/statics: Dr.-Ing. Zauft, Potsdam; fire protection inspection: Technische Prüfgesellschaft Lehmann, Berlin.

Executing companies

Shell construction: Bateg Ingenieurbau GmbH, Berlin; façade: Hupfeld & Schlöffel Metallbau, Berkatal; metalwork/locksmith: Mebatec Stahlbau GmbH, Neuruppin; roof insulation: BDG Bedachungen GmbH, Teltow; flooring and surfaces: SFT Saale Fußbodentechnik, Ammelsstadt; interior decoration/painting: Hornstein GmbH, Neustrelitz; elevator: A.S. Aufzug und Service, Magdeburg.

Facts and numbers

Total area (together with IAP): 43 922 m², of which ca. 22 000 m² make up the IBMT branch Potsdam-Golm
Total number of employees after moving in: 142
Total area: 4 095 m² (office and utility rooms: 1 400 m²; work and laboratory rooms: 2 700 m²).

Competencies and applications

	Miniaturization/microstructuring (or alternative materials)	Thick film/thin film sensors (hybrids)	Ultrasound sensors and systems (1-D/2-D array technology/hardware/software)	Medical telematics (sensors, communication and information technology)	Magnetic resonance (microscopy, spectroscopy, imaging)	Multiloal sensors and telecommunication	In-line process control	Biosystems/biocompatibility (cell and animal models)	Overall systems (health, environment)	Sensor manufacturing (development, service)	Nanobiotechnology	In vitro cell and tissue culture	Immunology and HIV repository
Imaging systems (sonography, NMR)													
Monitoring systems (volume flow, vital parameters)													
Process monitoring (airborne ultrasound, fluid control)													
Plate wave sensors (biosensors, mass sensitive sensors)													
Tactile sensors, endosystems (e.g. endosensors)													
NMR probe head development (high frequency systems)													
Material characterization (polymers, pharmaceuticals, cosmetics)													
Bio-interfaces (wetware, neuronal interfaces, micro-implants)													
Cryobiotechnology													
Biochip technologies													
Regenerative medicine													
Laser medicine technology													

Competency matrix.

 Rapidly developing.

 Central IBMT areas.

The scientific insights and practical results from many years of experience in the areas microsystems/laser medicine, ultrasound and magnetic resonance, as well as more recent experiences in the fields of sensor manufacturing, (nano)biotechnology, biosystems, cryotechnology, biochip technology and medical telematics, guarantee high quality performance in research and development and flexible customer and problem-oriented definition of tasks. Numerous talks, publications and patents document the qualification of the personnel and the modern state-of-the-art level of the installations and equipment in all the IBMT institute's departments.

In 2002, the IBMT began to restructure its patent policy and now offers more than 150 patents for licensing via the competence center in Sulzbach. Income from patents exceeded the costs by about four-fold in 2006.

Advisory committee

The advisory committee comprises excellent physicians and scientists as well as decision-makers from industry, commerce, politics, federal state authorities and academia. It advises the Institute directors and the executive board and assesses the Institute's performance annually.

Members of the advisory committee are:

Dr. Christian Ege, State Secretary, Ministry for Economy and Employment of Saarland, Saarbrücken

Prof. Dr. Emmeran Gams, Director of the Hospital for Thorax and Cardiovascular Surgery at the Heinrich Heine University, Düsseldorf

Dr. Karsten Henco, CEO, U3 Pharma, Martinsried

Prof. Dr. Hartmut Juhl, Managing Director, Indivumed GmbH, Hamburg

Prof. Dr. Michael Menger, Director, Department for Surgical Research, Faculty of Medicine, University of Saarland, Homburg/Saar

Dipl.-Ing. (diploma in engineering) Otmar Peter Schön, Chairman of the Board of Members, Hydac Technology GmbH, Sulzbach/Saar

Dr.-Ing. (PhD in engineering) Harald Stallforth, Member of the Board of Management, Research & Development, Aesculap AG & Co. KG, Tuttlingen

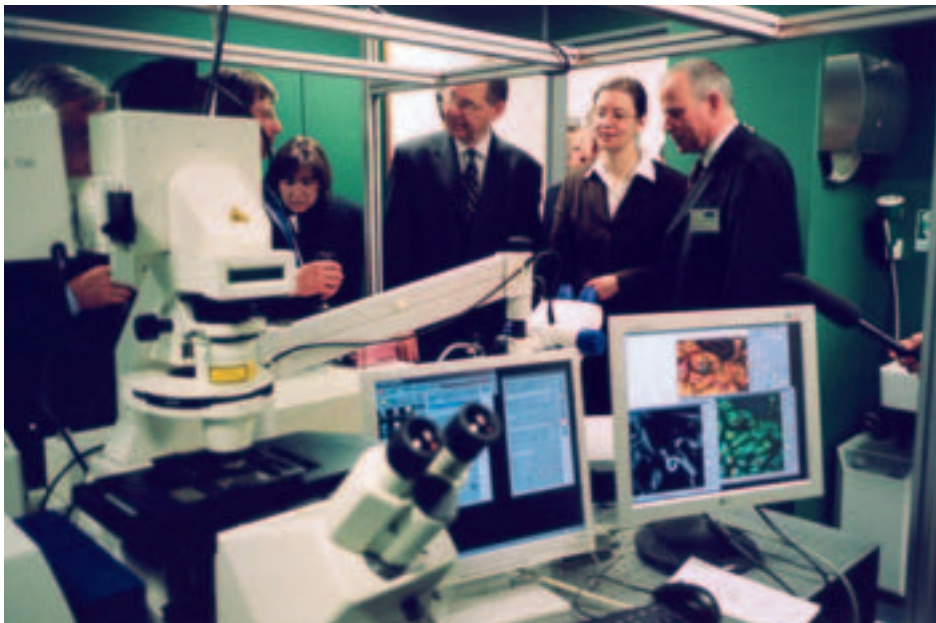
Dr. Ekkehard Warmuth, Head of the Department for Biological Research and Technology, Federal Ministry of Education and Research, Berlin

Prof. Dr. Volker Linneweber, President of the University of Saarland, Saarbrücken

Inauguration of the new ground floor laboratories at the Fraunhofer IBMT in St. Ingbert in parallel to the start of the BMBF project "Multiphoton Endoscope"



Symbolic inauguration of the laboratories, from left to right: Prof. Dr. Karsten König, Head of the department Microsystems/Laser Medicine, Dr. Susanne Reichrath, State Secretary for the Ministry of Education, Culture and Science of Saarland, Dr. Hanspeter Georgi, Minister for Economic Affairs and Labor of Saarland, Georg Jung, Mayor of the town of St. Ingbert, Prof. Dr. Günter Fuhr, Director of the Fraunhofer IBMT.



Glimpse into one of the new laser laboratories.

The Minister for Economic Affairs and Labor of Saarland, Dr. Hanspeter Georgi, the State Secretary for the Ministry of Education, Culture and Science of Saarland, Dr. Susanne Reichrath, representatives of the BMBF (Federal Ministry of Education and Research) and guests from the networks NanoBioNet e.V., OptoNet e.V., BioRegio Jena e.V., and the companies GrinTech GmbH, JenLab GmbH and Carl Zeiss Jena AG participated in the opening of the Fraunhofer IBMT new laboratory wing in St. Ingbert. This coincided with the start of the BioChance Plus project "Multiphoton Endoscope", supported by the Federal Ministry of Education and Research, on January 10, 2006. This joint project is led by Professor König. In addition to developing medical technology, the funding of approx. 1 million € will be used to establish links between the nanobiotechnology network in the region Saarland/Rheinland-Pfalz and the optical networks in Thüringen. Thus nanobiotechnology opens the way for Saarland to enter new attractive areas of medical femtosecond laser applications.

Medical technology is the major end-user of such applications and has also developed into a starting point for future advanced technologies. In addition to classical device engineering and basic medical research, new potential application areas for automation technologies are, for example, in pharmaceutical research, imaging, blood analysis, molecular diagnostics, and rapid prototyping for the production of dentures and prosthetics. Moreover, modern information and communication technologies also play a role in stimulating innovation in the medical

sector. Important impulses for medical technology also come from laser and nanotechnology, information technology and increasingly cognitive sciences. Since small and medium size enterprises typically cannot pursue basic research and can only undertake applied research to a certain extent, funded academic research (at universities or extramural) represents an important innovation potential for medical technology.

The development of the IBMT in St. Ingbert reflects the current rate of growth in medical technology. To be efficiently prepared for future challenges, new laboratories were put into operation six months ago by scientists from the three departments of Microsystems/Laser Medicine, Cryobiophysics & Cryotechnology and Medical Engineering & Neuroprosthetics.

The Fraunhofer IBMT attracts a significant amount of industrial and public funding to Saarland. As the new BioChance Plus project clearly demonstrates, this creates new high-quality jobs with good future prospects for technical engineers and academic scientists.

For two years now the Fraunhofer IBMT has been developing new technologies and systems for laser microscopy, laser nanobiotechnology and laser nanomedicine in Saarland. These research activities gained outstanding recognition in 2005 with the

International Pascal Rol Award, the International Award for Skin Pharmacology and the newly created Fraunhofer Award "Technology for People". The research results open up perspectives for a new generation of novel laser biodevices. Currently, the most modern femtosecond laser tomography system for the detection of pathological skin changes is located at the Fraunhofer IBMT. In the context of the planned network project "Multiphoton Endoscope" the spectrum of laser diagnostics should be extended by also enabling innovative high-resolution optical imaging of the inner body.

Together with the Fraunhofer IBMT, in the context of the BMBF-funded BioChance Plus, two young innovative spin-off companies from the Fraunhofer Venture Group and the network Optonet e.V. and BioRegio Jena e.V. from Thüringen will develop a multiphoton laser endoscope over the next three years. The BioChance Plus program promotes the startup and growth of young biotechnology companies and at the same time creates room for new developments, networks and basic medical research.

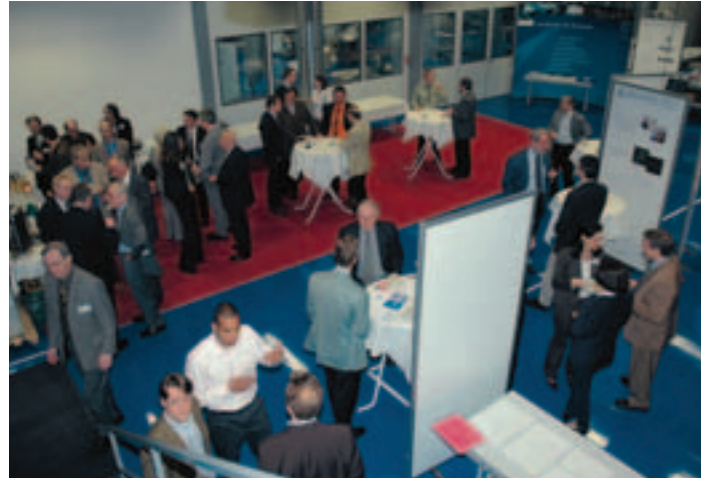
The project aims to develop a novel laser endoscope, which for the first time will conduct near infrared femtosecond laser impulses via a microstructured fiber into the body. Localization of pathological changes will be traced due to the autofluorescence of the tissues. This research will be carried out together with partners of the networks NanoBioNet e.V. from the region Saarland/Rheinland Pfalz as well as OptoNet e.V. and Bioinstruments Jena e.V. from Thüringen.

During the inauguration event the new laser laboratories at the Fraunhofer IBMT were handed over to the scientists and presented to the public. Currently, three femtosecond laser scanning microscopes for novel cancer diagnostics and the development of a nano-scalpel are in operation at the IBMT.

Entrepreneur day “Medical engineering as a driving force for innovation: applications beyond medicine”



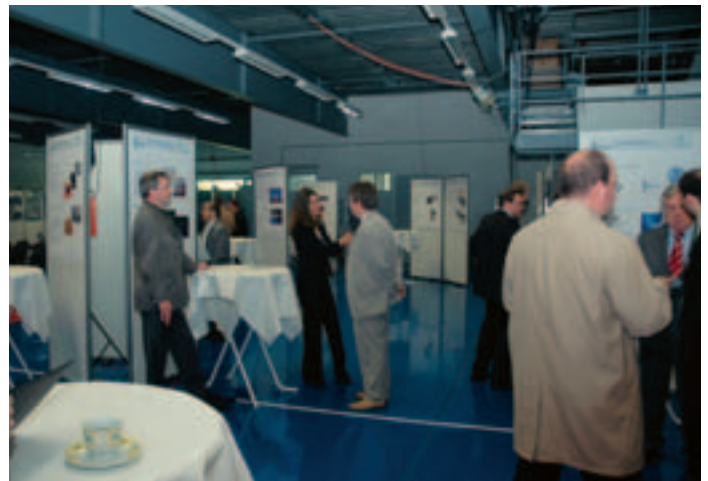
The Minister for Economic Affairs and Labor of Saarland and President of the Center for Productivity and Technology (ZPT Saar e.V.), Dr. Hanspeter Georgi, welcomes the guests to the entrepreneur day.



View of the exhibition area.



Hermann Götzingler, Managing Director of the ZPT Saar e.V., during his welcome address.



View of the accompanying exhibition with opportunities to meet IBMT workgroup leaders.



Businessmen from different industrial branches in Saarland during the talks.

Today, the medical industry is as an important driving force for technological innovation. On average, companies in this sector realize more than half their turnover with products that have existed for less than two years. This fact alone proves the exceptionally high innovation rate in medical engineering.

Companies operating in other areas can capitalize on this innovation capacity, since observing medical technology approaches can provide inspiring novel technical ideas for their own product

The Long Night of Sciences 2006

development. There are many examples for applications spanning different sectors. Methods for measuring blood flow are now used in gas meters, and an ultrasound application for wound cleaning has been adopted for gentle cleaning of construction parts. Electronic components that operate at low temperatures are not only used for cryobanks but also in the space industry.

To open up this innovation potential to interested companies, the Center for Productivity and Technology Saar e.V. (ZPT) and the Fraunhofer IBMT organized the forum "Medical engineering as a driving force for innovation: applications beyond medicine" on May 11, 2006, in Sulzbach/Saar.

Addressing the audience of approx. 50 entrepreneurs from Saarland and political representatives, the morning talks outlined those developments from the fields of classical medical engineering, device engineering, information technology, biomedicine and biotechnology that can be transferred to applications in other areas. Mr. Steck, CEO of Prosensys GmbH (an IBMT spin-off), presented further examples of this know-how transfer from the perspective of a Saarland company. In the afternoon session, the guests had the opportunity to discuss ideas and concrete questions with department and workgroup leaders of the Fraunhofer IBMT.

On May 13, 2006, the Fraunhofer IBMT's Berlin department of "Cellular Biotechnology & Biochips" participated in the sixth "Long Night of Sciences" in Berlin. Almost 9 000 interested people took advantage of the more than 1 600 demonstrations from science, technology and research. The program, particularly designed for children and young people, included numerous experiments, guided tours and presentations – ranging from a glimpse into nanoworlds to a paper chase using GPS and a football match between robot dogs.

Over 300 visitors made their way to the IBMT until late in the night, marveling at the trained non-contacting

"cells in the arena of biochips" and learning which tools can position the cells so precisely. The theme "Red Snow – Green Snow" answered questions about the microscopically small, cryophilic Arctic algae, e.g. why green snow algae appear red ("blood-red snow") and what enables them to survive in Polar regions.

Another "Long Night of Sciences" followed on November 29, 2006, at the hospital campus of the University of Saarland in Homburg. The IBMT also actively participated in this event. Professor Fuhr held a talk on the topic "Frozen, but living world – deep-frozen cells for regenerative medicine."



Dr. Thomas Leya, leader of the workgroup on extremophilic organisms at the Fraunhofer IBMT, gives an introduction to snow algae research: algae cultures in tubes with tilted agar.



Ulrike Bley (student at the Humboldt University Berlin and student assistant at the Fraunhofer IBMT) explains her poster on the search for enzymes active at low temperatures using molecular biological methods.

Tree researchers from Würzburg use old and infirm oak tree from the former Schmelz forest on the IBMT grounds



Oak tree on the grounds of the Fraunhofer IBMT, Ensheimer Strasse 50, in St. Ingbert.

The question of how leaves at the tops of trees over 100 meters high (e.g. Douglas firs and Sequoias) are supplied with water has been controversially discussed among scientists for more than two hundred years, because trees do not possess pumps as we understand them technically. The textbook explanation is that water evaporation through the stomata of the leaves creates a suction (pulling) tension in the vessel system of the trunk and branches (xylem), which pulls water up against gravity from the roots to the

treetop. Upon closer inspection this process turns out to be more complex, since in fact transport is a coupled system similar to a paternoster lift. While water is transported from the roots to the treetop, the energy-rich metabolic products of the leaves (assimilates) also dissolved in water are reciprocally channeled through a separate vessel system (phloem) downwards to supply the roots and keep them alive. Therefore, not all the water should evaporate, since some of the available water is needed for growth and some for the phloem transport just described. Moreover, the transport system of trees is not absolutely watertight, i.e. evaporation through the leaves cannot be completely prevented in times of drought even with all the stomata closed. In spring, the situation becomes even more complicated for deciduous trees, since unlike the evergreen conifers they do not yet have leaves to trigger the evaporation process. Apparently, considerably lower root pressure, another coupled osmotic phenomenon, presses water into the trunk under these conditions. This can be impressively demonstrated on the stump surface of felled trees in spring, which exude a watery carbohydrate mixture. In addition, the xylem of most trees is not continuously filled with water – an essential requirement for a purely suction mechanism. As early as the end of the 19th century, Julius von Sachs knew that during the summer months the xylem of trees contain more air than water, in other words that there is no continuous water column in trees. Even more disturbing is that a continuous water column exposed to tensile stress becomes unstable if it is higher than 10 meters. This is due to the weight of the water column and the pressure the water

column exerts, which must be compensated for by the tensile stress. A height of 10 meters must generate a tensile stress of 1 atm, i.e. there must be a vacuum in the xylem. At 20 meters the tensile stress would have to reach 2 atm, meaning the pressure in the xylem must have a negative value. Supplying a 100 meter-high tree would require negative pressures in the order of -20 to -30 atm in the xylem of the tree (if in addition to the weight of the water column, one also takes into account flow resistance). Water under negative pressure is comparable to super-heated water, i.e. water prevented from boiling. In both cases any minor vibrations lead to an explosive evaporation of water (so-called cavitation) and thus to a breakdown of the transport system. Such embolisms actually do occur.

Nowadays, we know from investigations of different kinds of trees that depending on the species, location and season, different forces are involved in supplying leaves with water. In particular, it seems that water is transported to the treetops in phases, cushioned by air, analogous to lifting ships in canal locks. Capillary and osmotic forces as well as transpiration-related tensile stress play important roles in this mechanism. The importance of osmotic forces was already realized by Wilhelm Friedrich Philipp Pfeffer more than 100 years ago. Osmotic and capillary forces are particularly important for filling the xylem of deciduous trees in spring before the leaves appear. Osmotic processes in the roots generate positive pressure, which pushes the water plus dissolved nutrients upwards. At the same time, photosynthesis and enzymatic processes in branches and twigs supply the xylem with osmotically active sugars, which pull the water up into the highest tips of the tree so that the leaves can start to bud. The xylem and phloem are

coupled transport systems. As early as around 1900, Haberlandt postulated that the water in the xylem is partly driven upwards by the flow pressure in the phloem. Today, we know that this paternoster lift or cable railway mechanism for transporting water in the xylem against gravity is also a critical component of the water transport system.

Although today much is known about the water transport in trees, many particular aspects are still not understood, since it involves a very complex interplay of different forces all strongly influenced by the tree species, climate and the environment. However, detailed understanding of how these forces act is important, for example when trying to recultivate salty soil or use rapidly growing trees for "energy farming", i.e. for energy and fuel production. New insights can be expected if one could visualize the water distribution, water flow and air cushions in the xylem of trees. However, this is a technically demanding task and only a few research groups worldwide are investigating this. In principal, the water transport in both vessel systems (phloem and xylem) can be visualized with contrast media, which can be traced in the laboratory with modern imaging procedures in wood blocks, trunk segments and branches after felling the tree. But the injection of contrast media into the vessels in the upper parts of a tree requires experienced tree climbers, and there are only a very few qualified people in Germany. These techniques have been tested for smaller and less precious trees and have delivered valuable results. There is rarely an opportunity to apply these techniques to large, and especially old trees such as oaks.

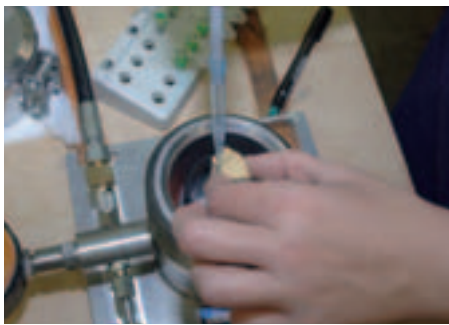


Working with the oak tree in preparation and during the scientific experiments.

The landscape remodeling on the IBMT grounds in the Ensheimer Strasse in St. Ingbert provided this opportunity. An approximately 200-year-old oak with some signs of infirmity but partially still in a suitable state for research had to be felled and offered the chance to investigate water transport. In the course of obtaining permission to remove the tree, which was originally part of the forest of Schmelz, the Fraunhofer IBMT contacted the biophysicist Professor Ulrich Zimmermann in Würzburg. He at once agreed to



had been distributed throughout the tree, it was cut down piece by piece and subjected (among other tests) to high resolution nuclear magnetic resonance imaging in the IBMT laboratories. This revealed the distribution of the water and contrast medium, which will yield valuable insights into the mode of water transport in this tree species.



Obviously, the time between cutting off sections and the analysis plays an important role, so it was lucky that this tree, which had to be felled, stood on the grounds of an institute with such excellent medical technology facilities. In parallel, how intact the tree was and what age-related diseases it had could be investigated and documented. Hence, the removal of the oak tree, which incidentally will be replaced by two new trees, had a particular value: first as part of a forest, then contributing to the city landscape of St. Ingbert, the oak tree finally served an important role in science.



Treatment of the wood samples and cross-section view of a labeled branch.

take the opportunity to examine the tree and use the excellent technical facilities of the Fraunhofer Institute in the direct vicinity. Contrast medium for NMR imaging and labeling was injected into the tree on May 22, 2006. The contrast medium used was Gadolinium, a chemical element with the atomic number 64, and a paramagnetic substance that amplifies nuclear resonance signals. As with humans in medicine, trees or at least major parts of them can be imaged by nuclear magnetic spin tomography. On the next day, after the contrast medium

Scientists of the Fraunhofer IBMT name area on Svalbard



Raudalgeura on the south coast of Hamiltonbukta (Spitsbergen, Svalbard – 79°47' N- 11°52' E)

View from the north towards the southern coast of Hamiltonbukta with the Raudalgeura area (centre). Snowfields on the slopes stained red by the long-term stages of algae are already visible from a distance.

In June 2006, the Norwegian Polar Institute announced that it had accepted the proposal made by the expedition members of the DFG project "CCCryo Resource" to name a slope on Spitsbergen (Svalbard, Norway) after the algae found there. The area will be called **Raudalgeura** (red algae scree field) in the future and be recorded on the relevant maps.

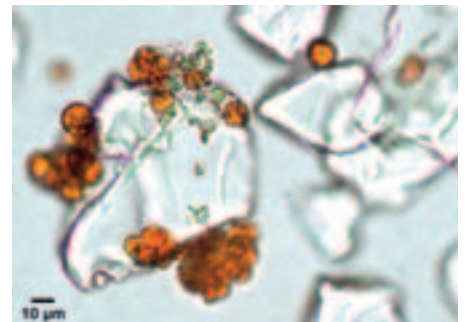
The Fraunhofer IBMT has launched expeditions to Spitsbergen for a number of years to collect and investigate extremophilic microalgae, so-called snow algae, that have adapted extremely well to low temperatures. Different cell stages of these algae cause the snow to turn red or green. The collection of cryophilic algae (CCCryo Culture Collection of Cryophilic Algae) set up in 1999 at the institute division for Biomedical Engineering (AMBT) in Berlin represents a unique bioresource for research on extremophilic organisms in Germany and Europe.

The idea of naming the location was developed during the expedition KOL 07/2000 to the Northwest of Spitsbergen (Svalbard). Members of the expedition were:

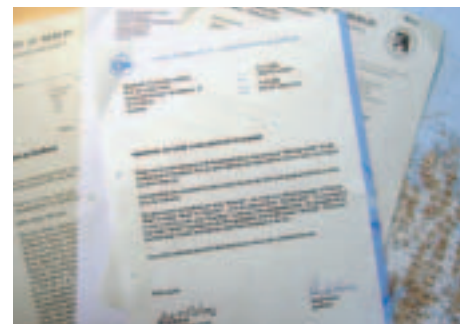


A red snowfield at the foot of Raudalgeura on Hamiltonbukta reaches down to sea level.

Dr. Günter R. Fuhr, Fraunhofer IBMT (leader of the expedition)
 Dr. Thomas Leya, Fraunhofer IBMT
 Dr. Hau U. Ling, Australian colleague, formerly Australian Antarctic Division, Hobart, Australia
 Hans Lund, Danish captain of the "Arctica"
 Dr. Torsten Müller, Evotec AOI AG, at the time of the expedition still at the Humboldt University Berlin



Long-term stages of a snow algae stained red by different carotinoids. These cell stages of normally chlorophyll-stained green algae macroscopically cause the phenomenon known since the Middle Ages as "blood snow" or "red snow", now acknowledged in the name given to the area (Raudalgeura means "scree field with red-colored algae").



Correspondence dating between 2000 and 2006 with the Norsk Polarinstitutt concerning naming the area.

29th Annual Meeting of the Working Group "Technology in Medicine" from June 15-16, 2006 in St. Ingbert and Saarbrücken



Members of the Working Group "Technology in Medicine" during a tour through the Fraunhofer IBMT (from left to right, 1st row: Prof. Dr. Klaus-Peter Hoffmann, Fraunhofer IBMT and HTW of Saarland, Prof. Dr. Werner Trampisch, Technical University of Gießen; 2nd row: Prof. Dr. Jürgen Dräger, Technical University of Stralsund, Prof. Dr. Rainer Dammer, University of Bremerhaven, Prof. Dr. Hans-Dieter Reidenbach, Technical University of Köln; 3rd row: Stephan Klein, Technical University of Lübeck, Prof. Dr. Leonore Heiland, Technical University of Zwickau, Vera Damman, Technical University of Gießen; center: Prof. Dr. Wolfgang Cornetz, Rector of the University for Technology and Industry and Commerce of Saarland).

The Working Group "Technology in Medicine" was founded in 1977 and is an autonomous network of higher education institutions, which offer study courses in this field, plus representatives from industry and state authorities who are committed to the education and training of new young scientists. The group particularly focuses on education and training in the areas of biomedical technology, medical technology, hospital operational technologies and medical information technology. Among other things, the group defines its tasks as promoting:

- education by direct, further and remote studies and in international courses,
- certification of study courses and quality control in education and training,
- national and international student and teaching staff exchange,
- further development of study subjects and the profile of graduates,
- recognition of the subjects and respective professions
- public relations for these fields.

This year the 29th annual meeting of the Working Group "Technology in Medicine" was organized by Professor Klaus-Peter Hoffmann in cooperation with Professor Wolfgang Langguth of the University for Technology, Industry and Commerce of Saarland (HTW) and took place on June 15 and 16, 2006, for the first time in Saarland. The reason the members of the group wanted to come to Saarbrücken and St. Ingbert was because they wished to learn more about the study program "Biomedical Technology" as well as research at the IBMT. This study program was very successfully launched in the winter semester of 2005 at the department of Electrical Engineering at the University for Technology, Industry and Commerce of Saarland (HTW)

with a Master's degree, followed last semester with a Bachelors degree. Currently, a total of 116 students are registered in this program at the HTW.

The study course is an integral component of the trilateral initiative of Saarland to create a biotechnology platform. In close cooperation between the Ministry of Economic Affairs and Labor and the Ministry of Education, Culture and Research, the University of Saarland, the HTW and the Fraunhofer-Gesellschaft, the study program is intended to make an essential contribution to the structural change from coal and steel industries to biological and information technologies, including biomedical technology. The qualified personnel trained in these courses will be a crucial requirement for continuing the successful trend of spin-offs and establishing companies in these sectors.

The members of the group were impressed by this unique study program featuring:

- Broad basic knowledge with project-oriented knowledge transfer in the Bachelors program involving the cooperation partners and regional companies.
- Highly specialized training in the Master's program with a strong emphasis on research-oriented components and courses in English when specializing in "Neural Engineering", particularly run by the IBMT and the University Clinics of Saarland, and an application-orientated component for specializing in medical physics.

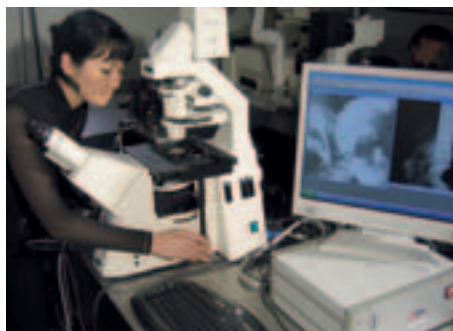
Further topics on the agenda were the career prospects for graduates, certification of the degree courses, the Internet presentation of the Working Group and the short reports from individual higher education institutions. It became apparent that the sustained positive development of the medical technology sector in Germany continues to open up enormous opportunities in the labor market for graduates of these study programs.

In connection with these discussions the members of the Working Group were impressed by the excellence of research at the Fraunhofer IBMT. Klaus-Peter Hoffmann, founding professor of this study course and head of the IBMT department of Medical Engineering & Neuroprosthetics, led a guided tour through his laboratories at the IBMT. Particularly impressive were the implantable microelectrodes, which could serve as a biotechnological interface between neuroprostheses and the peripheral nervous system. Examples of joint developments with international project partners are the retina implant, the hand prosthesis with a sense of touch and a stimulator for bladder control. But the department also focuses on the monitoring and telemetric transmission of vital parameters during the process of active aging in cooperation with the University for Technology, Industry and Commerce of Saarland and the interdisciplinary network "Products and services for all generations". For example, it collaborates in a project for long-term monitoring of cardiovascular parameters. The goal is to support patients with a high risk of severe cardiovascular diseases in order to increase their autonomy in their everyday life and protect them against emergencies. This involves developing novel intelligent sensors.

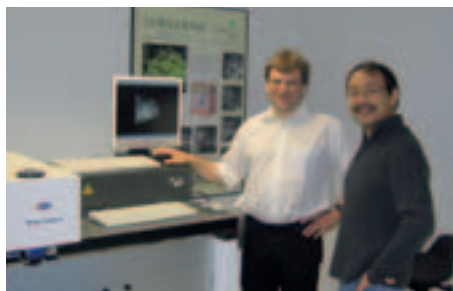
International laser workshop on “Advanced Multiphoton and Fluorescence Lifetime Imaging Techniques” at the Fraunhofer Institute in St. Ingbert from June 19-21, 2006



Dr. Michelle Digman, University of California, Dr. Klaus Suhling, King's College London and the organizer Professor Karsten König in front of the Fraunhofer IBMT in St. Ingbert.



Aisada Uchugonova, a participant from Kirghizia, examining stem cells with a novel femtosecond laser scanning microscope.



The organizer of a workshop explains the multiphoton tomograph used for examining black pigmented skin cancer to Professor Peter So from the MIT in Cambridge, USA.



Professor Peter So from MIT, Dr. Klaus Suhling from King's College London, Dr. Christoph Biskup from the University of Jena and the organizer Professor Karsten König during their morning run in the German-French Garden.



The talks were held in the mornings in the Eurocryo hall in Sulzbach before it was completely converted into a depository for HIV samples at the end of the year. The workstation projects took place at the Fraunhofer site in St. Ingbert.

Approximately 100 life scientists, clinicians and students from 16 countries and 40 different institutions traveled to St. Ingbert and Sulzbach in June to attend the first laser workshop on multiphoton fluorescence techniques and their biomedical applications. Even companies and universities from Australia, Singapore, the USA and Thailand sent participants to Saarland. The workshop was supported by the German companies Zeiss, Becker & Hickl GmbH, Berlin, and JenLab GmbH, Jena, as well as by the Fraunhofer-Gesellschaft and the NanoBioNet e.V. network.

Professor Peter So from MIT in Cambridge, USA, Professor Brian Bacskai from the Massachusetts General Hospital (MGH) in Boston, Professor Paul French from Imperial College London and 13 other worldwide renowned experts in the field of high resolution imaging accepted an invitation from Professor Karsten König and Dr. Wolfgang Becker to talk about the most promising biomedical applications of these technologies at the European Fraunhofer Cryoresearch bank in Sulzbach. Afterwards, the participants could work with state-of-the-art microscopes and tomographs equipped with femtosecond laser technology and also examine their own samples. The greatest interest concentrated on a multiphoton tomograph for early diagnosis of black pigmented skin cancer and a novel opto-acoustic microscope, which was developed at the IBMT to investigate the optical and mechanical characteristics of single cells.

Joint morning jogging in the German-French Garden in Saarbrücken, the poster session at Karlsberg Beer, the Crémant reception with the IBMT director Professor Fuhr and the final

Visit of the Presidents of the Federal and State Audit Offices

dinner in the Archipenko, combined with guided tours of the Saarland museum also all contributed to the extraordinary success of this first international workshop. One of the participating companies was so impressed by the research and development know-how of the Fraunhofer IBMT that only a few days after the workshop they placed their first orders with the department of Microsystems/Laser Medicine headed by Professor König. Further companies and universities have signaled their interest with respect to cooperating in joint projects in the future. It is intended to organize this international event of the highest scientific level in St. Ingbert every year.



The presidents of the Federal and State Audit Offices visiting the cryohall, led by Manfred Plaetrich, President of the State Audit Office of Saarland (foreground).

On September 25, 2006, the Presidents of the Federal and State Audit Offices of Germany, Switzerland and Austria visited the cryoresearch bank of the Fraunhofer IBMT in Sulzbach

after their annual conference in Saarbrücken and took advantage of the opportunity to find out about cryoresearch activities at the IBMT.

Nanotechnology for the application of high resolution, high frequency ultrasound in medicine – Fraunhofer IBMT receives funding from the Ministry of Education, Culture and Research



Handing over of the funding agreement (from left to right: Dr. Robert Lemor, head of the department for Ultrasound of the Fraunhofer IBMT, Minister Jürgen Schreier, Dr. Frank Tiefensee, project leader at the Fraunhofer IBMT, Prof. Dr. Günter Fuhr, director of the Fraunhofer IBMT, Dr. Wolfgang Bach, head of the department for Science and Research, Universities and Teacher Training at the Ministry of Education, Culture and Research of Saarland).

The development of ultrasound applications for medicine in recent years has been striving to include higher and higher frequencies. While established ultrasound technology works at a frequency range of up to 15 MHz, current developments can reach as high as 2 GHz. Increasing the frequency range by a factor of 100 means an improvement in the spatial resolution by approximately the same factor. In basic biological research as well as in application areas such as ophthalmology, dermatology and investigating blood vessel linings, the use of high frequency ultrasound promises significantly improved diagnosis by visualizing smaller and smaller anatomical structures. Nanotechnology can contribute significantly to this progress with novel nano-treated materials.

To comprehensively pursue this objective, which will be of great scientific and economical importance, two research institutes in Saarland with complementary research and technology skills launched a research alliance: the Institute for New Materials of the Leibniz Association and the Fraunhofer IBMT.

The department “Technology of Non-Metal Inorganic Materials” of the Leibniz Institute for New Materials (INM) has the know-how for developing and producing materials with entirely novel characteristics using solid/gel technologies.

Since its foundation in 1987, the Fraunhofer IBMT department of Ultrasound in St. Ingbert has developed into Europe’s largest R&D institution in this field with a staff of almost 40. The Chair of Medical Biotechnology & Medical Engineering and the IBMT workgroup “Biomedical Ultrasound” both possess the necessary experience and resources to support and rapidly realize the application of novel technical ultrasound developments based on high technology.

Taken together, these comprise exactly the requirements necessary for developing the desired medical applications.

The project is supported by funds from the Ministry of Education, Culture and Research of Saarland. Minister Jürgen Schreier handed over the funding agreement in person during a visit to the IBMT in St. Ingbert on September 29, 2006.

Presentation of the 7th SaarLB Research Award to Prof. Dr. Heiko Zimmermann



Presentation of the SaarLB Research Award 2005 (from left to right: Prof. Dr. Hans-Jörg Bullinger, President of the Fraunhofer-Gesellschaft, Prof. Dr. Günter Fuhr, Director of the Fraunhofer IBMT, Prof. Dr. Heiko Zimmermann, award-winner, Dr. Max Häring, chair of the SaarLB board of directors). Photograph: Wolfgang Klauke.

The SaarLB (State Bank Saar) sponsors arts, culture and science. As part of the science initiative, the SaarLB Research Award, endowed with 25 000 €, was first created in 1999 together with the Ministry of Education, Culture and Research of Saarland. The award pays tribute to scientific work leading to results and information that can be applied to economically strengthening the Saarland region. An independent jury evaluates the submitted work.

On October 20, 2006, Prof. Dr. Heiko Zimmermann, head of the department of Cryobiophysics & Cryotechnology at the Fraunhofer IBMT and junior professor at the University of Saarland, was honored with the SaarLB 2005 Research Award. He received the prize in recognition for his work in developing methods for cryopreservation and linking microcapsules for the treatment of diabetes mellitus. Diabetes is currently treated by injection of molecules

not produced by the body, which therefore have a short half-life. The methods developed by Heiko Zimmermann allow one to surround micro-encapsulated islets of Langerhans cells of allogeneic or animal origin with biocompatible alginate capsules of defined characteristics, so that the body does not mount an immune response against the foreign, cryopreserved cells. Another result of the work is a significantly higher survival rate of the cells after cryostorage. Cryopreservation is indispensable for later use of such transplants. The junior professor's considerable contribution to these processes was the reason why the jury decided to grant him the award.

Innovation competition Medical Technology 2006 of the Federal Ministry of Education and Research – Bodyguards for the nerves, nerve monitoring lowers injury risk

On November 14, 2006 the innovation competition prizes to promote medical technology were awarded to selected projects during the opening of the Medica 2006 exhibition. Dr. Klaus Peter Koch from the Fraunhofer IBMT, as the coordinator, received the prize granted to the project "Continuous Intraoperative Nerve Monitoring as a Microtechnological Navigation Tool" from the Federal Minister of Education and Research, Dr. Annette Schavan.

Intelligent and autonomous nerve cell monitoring can protect nerves during surgery against damage due to the effects of tension, pressure or temperature: electrodes constantly register changes in conductivity of the nerves. The signals are recorded immediately and processed by computer. This should considerably reduce the risk of injury. Dr. Klaus Peter Koch's group was one of the winners of the innovation competition 2006 and will receive approximately 1.5 million € in funding from the Federal Ministry of Education and Research (BMBF).

Damage to nerves is a frequent and potentially life-threatening consequence of surgery. Nerve fibers are similar in structure and color to connective tissue and small blood vessels, so the risk of confusion and resulting damage is high. This can have fatal consequences: Nervous dysfunctions after surgery can lead to severe handicaps that can affect the ability to continue in any employment or cause a withdrawal from social life. Surgery involving the thyroid gland, for example, carries the risk of injuries to the vocal chord nerves, which can lead to chronic hoarseness, loss of vocal abilities or even to life-threatening breathing difficulties. Nerve injuries from surgery in the lower abdomen, e.g.

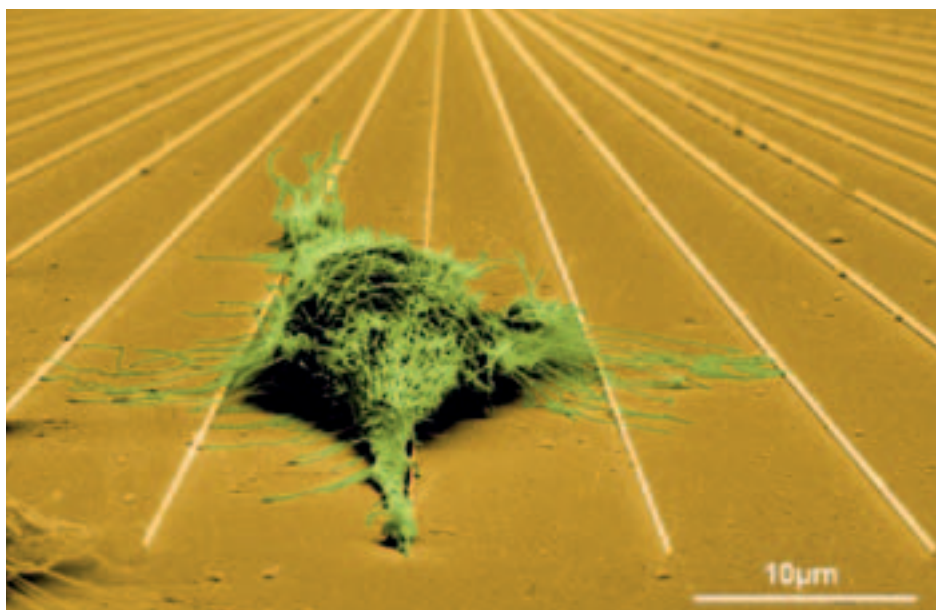
rectal operations, can disturb normal bladder and sexual functions. These are only a few of many other examples of the post-operative consequences of nerve injuries. To minimize these risks and better control potential complications, the nerves should be monitored during an operation. This would allow pressure and tension forces as well as the effects of temperature to be detected and avoided before any injury occurs.

Electrodes are the best security system for nerve cells. They are highly sensitive at registering everything that could threaten the nerves and immediately trigger an alarm – both visually and acoustically. The flexible electrodes developed during the project are made from a biocompatible material. They should be easy to use and not disturb or obstruct the surgical procedure. Furthermore, it is important that the signal transmission is relatively independent from errors in placing the electrodes correctly or displacement of the electrodes during the operation. All this is guaranteed by combining the electrodes with intelligent software, which automatically searches for the optimal stimulation and conductivity point. Dr. Klaus Peter Koch from the Fraunhofer IBMT and his team expect that continuous monitoring during surgery will reduce surgery-related nerve injuries by at least 50%. This would also be of national economic importance, since for thyroid gland surgery alone, follow-up costs due to nerve injuries amount to some 70 million € per year in Germany.

Contact

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Nanobiotechnology as a future research area



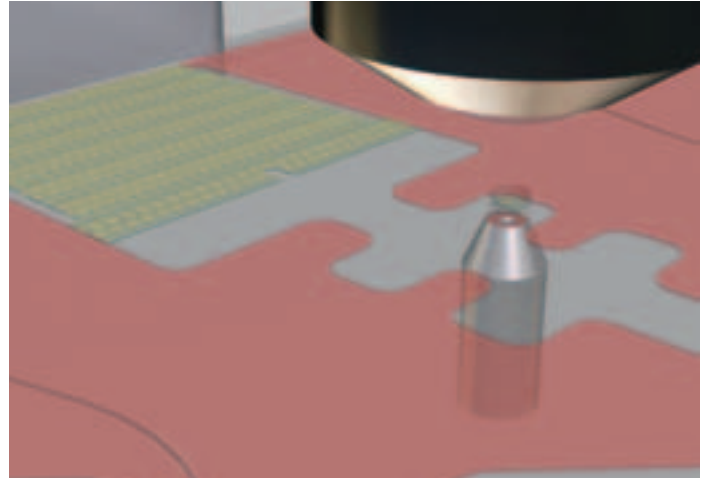
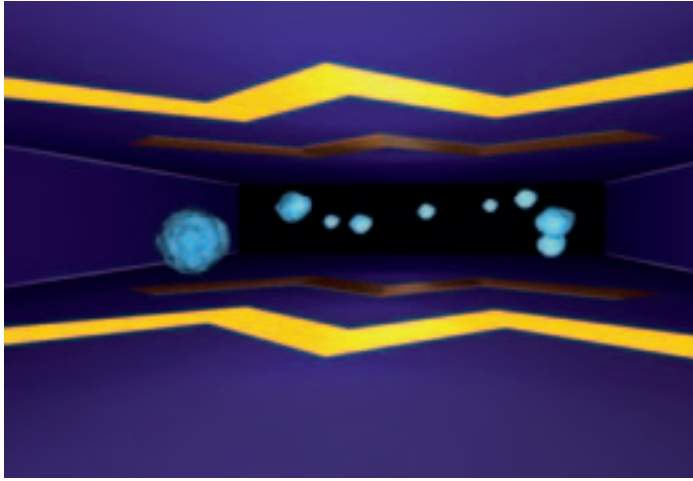
A human fibroblast on a nanostructured silicon surface photographed with a scanning electron microscope (Courtesy of Dr. Alisa Katsen).

CellPROM – Integrated EU research program

The 6th Research Framework Program of the European Union is a new funding scheme designed to stimulate the development and application of promising future technologies in the European research area, in addition to the proven funding instruments such as STREP and CRAFT projects. Examples of this new funding scheme are the Integrated Projects, where numerous partners from European research areas collaborate on an innovative large-scale project.

With a funding volume of 27 million €, *CellPROM* is the largest Integrated Project in the area of nanobiotechnology and links 27 academic and industrial partners from 12 countries for a period of four years. It is headed by Prof. Dr. Günter Fuhr and coordinated by the Fraunhofer IBMT. The abbreviation *CellPROM* stands for "Cell PROGRAMming by nanoscaled devices". The project's objective is surface-supported cell differentiation on a large technological scale. For this, artificial

macromolecular landscapes based on the model of cell surfaces will be developed and tested by nanotechnological procedures. In addition to soluble signaling molecules such as differentiation and growth factors, these artificial landscapes support the differentiation of cells via multiple surface contacts in a way that resembles the normal biological situation: these macromolecular landscapes (*NanoScapes*) imitate functions performed by cell surface contacts to matrix elements and adjacent cells in the tissue and body. This approach is meant to fill a technological gap and to create a new generation of novel modules for in vitro cell imprinting. Mastering these processes on an industrial scale is a prerequisite for opening up important application areas in the fields of biotechnology, medicine or pharmacy and for accelerating the technology development. The *CellPROM* project will enter new



Figures 1 and 2: Simulations to illustrate the modules currently being realized. Left: Manipulation of cells without any surface contact via miniaturized high frequency fields. Right: Magnetic manipulation of "nanoscapes" on microcarriers in a complex channel system.

interdisciplinary territory and contribute to the development of nanoscopic tools for cell handling in biotechnology and regenerative medicine. Upon completion, the four-year project should provide functional modules that can demonstrate the technical solutions and biological processes, forming the basis for scaling-up production and conceiving ideas for further applications, altogether considerably strengthening Europe's position in the promising future market of nanobiotechnology.

The Integrated Project *CellPROM* started in March 2004, with the kick-off meeting held on March 25 and 26. Work meetings are held quarterly with all partners, supplemented by regular meetings with 8 work package leaders and their representatives. On March 14 / 15, 2006, the second annual assessment meeting took place in St. Ingbert. Establishment of an operational

and effective management structure, evaluation and preparation of possible device concepts for different modules, first biological cell experiments and integration of technological prototypes dominated the second project year, and all aspects were evaluated very positively in the March 2006 assessment.

Two different concepts for handling cells were developed and presented: one concept is based on magnetically manipulated targets and allows manipulation of adherent cells by miniaturized surface carrier substrates (see Figure 2).

The second approach, based on a fluid lab-on-chip concept, involves manipulating cells without any direct contact (see Figure 1). Both concepts will be pursued in parallel during the next phase of the project and the corresponding modules will be developed and evaluated.

Partners of the project are companies such as Evotec Technologies (Germany), Leister Process Technologies (Switzerland), GeSIM (Germany), Symelec (Switzerland), Eurogentec (Belgium), Silex (Sweden), Surface Imaging Systems, AMO, Eurice and tp21 (Germany) as well as institutes such as the Royal Institute of Technology (Sweden), the Institute of Experimental Biology and Technology (Portugal), the Pasteur Institute (France), the Institute for Spectrochemistry and Applied Spectroscopy, the Institute for New Materials, the Georg Speyer House and the Max Planck Institute for Biophysical

Chemistry (Germany) and the universities of Lausanne (Switzerland), Barcelona (Spain), Saarbrücken (Germany), Vienna (Austria), Kaiserslautern (Germany), Pavia (Italy), Ljubljana (Slovenia), Tel Aviv (Israel) and Vilnius (Lithuania): in other words, a cooperation almost unique of its kind.

Coordinating such a large-scale project is a challenge not only in terms of scientific themes, but also with respect to management and requires novel administration tools. The Fraunhofer IBMT is supported in this task by its integration into the Fraunhofer Life Sciences Alliance and the administration department of the Fraunhofer-Gesellschaft.

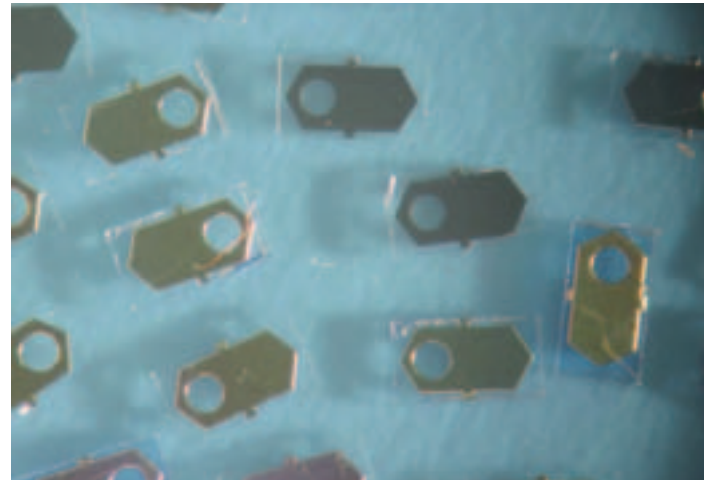


Figure 3: Magnetically manipulated microcarriers for cell culture in the circular holes (width of one target is 1 mm).

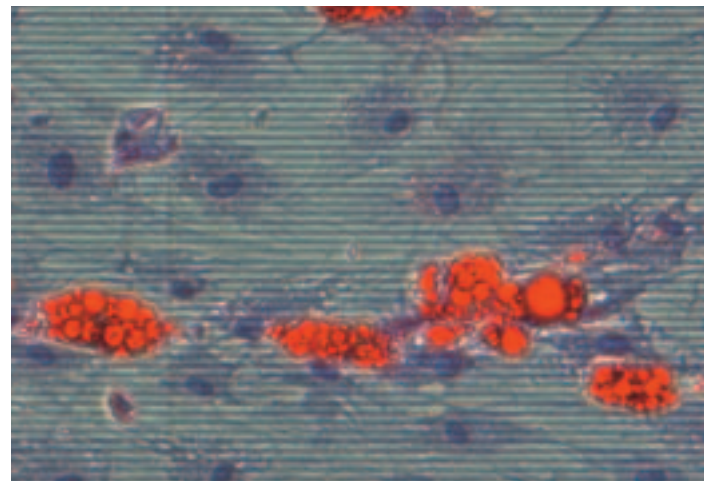


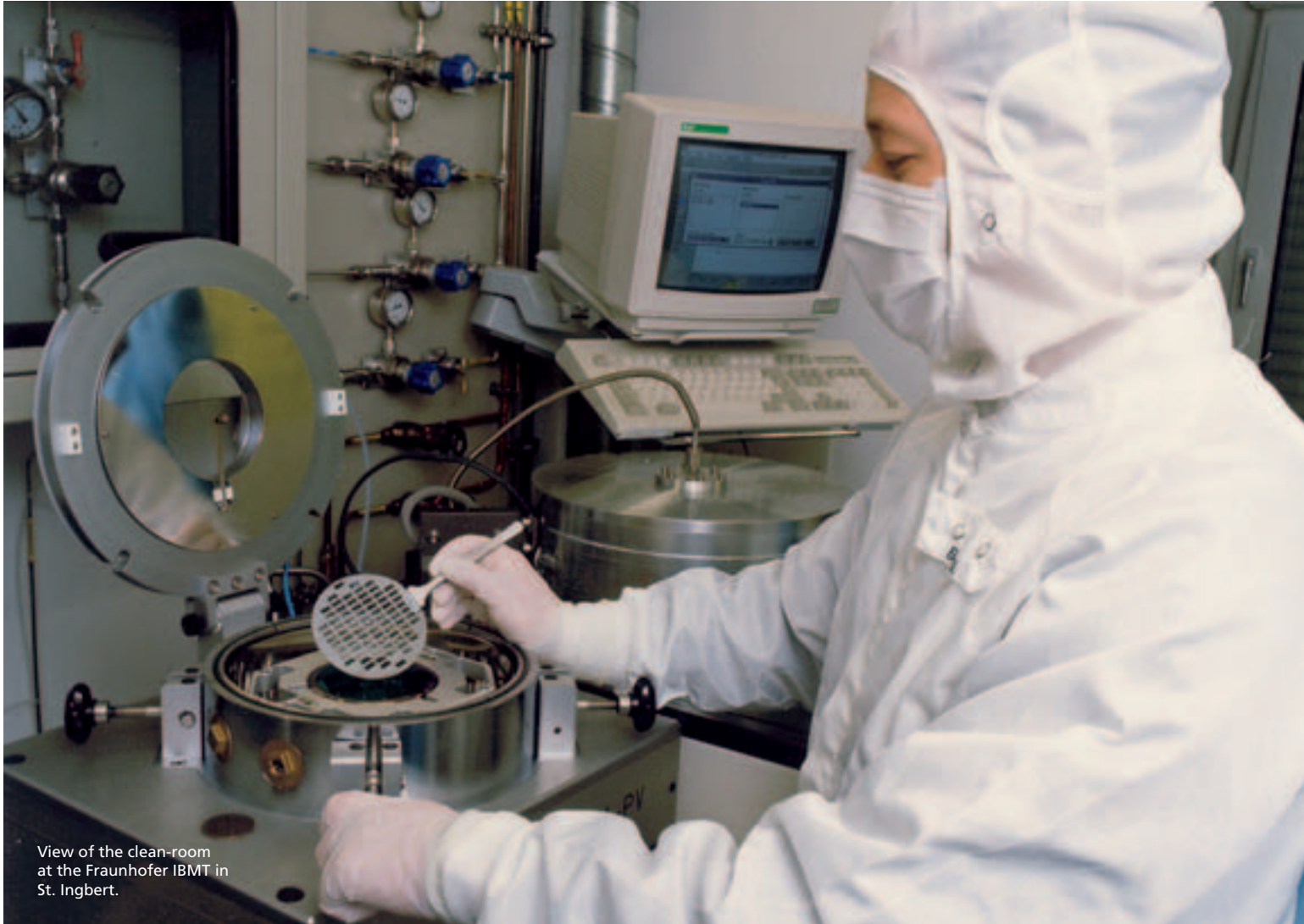
Figure 4: Cell programming in the CellPROM project. Differentiation of human adult stem cells into adipocytes on microstructured surfaces (Photograph: Claudia Brose).

Contact

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Contract Research and Services



View of the clean-room
at the Fraunhofer IBMT in
St. Ingbert.

- Institute-specific offers for contract research
- Contract and patent agreements
- Customers
- Product catalogue
- Contact and further information

Institute-specific offers for contract research

Procedure:

R&D projects are performed in success-oriented phases, starting with an initial technical market survey, the feasibility study deduced from this, then prototype development, field tests (clinical studies), the development of cost-optimized production processes and the required technology. Companies can be suggested for outsourcing sensor and microsystem production.

Relevance to practice:

Projects are pursued at the Fraunhofer IBMT in close coordination with the respective customer in order to establish the maximum relevance to practice. Close contact with the customer is a specific feature and an important requirement to meet the market demands when starting out from basic research.

Flexibility:

The concrete form, the orientation and the extent of the project work follow the requirements and ideas of the customer.

Synergy:

Integration into the research strategy of the Fraunhofer-Gesellschaft with its 58 institutes, and the Life Sciences Alliance of five Fraunhofer Institutes (IBMT, IGB, IME, ITEM, IZI) established in 2001, creates synergistic effects. Expertise from diverse research fields can be utilized in collaborations, allowing competent approaches even to multidisciplinary topics. Cooperation contracts offer IBMT customers complete product pipelines.

Quality:

Punctual delivery and reliability are characteristic for the work of the Fraunhofer IBMT. The creation of a "duty list" in cooperation with the customer guarantees that work on the project adheres to the agreed upon theme and projected time-frame.

Prices:

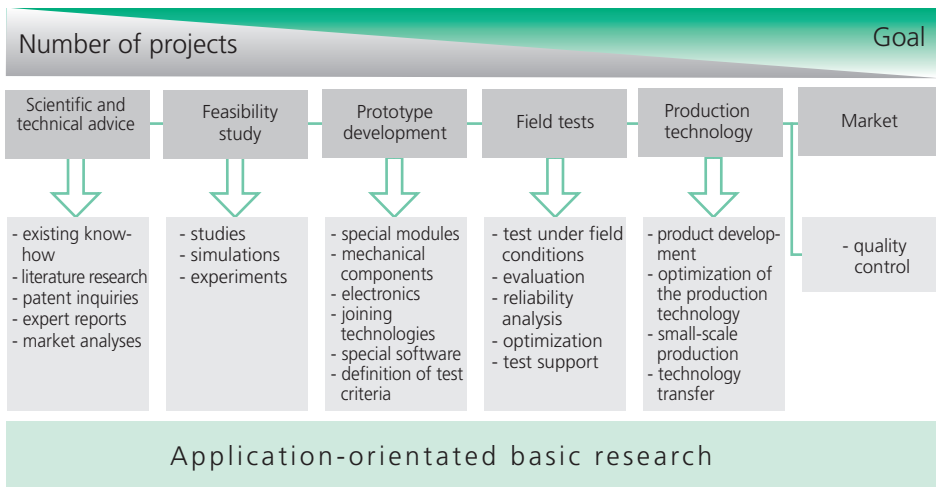
Commissioned research and development are carried out on a customer-paid basis. As an institute of the Fraunhofer-Gesellschaft, the IBMT is a charitable (non-profit) institution and mainly finances necessary application-oriented and preliminary research through public contractor participation.

R&D results:

The customer receives all the results after successful completion of the R&D project.

Confidentiality:

If the customer wishes, enquiries are handled with absolute confidentiality.



Risk-minimized product development.

Phase model:

Work on projects at the Fraunhofer IBMT is performed in stages: the start of a project involves scientific and technical consultation. This serves to reveal possible problems and assesses the risks of the project based on existing know-how, as well as applying literature, patent and market research. The second phase comprises a feasibility study, which specifically defines the project and evaluates the necessary efforts. Development of a laboratory prototype then demonstrates the practical operation. This stage leads to the development of a field prototype ending up with its extensive testing. Subsequently, re-design, technology optimization, small-scale production and technology transfer are all essential elements in preparing for large-scale production. As an auxiliary service, the Fraunhofer IBMT offers support with marketing and quality control, which

serves to get production started smoothly and eliminates risks involved in manufacturing. The client can subdivide their commission according to these phases and decide at the end of each individual stage whether it is worthwhile embarking on the next stage. These criteria make it easier for the customer as well as the IBMT to place or accept a commission and they produce transparent and calculable project times and costs.

Contracts and patent agreements

Drawing up a contract:

Fair and reliable contract conditions for the customer are of primary importance. Here, the scientists and engineers are supported by an experienced contract department of the Fraunhofer-Gesellschaft.

Beneficial interest:

The customer possesses exclusive rights to the patents generated in the course of the project. If the customer wishes, individual agreements can be settled. The IBMT is represented by more than five well-known patent attorney agencies.

Coordination:

The Fraunhofer IBMT is experienced in the coordination of complex multi-partner programs and generic lead projects. In this context, the IBMT takes on administration and coordination tasks and ensures excellent communication between the project partners to minimize "frictional loss".

Training:

The IBMT also offers the customer training of personnel if required, to introduce new methods and technologies. The training can take place on-site at the customer's company location.

Quality control:

The scientists and development engineers of the Fraunhofer IBMT work according to the rules of modern project management. The projects and operations are thoroughly and constantly audited with regard to time and costs and are oriented towards successful termination of the project. Each commission is monitored by computer-aided project controlling.

Funding possibilities:

The Fraunhofer-Gesellschaft helps the customer to locate every possible source of project funding. With long-standing experience in applying for research funding from the European Union, the Federal Ministry of Education and Research (BMBF) or other funding sources we proactively support the customer in matters of financing research projects.

Customers

In addition to customers from the biomedical and medical engineering sector including biotechnology, other industry branches (biotechnology, environmental technology, chemistry, pharmacy, material technology, automobile technology, hydraulics, mechanical engineering, installation engineering, sensor systems) are also clients of the Fraunhofer IBMT. Since its foundation the IBMT has worked together with companies of all sizes.

Product catalogue

The Fraunhofer IBMT offers its partners new products, technologies and processes, also for manufacturing, marketing or exploitation of patents and licenses. Please refer to the competence matrix on page 19 and the following product catalogue.

Product	Market	IBMT contact person
PaDok® – Secure communication and case-based network of records in the health service	medicine, healthcare, telematics	Dipl.-Phys. Bertram Bresser Tel.: +49 (0) 6894/980-206
TOPCARE – Home care and tele-medicine platform	medicine, health care, telematics, home care	Dipl.-Inform. Stephan Kiefer Tel.: +49 (0) 6894/980-156
Flow sensors	medicine, food industry, chemistry, environmental testing	Dr. Thomas Velten Tel.: +49 (0) 6894/980-301
NMR sample heads for spectroscopy and micro-imaging with a coil diameter between 2 and 40 mm, adapted to respective samples	medicine, material research, biomedical technology, environment, food, chemical and cosmetics industry	Priv.-Doz. Dr. Frank Volke Tel.: +49 (0) 6894/980-405
State-of-the-art gradient coils for NMR micro-imaging, e.g. 200 G/cm gradient systems in x,y,z dimensions and measurement time lapses starting with 50 microseconds	clinical medicine	Priv.-Doz. Dr. Frank Volke Tel.: +49 (0) 6894/980-405
NMR coils for medical whole body tomographs, e.g. lung coils for MRI with clinical equipment for (polarized) helium and/or xenon	clinical medicine	Priv.-Doz. Dr. Frank Volke Tel.: +49 (0) 6894/980-405
Minimally invasive NMR technology, e.g. NMR coils in conjunction with endoscopic operations	clinical medicine	Priv.-Doz. Dr. Frank Volke Tel.: +49 (0) 6894/980-405
Magnetic resonance positioning systems for medical operations	online MRI-aided operations, clinical medicine	Priv.-Doz. Dr. Frank Volke Tel.: +49 (0) 6894/980-405
Training courses for NMR spectroscopy and micro-imaging	pharmaceutical, life and material sciences, industry	Priv.-Doz. Dr. Frank Volke Tel.: +49 (0) 6894/980-405
Imaging software	medicine, material sciences	Priv.-Doz. Dr. Frank Volke Tel.: +49 (0) 6894/980-405
Biochemical structured surface substrates	biotechnology, stem cell research	Dr. Andreas Lankenau Tel.: +49 (0) 331/58187-303
Strains from the algae culture collection of psychrophilic microalgae (CCCr _{yo})	detergent, pharmaceutical, food and cosmetics industry	Dr. Thomas Leya Tel.: +49 (0) 331/58187-304
Algae raw material from customer-specific cultivation	detergent, pharmaceutical, food and cosmetics industry	Dr. Thomas Leya Tel.: +49 (0) 331/58187-304
DNA, RNA, cDNA for downstream processes	detergent, pharmaceutical, food and cosmetics industry	Dr. Thomas Leya Tel.: +49 (0) 331/58187-304
Immunosensor analyzer for automatic competitive immunoassays	biotechnology, pharmaceutical industry, environmental analytics	Dr. Nenad Gajovic-Eichelmann Tel.: +49 (0) 331/58187-204

Contact and further information

Please do not hesitate to call us if you have any questions, or if you wish further information or a concrete offer. We are happy to send you publications and brochures. Please visit our website:

<http://www.ibmt.fraunhofer.de>.

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The Institute in Numbers



Employees of the IBMT during a works outing in 2006 to visit the coal mining training tunnel of the RAG-Deutsche Steinkohle AG (DSK).

- Personnel development
- Operative budget
- Contract research with industry

Personnel development

In 2006, there were 194 scientific, technical and administrative personnel (including professorships), 29 student assistants and 57 practical students at the Fraunhofer IBMT. In addition, 10 guest scientists were carrying out research at the institute for a longer time period.

Operative budget

The estimated operative budget for 2006 will amount to 11.4 million €.

Income from industry to cover overall expenses is predicted to be 2.8 million € in 2006.

Contract research with industry

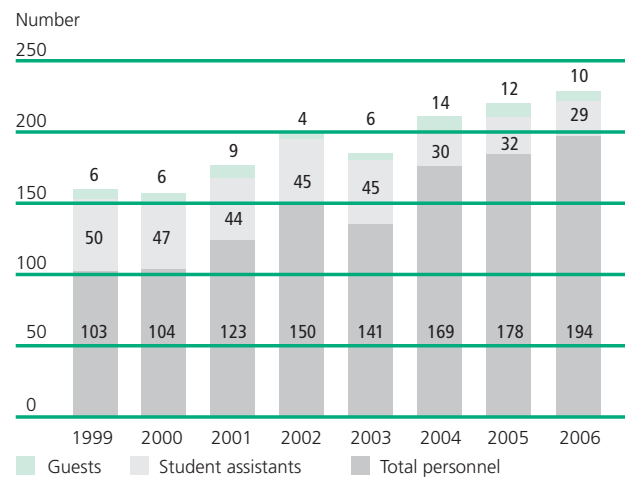
Project work predominates the research activities at the Institute. The goal in 2006 was to reduce the overall number of projects in 2000 to 2002 in favor of larger projects. This objective was achieved in 2006 with an overall increase in project scope but limited to 355 projects. 145 projects (i.e. approx. 41%) were for industrial customers.

Head of Administration

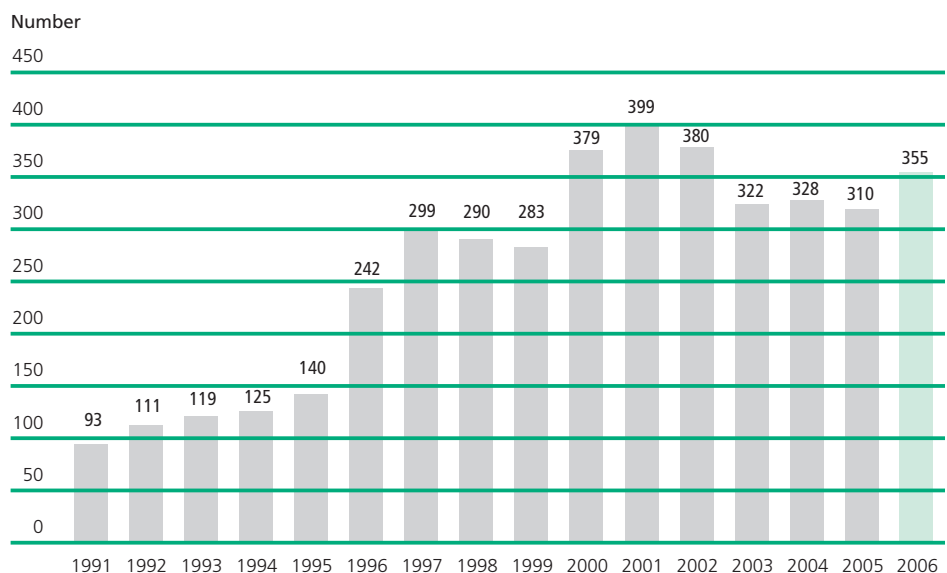
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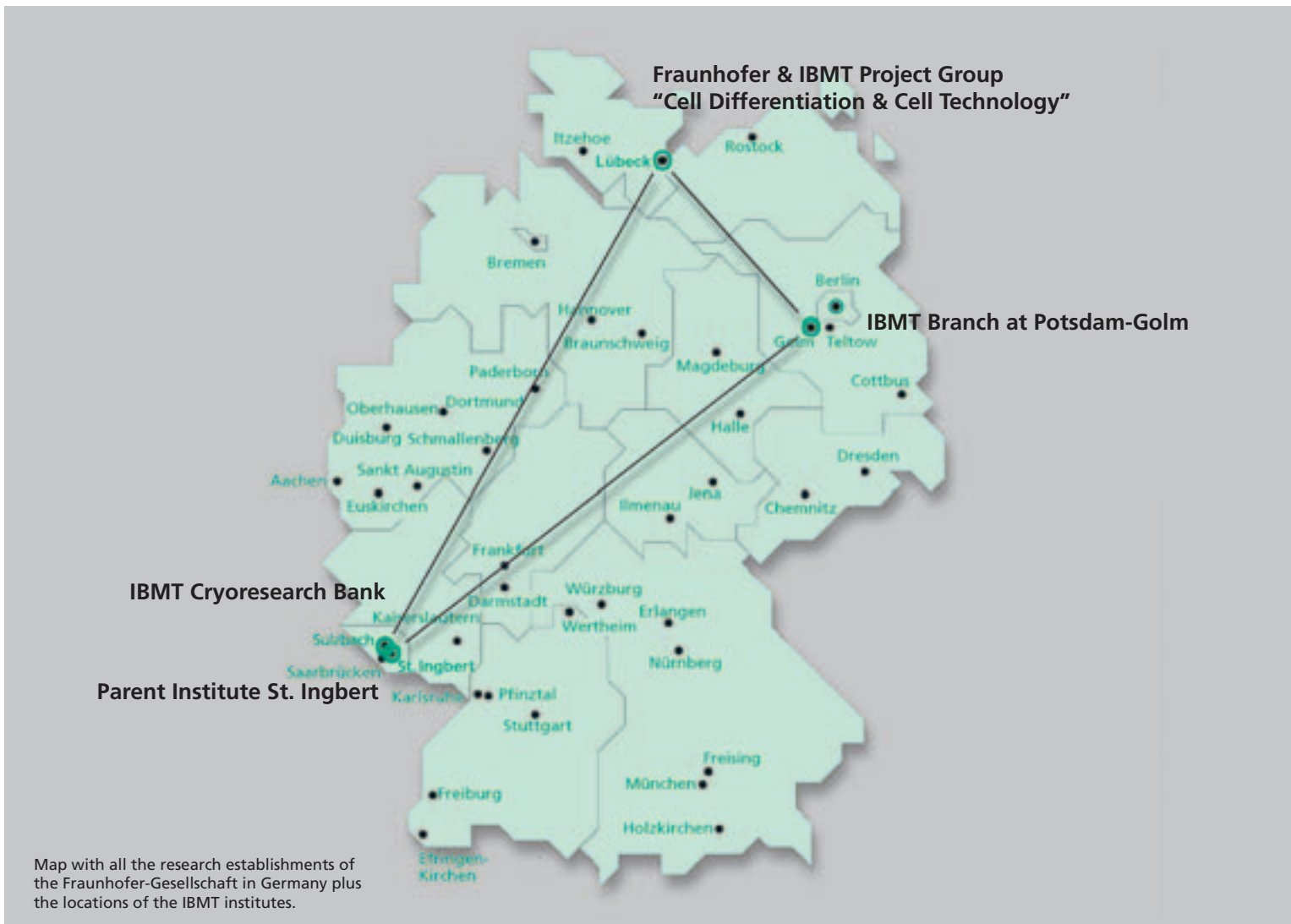
Personnel development from 1999 to 2006.



Project development from 1991 to 2006.



The Fraunhofer-Gesellschaft at a Glance



- Summary of overall competence
- Research areas
- Target groups
- Services offered
- Advantages of contract research

The Fraunhofer-Gesellschaft presently comprises 58 institutes that are thematically organized into eight research fields. Due to the strong interdisciplinary nature of biotechnology, a decisive advantage of the Fraunhofer-Gesellschaft, with its institutes and associations, is that it can cover almost all technology areas from research and industry. To enable our customers to optimally utilize these competences, the core areas of the Fraunhofer-Gesellschaft are summarized below.

Summary of overall competence

Research of practical utility lies at the heart of all activities pursued by the Fraunhofer-Gesellschaft. Founded in 1949, the research organization undertakes applied research that drives economic development and serves the wider benefit of society. Its services are solicited by customers and contractual partners in industry, the service sector and public administration. The organization also accepts commissions from German federal and Länder ministries and government departments to participate in future-oriented research projects with the aim of finding innovative solutions to issues concerning the industrial economy and society in general.

Applied research has a knock-on effect that extends beyond the direct benefits perceived by the customer: Through their research and development work, the Fraunhofer Institutes help to reinforce the competitive strength of the economy in their local region, and throughout Germany and Europe. They do so by promoting innovation, accelerating technological progress, improving the acceptance of new technologies, and not least by disseminating their knowledge and helping to train the urgently needed future generation of scientists and engineers.

As an employer, the Fraunhofer-Gesellschaft offers its staff the opportunity to develop the professional and personal skills that will allow them to take up positions of responsibility within their institute, in other scientific domains, in industry and in society. Students working at the Fraunhofer Institutes have excellent prospects of starting and developing a career in industry by virtue of the practical training and experience they have acquired.

At present, the Fraunhofer-Gesellschaft maintains more than 80 research units, including 58 Fraunhofer Institutes, at 40 different locations in Germany. The majority of the 12 500 staff are qualified scientists and engineers, who work with an annual research budget of 1.2 billion €. Of this sum, more than 1 billion € is generated through contract research. Two thirds of the Fraunhofer-Gesellschaft's contract research revenue is derived from contracts with industry and from publicly financed research projects. Only one third is contributed by the German federal and Länder governments in the form of institutional funding, enabling



Joseph von Fraunhofer (1787-1826).

the institutes to work ahead on solutions to problems that will not become acutely relevant to industry and society until five or ten years from now.

Affiliated research centers and representative offices in Europe, the USA and Asia provide contact with the regions of greatest importance to present and future scientific progress and economic development.

The Fraunhofer-Gesellschaft is a recognized non-profit organization which takes its name from Joseph von Fraunhofer (1787-1826), the illustrious Munich researcher, inventor and entrepreneur.

Research areas

Research and development are organized into eight institute groups (clusters) within the Fraunhofer-Gesellschaft:

- Material technology/construction component properties
- Production technology/manufacturing technology
- Information and communications technology
- Microelectronics/microsystems technology
- Sensor technology and sensor systems
- Process engineering
- Energy and construction technology, environment and health research
- Technical and economical studies/information transfer

To strengthen the biological sciences, a Life Sciences Alliance was established in 2001, comprising the four founding institutes (IBMT, IGB, IME, ITEM) and the IZI, which is currently under development.

Target groups

The target groups of the Fraunhofer-Gesellschaft are industry and the public sector.

- For customers from industry the Fraunhofer-Gesellschaft develops technical and organizational solutions up to the point of operational use. If system solutions are needed, several Fraunhofer Institutes cooperate under the direction and coordination of one commissioned institute.

- Strategic research projects are carried out upon request from German Federal or State authorities. These are aimed at promoting key technologies and innovations in areas of particular public interest, e.g. environmental protection, energy technologies and healthcare. Within the context of the European Union the Fraunhofer-Gesellschaft participates in technology programs that serve to increase the competitiveness of the European economy.

Services offered

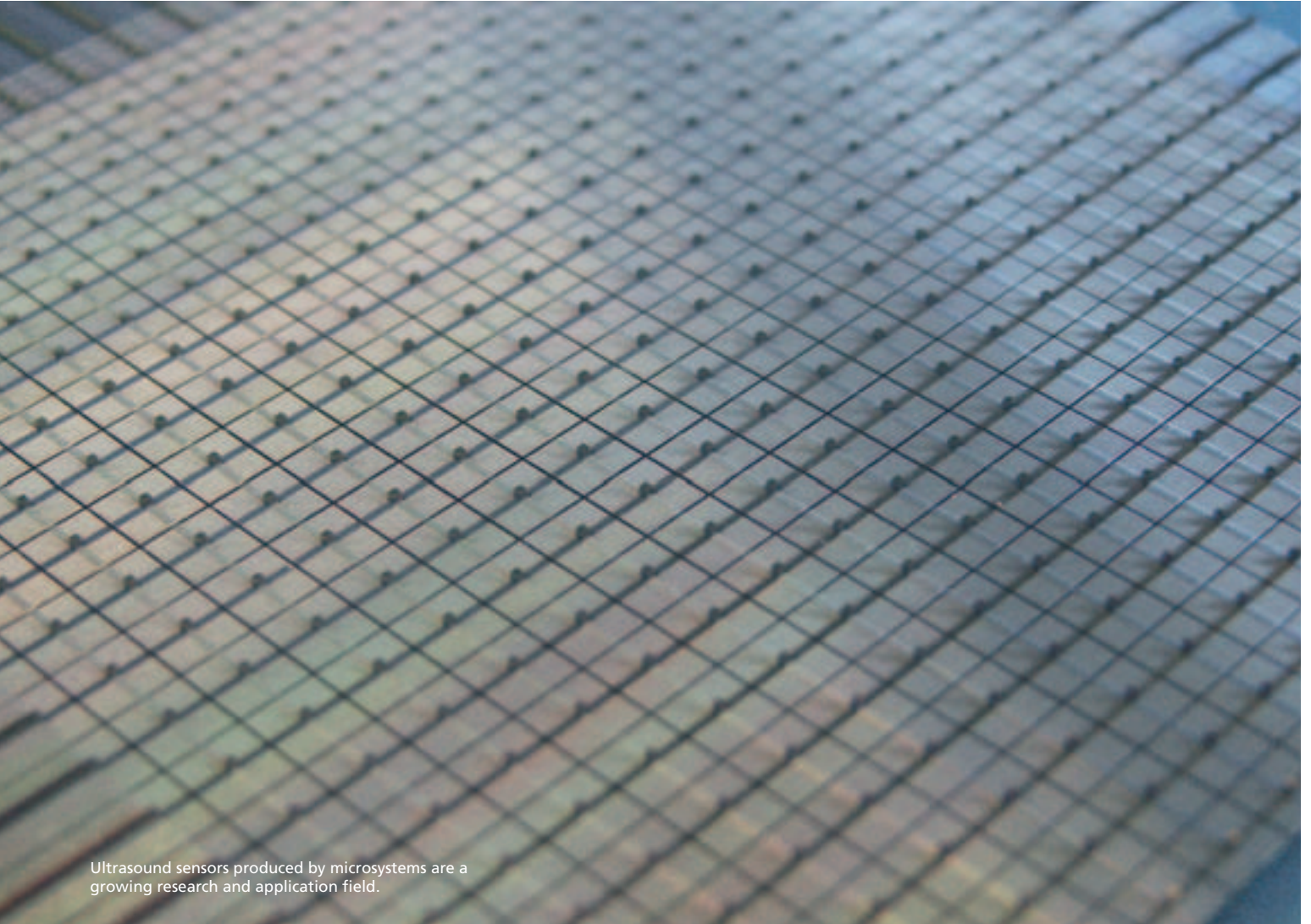
The Fraunhofer-Gesellschaft offers research and development in many service areas:

- Product optimization, development of prototypes, optimization of processes and development of new processes
- Support in introducing new organization schemes and technologies by
 - Testing in demonstration centers with state-of-the-art equipment
 - On-site training of the personnel involved
 - Services after introducing new processes and products
- Technology advice through
 - Feasibility studies
 - Market observation
 - Trend analyses
 - Evaluation of economic efficiency
 - Funding advice, especially for SMEs
- Testing services and granting of test certificates
- Helping companies start up
- Advice on company concepts and business plans
- Generation of economic concepts

Advantages of contract research

The cooperation of all the institutes ensures that the customers of the Fraunhofer-Gesellschaft can access numerous specialists with a broad spectrum of competences. Uniform quality standards and the professional project management of the Fraunhofer Institutes guarantee reliable results for the commissioned research. State-of-the-art laboratory equipment makes the Fraunhofer-Gesellschaft attractive for companies of all sizes and from all branches. In addition to the reliability of a strong association, a cooperation also has economical advantages, since the Fraunhofer-Gesellschaft contributes valuable starting capital to the partnership in the form of cost-intensive preliminary research.

Selected Research Results and Applications



Ultrasound sensors produced by microsystems are a growing research and application field.

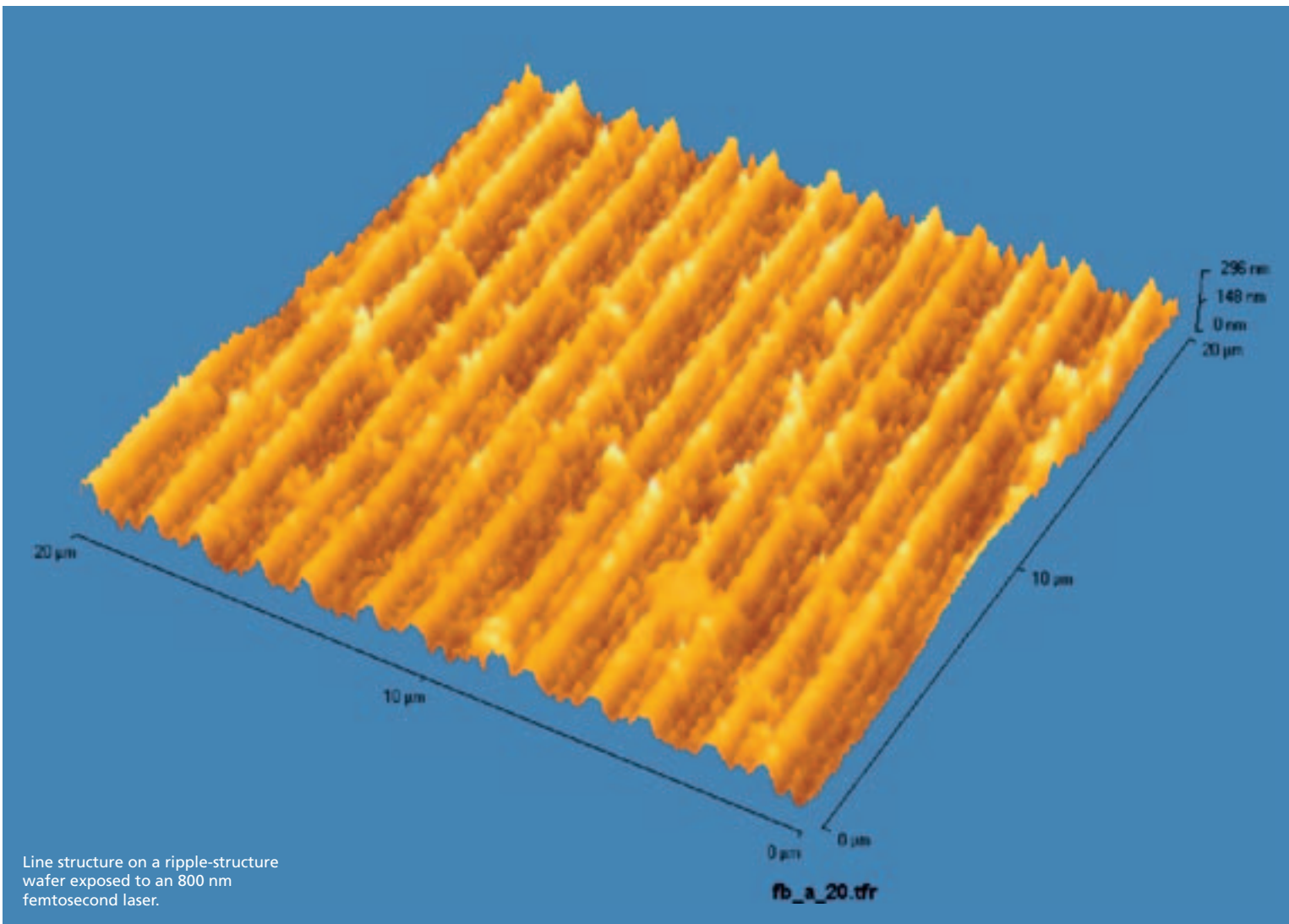
- Microsystems/Laser Medicine
- Ultrasound
- Telematics/Tele-Medicine
- Medical Engineering & Neuroprosthetics
- Cryobiophysics & Cryotechnology
- Cryoresearch and Cryodemonstration Bank
- Biohybrid Systems
- Computer-aided Simulations
- Cell Differentiation & Cell Technology

Branch Potsdam-Golm

- Cellular Biotechnology & Biochips
- Molecular Bioanalytics & Bioelectronics

Biomedical Competence Centers

Microsystems/Laser Medicine



Services, results and products of the workgroups

- Miniaturized Systems
- Magnetic Resonance
- Laser Medicine

Project example: Non-invasive, high-resolution imaging with magnetic resonance tomography in combination with multiphoton tomography

Equipment

Photolithography as a core technology for chip production, microsensors, microactuators and rapid prototyping is based on UV exposure of photosensitive polymers (photoresist) applied to silicon wafers and a subsequent etching process. From year to year the packing density on the chips has increased due to the ever-decreasing area of polymer exposed to UV. Since, according to Abbé, the size of the exposed spots correlates with the wavelength, UV excimer lasers are used. Currently, 90 nm technology is used to produce the Pentium 4 processor. Surprisingly, even sub-200 nm and sub-100 nm structures on silicon wafers and photoresist can be achieved with lasers of longer wavelengths in the near infrared (NIR) spectral range. Such sub-wavelength nanostructuring results from multiphoton effects, which are induced when the light passes through wide aperture lens optics within the focal range. At the IBMT, we used ultracompact turn-key NIR femtosecond laser pulses with low picojoule pulse energy in combination with scanning microscopes to expose SU-8 photoresist using a two-photon effect. Exact exposure of the photoresist in all three dimensions, with a precision of 40 nm within the photoresist, was achieved by varying the focus plane with a piezo-controlled lens system. Hence, it was possible to generate 3-dimensional structuring and bulk structures. The figure (on the left, p. 56) illustrates an example of such a 3-D two-photon polymerization of SU-8 photoresist applied to a wafer after exposure to 730 nm femtosecond laser pulses from an 80 MHz titanium sapphire laser.

The resulting structure, an "IBMT cube" with an edge length of 60 μm , was generated by initial irradiation of a base in 60 μm coating depth and subsequent exposure of the overlying areas by suitable beam scanning with an x,y-galvoscan. Interestingly, the detailed topography of the structured micro-cube featured a periodic nanostructure. Analyses by electron and atomic force microscopy revealed nanogrooves with an average depth of 150 nm. The distance between these nanogrooves can be modified by varying the scanning parameters. The generated 3-D structure with its periodic nanotopography impressively demonstrates the new technological potential of ultra-short long-wave laser pulses for precise three-dimensional photolithography using multiphoton photochemistry.

If the laser pulse energy is raised to a few nanojoules, even direct nanostructuring (laser writing) of silicon wafers can be achieved without the use of photochemical processes (photopolymerization). The figure on the left shows a ripple-structure in a wafer exposed to an 800 nm femtosecond laser. As yet poorly understood self-organizing processes created a sub-80 nm nanostructure. This means that the width of the structure is more than an order of magnitude smaller than the laser wavelength. Thus, we generated the smallest sub-wavelength structures to date.

Currently, we are investigating the biocompatibility of such nanostructures generated by femtosecond lasers and their potential as tools for manipulating single cells and cell clusters, especially stem cells.



Further application fields for this novel nanostructuring laser technology exist in tissue engineering (e.g. the production of artificial extracellular matrices), the preparation of prostheses, the production of novel optical 3-D data storage media, photonic crystals and nanosystems, as well as rapid prototyping.

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Miniaturized Systems



Miniaturized systems, if requested with wireless control and data acquisition:

- Sensor systems
- Actuator systems
- Active medical implants

Miniaturized telemetric systems (not only) for medical applications:

- Transmitted by induced current
- Infrared telemetrics
- Radio telemetrics
- Production of microcoils

Development of size-optimized sensor, actuator and communication electronics:

- Microsensors
- Mass flow sensors with integrated conductivity measurement
- Sensors to measure the thickness of films
- Tactile sensors (endoscopy, robotics)

Micro-fluidics and biocell handling systems:

- Micro-fluidic systems as fluid interface to biosensors and biochips
- Multi-jet structure to handle several cells in parallel
- Micro-injection chips for cell injections (needle + pump on one microchip)

Construction and bonding technology:

- Packaging of bioanalysis chips
- Packaging of micro-implants
- Design and production of ultra-thin (5-10 μm), flexible printed circuit boards with conductor widths $\geq 5 \mu\text{m}$
- Patented “MicroFlex bonding technology” for flexible printed circuit boards
- Hybrid-integrated layer technologies (thick layer or thin film technology)

Thin layer technology:

- Preparation of low-stress silicon nitride layers (PECVD)
- Preparation of water impermeable parylene layers
- Preparation of metallic and dielectric layers (vapor-coating, sputtering)

Microstructuring:

- 3-D rapid prototyping of SU-8 photoresist with femtosecond laser pulses (resolution: 300 nm)
- Masking via photolithography
- Wet chemistry etching
- Reactive ion etching (RIE)
- Dry etching of parylene and polyimide

Replication technologies:

- Silicon molding
- Rotary hot embossing of (fluidic) microstructures on large surface, continuous polymer foils

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Magnetic Resonance

Biomedical research (NMR, FT-IR):

- Evaluation of active compounds by NMR spectroscopy and MR imaging
- NMR micro-imaging and MRI (magnetic resonance tomography)
- Formulation of compounds, creams, gels, etc.
- Permeation characteristics of vesicles, drug carriers and cells
- Interactions between membrane-active pharmaceuticals and model or bio-membranes
- Liposomes as carriers of active compounds
- Characterization (in vitro) of cellular components and metabolic processes with high-resolution solid-state NMR technologies
- Molecular characterization of biomineralization processes
- Ageing processes in gels, creams, etc.
- Hydration characteristics of biopolymers and active agents
- Coating of surfaces (biocompatibility)
- In vitro and in vivo studies on the effects of creams and lotions on the skin
- Analysis of bio-glues
- Analysis of biosensors
- Cells under extreme conditions (e.g. cryopreservation, cryoprotection)
- Cell-cell and cell-surface interactions with high-resolution NMR spectroscopy
- Structure and dynamics of biofilms under flow conditions
- Image analysis with the software BodyScan® developed in the NMR/MRI workgroup

Material research (NMR, FT-IR, AFM):

- Molecular structure and dynamics in polymers and biopolymers
- Diffusion behavior of fluids in polymers

Laser Medicine

- NMR micro-imaging of composite materials
- Swelling capacity of polymers and biopolymers
- Evaluation of filter material
- Evaluation of the protective effect of waxes

NMR technology:

- Non-invasive high-resolution NMR flow measurements, rapid imaging procedures for on-line control, flow characteristics on different physico-chemical surfaces (biocompatibility)
- Rapid 3-D MR imaging also for solid material
- NMR probes for spectroscopy and micro-imaging with coil diameters between 2 and 40 mm, specifically adapted to the samples
- State-of-the-art gradient coils for NMR micro-imaging, e.g. 200 G/cm gradient systems in x,y,z dimensions and measurement time lapses starting with 50 microseconds
- NMR coils for medical whole body scanners, e.g. lung coils for MRI with clinical equipment for polarized helium and/or xenon
- Minimally invasive NMR technology, e.g. NMR coils in conjunction with endoscopic operations
- Magnetic resonance positioning systems for MR-guided surgery
- CAD/CAM for life and material sciences

Others:

- Consulting and studies (research institutions, courts, companies, authorities)
- Training courses for NMR spectroscopy and micro-imaging (industry)

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- Multiphoton laser microscopy with femtosecond lasers in the near infrared (NIR) spectrum
- Optical tomography of cells and tissues
- Optical melanoma diagnostics and drug screening
- Nanosurgery within cells and tissues
- Microstructuring
- Nanostructuring of polymers, metal foils, silicon
- Optical trapping
- Stationary and time-correlated fluorescence spectroscopy
- Fluorescence lifetime imaging (FLIM)
- Raman spectroscopy and imaging
- Two-photon fluorescence correlation spectroscopy
- Atomic force microscopy (AFM)
- Electron microscopy
- Viability test
- Cell cloning assay
- Reactive oxygen species (ROS) detection
- Imaging of ECM structures (elastin, collagen)
- Detection of pathogenic microorganisms
- Detection of accumulated nanoparticles in tissue
- Multiphoton acoustic microscopy

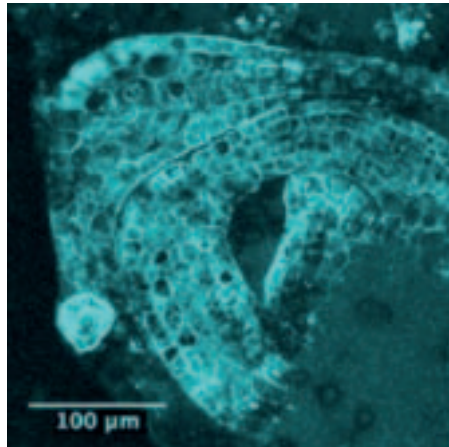
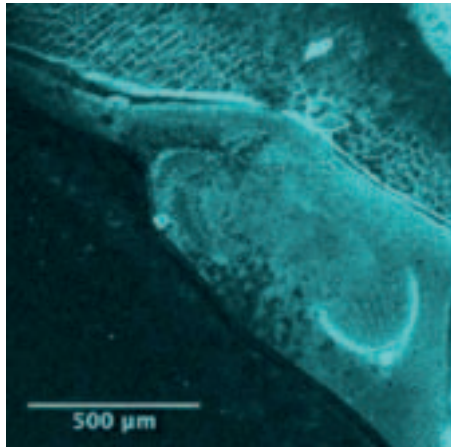
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Project example: Non-invasive, high-resolution imaging with magnetic resonance tomography in combination with multiphoton tomography

Magnetic Resonance



Images of a barley embryo (day 14 post fertilization), autofluorescence image, excitation by multiphoton absorption in the near infrared. Left: overview (scale bar 500 μm); right: cellular details in the area of the primordial cotyledon (scale bar 100 μm).

Initial situation

Medicine, cell biology and biotechnology are increasingly searching for new, rapid and reliable imaging processes and algorithms for evaluating the huge amount of data being generated. Basic and applied research focuses more and more on non-invasive observation with high temporal and spatial resolution in correlation with morphological and biochemical changes and processes in the studied object. Furthermore, analyses of single cells and cell aggregates (tissue engineering) are of particular interest for understanding tumor genesis, contact inhibition during cell-to-cell contacts and the influence of external stress factors on cells. Solving such complex tasks requires an innovative approach that takes into account both imaging technologies and handling of the studied object. For instance, the size of MRI/NMR coils can be reduced enormously by microsystems technology without deterioration of the signal-to-noise ratio. This gives rise to new application areas, which among other things could lead to a lab-on-chip

device. The challenge is to combine different imaging techniques that efficiently exploit the information available at different observable size scales, from the nanometer to centimeter range, and allow the detection of specific biomolecules.

For the first time, micro-imaging of seed embryos using magnetic resonance and multiphoton tomography was performed at the Fraunhofer IBMT. In particular, developing seeds were analyzed from fertilization to grain maturity.

Project description

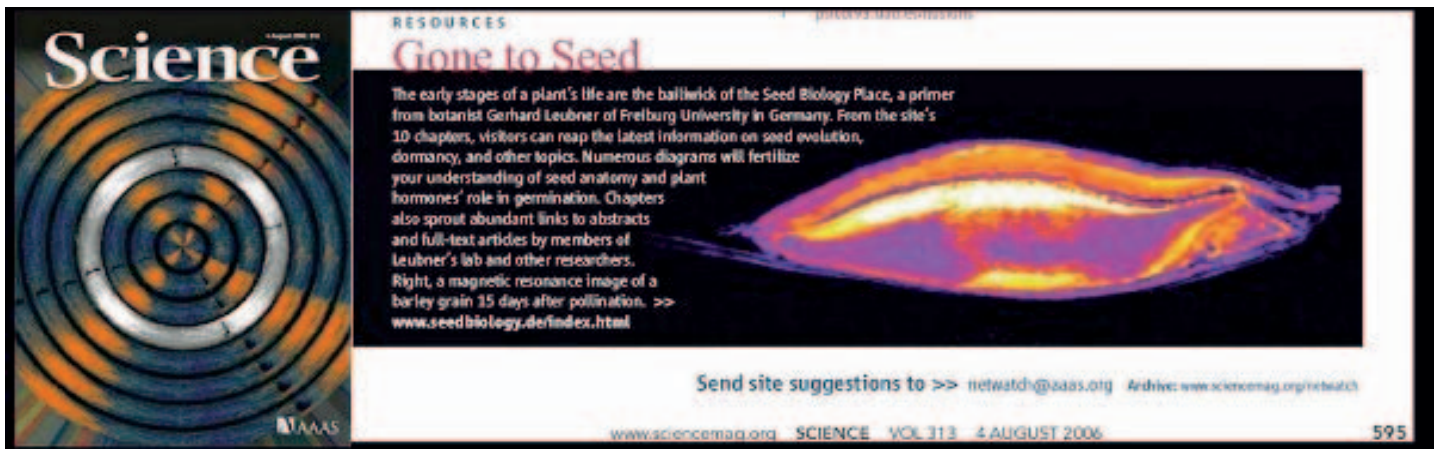
In the context of a project funded by the German Research Council (DFG), in collaboration with the Institute for Genetics and Research of Cultured Plants (IPK) Gatersleben, barley seeds were analyzed with micro-MRI based on miniaturized coils and with two-photon autofluorescence imaging. This method does not require any staining or addition of contrast medium. Both techniques allowed non-invasive imaging and subsequent three-dimensional

reconstruction of the studied object. Changes in internal structures and the distribution of molecular components during the maturation process were monitored. MRT resolution in the range of 40 μm could be attained using custom-made microcoils. The microcoil yielded a very good signal-to-noise ratio due to the homogeneity of the magnetic field and an optimal filling factor.

Moreover, using a high aperture objective allowed the detection of specifically fluorescing biomolecules at submicrometer resolution after multiphoton excitation. Objectives with lower apertures were used for overview pictures. Both detailed and lower resolution image information were combined with suitable software. At the same time, the seed embryo was analyzed three-dimensionally by multiphoton tomography, and information from both imaging techniques were combined.

Tasks

As a partner in the DFG seeds project, the Fraunhofer IBMT is responsible for the development and analysis of appropriate imaging technologies, and in the context of a VDI project the Fraunhofer IBMT works on further miniaturization (MST) of NMR/MRI equipment with the aim of making a robust lab-on-chip NMR/MRI system, which should also find applications in medical, pharmaceutical and food industry areas.



Results

For the first time, μ -MRT was successfully combined with high-resolution multiphoton tomography. The results were submitted for publication (Stark et al., Multiparametric high-resolution imaging of barley embryos by multiphoton microscopy and magnetic resonance micro-imaging).

The quality of the μ -MRT images of barley embryos from the IBMT convinced the renowned journal SCIENCE to print a picture of a developing embryo taken 15 days after fertilization (Volke, F., Manz B., and Weschke, W., SCIENCE, August 4th, 313, page 595, 2006).

Furthermore, we succeeded in achieving femtosecond laser induced polymerization of photo-coatings, which allows the precise production of miniaturized MRT microcoils. Exposure of the photoresist was also achieved with the multiphoton tomograph. An example is the laser treatment of SU-8 photoresist (see Microsystems/Laser Medicine). In principal, very small structures can be generated with the rapid prototyping process.

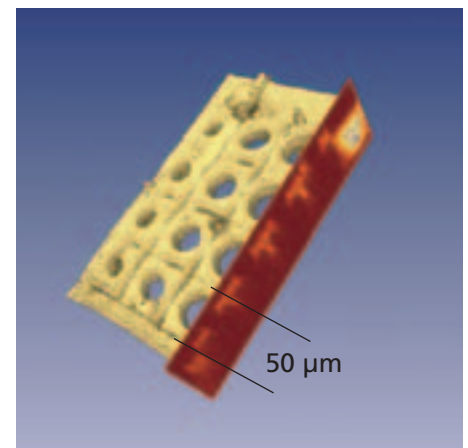
Project funding

The project is funded by the DFG, the IPK Gatersleben and the VDI (BMBF).

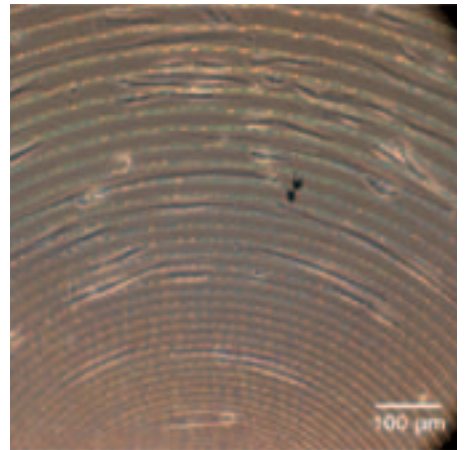
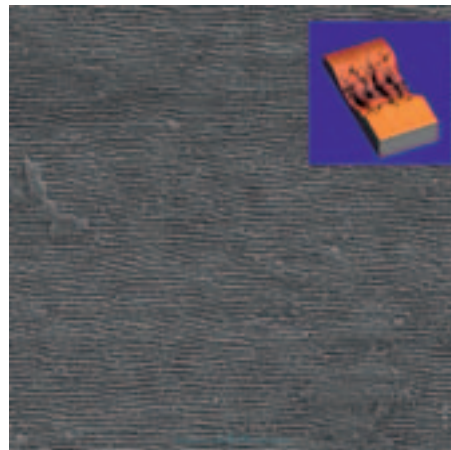
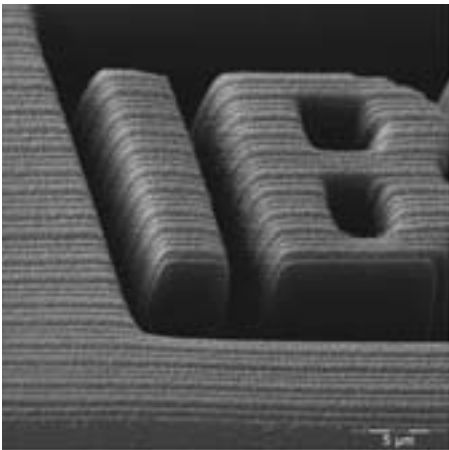
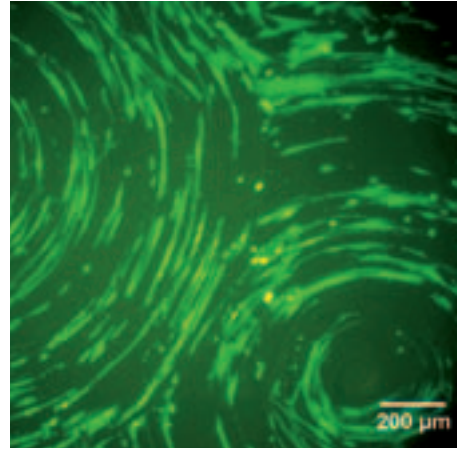
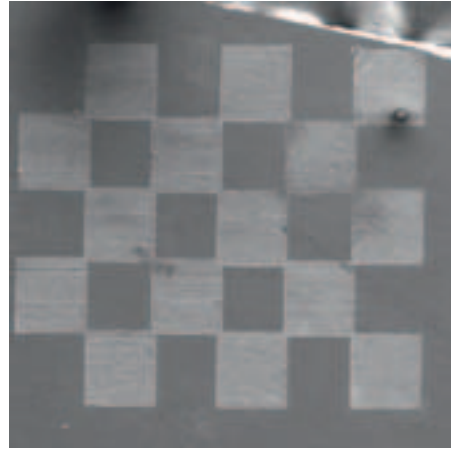
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Laser treatment of SU-8 photoresist, e.g. for miniaturized MRT coils and cell containers.



"IBMT cube" (60 μm) generated with an 80 MHz titanium sapphire laser.

Nanopatterns created on silicon wafers with sub-nJ pulses.

Laser-induced modification of the morphology of human dental pulp stem cells.

Equipment

Miniaturized Systems

- Complete photolithography with resist processor and double-sided mask aligner for microstructuring
- Dry etching facilities (reactive ion etching, RIE) for silicon wafers as well as polymer substrates
- Facilities for anisotropic silicon etching
- Laser for drilling and cutting (e.g. of silicon or aluminium oxide ceramics)
- Construction and bonding technology (die bonder, ball-wedge bonder, wedge-wedge bonder)
- Anodic bonder
- Thin film processing facilities (sputtering, vapor-coating, PECVD)
- Coating facilities for parylene C
- Hot embossing facilities
- Rotary hot embossing facilities for large surface foils (reel to reel)
- Foil laminator
- Laboratory for silicon remolding
- Hybrid laboratories
- Design technology for mask and circuit layouts
- 3-D laser profilometer
- Scanning electron microscope (SEM, EDX)
- Atomic force microscope (SPM, AFM)

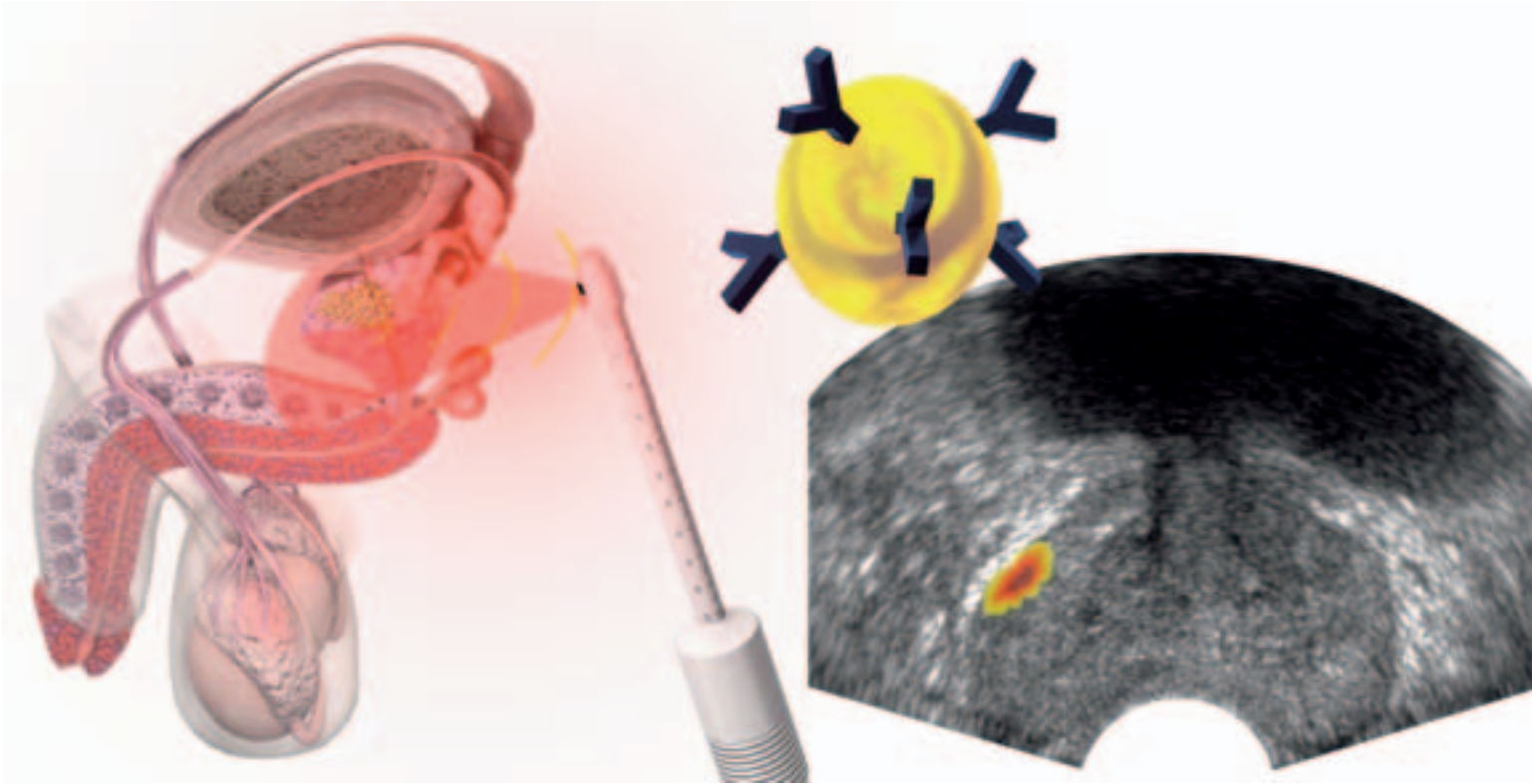
Magnetic Resonance

- Two 9.4 Tesla high-frequency NMR spectrometers for spectroscopy (fluids, gels, solid material) and micro-imaging (resolution down to 6 μm)
- Rapid MR 3-D imaging and non-invasive flow measurements
- High-resolution MAS (Magic Angle Spinning) NMR spectroscopy of viscous and solid material in combination with multi-dimensional NMR
- Diffusion measurements (self-diffusion coefficient) up to 10-14 m^2/s with pulsed-field gradient NMR
- CAD and CAM of NMR probes (up to 800 MHz) and magnetic field gradient units (up to 500 G/cm) for micro-imaging and custom-made solutions for clinical MRT systems
- CAD and CAM of MRI and NMR accessories, e.g. positioning systems, as well as other applications
- 200 MHz NMR spectrometer with extension for high resolution of solid material (MAS)
- Access to clinical MRI scanners with 0.5, 1.5 and 3.0 Tesla
- Access to 600, 750 and 800 MHz widebore NMR spectroscopy including Magic Angle Spinning (MAS)
- FT-IT spectrometer with ATR extension for spectroscopy of interfaces
- Medical software (e.g. early diagnosis of skin cancer)
- RF and magnetic field measurements
- Photofinder (TeachScreen)
- Device for magnetic field measurements (3-D)

Laser Medicine

- Femtosecond lasers (titanium sapphire laser) MaiTai (710 - 990 nm, 80 MHz), Chameleon (720 - 930 nm, 90 MHz) and Vitesse (800 nm, 80 MHz)
- Ruby laser
- Carbon dioxide laser
- Modified confocal laser scanning microscope
- Compact scanning microscope for nanosurgery
- Multiphoton laser scanning microscope with spectral imaging module (Zeiss LSM5 10-Meta-NLO)
- Multiphoton imaging system Dermalinspect for in vivo examination of skin
- Autocorrelator
- Pulse picker
- Frequency doubler
- Beam analysis system (Spiricon)
- Module for time-correlated single photon counting and fluorescence lifetime imaging
- Laser tweezers
- Miniaturized cell chambers for long-term studies (cell cloning assay)
- Animal operation room
- Cell culture facility

Ultrasound



“ADONIS” – Concept for highly sensitive diagnosis of prostate cancer using opto-acoustic molecular imaging. The hybrid imaging combination between optical excitation of a biologically functionalized nanoscale contrast medium and acoustic detection allows selective high-resolution imaging with penetration depths of some centimeters. The concept is not restricted to visualizing prostate disorders but can be applied to the diagnosis and study of many different diseases. The development of this concept is being carried out in conjunction with the EU-funded project “ADONIS” (www.fp6-adonis.net).

Services, results and products of the workgroups

- Active Materials
- Piezosystems & Manufacturing Technology
- Ultrasound Systems Development
- Biomedical Ultrasound Research

Portfolio of the Department

Equipment

The usefulness and value of a technology is determined by the scope and number of possible applications. A general rule is: The simpler the basic principle, the more successful the technology. The use of mechanical waves in the high frequency, inaudible range – ultrasound – is a convincing example of this principle.

Ultrasound was discovered in the late 19th century; however, it took about 100 years before the technology matured to its current significance due to the much later development of electronic real-time signal processing that it requires. After the first, now well-established application as sonar signals for locating ships and mines and for characterizing industrial construction materials and components, ultrasound has been used for more than 50 years in medical diagnostics. Indeed, it has become the most frequently used imaging technology in this area. Routine examinations in various medical fields, particularly prenatal diagnostics, first became feasible due to the non-invasiveness and low costs of this technology. In addition to these properties, the robustness and ability to scale down/up this technology means the spectrum of applications is still increasing today. By scaling up the frequency one can visualize and characterize very small structures such as single biological cells in the sub-micrometer range,

analyze tiny sample volumes and gently manipulate samples and particles down to the nanometer range. Scaling the power means ultrasound can be used to modify and accelerate processes in chemical and biotechnological processing technologies and, in medicine, as a therapy to treat diseases. A trend in all applications is the use of increasingly integrated, higher resolution systems and the combination of different complementary technologies. For instance, a combination of dielectrophoretic and ultrasound-based generation of forces can be used for gentle handling of single cells in lab-on-chip systems. The area of molecular imaging is currently pursuing combination systems of optical excitation, acoustic detection and molecular biologically activated micro- and nano-scale contrast media.

The department for Ultrasound, with 40 personnel, is the largest department of the Fraunhofer IBMT. With 18 years of experience and divided into four workgroups, it offers overall competence for medical, biotechnological and technical ultrasound solutions. The development services offered range from consulting and feasibility studies, laboratory samples and prototype development, to certified product development and evaluation. The competences in the workgroups permit in-house development of all system components, ranging from an ultrasound transducer with specifically adapted material properties, electronic system components and processes, to manufacturing sensors.



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Active Materials



- Piezoelectric materials
- Nanocomposite materials
- Thin and thick layer coating
- Laser structuring
- Microsystems technology

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Piezosystems & Manufacturing Technology

- Sensors for distance measurement and flow measurements in gases and fluids
- Ultrasound sensors for special applications and environments
- Sensors for material testing
- Sonar sensors
- Piezoelectric composites
- Miniaturized ultrasound transducers
- Catheter-integrated sensors for medical technology
- Imaging multi-element transducers (arrays)
- Power ultrasound transducers (e.g. sonotrodes)
- Cleaning systems (e.g. mega sound cleaning)
- Sensor manufacturing and quality control
- Consulting for sensor development and production

Contact

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Ultrasound Systems Development

- Analogue & digital circuit development
- Ultrasound single- and multi-channel systems
- Embedded systems
- Ultrasound phased array systems
- Portable systems
- High-power sound systems
- Flow, distance and level measurement systems

Contact

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Biomedical Ultrasound Research

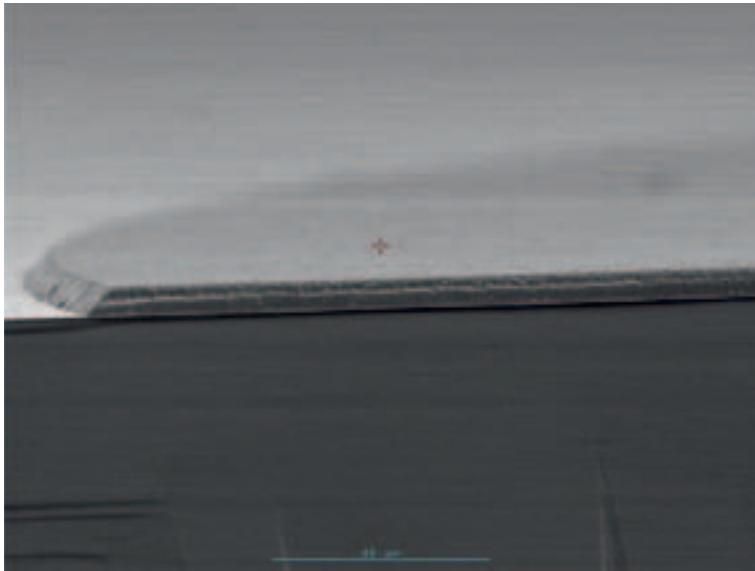
- Application-specific ultrasound research and development
- Material characterization
- Signal processing and parameter extraction
- Reconstruction and visualization
- Navigation
- Therapy monitoring
- Microscopy
- Manipulation systems
- Hybrid imaging systems

Contact

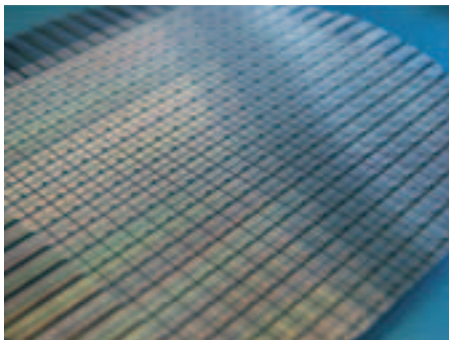
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Workgroup Active Materials



Section of a circular piezoelectric zinc oxide layer on a silicon wafer. The zinc oxide was applied with a PVD (physical vapor deposition) process. The layer thickness can be varied between 1 to 20 μm . Depending on the thickness, the layers have resonance frequencies between 100 MHz and 1 GHz. Together with acoustic lenses made of silicon or sapphire, the piezoelectric zinc oxide layers are used as ultrasound sources in acoustic microscopes.



The dots in the structure are acoustic ultrasound sensors produced with microsystems technology. The procedure allows the generation of 256 acoustic sensors on one silicon wafer.

Within the department for Ultrasound, the workgroup Active Materials focuses on material technology solutions for applications in ultrasound technologies. The research areas include developing new materials, adapting existing materials and establishing new processes such as laser structuring to create modern ultrasound systems.

While the adaptation of existing materials and development of processes are carried out exclusively in the workgroup, novel materials are also developed in collaboration with other material sciences research establishments. The impetus to create a workgroup oriented to material sciences within the department for Ultrasound came particularly from frequency ranges in ultrasound technology extending beyond 100 MHz and up to several GHz. This frequency range allows improved spatial resolution of diagnostic systems for ophthalmology, dermatology and analysis of blood vessel walls, as well as further developments in ultrasound microscopy. The development of these systems can certainly be enhanced by using novel nano-coated materials, where material parameters such as speed of sound, absorption

and acoustic impedance can be adjusted by the composition of the nanoparticles and the way they are synthesized. In addition to applications in high-frequency ultrasound, nano-coated materials have advantages for processes in established conventional ultrasound, such as adjustable rheology during material synthesis. Research activities in the novel material field are performed in cooperation with industry partners and with external project funding. Currently, projects are being funded by the Ministry of Culture and Education of Saarland and the Federal Ministry of Education and Research (BMBF), although the majority of projects are bilateral collaborations with industry.

Core competences:

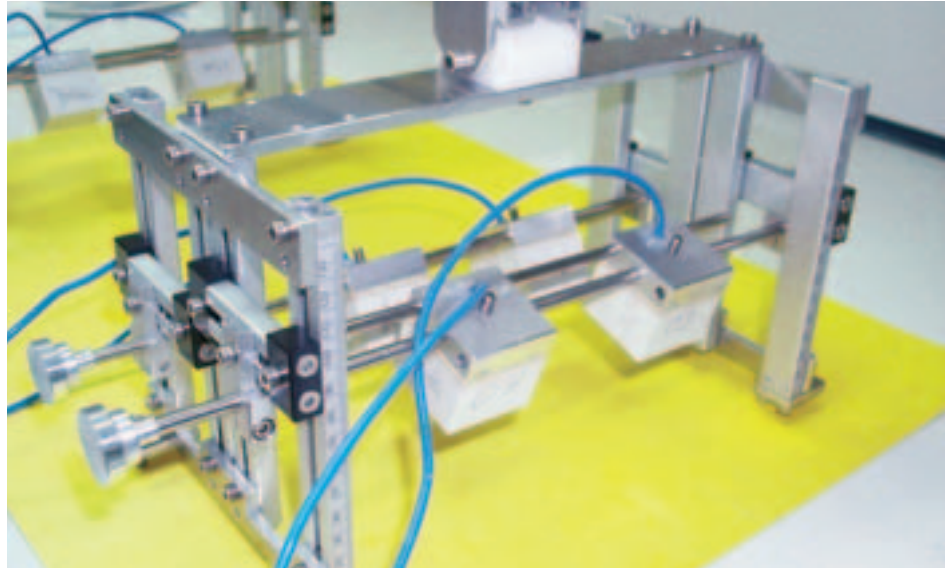
- Piezoelectric materials
- Nanocomposite materials
- Thin and thick layer coating
- Laser structuring
- Microsystems technology

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Workgroup Piezosystems & Manufacturing Technology

The workgroup Piezosystems & Manufacturing Technology offers application-specific development and prototype production of ultrasound transducers, arrays and high-power application devices in nearly all application areas. Due to the broad scope of the workgroup, know-how can be used to advantage over a wide spectrum in various fields such as medicine or technical and industrial applications. The electro-mechanical coupling used in ultrasound transducers, as well as the necessary transmission mode, demand in-depth knowledge about the application-specific setup of ultrasound probes. Based on their long-standing experience, the workgroup designs new sensors and builds initial test transducers and prototypes for evaluation and life-span testing that take into account specific operation environments and subsequent signal processing. To transfer a finished prototype into a mass-produced product, we develop suitable production technologies and installations, and ensure the small to medium-scale production of different ultrasound systems. We also offer the development and manufacturing of piezoelectric components and composite materials (1-3 composites), which are used as OEM components in many sensors.



Core competences:

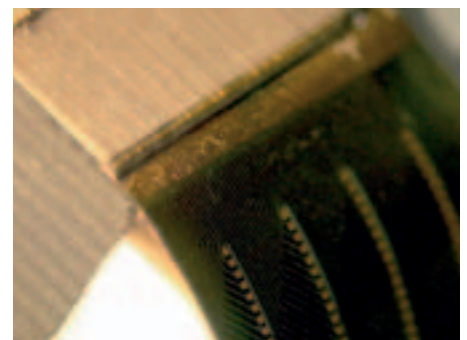
- Sensors for distance measurement and flow measurements in gases and fluids
- Ultrasound sensors for special applications and environments
- Sensors for material testing
- Sonar sensors
- Piezoelectric composites
- Miniaturized ultrasound transducers
- Catheter-integrated sensors for medical technology
- Imaging multi-element transducers (arrays)
- Power ultrasound transducers (e.g. sonotrodes)
- Cleaning systems (e.g. mega sound cleaning)
- Sensor production and quality control
- Consulting for sensor development and production

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Ultrasound sensor system to measure defective regions in sewer pipelines.



Picture of a miniaturized acoustic block for medical imaging produced with the sandwich construction method. The acoustic block consists of many ultrasound transducers with separate electrical contacts. With a time controlled excitation of the single transducer it is possible to generate well defined sound beams which scan the tissue line by line.

Workgroup Ultrasound Systems Development

The workgroup Ultrasound Systems Development is specialized on the development of single and multi-channel ultrasound systems for medical and non-medical applications. The group has a long-term experience and know-how in designing analogue and digital hardware. The targeted evaluation of innovative approaches and a rapid product development is supplied by proven and continuously improved technology platforms like the single-channel Transmit Receive Module (TRM) and the multi-channel imaging systems Digital Phased Array System (DiPhAS). These platforms are the basis for developing systems for medical diagnostics (e.g. imaging, navigation,

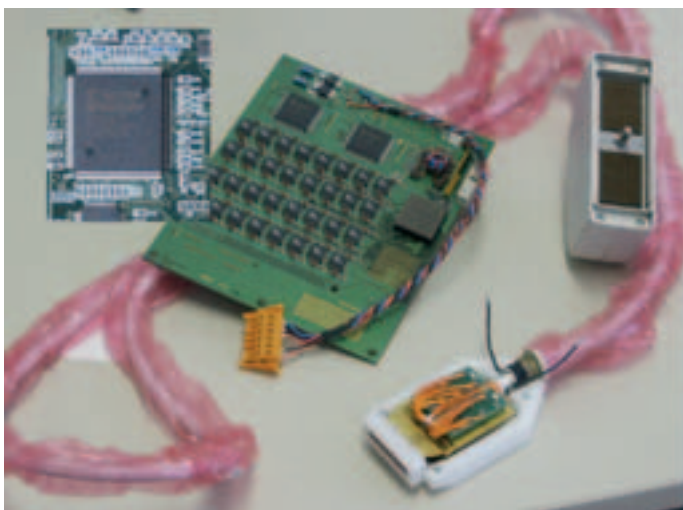
therapy control and monitoring) and therapy (high-power ultrasound) as well as for industrial measuring tasks (e.g. flow meters, distance and level metering, quality control). In addition to developments in the "classical" medical diagnostic ultrasound area, we offer developments in the kilohertz, megahertz and gigahertz range. Intelligent components (DSP, FPGA) are also used for "embedded systems". Measuring tasks including complex signal processing can be done without a computer. The experience of the workgroup covers the whole spectrum from the concept-phase to the development of partial and complete technological system solutions for applying ultrasound technology in medical and biotechnological applications as well as technical environments.



Flow measurement device "deltaflow" offered by the company Systec Controls. The one-channel ultrasound board was developed in the workgroup Ultrasound Systems Development. The device is an "embedded system". The entire signal processing is performed by a Digital Signal Processor (DSP). The system parameters can be adapted to various applications like sewage plants, power stations or pipelines by an appropriate DSP programming. The critical time control is done by a Programmable Logic Device (PLD).

Core competences:

- Analogue & digital circuit development
- Ultrasound single- and multi-channel systems
- Embedded systems
- Ultrasound phased array systems
- Portable systems
- High-power sound systems
- Flow, distance and level measurement systems



High-frequency ultrasound front-end for blood vessel diagnostics in young children. The ultrasonic probe is connected through a multiplexor board with the multi-channel ultrasound system DiPhAS (Digital Phased Array System). The probe is a microsystem comprising 288 single ultrasound elements. Each of them is connected to an interface board by a flex-tape technology cable. The multiplexor distributes the 288 elements to the 64 electronic channels of the DiPhAS. The device is controlled by application-specific programmed FPGA (field programmable gate array).

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Workgroup Biomedical Ultrasound Research

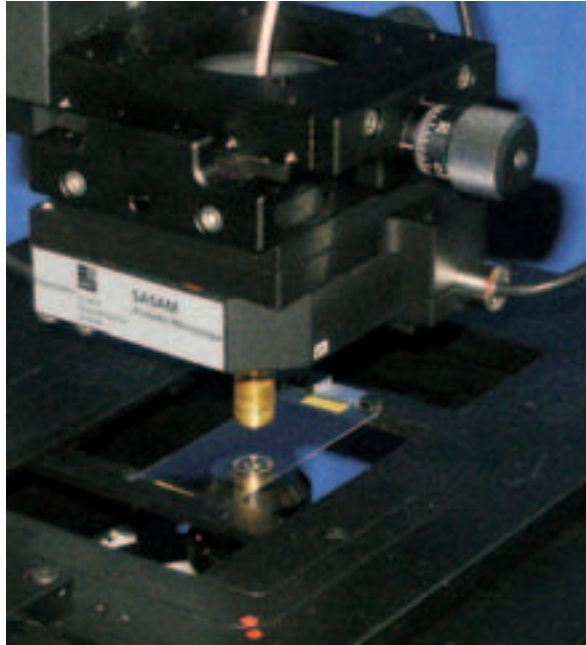
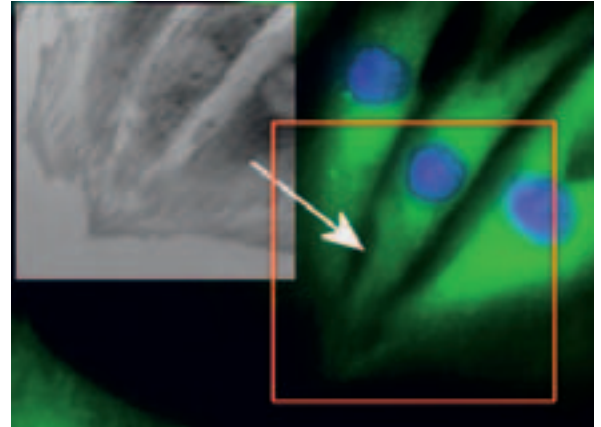


Figure left: Scan head of the acoustic microscopy system SASAM.



Right: Fluorescence-optical and acoustic visualization of adult human stem cells. Due to its non-invasiveness acoustic microscopy is suitable for gentle characterization of stem cells and other microscopic objects. Acoustic microscopy does not need light and can be performed on non-transparent substrates.

The workgroup Biomedical Ultrasound Research focuses on novel applications of ultrasound technology in medical diagnostics and therapy as well as in biological research and technology.

In the medical field this includes non-invasive data acquisition for diagnostics and the targeted destruction of tissue or release of medical drugs during therapy. In biology ultrasound can be used for non-destructive characterization of biological materials and living organisms and their targeted manipulation as well as an enabling technology for biotechnological processes. In addition to close collaboration with the other workgroups in the Department for Ultrasound to generate and process application-specific signals and to reconstruct and visualize ultrasound data for diagnostics and interventional imaging (navigation, therapy control), our group pursues intensive research on novel application areas for ultrasound technology. High and very high frequency systems facilitate new

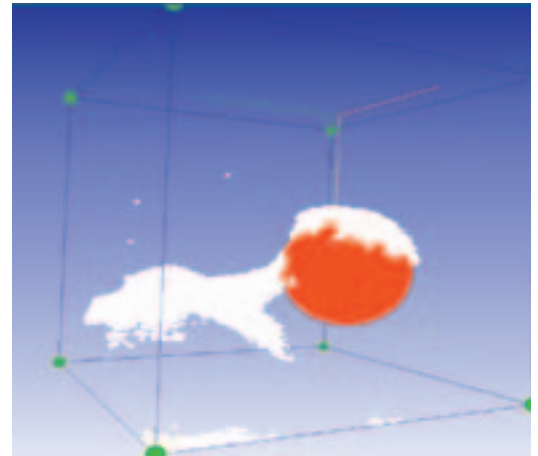
research approaches and more precise diagnostic procedures. In particular, the use of acoustic microscopy in cell biology research, as well as in systems for high resolution imaging of small animal models in preclinical research, enables non-invasive and inexpensive morphological and anatomical investigations. In this area our workgroup concentrates on combining ultrasound technology with other imaging technologies and modules in combined and hybrid procedures for molecular imaging. Furthermore, the workgroup studies the effect of ultrasound on biological tissue and related applications in biotechnology.

Core competences:

- Application-specific ultrasound research and development
- Material characterization
- Signal processing and parameter extraction
- Reconstruction and visualization
- Navigation
- Therapy control and monitoring
- Microscopy
- Manipulation systems
- Hybrid imaging systems

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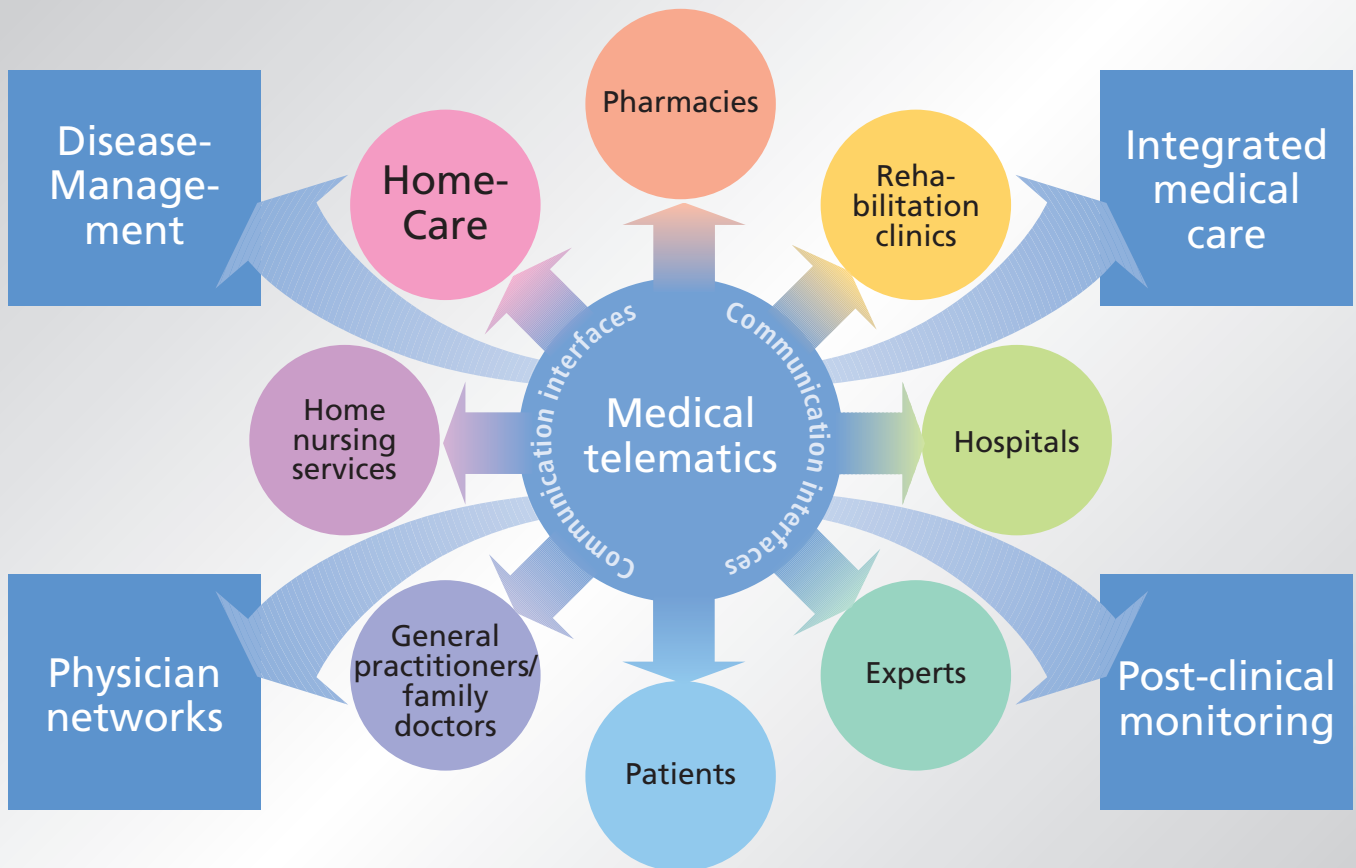
Left: Prototype of the "SonoPilot@ortho". Right: 3-D reconstruction of a femur with merged, automatically detected position and size of the femur head. The automatic detection of anatomical landmarks provides a basis for using imaging in navigation systems.

Equipment

Ultrasound

- Photolithography, mask aligner
- Sputtering devices, PCD, PECVD, cleanroom
- Sinter ovens
- Precision dispensers
- Polarizer
- Full-parametric 3-D-CAD systems (Pro/Engineer)
- Component preparation: interior hole diamond circular saw for direct cutting of precision components, vacuum mixer for casting, lapping machine
- Bonding/sensor technology: lateral moving glue sandwicher, soldering and bonding technology
- Production installation for a low to moderate number of ultrasound sensors
- CNC flat bed sanding machine (Ziersch & Baltrusch)
- Precision lapping and polishing machines (Wolters)
- CNC universal milling machine (Mikron UM 600), work area: 600 x 500 x 450 mm
- CNC tool milling machine (Korrad UW 10 CNC), work area: 500 x 300 x 400 mm
- CNC lathe center (Weiler DZ 32 CNC), working diameter 100 mm, length 150 mm, power driven tools
- CNC universal lathe (Rael Meka RT 5, cycle-controlled), transverse adjustment 200 mm, longitudinal adjustment 600 mm, driven tools
- Lathe (Colchester Master VS 3250), working diameter 1-300 mm, length 650 mm
- CNC high precision separating and profile sanding machine (Berney T 38-4 CNC), working area: 160 x 220 x 120 mm, NC circular table 360°, cut width min. ca. 20 µm
- CNC diamond circular saws (Disco DAD 321)
- CNC micro drilling-milling-sanding machine (Kern), working area: 220 x 160 x 200 mm, movable NC circular table with five axles
- CNC laser cutting and welding installation (Haas), YAG laser with variable lens optics, cut width 60-200 µm, cutting of ceramics, metals, hollow bodies and metal plates, material thickness 5 µm - 2 mm
- Conventional drilling-milling lathe (incl. circular sanding facilities)
- Fully automatic band saw, sawing area: 200 x 200 mm, precision ± 0.1 mm
- Sand jet installation
- Screw thread cutting machine
- Motorized table scissors
- Test station for static and dynamic pressure tolerance
- 5-basin ultrasound cleaning facilities
- Plasma cleaning installation
- Measuring equipment: pygrometer, 3-D sound field scanner, impedance measurement site
- Device for measuring contact angles
- Scanning electron microscope
- Scanning probe microscope (AFM, STM, MFM)
- Special measurement software for development areas, impurity measurement station
- Laser interferometer measurements
- Impedance measurement station
- Insertion-loss measurement station
- Climate chamber measurement station
- Temperature shock measurement station
- 3-axis measuring microscope incl. image storage and processing
- Cryostat measurements for sensor characterization and zero-flow measurements
- Wave pressure scales
- Sound field measurement station
- DSP and microcontroller development area (microchip, Motorola)
- FPGA development area
- Computer-aided development area for electronic boards (ORCAD)
- Fitting technology: SMD fine-pitch fitting
- Electronics for bonding technology: micro-soldering station, surge soldering facilities, reflow soldering facilities
- SPS development station (Siemens S 6)
- Single and multi-channel ultrasound systems
- Phased array and linear array ultrasound development systems
- Universal ultrasound measurements for industrial applications (concrete, steel, synthetic materials)
- 8-channel run-time difference measurement system for airborne sound applications
- Airborne sound sensors (3-D surface scanner, volume measurements and position detectors)
- Doppler systems
- Flow-through measurement technology: laboratory measurement stands for flow-through (Speckle Tracking, run-time difference; liquid: 7 m/s, DN 50/100/200; gas: variable up to 30 m/s, DN 200)
- Zero-flow measurements
- Development systems for industrial imaging (setting, position, OCR, pattern matching)
- Ultrasound sensor systems for therapy control (minimally invasive surgery, laser-induced therapy)
- Ultrasound navigation system development platform - SonoPilot®
- Opto-acoustic laboratory
- Acoustic microscope systems SASAM
- Biological laboratory, cell culture

Telematics/Tele-Medicine



The protagonists in the area of health telematics.

Services, results and products of the workgroups

- Medical Networks
- Home Care

Project example: SmartHEALTH - Smart, integrated biodiagnostic systems for cancer diagnosis

Equipment

The term "eHealth" is currently linked with the possibility of reducing problematic costs and increasing efficiency in the health sector by using information technologies. This expectation is apparent in the efforts to introduce the electronic health card and the corresponding required telematic infrastructure throughout the whole of Germany. The potential of combining telecommunication and informatics (telematics) was already recognized and used a decade ago in the Fraunhofer IBMT when it created a separate research unit "Medical Telematics". The medical telematics section of the IBMT delivers R&D services to industrial and public customers that cover a broad range, from studies to practically tested, pre-product systems. During the last two years this has led to the formation of the two different, yet overlapping, activity areas of "Medical Networks" and "Home Care", which starting this year are organized as separate workgroups in the department "Telematics/Tele-Medicine".

After a thorough, sector-wide analysis of the medical and organizational operations of healthcare providers, the workgroup "Medical Networks" developed the communication model **PaDok**[®]. This model is gaining more

and more acceptance and new customers, which underpins the relevance of the department's work. As a communication model, **PaDok**[®] and the subsequent product **D2D** are becoming increasingly integrated into everyday processes of the German public health system.

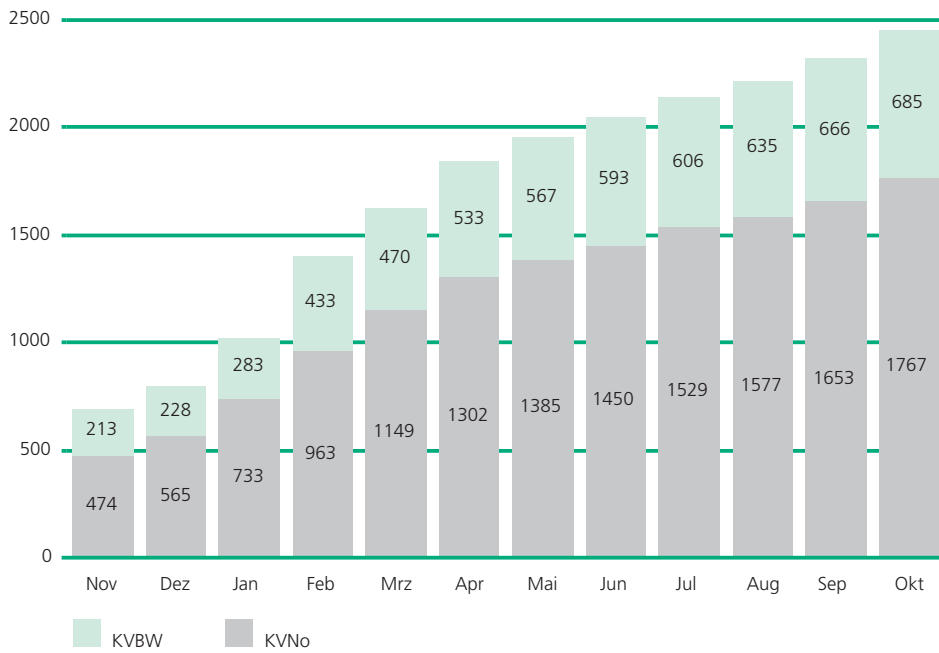
As the table (p. 70) listing registration of physicians for the D2D network within the Associations of CHI Physicians (Kassenärztliche Vereinigungen, KV) in Nordrhein and Baden-Württemberg impressively shows, concomitantly with growing numbers of participating doctors, D2D is having the effect of making platforms and information exchange services more and more interesting and useful. Apart from the KV in Nordrhein and Baden-Württemberg, the KV Bayern will also implement D2D as an eHealth platform, which will again increase the number of participants. Nearly half of Germany, in terms of insured persons and physicians are now accessible via the currently installed D2D platform. The proportion of D2D-supported primary systems for outpatient medical care has now reached far more than 50%. At the moment, hospital systems in particular are increasing their D2D participation. They are especially interested in electronic communication via D2D with the professional association (Berufsgenossenschaft) and the so-called VHITG doctor's record (Arztbrief) according to the guidelines of the new CDA rel. 2 (Clinical Document Architecture) since D2D is the very first system adapted to this.



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Number of registered physician in 2005.

Furthermore, our current demographical development urges us to develop novel IT-based concepts for domestic and outpatient care and medical prevention. The workgroup "Home Care" is very successfully developing such adapted concepts and technologies. Comparable models also address under-developed rural regions with insufficient access to basic medical treatment. For example, the project T@lemed, a collaboration of European and Latin American partners coordinated by the IBMT, managed to successfully establish tele-medical services in Colombia based on our **TOPCARE** home care and tele-medicine platform. Besides the system development for personal healthcare, the Home Care group also supports biomedical research, for example by an information system for setting up an HIV cryosample bank at the IBMT.

The development of applications towards implementing new, mostly still unfamiliar civil techniques such as electronic documenting, electronic signatures and electronic representative roles will ensure a broad range of activities for medical telematics at the IBMT in the years to come. The successful path of medical telematics is also reflected in this year's promotion of the workgroup to a department at the IBMT and will be pursued in the same way in the future. The IBMT workgroups combine expertise in informatics with know-how in setting up networks and knowledge about operators/users. It is obvious that telematic challenges cannot be solved by software manufacturers alone; rather a complex understanding of all participants and their expectations is needed.

Medical Networks

Products:

- PaDok® – Secure communication and shared case-based patient record in the public health system

Applied research and development:

- Solutions for linking service suppliers of the public health system
- Electronic patient-linked documentation and shared case-based patient record
- Concepts for data protection and data security in medicine
- Integration of general practice and hospital information systems, home-based stations and medical equipment into medical communication networks
- Medical standards (DICOM 3.0, HL7, xDT, ICD10, XML, CDA, etc.)
- Electronic disease management

Service:

- Linking-up of service suppliers of the public health system with the health telematics solution PaDok®
- Data safety assessments

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Home Care

Products:

- TOPCARE – a home care and tele-medicine platform

Applied research and development:

- Tele-medicine solutions for home and portable healthcare for high-risk, elderly and disabled patients
- Tele-medicine solutions for underprovided rural regions and epidemiology
- Health-related prevention systems
- Gerontological sensors
- Smart, linked-up medical equipment and intelligent environments
- Medical standards (HL7, POCT1A, ICD10, XML, CDISK, etc.)
- eLearning environments for primary care
- Semantic integration of biomedical databases
- Integrated IT tools for clinical trials and epidemiological studies
- Information systems for biobanks

Service:

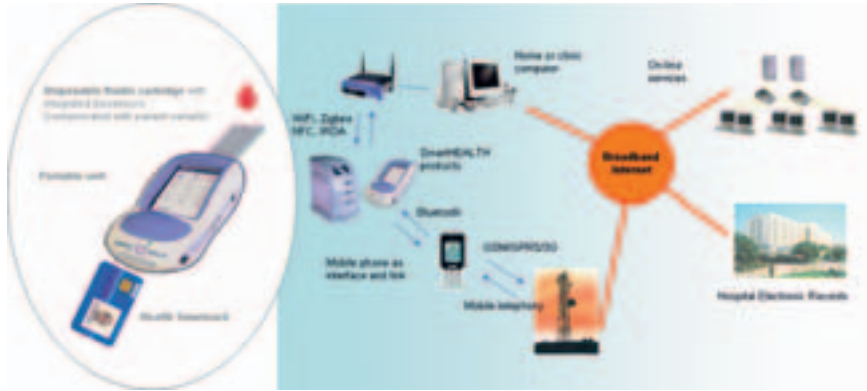
- Pilot testing of new home care and tele-medicine services on the basis of the IBMT TOPCARE platform

Contact Home Care

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Project example: *SmartHEALTH* – Smart, integrated, biodiagnostic systems for cancer diagnosis

Home Care



Objectives of the SmartHEALTH project: flexible, intelligent and communicating biodiagnostic equipment for cancer diagnostics.

Initial situation

In Germany over 400 000 people fall ill with cancer every year, approx. 360 000 of them for the first time. Although today many patients are cured permanently, about 42% of the affected women and 54% of the male patients do not survive the next five years. Hence, it is of utmost importance to detect tumors as early as possible with screening procedures to increase the chance of a permanent cure, or to reduce and control tumor growth by suitable long-term therapies in not completely curable cases, in order to maintain a patient's lifetime and quality of life. Long-term therapy of chronic cancers requires close and individualized monitoring, if possible outside a hospital. Likewise, successful early diagnosis needs reliable and powerful biodiagnostic systems at the so-called point of care. New molecular and protein-based cancer markers, progress in microsystems technology and nanobiotechnology linked with information and communication technologies create the basis for developing a new generation of intelligent, integrated, biodiagnostic systems for the diagnosis and monitoring of cancer diseases. These all fall within the

framework of the EU-funded integrated Research & Development project SmartHEALTH (project number FP6-2004-IST-NMP-2-016817).

Task

Prevention, early diagnosis, and targeted and effective therapies form the cornerstones of an efficient health system. Therefore, new diagnostic cancer tests have to deliver precise and reliable results for therapy decisions and be optimally integrated into the healthcare process to avoid unnecessary treatment and stress for the patients. SmartHEALTH addresses these challenges and is developing a new generation of intelligent, biodiagnostic systems that allow, or support and complement optimized disease management and screening programs in health services.

Driven by three key applications in cancer diagnosis (breast, intestinal and cervical cancers) the project is developing intelligent, linked, prototypical diagnosis systems for multi-parametric cancer marker analysis for the point of care.

The objectives of SmartHEALTH include:

- Implementation of new sensor systems for biomarker analysis integrated into future healthcare services to improve current healthcare concepts.
- Clinical validation of the systems for target applications (breast, intestinal and cervical cancers).
- Demonstrating the usefulness of “ambient intelligence” technologies in medical diagnostic systems and coupled online services for “pervasive” healthcare.
- Development of new production technologies to achieve uniform sensor solutions that integrate microfluidic components, transducers and biological assays.

Solution

Driven by clinical oncological applications, micro- and nanobiotechnology and information and communication technologies, the Integrated Project SmartHEALTH is developing an open, integrated system platform for novel biodiagnostic devices to support the industry in exploiting bioassays and new application concepts for cancer diagnosis. The initial system comprises a disposable microfluidics chip. The chip is loaded with the biosample and connected to a desktop reader device, which integrates dynamically into the surrounding e-health infrastructure and allows wireless communication with other instruments.

Subsequently, this system concept will be cost-optimized and miniaturized, eventually leading to various portable and easily accessible products. The system platform will allow simultaneous measurements and analyses of several analytes based on nucleic acids and proteins and can process different types of biological samples. The results will be interpreted using artificial neu-

Telematics/Tele-Medicine

ronal networks and further analysis tools. The adaptive systems will know their user, the patient and the current context. Based on medical standards they will maintain wireless communication with patient records at the respective laboratory, hospital or online information system, strictly complying with data protection regulations. In addition, they will support public key infrastructures.

The project was initiated in December 2005 with 25 European R&D partners and promises to improve medical cancer diagnosis by earlier and more precise cancer marker analysis. This will improve the quality of life of the patients and strengthen the competitiveness of the European industry in the area of in vitro diagnostics. The tasks for the IBMT include the integration of microfluidics and sensor components (workgroup Miniaturized Systems), and particularly pioneering the development of software that integrates the system with technologies such as "Ambient Intelligence", "Ubiquitous Computing" and the "Semantic Web" with the goal of making biodiagnostic devices more intelligent so they can be easily integrated into the surrounding IT infrastructure.

Results of the IBMT

The IBMT department Telematics/Tele-Medicine has developed a promising software architecture, the so-called "Semantic Medical Device Space (SMDS)", to integrate system intelligence into biodiagnostic devices so that they adapt to changes in their environment, dynamically recognize and use offered services and/or supply services to their surroundings, and auto-adapt to communicate with existing medical information systems. The SMDS is a pervasive software concept that uses semantic web and web service technologies to equip medical devices with intelligence and communication abilities, allowing semantic

interoperability with other information systems and devices. To take into account data privacy issues and to consider adequate data safety measures in the SMDS concept, we performed a safety analysis according to the Common Criteria Standard, derived a so-called protection profile for intelligent biodiagnostic medical devices and incorporated this into the SMDS.

In an initial step, the SMDS concept will be integrated into the initial SmartHEALTH instrument and evaluated by users. For this, communication standards such as HL7 V2.3 and POCT1A will be implemented on the basis of web service technologies. In addition, the department is developing a SmartHEALTH information system that is meant to support the clinical validation of cancer markers and offers new online services for the interpretation of analysis results.

Potential

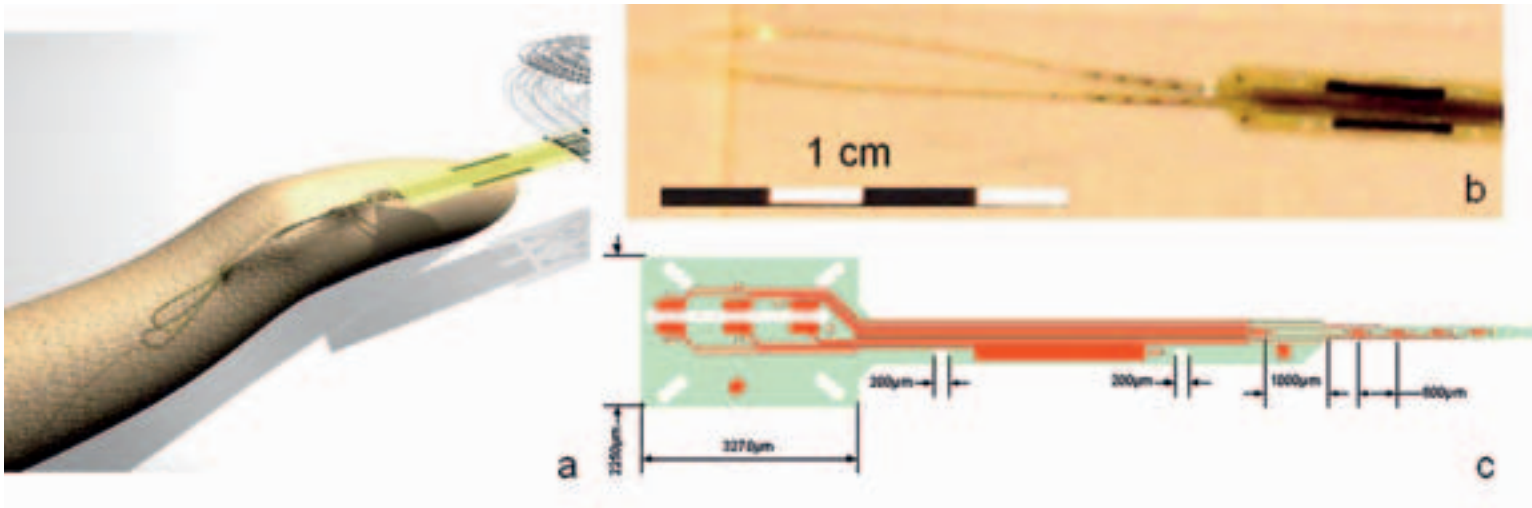
The "Semantic Medical Device Space (SMDS)" concept is an exemplary model for the design of intelligent and interoperable medical diagnostic devices. Reusable software components will allow the transfer to, and adaptation of medical devices of the medical technology industry. The first demonstration setups are expected to be completed in 2007.

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- Hardware platforms, in addition to standard PCs, particularly HP, SUN, DELL and SGI computers (desktop and server computers)
- Video conferencing systems of different bandwidth and quality for various application areas
- Devices for the monitoring of vital parameters, also online
- Communication systems for continuous wireless monitoring of patients
- Software tools for the elaboration of presentations, also online
- Software development tools for Internet and database applications (Oracle, SQL servers)
- Software development tools for embedded platforms

Medical Engineering & Neuroprosthetics



Structure and application of a thread electrode (tf-LIFE) at a peripheral nerve to detect electrical potentials and stimulate single nerve fibers.

Services, results and products of the workgroups

- Neuromonitoring
- Neuroprosthetics

Project example: Highly flexible, textile-integrable electrode material to record ECGs within a 24/7 monitoring scheme

Equipment

The research of the department of Medical Engineering & Neuroprosthetics focuses on the development and application of intelligent invasive and non-invasive interfaces with biological systems. Special emphasis is put on interfaces with the nervous system and their use in stimulating neuronal structures and detecting bioelectric potentials. The necessary hardware and software components are developed and produced at the Institute. The spectrum ranges from miniaturized, implantable electrodes, to monitoring systems, including signal processing and applications. All essential technological requirements, such as clean-rooms, plasma facilities, parylene coating, electrode characterization, simulation environment, reference systems, etc., exist in the department. The department has gathered over 15 years of experience with implant-based projects.

Neuromonitoring uses in particular electric processes in neuronal and myogenic structures for diagnostic decisions and the control of chosen therapeutic measures such as electroencephalography (EEG), electromyography (EMG) and evoked potentials (EP). The focus of the workgroup Neuromonitoring is on the required device

technology and methods for appropriate measurements and data acquisition. Also included are vital parameters that can be influenced by neuronal structures (e.g. temperature, blood pressure, breathing, eye movements, skin conductivity, etc.). This creates challenges with respect to sensors, signal processing, data transfer and signal analysis. A further approach includes using suitable stimulators for setting up closed-loop systems.

Neuroprotheses are used with the aim of trying to compensate for an existing neuronal malfunction within a motor or sensory context. They electrically stimulate myogenic and neuronal structures in the peripheral, spinal, central or increasingly in the vegetative nervous system. Pacemakers, cochlea implants and implants for deep brain stimulation, e.g. in paraplegics and stroke patients, are another important application area. Neuromodulatory therapy of chronic pain and incontinence is more and more based on implantable electrostimulators. The core competence in the field of neuroprosthetics is the development and production of implantable microelectrodes.

The department of Medical Engineering & Neuroprosthetics sees the enhanced integration of cognitive systems into their research as a further step towards the development of intelligent implants. Especially modern monitoring systems, e.g. intra-operative monitoring or monitoring of elderly people at home, increasingly include cognitive technology.



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Neuroprosthetics & Neuromonitoring



- Deduction of nerve and muscle signals
- Examination of implant materials under physiological conditions and accelerated aging
- Development of biotelemetry for the control of implants
- Development of stimulation patterns for bladder stimulation
- Development of deduction systems for examining intestine mobility
- Microelectrode characterization
- Design of cuff electrodes
- Design of epimysial electrodes
- Development of external electrostimulators
- Studies on the functional electrostimulation of peripheral nerves
- Parametric characterization of stimulation and deduction systems for prehensile prostheses
- Development of implantable stimulators
- Implant technology for different application areas
- Encapsulation methods for microimplants
- Examination methods for encapsulation materials
- Mask design for 2-D and 3-D microelectrodes
- Production of microelectrodes
- Production of microimplants with integrated electronics
- Neuromodulation for selective stimulation of nerves
- Development of neuroprostheses
- Encapsulation with parylene
- Microsystems on polyimide basis
- Retina stimulators
- Design of sieve electrodes with tracking system
- Production of silicon implants for neuroprosthetics
- Development of electrodes for stand-walk prostheses
- Microelectrodes with SU-8 patterning
- Investigating novel organic electrode materials
- Preparation and supervision of clinical trials
- Technical assistance for implantations and experiments
- Development and characterization of surface electrodes
- Investigating material characteristics of surface electrodes
- Investigating long-term reactivity of surface electrodes

Contact Neuromonitoring

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Contact Neuroprosthetics

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Project example: Highly flexible, textile-integrable electrode material to record ECGs within a 24/7 monitoring scheme

Neuromonitoring

Initial situation

The current demographic development poses increasingly difficult challenges for our society, especially for the health service. In this context, it is extremely important to leave elderly people in their accustomed home environment to maintain their maximum quality of life. This also includes ensuring adequate medical care. Especially in the case of an emergency, rapid and direct intervention by medical staff should be guaranteed. This requires monitoring different vital parameters over a long time-span. ECG is especially important for this long-term monitoring because it not only records changes in the heart rate, but also variations in the pattern of the heartbeat, providing information about the autonomous nervous system. It has been known for a long time that especially the elderly have a higher risk of cardiovascular diseases.

Project description

The goal of the project senSAVE is to support patients with a higher risk of severe cardiovascular diseases in their everyday life, enhance their autonomy and prevent emergencies. This becomes possible by real-time vital monitoring based on a novel intelligent sensor network. This new monitoring concept can be especially useful for outpatient treatment of chronic diseases, the healthcare of elderly people and areas such as sports, leisure time and wellness. An essential requirement is easy handling of the sensors, which include

special electrodes. Here, a novel, modular multi-parameter monitoring system consisting of sensors, intelligent signal processing and radio transmission is being developed for portable long-term operation.

Task

The department of Medical Engineering & Neuroprosthetics of the IBMT took on the task within the project for developing a special electrode material for an innovative surface electrode. This material should make it possible to record a dry ECG, i.e. without the use of electrode gel. Furthermore, it ought to be highly flexible so that it can be integrated into fabrics. This would mean electrodes made of such a material can be correctly placed on the appropriate monitoring sites even by medically untrained staff. The material should also comply with further requirements such as skin compatibility, long-term stability, and be washable, etc.

Results

An electrode material was developed based on polysiloxan, which is both flexible and can be integrated into textiles. Moreover, the material is especially gentle to the skin and possesses high wearing comfort. The polysiloxan is coated with different nanoparticles to achieve electrical conductivity.

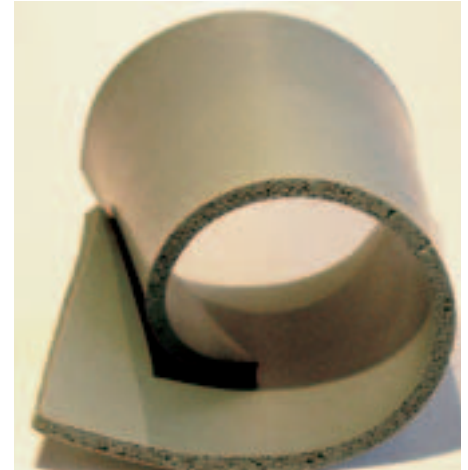


Figure 1: Highly flexible electrode material.

Figure 1 shows an example of such an electrode material. This material was characterized in a first measurement run over 10 days by impedance spectroscopy. The test signal was supplied by a frequency analyzer (1255, Solartron Analytical). The frequency range was between 0.1 Hz and 100 kHz with an amplitude of 50 mV. The impedance was measured by electrochemical interfaces (1287, Solartron Analytical) in a 3-electrode setup. The counter electrode was a platinum wire (150 μm , 20 coils around a diameter of 3 cm) in the center of the measurement setup. The reference electrodes were made of Ag/AgCl. It was possible to measure 128 regions of the electrode material simultaneously. The test object with a surface of 1 cm^2 was placed in a circle around the counter electrode.

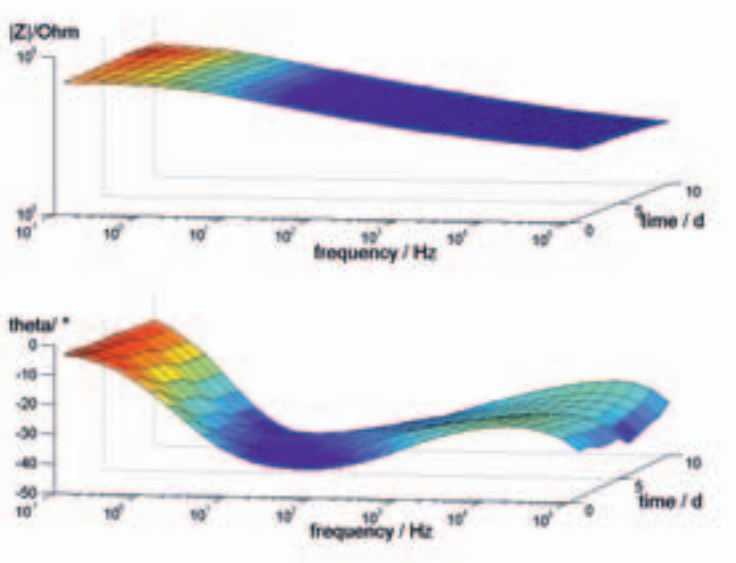


Figure 2: Results of characterizing the electrode material over a period of 10 days in a frequency range from 0.1 Hz to 100 kHz.



Figure 3: Proof of the signal quality exemplified by an ECG recording of a volunteer (recording at the extremities according to Einthoven).

The result of the analysis is shown in Figure 2. Both the change in the impedance and phase angle are plotted against the frequency. The third dimension is the time over 10 days. It shows that the observed mean values remain stable for a long time. This is of utmost importance for monitoring 24 hours a day, and 7 days a week (24/7 monitoring).

After connecting the electrode material and placing it on the skin surface, the first electrocardiographs could be recorded. It was not necessary to use any kind of electrode gel to obtain useful ECG traces. Figure 3 shows some example ECGs recorded with dry electrodes (recorded at the extremities according to Einthoven). The good signal quality of this new electrode material can be easily seen.

The characteristics of the newly developed electrode materials based on polysiloxan can be summarized as follows:

- Highly flexible
- Dry acquisition of bioelectric signals without the use of conductive gels or electrolytes
- Can be integrated into fabrics
- Signal quality comparable to commercial Ag/AgCl gel electrodes
- Stable for a long time
- Biocompatible
- Can be disinfected
- Washable in a washing machine

Medical Engineering & Neuroprosthetics

Project funding

Fraunhofer-Gesellschaft
MAVO project INMUSENS

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Project consortium

INMUSENS (Intelligent multimodal sensors):

- Institute for Occupational Economy and Organization, IAO, Stuttgart
- IBMT, St. Ingbert
- Institute for Integrated Circuits, IIS, Erlangen
- Institute for Photon Microsystems, IPMS, Dresden
- Institute for Applied Information Technology, FIT, St. Augustin

- Production of implants
- Characterization of electrodes
- Laboratory for measurements
- Research laboratory for visual systems
- Laboratory for methods of clinical neurophysiology
- Software laboratory
- Simulation
- Development tools for flexible substrates with integrated electrodes for neuro-implants (CAD: LASI, electro-mechanical simulation: FlexPDE)
- Access to cleanroom facilities for production and assembly of neuro-implants with a minimum size of about 5 μm (lithography, metal coating, reactive ion etching, polyimide oven, parylene C coating, bonder)
- Laboratory for assembly (gluing, soldering, welding) and encapsulation (parylene, silicon) of electrodes, wires and implants; production of molds
- PC-controlled measurement workplace for characterization of electrodes: impedance, transient electric pulses, cyclic voltametry (HP 3245 A, HP 3458 A, EG&G 5302); scanner for measuring the distribution of the electric potential in physiological media; stability under mechanical stress
- PC-controlled measurement workplace for examination of field distributions of microelectrodes
- PC-controlled measurement workplace for electric impedance spectroscopy (Solartron 1255B/1287)
- PC-controlled measurement workplace for measuring organic semiconductors
- PC-controlled measurement workplace for characterizing the conductivity of insulation layers for leakage currents as low as in the sub-picoampere range in physiological media at room temperature and accelerated aging (Keithley 617 E electrometer)
- Tools for developing analog and digital circuits and systems for physiological measurement technology and electrostimulation, as well as test environments for characterizing miniaturized (neuro)implants (OrCAD, Visual C++, LabWindows/CVI, logic analyzer Philips PM 3585, emulation systems for 80C31, PIC and 8051 family, PIC and EPROM programmer, digital oscilloscope HP 54504-400 MHz)
- PC-controlled measurement workplace for examining noise in electronic circuits and systems as well as in electrodes in physiological media (FFT Servo Analyzer Advantest R 924 C, Spectrum Analyzer Advantest R 3361 C, multimeter Keithley 199, function generators)
- Facilities for non-invasive measurements of prehensile force and momentum at the lower extremity
- Multi-channel stimulator with arbitrary pulse forms (constant wattage/voltage) for electrostimulation and multi-channel recording systems for electrophysiological measurements
- Pneumatic stimulator for studying sensory nervous signals

Cryobiophysics & Cryotechnology

Cryoresearch and -demonstration Bank



Cryoelectronics in liquid nitrogen are being tested in the cryoresearch bank in Sulzbach (Photo: Bernd Müller).

Services, results and products of the workgroups

- Cryoequipment & Cryorobotics
- BMBF Junior Research Group Cryonanobiotechnology
- Cryoresearch and -demonstration Bank

Project example: Development of tumor models for the cryobanks of personalized medicine

Equipment

Until now the young “science of extremely cold life” (a literal translation of the Greek terms used in the word “cryobiology”) has managed to successfully conserve cells primarily by empirical methods. One reason for this is that the causes of damage to cells during freezing, storage at the low temperatures of liquid nitrogen (usually below -150°C) and thawing are highly complex. The empirical discovery of suitable freezing and thawing rates and tolerable cryoprotectives is justified if a sufficient proportion of a cell population “survives”, as it is usually the case for most cell cultures. However, substituting the empirical approach in applied cryobiology by a more systematic procedure is of fundamental importance for successful application in those areas where the single cell and its state are increasingly critical, e.g. in stem cell research, therapy with “programmed” cells, regenerative medicine and also for the sustainable use of bioresources by conservation of viable cell samples. Systematic and knowledge-based optimization of a cryopreservation process, i.e. a cycle of freezing, storage and thawing, requires suitable tools. The development of such tools is the task of the department of Cryobiophysics & Cryotechnology with its workgroups Cryoequipment & Cryorobotics and the BMBF junior research group Cryonanobiotechnology. For instance, the department devises miniaturized cryosubstrates made of different materials and varying in size, optimized freezing and thawing machines, manipulation systems for sterile access to cold samples that are suitable for use in industry, and last but not least nanotechnologically optimized surfaces for surface-

based cryopreservation (see figure). These developments form the basis of a future tool box for systematic cryobiophysics. Professor Heiko Zimmermann and his workgroups were granted approval No. 18 by the Robert Koch Institute (Berlin) to import human embryonic stem cells (isolated before the stipulated date of 01.01.2002). The freezing and thawing protocols for these cells should be optimized and standardized and compared to those of other cells.

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Contact Cryoresearch and -demonstration Bank

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Cryobiophysics & Cryotechnology



- Research and development in the area of low temperature biophysics and cryobiotechnology
- Development of cryoequipment (substrates, heating/cooling tables, microscopes, etc.)
- Development of freezing procedures for single cells, cell groups and tissues
- Development of workplaces for measuring parameters of low temperature electronics
- Low temperature tolerant and optimized digital storage systems
- Database concepts for sample banks at industrial scales
- Research and development in the area of chip-based, adaptive laboratory and workflow management (“ChameleonLab” technology)
- Dynamic infrared thermography
- Research and development in the area of microsystem-based cryopreservation

Contact

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Cryoequipment & Cryorobotics

- Development of cryoequipment (substrates, heating/cooling tables, microscopes, etc.)
- Development of automation concepts for cryobanks and cryocontainers
- Special-purpose production of cryo-infrastructure components (e.g. “intelligent” transport containers, installations for sample security)
- Tool design for cryobiotechnology
- Low temperature imaging (special video solutions), low temperature sensors
- Research and development in the area of cryorobotics
- Special-purpose developments for low temperature measurements and process control
- Development and production of laboratory containers

Contact

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BMBF Junior Research Group “Cryonanobiotechnology”

- Research on surface-based freezing of cells
- Research in the area of nanostructure-aided cryopreservation
- Development of novel nanostructuring methods
- Research on hydrogel micro-encapsulation (2-D/3-D) and cell programming for cryopreservation

Contact

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Cryoresearch & -demonstration Bank

- Storage of biological material for research purposes
- Testing of customer-specific cryoequipment (substrates, heating/cooling tables, microscopes, etc.)
- Testing of cryoprotocols
- Prototypes of cryobanks
- Testing of cryobank concepts
- Development and validation of cryo-databases
- Consulting on the setup of customer-owned cryobanks with specific software solutions

Contact

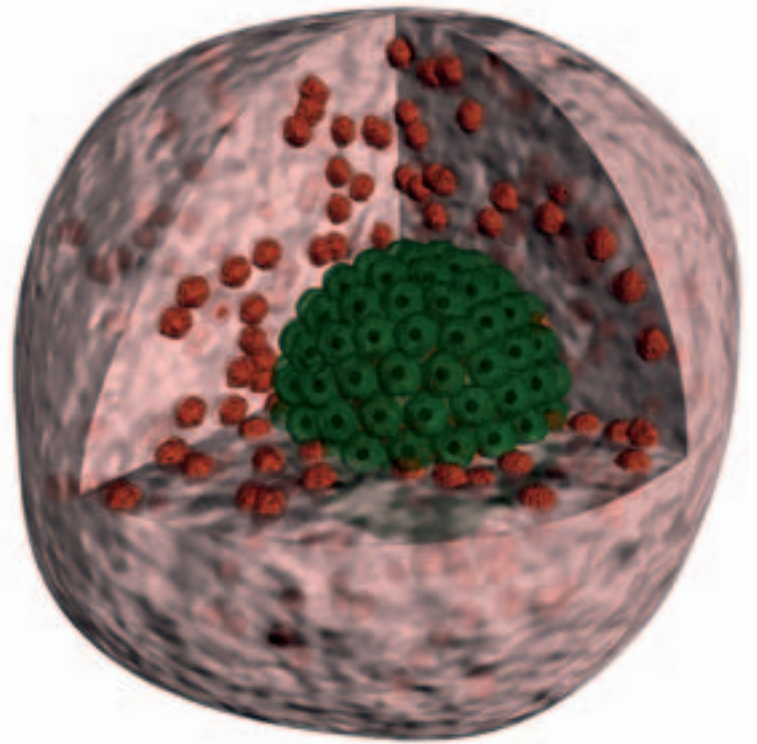
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Project example: Development of tumor models for the cryobanks of personalized medicine

Cryobiophysics & Cryotechnology

Initial situation

The increasing application of cell-based therapies in medicine and the storage of samples for later, not yet feasible, analysis is leading to a high-throughput deposition of samples in cryobanks. High-quality sample banks of viable cells are particularly necessary for the detection of molecular patterns and the ensuing search for personalized therapeutic approaches. This is why industry and research from areas such as biotechnology, medicine and pharmacy are storing valuable cells and microorganisms in biobanks, e.g. cell lines, genetically transformed or modified cells, medical samples (such as tumors, blood samples, biopsy samples), as well as primary material for regenerative medicine (e.g. hematopoietic stem cells from the umbilical cord, adult and embryonic stem cells) and for reproductive medicine (e.g. sperm, oocytes, embryos, ovary tissue). The differences in cell types and configurations (e.g. suspension cultures, multi-cellular systems, tissue regions, adherent cells) with respect to their biological and biophysical properties require specific cryopreservation protocols. Especially for multi-cellular systems, i.e. associations of hundreds to about 10 000 single cells, that engage in specific interactions, for example in tumors and tissues, no successful cryopreservation methods are as yet known.



Computer-generated model of a cover-encapsulated system consisting of a multi-cellular spheroid covered by a hydrogel matrix that contains single cells (Illustration: H. G6rger, IBMT).

Approach towards a solution

A modular construction system consisting of cell spheroids and biocompatible materials will be developed at the IBMT to help better understand the processes during cryopreservation of multi-cellular systems and to optimize the protocols. The goal is to adapt the model system to primary systems, i.e. actual samples from patients, so that a systematic search for optimal cryopreservation protocols can be performed. This will involve combining established spheroid culture techniques with novel biomaterials and processing procedures to develop a model that suits the initial sample. Parallel experiments with primary material, e.g. human tumors, will be carried out to determine the agreement between the model and the original. A novel nanoplotter will be used for cryopreservation, which allows the exact addition of DMSO (currently the most common cryoprotective) in the picoliter



Nanoplotter (GeSIM mbH) during loading of a cryosubstrate with a capacity of 30 x 25 µl. The addition of cryoprotectives such as glycerol or DMSO can be precisely controlled in the picoliter range.

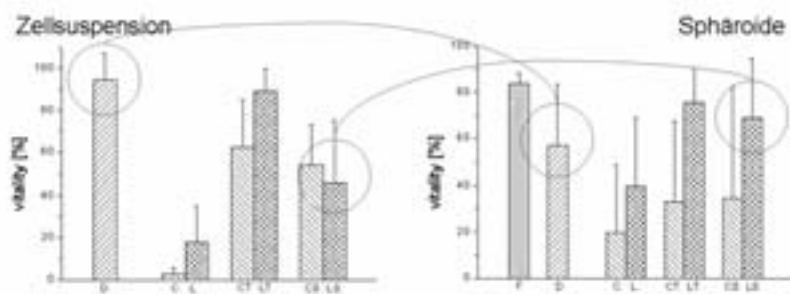


Figure 3: Screening experiment: viability of L929 cells (murine fibroblasts) in suspension and as multi-cellular spheroids after cryopreservation in different cryomedia. (F: before freezing; D, C, L, CT, LT, CS, LS: various cryomedia).

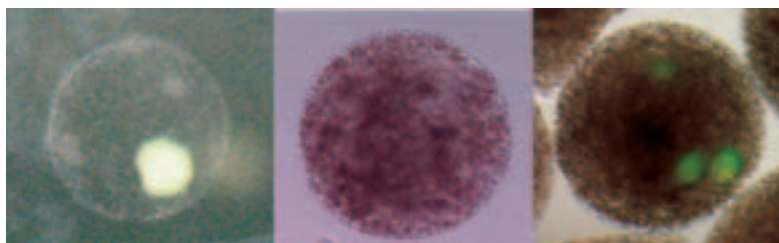


Figure 4: Different possibilities for encapsulation (from left to right): L929 spheroid, human erythrocytes, L929 spheroids (green) and human erythrocytes in a capsule.

range. This application method has already significantly improved the cryopreservation of Islets of Langerhans cells. Miniaturization of the cryovessels is also believed to have a positive effect: in contrast to traditional 1 ml tubes, HDPE plates with 30 x 25 µl wells are used. Since DMSO disrupts cellular metabolism at physiological temperatures, and must be washed away as rapidly as possible after thawing, alternative cryoprotectives are being investigated following the example of extremophilic organisms. Trehalose, starch hydrolysates and starch derivatives are some examples of protein-free alternative cryoprotectives. Besides maintaining viability and functionality after thawing, conserving the integrity of multi-cellular systems is difficult. Hydrogel capsules made of alginate offer a possible solution to this problem. They are already used for the immuno-isolated transplantation of

Islets of Langerhans or parathyroid gland tissue, for example.

Results

Despite being the same cell type, optimal cryopreservation conditions for multi-cellular systems differ from those for the corresponding cell suspension (see Figure 3). These optimal conditions can only be determined by extensive screening efforts. Model systems should help to reduce the use of primary material by first conducting preliminary studies with the model system and then using the best protocols with the primary system. The cryopreservation of human mammal gland or ovary carcinomas has already been improved in this manner.

In tissues, cells are often not directly linked to each other but adhere to a three-dimensional matrix. The distances between the cells can be simulated by incorporating the cells into an alginate matrix. It is also possible to use different combinations of various cell types, cultivation modes (single cells, spheroids, see Figure 4, left) as well as the addition of accessory components such as erythrocytes for enhanced oxygen supply (Figure 4, center and right), HSA for osmotic stabilization, collagen fibers or SiO₂ beads for mechanical consolidation, etc. However, the alginate encapsulation method not only possesses potential for the model system research, it also increases the success rate of cryopreservation. Alginate-encapsulated L929 spheroids have a 5-10% higher viability after thawing, and hemolysis of encapsulated erythrocytes is reduced by up to 90%.

Potential

The Fraunhofer IBMT has the facilities to establish model systems for diverse types of tissue. The different combination possibilities of cell systems (single cells, multi-cellular systems and monolayers), capsule characteristics (shape, size, mechanical stability and cell adhesiveness) and accessory ingredients (erythrocytes, SiO₂, collagen) allow specific adaptation to different primary systems. This drastically reduces the use of primary material. Improved cryopreservation protocols have been established for human tumors.

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Equipment

Cryobiophysics & Cryotechnology

- Low temperature storage systems (down to -196°C) with approval for medical use
- Modified, programmable freezing machines for applications in biology, material sciences and electronics
- Cell biology laboratory
- Modified research microscopes
- Inverted cryomicroscope (own development, Peltier-based)
- Combined reflection/scanning force microscope for measurements of biological objects in aqueous environments
- Testing equipment (digital/analog) for low temperature electronics
- Low temperature measuring chamber for testing electronics and materials
- Thermography system (temperature measurement range -20°C to 250°C)
- Micropipetting system/automation platform
- “ChameleonLab”-based laboratory management
- High-speed camera system for microdrop-based freezing

Cryoequipment & Cryorobotics

- Computer-controlled freezing machines (own developments)
- Cryotank sample handling systems
- Sample handling sluice systems
- Cold gas devices
- Cryotransport containers (own developments)
- 20-channel cryotemperature measuring systems
- Cryorobot for sample handling
- LN₂ gauge ultrasound measuring systems

BMBF Junior Research Group “Cryonanobiotechnology”

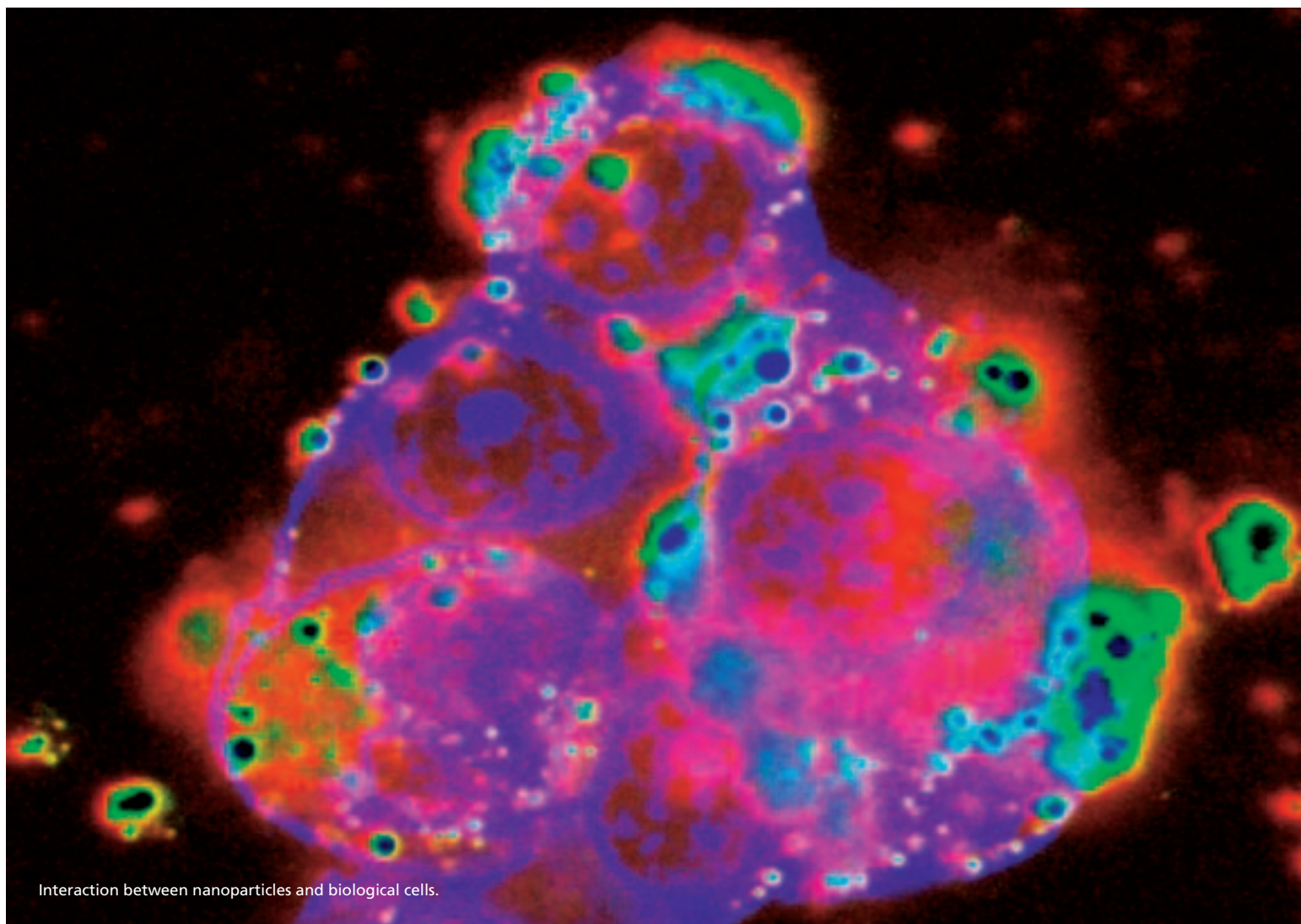
- Micro-encapsulation installation (crystal gun principle)
- Freezing spin coater for freezing of ultra-thin layers (own development)
- Infrared laser system for precise heating of thin layers (planned)

Cryoresearch & -demonstration Bank

First sub-sections of the European Center for Cryobiotechnology are already in operation.

- Low temperature storage systems (-130 to -196°C) with approval for medical use
- Programmable freezing machines
- Cell biological laboratory
- Cell culture microscope for bright field, phase contrast, variable relief contrast and fluorescence
- High security containers
- Ultra-cold freezer with CO₂ emergency cooling
- File server with RAID system
- Testing and development server
- Storage tank for 25 000 liters liquid nitrogen
- Sterile workbench
- CO₂ incubator
- Nanoplotter
- Emergency power generator 15 kVA
- Database server with RAID systems and LTO tape drive
- Oxygen depletion monitoring
- Burglar alarm

Biohybrid Systems



Interaction between nanoparticles and biological cells.

Services, results and products of the workgroups

- Cell-based Sensors & Biomonitoring
- Molecular Cell & Tissue Engineering

Project example: Technology platform for accelerated HIV vaccine development

Equipment

Ever increasing novel therapeutic approaches for treating many diseases are emerging from research in biopharmacy, regenerative medicine and nanobiotechnology. However, how quickly new therapeutic approaches can be introduced into broad clinical use depends greatly on cell technology requirements. There is a growing need to characterize, transfer and process diminutive biological samples. Suitable technologies have been developed during the last 10 years in the department of Biohybrid Systems at the Fraunhofer IBMT. To achieve high acceptance among customers, the developed technologies for the economically most promising application areas are currently being evaluated. Within the framework of international and national research projects this evaluation is taking place in cooperation with research groups and companies that specialize in particular applications. The following current projects are examples of applications that draw on the developed technologies: The clinical use of cell therapies requires stable, safe and well-characterized cell material. The objective of the EU project OsteoCord is optimizing the isolation and expansion of mesenchymal stem cells from blood of the umbilical cord. The differentiation potential of the stem cells is investigated with respect to their capacity to form bone cells. The EU project CARDIOWORK-BENCH endeavors to optimize the search for suitable drugs for treating cardiovascular diseases and resulting heart disorders. Another EU project, PolExGene, focuses on improving the biocompatibility of non-viral gene transfer systems for cell therapy approaches to treat retinal and cardiovascular diseases. Within the BMBF network project NanoDrug, the

department carries out preclinical tests on nanoparticle pharmaceutical substances for tumor therapy. The biological effects of nanoparticles are also relevant for environmental toxicology. As a partner within the EU project DIPNA, the department is involved in the development of a platform to elucidate the toxicological and ecotoxicological effects of nanoparticles. Once again, the technological basis determines how rapidly novel vaccines can be developed. An international consortium, coordinated by the IBMT, was awarded a grant from the Bill & Melinda Gates Foundation to develop technologies to accelerate the development of an HIV vaccine. Dr. Hagen Thielecke obtained approval No. 19 from the Robert Koch Institute to import human embryonic stem cells in the context of the OsteoCord project.

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Cell-based Sensors & Biomonitoring

- Cell and tissue-based biosensors for functional efficacy testing and for medical diagnostics in the areas of oncology, neurology and cardiology
- Electrochemical microsensors and methods for the functional, label-free testing of drugs, for in vivo monitoring and for bioprocess technologies
- Bioimpedance spectroscopy (in vitro and in vivo)
- Biointerfaces (e.g. implantable, controlled drug release modules)
- Sensor systems medical in vivo diagnostics
- Sensor systems and processes for toxicological investigations in the environment
- Development of methods for detection and monitoring of neurotoxins (e.g. biological and chemical warfare agents, environmental and food toxins)
- Technologies for the gentle characterization, manipulation and handling of single cells
- In-line sensors for the food industry and bioprocess control
- Performing theoretical and experimental studies in the areas mentioned above

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Molecular Cell & Tissue Engineering

- Applied research and development:
- Cell culture and cell aggregation models for medical technology and drug research
 - Three-dimensional, organ-specific cell culture technology (tumor, retina spheroids, in vitro retina, 3-D heart muscle cell spheroids)
 - Models of stem cell differentiation
 - In vitro cell culture model of the blood-brain barrier for determining drug transport rates
 - Development and preclinical testing of nanoparticles for directed drug transport into different target cells

Biocompatibility tests:

- Cytotoxicity of biomaterial and medical equipment according to medical product testing guidelines ISO 10993 and EN 30993

Virus safety:

- Virus validation of manufacturing processes for drugs from biological sources (e.g. coagulation factors, immunoglobulins, vaccines, monoclonal antibodies)
- Testing cell lines for virus contamination (cell bank characterization)
- Detection of replication-competent retroviruses and adenoviruses during gene therapy trials (RCR and RCA)

Validation of microbicides:

- Against viruses (enveloped/non-enveloped)
- Against bacteria (*Staphylococcus aureus*, *Pseudomonas aeruginosa*, *E. coli*)
- Against fungi (*Candida albicans*, *Aspergillus niger*)

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Project example: Technology platform for accelerated HIV vaccine development

Molecular Cell & Tissue Engineering

Situation

In 1981, the first cases of a lethal disease appeared among young men in California and New York, a disease previously completely unknown to physicians. It seemed to switch off the human immune system and was therefore called AIDS (**A**cquired **I**mmuno **D**eficiency **S**yndrome). The virus causing the disease, the Human Immunodeficiency Virus (HIV), was discovered a few years later. Researchers were extremely optimistic at that time that a first vaccine trial would be underway within the next two years.

The first HIV vaccines that were supposed to protect against the disease were tested in 1987 in the USA. Initially, purified inactivated HIV particles were used to elicit an immune response. Since this was unsuccessful, a second approach concentrated on immunization with separate viral protein components. But as yet, no viral protein has functioned as an effective vaccine against HIV. These difficulties in the development of an HIV vaccine are mostly explained by the incredibly high variability of the virus. Replication of the AIDS pathogen requires many steps during which numerous changes (mutations) accumulate in its genome. It was observed that the viruses isolated from infected persons differed significantly from the viruses originally causing the infections. It is precisely this high mutation rate that makes it difficult for the immune system to combat the virus. Now there are numerous HIV subtypes, which a priori seems to exclude that a single vaccine could be effective throughout the world.

Project description

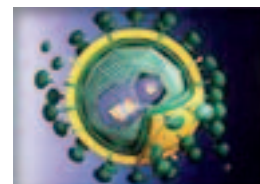
With the help of the global HIV vaccine development initiative (Collaboration for AIDS Vaccine Discovery – CAVD), propagated by the G8 countries and financially supported by a program initiated by the Bill & Melinda Gates Foundation, the first vaccine is intended to be actually produced in five to ten years. This global activity is considered to be an essential component for the development of an HIV vaccine. Within this project an international consortium, coordinated by the Fraunhofer IBMT, was granted funding in 2006 to develop and implement one of the most modern global HIV cryobanks (Global HIV Vaccine Research Cryobank – GHRC). This is the first project of the Gates Foundation to be coordinated in, and by a German institution.

Overall, it is important for the development of effective vaccines to establish and continuously maintain a collection of current virus variants. These viruses form the basis for virus research in general, and for the development of specific HIV vaccines in particular. The comparative analysis of virus variants requires their collection and systematic storage. The task of the mainly European consortium is to set up a central HIV bank in the form of an exemplary, modern cryobank with the highest safety standards, as fast as possible, and to provide HIV research groups worldwide access to this resource.

Task

The task of the GHRC consortium is to establish a large-scale centralized facility for long-term cryopreservation of reagents and biological samples that will be generated during HIV vaccine research and stored in the HIV cryobank. During the three years of funding, set up as a pilot phase, a completely new cryobank concept should

HI-Virus.



be realized that creates the technological and biophysical basis for safe and expandable cryobiotechnology serving the entire CAVD initiative. The network will develop new procedures for optimized sample preparation, cryopreservation and storage of reagents, which will not only be valuable for clinical material from so-called “regional centers” in developing countries, but also reagents generated by the different CAVD consortia. In a reciprocal manner, reagents, samples and HIV strains with the corresponding data, as well as new technologies will be made available to the CAVD consortia for further research. Moreover, technology transfer and expansion of the capacities of “regional centers” are included in the program. The HIV cryobank together with the other partners of the GHRC consortium will jointly support the scientific plan of action of the CAVD initiative by developing state-of-the-art technologies for an international HIV-specific storage bank. These central activities and the resulting novel technologies will allow optimized characterization of circulating HIV strains and reproducible measurements of immune responses.

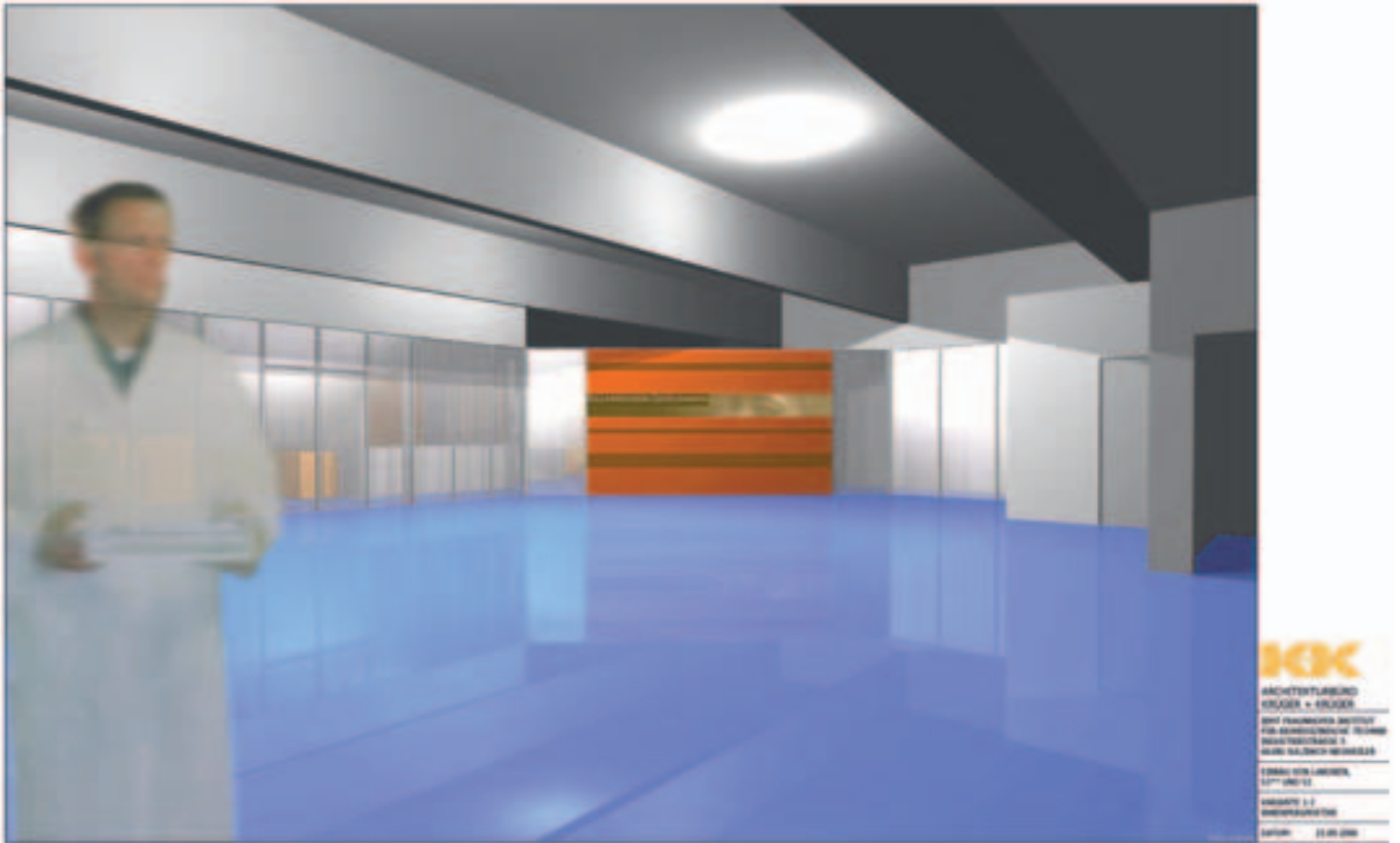


Illustration of the future containment level 3 laboratories in the cryohall for the HIV cryobank project funded by the Bill & Melinda Gates Foundation.

The objectives of the GHRC project in detail are:

- New strategies for sample collection (e.g. HIV isolates from so-called “early infections”).
- Optimized sample processing and cryopreservation.
- Establishment of a CAVD-specific global sample collection.
- Up-scaling of the HIV cryobank.
- Progressive technologies for collecting, preparing, preserving and distributing reagents for further networks.
- Technology transfer to the “regional centers” and the other CAVD consortia as well as to developing countries.

Outlook

The project should establish a unique virus bank within three years, which should contain the most diverse reagents necessary for, and arising from HIV vaccine research, and which will be available for extensive virological and immunological characterization. This material will be the basis for the further development of vaccines and new therapies against HIV. Scientists from all over the world will then be able to access the samples and the important bioinformatics derived from the primary biological data.

Contact

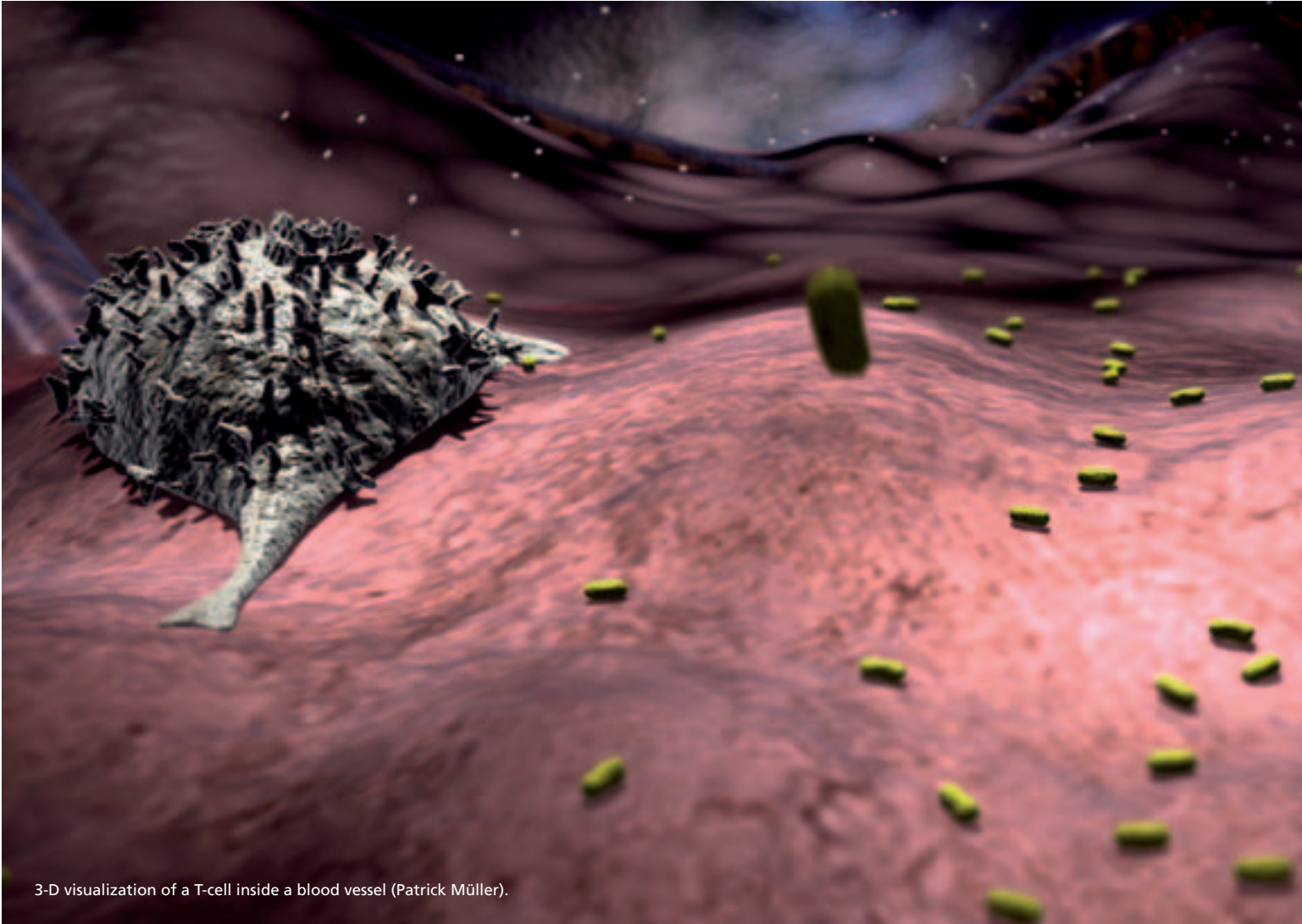
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Equipment

Biohybrid Systems

- Cell culture laboratories (genetic engineering containment level S1 and S2) with sluice area and separate media and autoclave rooms for 2 laminar flow class 2 sterile workbenches
- Genetic engineering laboratories (genetic engineering containment level S1 and S2) with 3 laminar flow class 1 and 2 sterile workbenches
- Phase contrast, differential interference contrast and fluorescence microscopes (reflected and transmitted light)
- Imaging system including 3-D video camera
- Spectral photometer for microtiter plates
- SNOM (optical near field microscope)
- Axiphot fluorescence microscope with photo and digital camera extension
- UV/VIS spectral photometer
- Automatic particle counter for cell concentration and diameter measurements (Multisizer II)
- Cryomicrotome
- Molecular biology equipment (PCR, electrophoretic equipment, etc.)
- Laboratory for bioelectronics (genetic engineering containment level S1)
- Electrochemical measurements of impedance with Solatron SI 1260, SI 1281, SI 1287, SI 1294
- Electrophysiological measurements with data recording system
- Dust stimulator
- BX-50-WI research microscope with micromanipulation unit and incubation hood
- Flow cytometer (BD FACSCalibur system)
- Cell counter (CASY Model TT)

Computer-aided Simulations



3-D visualization of a T-cell inside a blood vessel (Patrick Müller).

Services, results and products of the workgroup

– Computer-aided Simulations

Project example: Setup of the *CellPROM* application laboratory

Equipment

Over the years, tight interfacing between computer-aided design (CAD) and simulation has become a must. All major software manufacturers offer interfaces in both directions, in many cases even integration of both tools. Rapid data capture from the construction and direct feedback based on analyses from a simulation of the component setup seem to be standard. Is a group exclusively dedicated to simulations still up-to-date?

While testing a mechanical construction component under static load works relatively well, it becomes more complex for an electromechanical system under the influence of temperature and time-dependent forces. Thereby, simple determination of geometry recedes into the background, and definitions of differential equations to be solved and of boundary conditions become a major part of the analysis. Finally, the implementation of CAD software is oriented more towards later production than convenient handling of simulations; the CAD-constructed components are designed for transfer into production and not for straightforward integration into finite-element simulations. Typically, the construction details available are of minor importance for the analysis

and thus can be neglected in favor of reduced model complexity. Suppressing these details in the simulation is based on the experience of the person performing the analysis, hence, direct transfer of data from the CAD environment to the simulation, at least in these cases, remains an exception.

For instance, the design of piezoelectric ultrasound sensors still begins with the first step of generating simplified simulation models. This helps with understanding and optimizing the principle characteristics independently of any constructive constraints. Here, small compact models allow many variations and also the expansion of relevant and large parameter fields. Only in a second step are the CAD data incorporated directly into the simulation software. Despite the normally much larger size of the models, this is often the only possibility for integrating complex construction details into the simulation with relatively little effort.

The workgroup of Computer-aided Simulations focuses on the design of



complex microfluidic components and on the design and optimization of piezoelectric ultrasound sensors. The CAD environment Solidworks and the finite-element software Ansys provide our expert staff with highly efficient tools to develop and optimize components and systems in a project-oriented manner.

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Computer-aided Simulations

- Computer-aided development and testing of ultrasound transducers
- Computer-aided development of ultrasound arrays
- Sound field calculations
- Optimization of ultrasound sensors and systems
- Computer-aided development and testing of gradient coils
- Electromagnetic field calculations
- Computer-aided development and testing of MEMS
- Electrical current calculations
- Coupled electrical current-acoustics calculations
- Stress analyses and calculations
- FEA-based optimization of construction parts
- Simulation of microfluidics components and systems
- Temperature calculations
- 3-D construction
- 3-D visualization and animation in biology, chemistry, physics, medicine and engineering
- Medical imaging and 3-D reconstruction



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Computer-aided Simulations

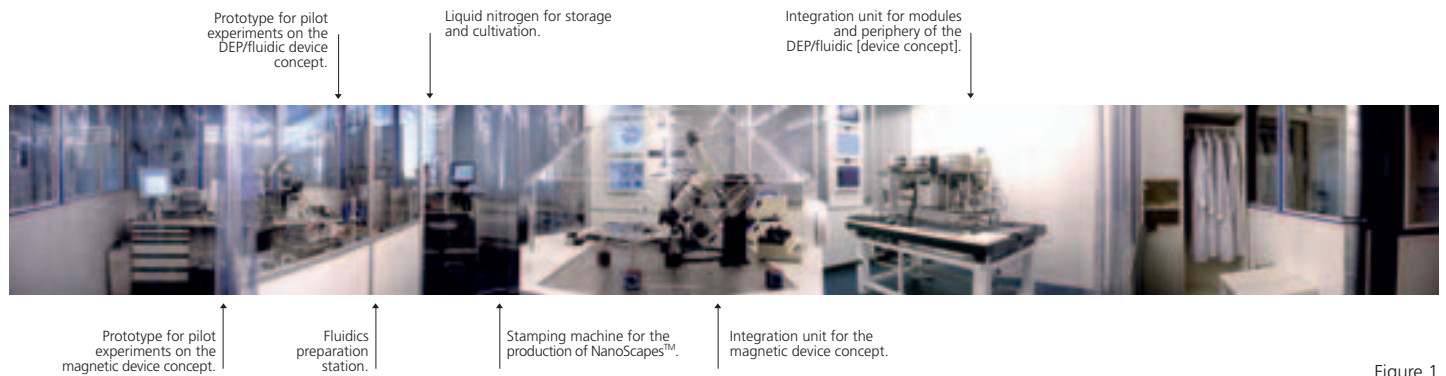


Figure 1

Situation

The controlled and documented in vitro differentiation of cells at the single cell level imposes very high requirements on the necessary technical systems. Until now, only a few devices were available that fulfilled these requirements in individual areas. Automation and easy handling seem to be diametrically opposed to the complexity and variability of biological cell models.

Task

Within the context of the EU-funded Integrated Project *CellPROM*, 26 scientific groups and companies are currently working on developing new technologies for the controlled differentiation of cells. The interactions between biology, nanotechnology, microsystems technology and automation impose high standards on the environment and core areas of the device systems. As the coordinator, the Fraunhofer IBMT is not only in charge of the scientific project management, but is also responsible for the integration of components, either developed by the IBMT or other partners, and the definition

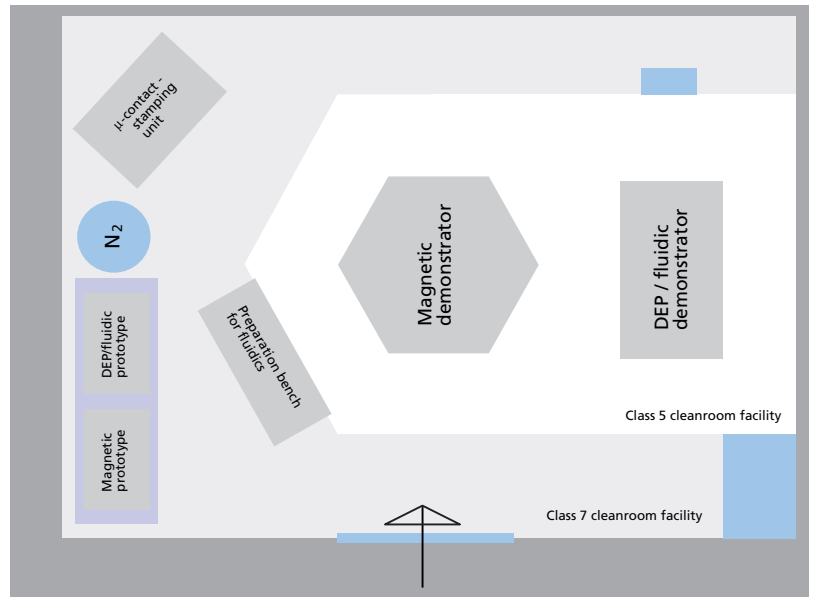


Figure 2: Workplaces and devices in the cleanroom (MagnaLab and NazcaLab).

and implementation of interfaces. Reaching its mid-point in February 2006, the project plans to create operational modules and test them in cell biology experiments within four years.

Results

Combining biology and nanotechnology demands high standards for sterile and particle-free environments. Furthermore, the modular approach calls for a high degree of flexibility in the device components. Therefore, a cleanroom microenvironment was installed initially (see Figures 1 and 2). Two workplaces with class 50 clean-

room facilities now allow the complex and flexible setup of systems comprising various components and the evaluation of two concepts in parallel.

An intricate microfluidic channel system forms the core of the first system (see Figure 3). Single cells can be manipulated and moved in it without physical contact by using dielectrophoresis and ultrasound. This allows characterization and differentiation of single cells under defined and constant conditions. Six fluidic and more than 30 electrical channels are concentrated



Figure 3: Integration of the modules around the NazcaLab chip.

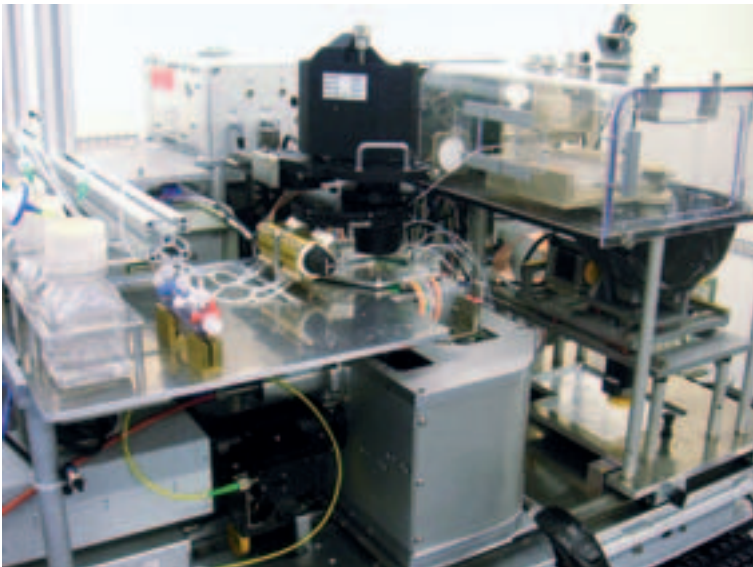


Figure 4: Prototype evaluation for the manipulation of cells on magnetic carriers (MagnaLab).

on a small area around the central chip. They are computer-controlled and can be used to plan and carry out experiments.

The second concept is also based on a central fluidic channel system (see Figure 4). Here, however, small magnetic carriers which the cells adhere to during growth can be moved inside this system by external electromagnets. Special areas of the 30 cm wide central cultivation unit serve as observation or cultivation zones for the cells. The cells are transported from station to station either interactively or according to a pre-defined sequence.

In addition to the two central work-places, further single components can be tested and installed in the clean-room environment.

Potential

During the project's duration, the *Cell-PROM* application laboratory is the central hub for the integration and testing of single system components. Already at the mid-point of the project all partners can test and improve their modules in functional prototypes. The integration of further modules and the redesign of existing components will increase the complexity of the systems during the second half of the project. The final goal is to create a technical platform that allows a multitude of novel and interesting experiments relating to the controlled differentiation of single cells.

Computer-aided Simulations

Hybrid computer environment with UNIX/Linux and Windows systems and the following software tools: ANSYS™ (FEA code), CFDRC™ (FEA code), Flo-tran™ (FEA code), ModuleF (FEA code), FlexPD (FEA code), ProEngineer™ (Standard CAD code), SolidWorks™ (Standard CAD code), AutoCAD™ (Standard CAD code), PiezoCad™ (design of ultrasound transducers based on the KLM model), Mathematica™, SCALP (own development for the calculation of the transient propagation of acoustic or electromagnetic waves), LabView™ (signal analysis code), 3D-Studio MAX™ (visualization and animation of complex physical and technical processes), Evoluti (own development for optimization based on genetic algorithms), AMIRA™ (3D imaging and reconstruction), Acapella™ (micrograph imaging).

Project collaborators at the IBMT

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Project funding

European Union, NMP4-CT2004-500039 (*CellPROM*)

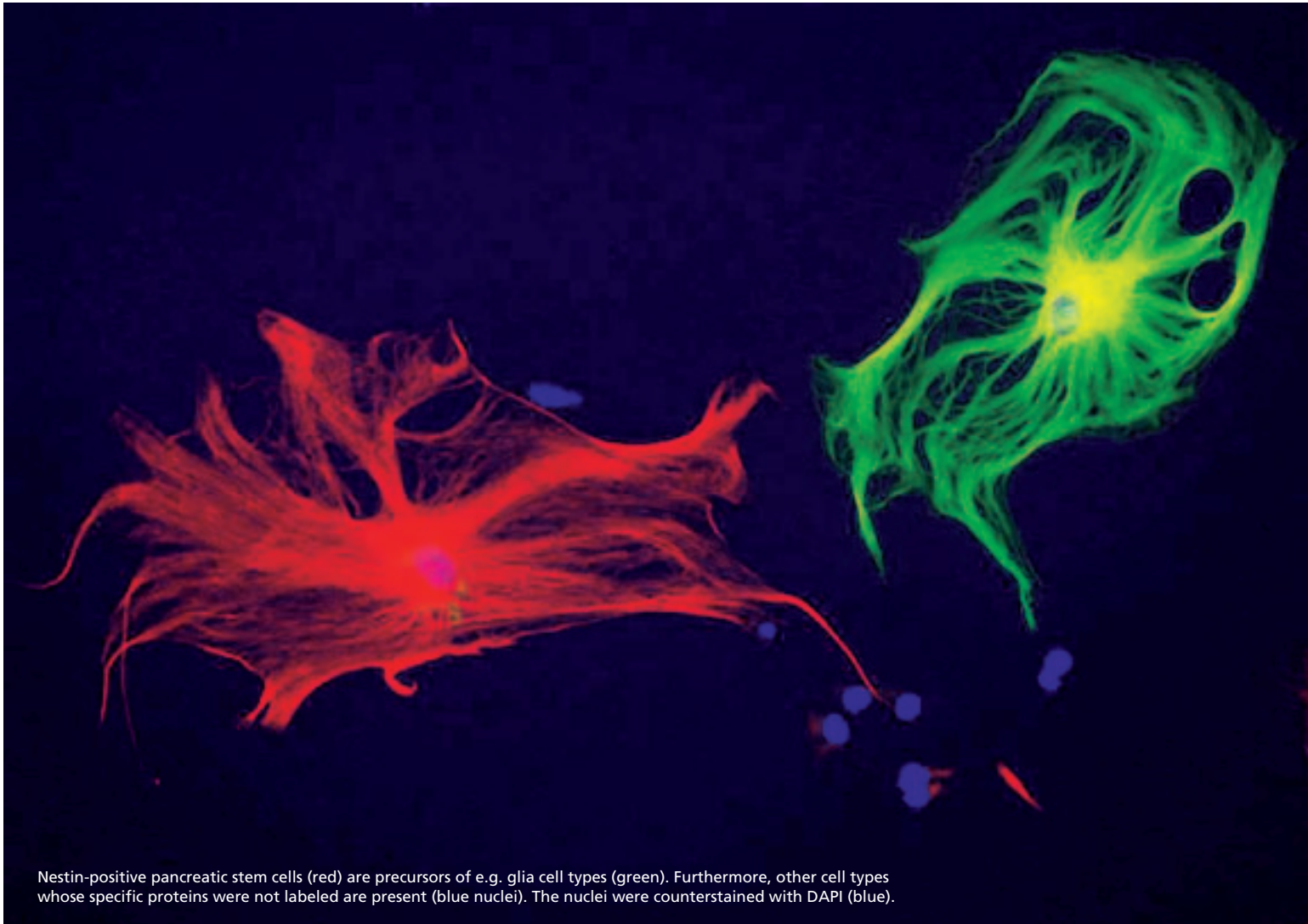


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Project Group Lübeck

Cell Differentiation & Cell Technology



Nestin-positive pancreatic stem cells (red) are precursors of e.g. glia cell types (green). Furthermore, other cell types whose specific proteins were not labeled are present (blue nuclei). The nuclei were counterstained with DAPI (blue).

Services, results and products of the workgroup

Cell Differentiation & Cell Technology

Project example: Human pancreatic stem cells differentiating into cardiac muscle cells

Equipment

Stem cells are among the most promising approaches for future regenerative medicine. The idea of isolating stem cells from patients and reprogramming them so that they differentiate to create cell types of dysfunctional organs or tissues has become more feasible over the last few years. In addition to their ability to generate specialized cells, stem cells possess a more active (although it varies) proliferation potential. The combination of both these characteristics opens up application areas beyond regenerative medicine and cell therapy. One could conceivably create custom-made testing systems for pharmaceutical and cosmetics industries with stem cells, employ them for tissue engineering or use them for the specific production of high-quality biomass.

Stem cells are subdivided according to various criteria: according to their origin, into embryonic and adult; and according to their ability to differentiate into specialized cells, into pluripotent, multipotent or unipotent. At present, embryonic stem cells, which are isolated from an early developmental stage of the organism, cannot be used for applications beyond basic research due to ethical objections. Adult stem cells, however, can be isolated without any ethical considerations, but they normally do not possess the same differentiation and proliferation potential as embryonic stem cells. Moreover, their precise localization in the organism is often unclear, which frequently means it is not possible to extract these cells.

Three years ago the workgroup of Cell Differentiation & Cell Technology, a Fraunhofer project group at the University of Lübeck for two and a half years now, published results on the astonishing characteristics of stem cells isolated from exocrine glands. Since then the outstanding reproducibility and their high differentiation potential have been confirmed in all respects, not only by external groups, but conclusively by the Lübeck group itself and two other cell culture groups at the IBMT in St. Ingbert and Potsdam-Golm. Moreover, in 2006 we succeeded in demonstrating their differentiation into contracting cardiomyoblasts (a cell type of the mesoderm), the cloning of cells and inducible tissue bodies derived from these cells, as well as myogenic, neuronal, adipogenic and chondrogenic transformations. Furthermore, for the first time cells could be characterized with distinct egg cell characteristics (see figure on p. 100). These results have been accepted for publication, and the patents from the years 2003/2004 have been granted in a number of countries. Thus, this source of highly potent stem cells from exocrine glands will gain an important position on the candidate list of adult stem cells for cell therapies. In many respects these stem cells resemble those of embryonic origin. For instance, a now optimized and stable procedure allows reproducible isolation of stem cells from exocrine pancreas (and salivary gland tissue) that show a growth rate comparable to embryonic stem cells (doubling time approx. 16 h; cultivation possible over 150 passages with rat-derived cells). In addition, they differentiate into cell types of all three germ cell layers (ectodermal, mesenchymal, endodermal). Furthermore, isolation is highly efficient: 50 million cells from the initial sample tissue (approx. 1 cm³) yield approx. 100 000 proliferating stem cells. This ratio of 1:500 is several orders of magnitude better than the 1:100 000 ratio of conventional mesenchymal stem cells.



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Cell Differentiation & Cell Technology

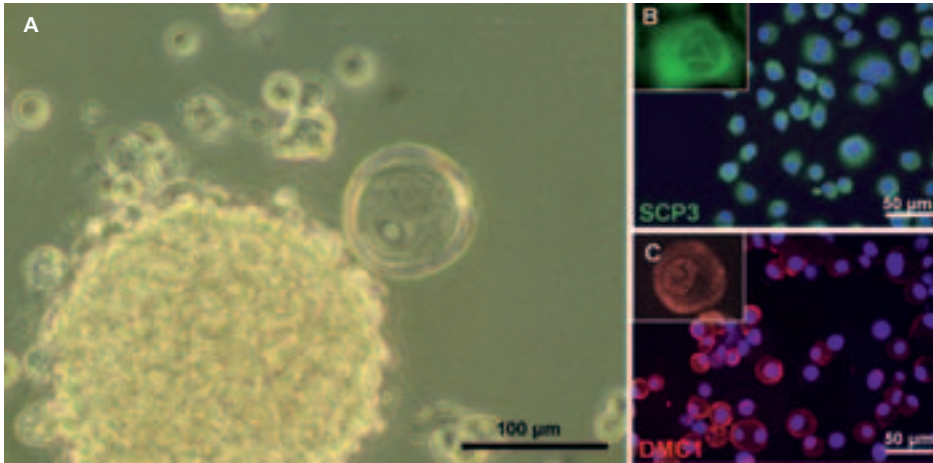


Figure 1: Clonal pancreatic stem cell aggregates from the rat produce oocyte-like cells. A: Oocyte-like cells in suspension. B-C: Immunocytochemical detection of meiosis-specific proteins. B: Immunostaining of the synaptonemal complex protein (SCP3, green). C: Immunostaining of the DMC1 protein (red). Nuclei were stained with DAPI (blue).

In addition to their excellent availability, stem cells from exocrine glands offer the great advantage of aggregating easily into small three-dimensional organoid-bodies. The intensified cell-to-cell contact in these aggregates leads to new differentiation stimuli and significantly expands the spectrum of possible applications for these cells. The Fraunhofer IBMT with its external workgroup at the University Lübeck is focusing on the obvious potential of these cells. Apart from human stem cells, the workgroup is one of the few stem cell institutions worldwide to succeed in efficiently isolating stem cells from animals, ranging from fish to mammals, and establishing these cells in *in vitro* cultures. In cooperation with the zoo in Neunkirchen, they are establishing a comprehensive stem cell collection of endangered animal species. Upon request and payment of basic costs the IBMT supplies such cell cultures from fish, spoonbill, crane, chicken, rat, mouse, goat, roe deer, boar, watussi cattle, guanaco, red deer

and long-tailed monkeys for research purposes. An industrial use is also possible on a project basis upon agreement. Currently, the Fraunhofer IBMT is working on seven large-scale projects centered on stem cells, in addition to two EU projects on comparative investigations with human embryonic stem cells for which the Fraunhofer IBMT was granted the import approvals No. 18 and 19 by the Robert Koch Institute after passing the stipulated application routes and an evaluation by the central ethics committee. The IBMT is the first, and at present only Fraunhofer Institute with such approval and probably possesses the broadest spectrum of available stem cell types.

- Isolation and differentiation of human and animal adult stem cells with the aim of harnessing them for regenerative medicine and biotechnology
- Primary cell isolates from different species and different exocrine tissues
- Cloning of cells, establishment of cell lines
- Induction of tissue systems from animal and human cell isolates
- Development of stem cell differentiation procedures
- Immunological characterization of cells
- Development of new tools and device components for stem cell handling
- Micromanipulation of cells
- Courses on cell manipulation
- Contract cell cultivation for customers

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Project example: Human pancreatic stem cells differentiating into cardiac muscle cells

Cell Differentiation & Cell Technology

State of the field

The number of tissues in which stem cells and progenitor cells have been found has significantly increased during recent years. Remarkably, the number of stem cell types described to possess pluripotent properties has also increased. These cells can differentiate into cells of all three germ layers. According to current knowledge there are at least four origins of these cells: mesenchymal stem cells, stem cells in blood from the umbilical cord, pancreatic stem cells and testicular stem cells. In addition, several adult stem cell types exist that can differentiate into cells of at least two germ layers (e.g. stem cells from hair follicles or the liver). The glandular stem cells described and investigated by the IBMT workgroup "Cell Differentiation & Cell Technology" at the University Lübeck were mainly isolated in cooperation with the Lübeck Surgical Clinic, and various proliferating cell populations have now been established. The glandular stem cells are of primary interest for investigations carried out here because they (1) are relatively easy to isolate, (2) show a high yield, (3) can be efficiently cryopreserved, (4) can be cultivated over extended periods, (5) form three-dimensional tissue bodies and (6) differentiate into cells of all three germ layers (ectoderm, mesenchym, endoderm) (see Figure 2). In addition to the IBMT workgroup, other renowned research groups from all over the world are investigating these interesting stem cells. This means it is important to maintain and increase the lead in some areas, in particular with respect to the targeted differentiation into specific cell types.

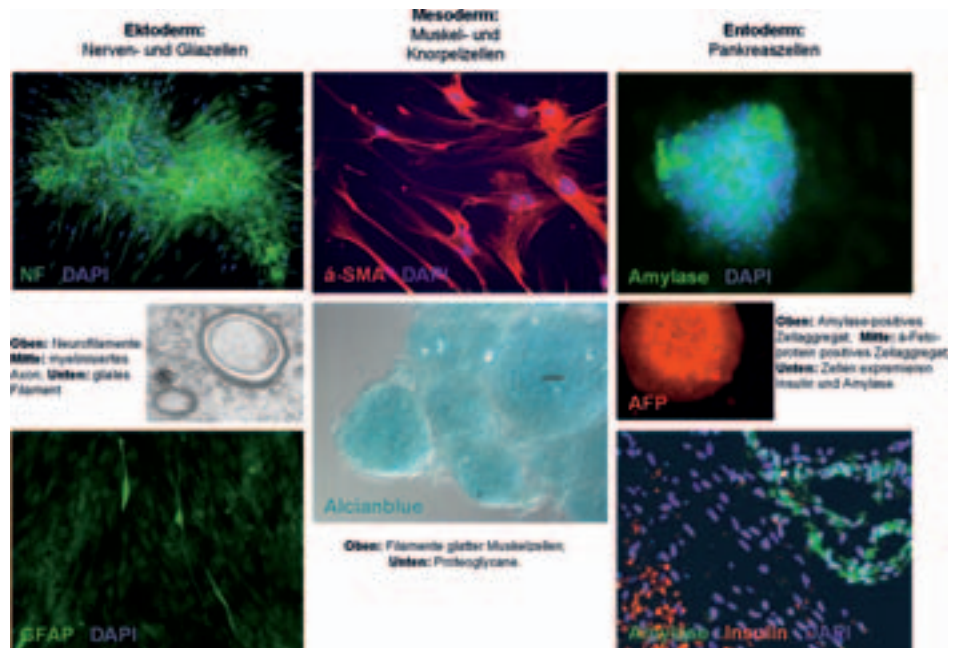


Figure 2: Spontaneous differentiation of stem cells/progenitor cells from the exocrine pancreas into cell types of all three germ layers.

Besides the differentiation of stem cells into quiescence, other processes of dedifferentiation and redifferentiation also seem to be partially responsible for the high plasticity of adult cells. Current results indicate that both processes are also relevant in the stem cell isolates from the exocrine pancreas.

Stem cells and progenitor cells from exocrine glands

Cells isolated from rats, mice, humans and other vertebrates have been cultivated in the laboratory for more than three and a half years. These spontaneously form tissue-like aggregations under certain conditions, which are described as "organoid tissue bodies". Fluorescence analyses with highly specific labeled molecules, high-resolution electron microscopic sections as well as PCR results indicate that tissue types emerge that can also be found in nerves, muscles, cartilage and skin.

These investigations were performed in collaboration with the Institute for Anatomy at the University Lübeck.

Differentiation into cardiac muscle cells

Heart failure is a major cause of death in industrialized countries, mainly due to the fact that adult cardiomyocytes hardly regenerate or renew themselves. This is why injections of stem cells might be an actual alternative for heart regeneration. Currently, such treatments are already being carried out using mesenchymal stem cells, although the results are not always very clear. Hence, the search for other suitable stem cells that can produce cardiac muscle cells is still in progress, and remarkable progress has been

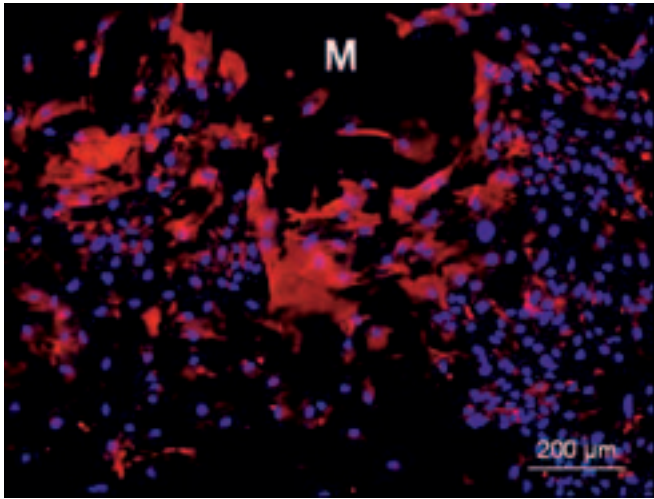


Figure 3: Immunocytochemical detection of heart cell-specific sarcomeric myosin (red) in a co-culture of pancreatic stem cells with myocardial tissue (M). Cells in the neighborhood of the myocardial tissue fragment show higher expression of this protein.

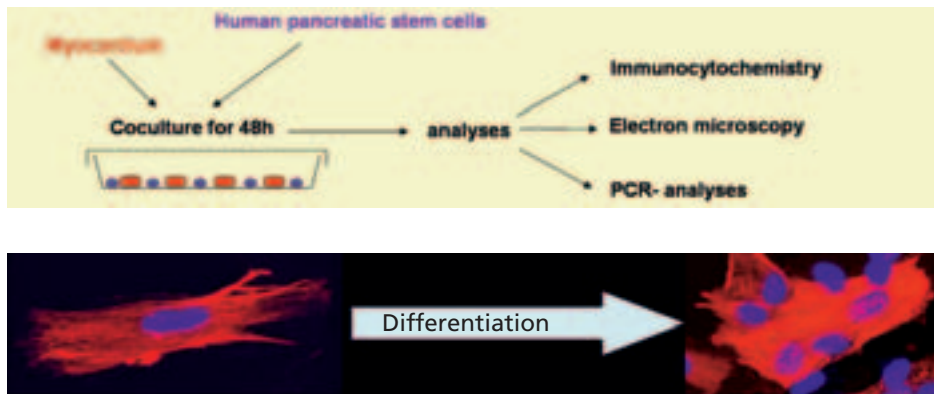


Figure 4: Pancreatic stem cells (nestin) spontaneously differentiate into cardiogenic cells (sarcomeric myosin). This process can be stimulated by co-cultivation with heart tissue.

achieved especially in animal models. In close cooperation with the Heart Surgery Department at the University of Lübeck the IBMT workgroup could demonstrate that cells with unmistakable cardiac muscle characteristics can spontaneously arise from human pancreatic stem cells. This process can be stimulated by co-cultivation with viable heart muscle tissue, simulating a situation resembling that after injection of stem cells into the heart muscle. Possible cell fusion cannot be fully ruled out in this method, but is negligible within the investigation period (48 h). Indeed,

certain heart muscle proteins can be detected most frequently in the cells directly adjoining the heart muscle tissue (see Figure 3).

Interestingly, the pancreatic stem cells often contain the intermediate filament nestin, a typical marker for adult stem cells, which was initially found in neuronal progenitor cells but is now considered a general marker for adult stem cells.

A general dilemma of different stem cell applications also becomes apparent in these experiments. If the heart tissue is removed, its stimulating effects are no longer observed after a while. Until now it cannot be unambiguously ascertained whether this is due to the differentiated cardiac muscle cells dedifferentiating or dying off. However, in the organism the stimulating effect would be maintained since the cells are introduced directly into the myocardium. In any case, the results described here point to new possibilities for successfully using stem cells in the regeneration of heart muscle tissue (see Figure 4).

Evaluation of the results

The fact that stem and progenitor cells from exocrine glands possess such properties is of enormous importance for stem cell research, since apparently adult stem cells also contain pluripotent cell types with a broad differentiation spectrum, and these can be isolated and cultivated. For later use it is not so important if they represent a pure stem cell type or a mixture of different precursor cells, or if they are derived from quiescent stem cells or from dedifferentiated somatic cells. Both alternatives are currently being tested. It is more important that these pluripotent stem cells can be differentiated into numerous cell types of all three germ layers. The findings represent a huge step forward towards the vision of being able to establish an expandable and adequately sized depository of various animal and also human stem cells for later use in agriculture, biotechnology and personalized medicine. It also means new adult stem cell cultures and lines of different origins will be available for tissue engineering. As described above, the different stem cell cultivation methods can be advantageously employed in this area.

Cell Differentiation & Cell Technology

- Basic equipment for the isolation and setup of any in vitro culture
- Differentiation and analysis of adult stem cells
- Microinjection technology
- Micro-dissection technology
- Equipment for characterization and isolation of single cells

Potential

As a consequence of the high impact of these results many collaborations with partners from Germany and other European countries have arisen. These aim to more thoroughly explore the possibilities of this new stem cell source and test their use in medicine, biotechnology and agriculture. The partners come from basic research, clinical research and industry. The IBMT workgroup has been integrated into the EU-funded Integrated Project *Cell-PROM* due to the high biotechnological and medical potential of the results. The project focuses on defined, surface-based induction of cell differentiation. Different pilot experiments have already been performed and produced the first results.

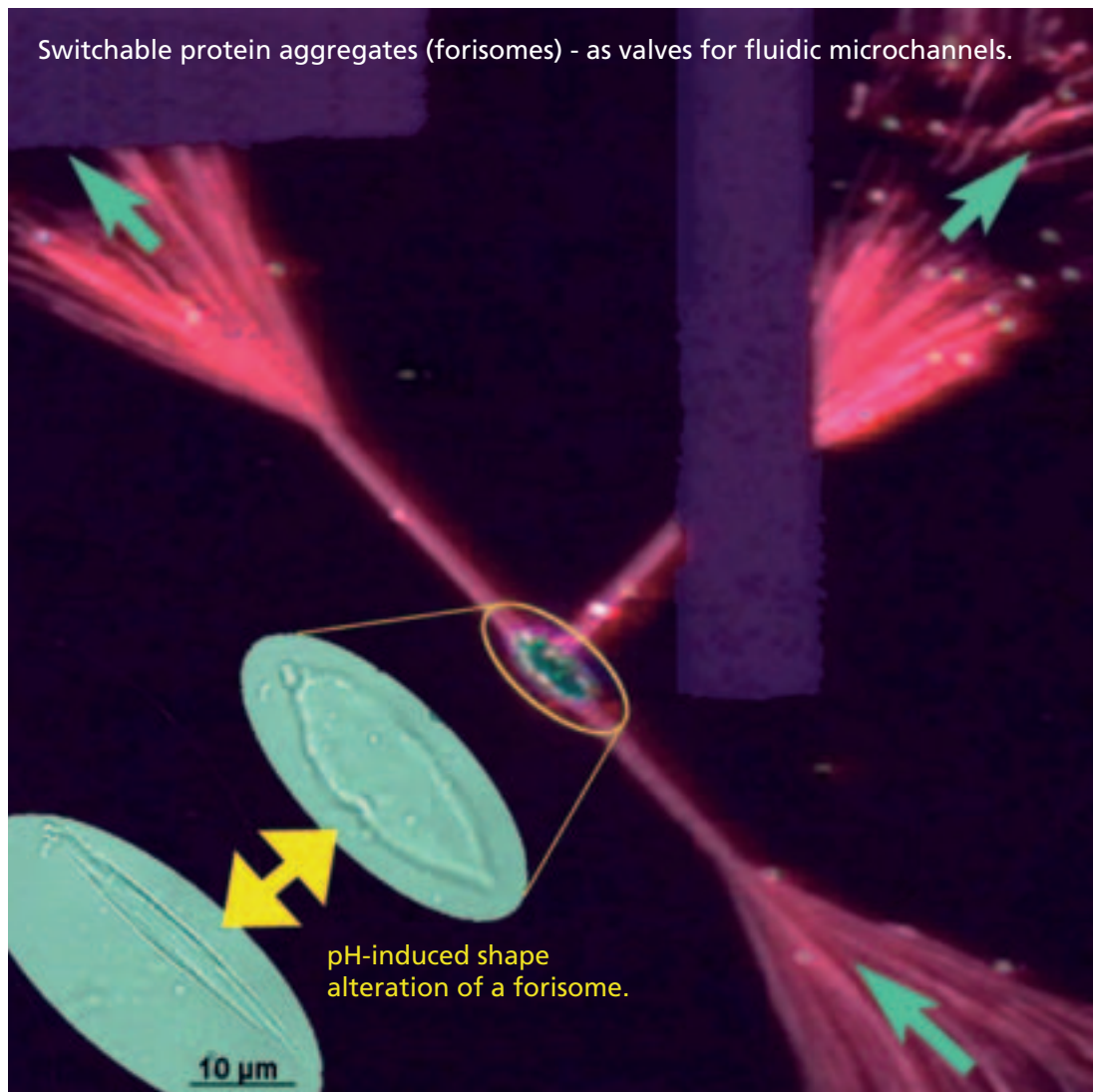
Germany now, as before, has the potential to occupy a key position in stem cell research and the efficient preservation of stem cells. It is necessary to take advantage of this lead and at the same time to extend it by concerted expansion of basic and applied research.



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Services, results and products of the workgroups

- Lab-on-Chip Technology
- Cell Assay Development
- Extremophile Research

Project example: Lab-on-Chip – Gentle handling of valuable cells

Equipment

In the future, cell-based diagnostics and therapy approaches will occupy key roles in medicine. However, advances in these fields will only be possible when the tools and technologies that allow the gentle and reproducible manipulation and characterization of cells become available. The department of Cellular Biotechnology & Biochips is developing such tools. The basis of this development is the assumption that the cellular stages and differentiation patterns must be adjustable with relative precision for such intended medical applications. This can only be achieved if one can control the information exchange between a cell and its environment. This exchange can be triggered by, both, biochemical and mechanical processes. Our solutions are based on two approaches: Single cells can be handled with high precision and stability in lab-on-chip systems without physical contact using high-frequency electromagnetic fields. A clever combination of microelectrodes and fluidic microchannels makes it possible to carry out important tasks in the chip: Precise positioning to the micrometer for

microscopy, assembly of cells and the formation of cell clusters, sorting of different cell populations, and separating and processing cells in very small samples. The second approach tries to control the attachment and migration of adherent cells on surfaces in a targeted manner through the presentation of various stimuli. Microfluidic systems can generate concentration profiles of soluble signal molecules with high spatial precision, which can be used to analyze the chemotactic response of cells. The coating of switchable polymers onto nanoscopically structured surfaces allows one to easily vary the adhesion conditions of cells. A technology platform is currently being established by combining both approaches. This will make it possible to precisely control the development and differentiation of stem cells, in particular via biochemically and topographically defined surface architectures.

Within the context of the department's research on extremophilic organisms, a snow algal bank under the acronym CCCryo is installed, which serves as a source of metabolites (enzymes, pigments, biopolymers) for biotechnological applications (e.g. process engineering).



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Lab-on-Chip Technology



- Design and development of microfluidic systems (chips, periphery, detection) for biotechnology and cell biology
- Design and construction of chip-based microsystems for cell-compatible injection of physiological suspensions into microfluidic systems, contact-free handling of single or low numbers of biological objects (cells, bacteria, viruses) and defined deposition of previously characterized particles for further cultivation
- Microsystems for the controlled translation and rotation of suspended microparticles
- Manual, semi-automatic and automatic sorting of micro-objects (e.g. living cells) in continuous flow systems
- Centrifugation-free washing and loading of living cells with, e.g. pharmaceutical agents in microfluidic flow systems

- Accumulation and detection of micro- and nanoparticles in biotechnologically relevant suspensions
- Dielectric characterization of complex particles on a single cell level
- Chip-based electromanipulation (e.g. fusion) of rare cells (e.g. stem cells)
- Transport of minute liquid volumes with chip-integrated micropumps
- Combination of dielectric field traps and optical tweezers for the simultaneous manipulation of several objects and for the characterization of interactions (binding forces) between particles
- Optical high-end microscopy, e.g. high-sensitivity fluorescence measurements
- Numerical calculation and modeling of electrical, optical and hydrodynamic forces in microsystems
- Influence of alternating electric fields (10 kHz to 250 MHz) on biological objects
- Time-resolved investigation of cell adhesion on functionalized surfaces with Total Internal Reflection Fluorescence Microscopy (TIRFM)
- Characterization of the topographical structure of artificial and biogenic surfaces with sub-micrometer resolution using Atomic Force Microscopy (AFM) and investigation of mechanical characteristics on the same size scale with micro-indentation
- Microprocessing with UV laser ablation
- Micromanipulation of single objects with capillary aspiration
- Cultivation of animal and yeast cells under S1 conditions before and after manipulation in microfluidic chips

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Cell Assay Development

- Protein analysis with high-resolution immunofluorescence microscopy
- Pulse chase technology for investigating expression kinetics
- Time-resolved characterization of manipulation-induced molecular changes in the cell using fluorescence time-lapse and TIRF time-lapse microscopy
- Development of microfluidics carriers for high-resolution microscopy
- Cancer diagnostics based on galvanotaxis and chemotaxis analyses
- Examination of single cells by non-invasive analysis of abandoned cell traces
- Design and fabrication of surfaces
- Development of methods for the differentiation of stem cells
- Non-invasive examination of stem cell differentiation status
- Control of cell trace deposition by surface modifications
- Development of quick assays for determining chemotactic properties
- Correlation of tumor progression stages with molecular processes during chemotactic cell movement
- Switchable surfaces for the control of cell adhesion
- Substrates for cell analysis with physiologically compatible surfaces
- Microcontact printing (“ μ -CP”) of biomolecules for the production of micro- and nanostructures for cell manipulation

Extremophile Research

- Design of surface topographies by μ -CP of coated micro- and nanoparticles on glass and gold surfaces
- Nanostructured gold surfaces for the control of cell functions
- Formation of self-assembled monolayers of thiolbearing biomolecule on gold surfaces

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- CCCryo: culture collection of cryophilic and mesophilic snow, ice and soil algae from polar and alpine regions (snow algae)
- Development of culture systems for large-scale cultivation of carotenoid producing microalgae in photobioreactor installations
- Contract cultivation of algae material under defined and/or differential conditions (UV radiation, light, temperature, nutrients)
- Delivery of isolated and purified DNA and RNA for corresponding studies
- Shipping of algal strains (on request)
- Research on extremozymes (differential transcriptomics, 2D-SDS-PAGE) and primary and secondary plant metabolites (natural cryoprotecta, polyunsaturated fatty acids, carotenoids, astaxanthin, alpha-tocopherol, biopolymers)
- Enzyme assays
- Basic research on the taxonomy of cryophilic freshwater microalgae
- Physiological investigations on cryophily (e.g. single cell microscopy)
- Phylogenetic analyses based on 18S rRNA and ITS gene sequences
- Population genetic investigations on the bipolar distribution of cryophilic algae to support climate modeling

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Project example: Lab-on-Chip – Gentle handling of valuable cells

Lab-on-Chip Technology

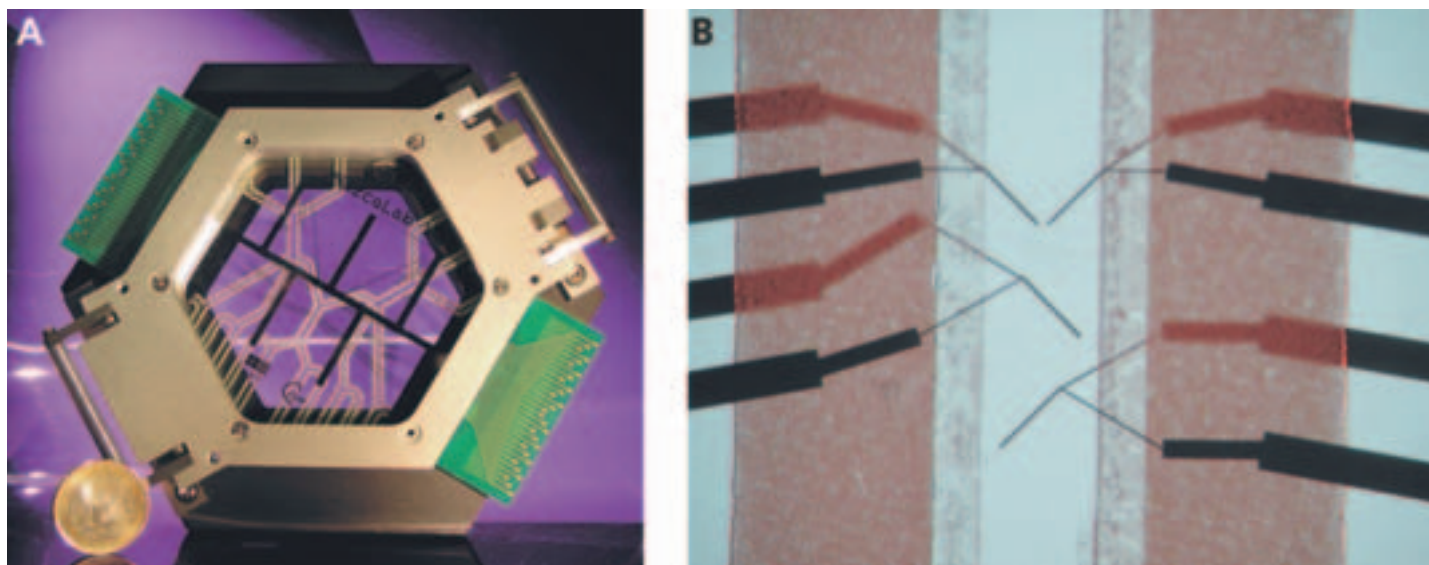


Figure 1: **A** “NazcaLab” chip with integrated fluidic channels and microelectrodes for the gentle handling of living cells. The cells can be sorted, separated and brought into contact with each other. **B** Magnified view of the chip. Microelectrodes with a width of 15 μm protrude in two different planes into the 900 μm -wide channel where the living cells are processed.

Initial situation

In 1600 the English doctor William Gilbert described one of his experiments with amber, which he had previously rubbed with a cloth:

“Hence it is probable that amber exhales something peculiar that attracts the bodies themselves, and not the air. It plainly attracts the body itself in the case of a spherical drop of water standing on a dry surface; for a piece of amber held at a suitable distance pulls toward itself the nearest particles and draws them up into a cone.”

What Gilbert had observed was the deformation of a dielectric body – the water drop – in the electric field around the piece of amber electrostatically charged by friction. Thanks to technological progress over the past four centuries we can generate much better defined electrical fields today than Gilbert could in his time. In particular, microelectrodes can now generate electrical fields, especially field gradients and high frequencies, on very small length scales. From a biotechnological perspective the ques-

tion is then: Can Gilbert’s insights be transferred to microscopic dielectric objects of medical relevance such as single living cells? If so, how can this be achieved technologically? Does this process make it possible to obtain information about the cells under examination without destroying them?

Project descriptions and tasks

Lab-on-chip systems are versatile tools for the manipulation of biological and medical samples. They aim at handling human cells, pathogenic bacteria or viruses under conditions that mimic their natural environment as closely as possible. Mostly these systems are set up as microfluidic channels through which suspended particles flow, and where they can be analyzed and manipulated.

The analysis and manipulation of cells can be achieved using different principles. For instance, many lab-on-chip systems are based on first lysing the cells and subsequently characterizing their contents. In other approaches cells are labeled with specific signaling substances and then classified according to the ability of these substances to bind to certain receptor molecules. Often these signaling compounds are immobilized in a grid-like layout on surfaces, and the preferential binding of the particles is detected locally. However, these methods have the inherent disadvantage of destroying or at least considerably disturbing the cells so that certain signaling pathways are switched on.

If one is seeking techniques for gentle, but at the same time efficient handling of living cells, gradients of ultrasound and electromagnetic fields, e.g. radio waves, provide numerous options. Radio waves are alternating electrical fields, which can exert forces in the pN range on biological objects (dielectrophoresis). Such high-frequency fields never arose during the course of

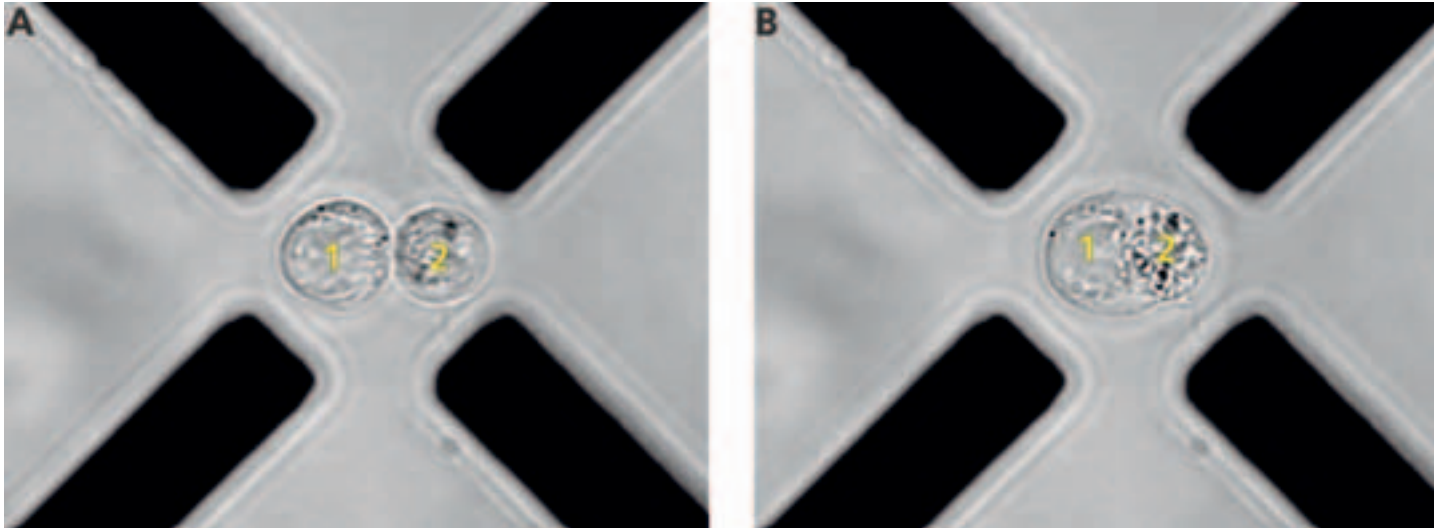


Figure 2: **A** Two human lymphocytes (U-937) are held without contact in a dielectrophoretic microelectrode structure comprising eight electrodes (black) – four at each level – a so-called octode. The two cell nuclei are labeled “1” and “2” (electrode width: 10 μm). **B** After applying a specific electrical signal the cells fuse. The two nuclei are now surrounded by a single cell membrane.

evolution on our planet. Therefore, cells probably do not possess signaling pathways that these fields can interfere with, given an appropriate setting of electrical parameters. So, influence on cells is minimal. Electrical fields can be applied with high temporal and spatial precision. Since this only requires the correct setup of circuits such processes can easily be automat-

Established processes of semiconductor production allow the integration of microelectrodes in microfluidic lab-on-chip systems, greatly increasing their operational scope. Eventually, these developments will lead to technological solutions in the form of chips that can be used in parallel. An example is the “NazcaLab” chip developed within the context of the EU project *Cell-PROM* (see Figure on p. 108). This completely new chip design features a microsystem of as yet unmatched proportions. It enables the simultaneous processing of biological microobjects in

parallel in many channels. Moreover, the new format allows one to easily increase the number of integrated manipulators, i.e. the microelectrodes, to more than a hundred.

Since they are constructed from high optical grade materials, these devices can easily be combined with other modern techniques such as high-resolution confocal microscopy or laser tweezers. They can be used to solve various different tasks in current biotechnological and medical research. Some of the following examples will be described in more detail below: (1) For instance, cell samples can be sorted according to optically detectable characteristics. These characteristics could be coupled to the expression of a genetic trait of interest. (2) Cells can be exposed to certain pharmaceuticals or other soluble effectors without cen-

trifugation and for a precisely defined period, and their reaction to these substances detected. (3) Two microobjects, e.g. cells, can be brought into contact in the chips for certain periods of time and then separated again. This is particularly useful for immunological and stem cell research. (4) In addition, the method allows a high level of control over the fusion of two selected cells. (5, 6) Depending on the setup of the microelectrodes, they also serve to transport liquid in the system or work as particle filters in the channel. (7) Finally, type-specific physical properties of the cells can be measured, allowing their identification and characterization.

Results

A particularly interesting challenge is to combine several advantageous characteristics in the same cell. In practice, a very frequent problem is that cells which produce valuable substances due to genetic modification or surface-mediated programming often become unstable during longer cultivation.

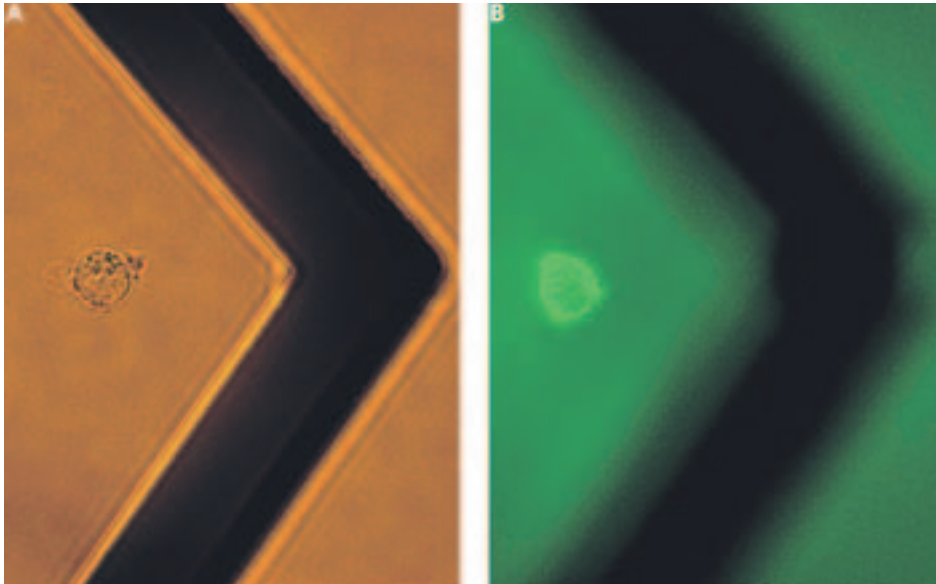


Figure 3: **A** A single human T-lymphocyte is dielectrophoretically anchored by a hook-shaped microelectrode (black) in a flow that comes from the left (width of the electrode: 20 μm). **B** The immunological activation of the cell can be successfully detected by a fluorescently labeled CD69 antibody.

On the contrary, other cells are often robust in comparison, but technically uninteresting. The positive properties of both cell lines can be combined by externally induced fusion (see Figure 2, p. 109). This makes it possible to establish not only stable cell cultures that produce a desired product, but also, for example, cultures that are resistant against a certain pathogenic factor. The same protocol can also produce cell aggregates, which can be used in pharmaceutical research to investigate cell membrane characteristics. A long-established method for inducing cell fusion is the application of pulsed electrical fields. The chip systems described above are perfectly suited for this application due to their integrated microelectrodes. The cells can first be selected electrically, i.e. without direct physical contact, and then positioned and eventually fused.

The example above referred to the “programming” of cells. This means that a cell receives an external input through surface contact, to which it

reacts with a defined response. This can be exploited particularly well in microsystems. An example is the activation of T-cells, a cell type of the adaptive immune system. In the body such information transfer occurs during an infection when certain B-cells come into surface contact with T-cells and thus program the T-cells for a specific immune response. In microchip systems this process is achieved by first anchoring a cell at a hook-shaped barrier by a suitable combination of hydrodynamic and electrical forces (Figure 3). The anchored cell in this configuration is then exposed to defined contacts with another cell or an artificial particle. The surface contact between the two particles results in information transfer between them, hence inducing “programming”.

To be able to select the correct target cells from the injected sample, one needs a process that can transport the sample through the channels onto the chip. A particularly elegant approach is to use the integrated microelectrodes for this as well. This avoids using complicated and costly pump systems that control the channels from the outside (Figure 4, p. 111). Similar to suspended objects, electrodes can also exert forces on liquids (traveling waves). The translation of this method into the design of pumps is obvious. In addition to the precise transport of very small volumes, such electrode setups also facilitate keeping cells in continuous motion around ring-shaped structures in channel systems so that the cells can be stored without adhering irreversibly to the surfaces of the channels.

Another application of traveling waves derives from the ability to generate appropriate flow profiles that lead to the accumulation of suspended particles at certain positions within the chip system. This makes it possible to concentrate dispersed nanoparticles at one location for carrying out a reliable analysis (Figure 5A, p. 112). Until now non-magnetic accumulation of nanoparticles was not possible in flow systems. The traveling wave method now opens up the possibility of concentrating the particles at certain sites on the chip. A requirement for the successful development of application-specific solutions is in-depth knowledge of the physical conditions in the chip. At present, numerical modeling approaches are absolutely essential, as exemplified by the finite element method (Figure 5B, p. 112). This enables one, even before producing a prototype, to make predictions about the probable reaction of a future sample in the system and to optimize the design.

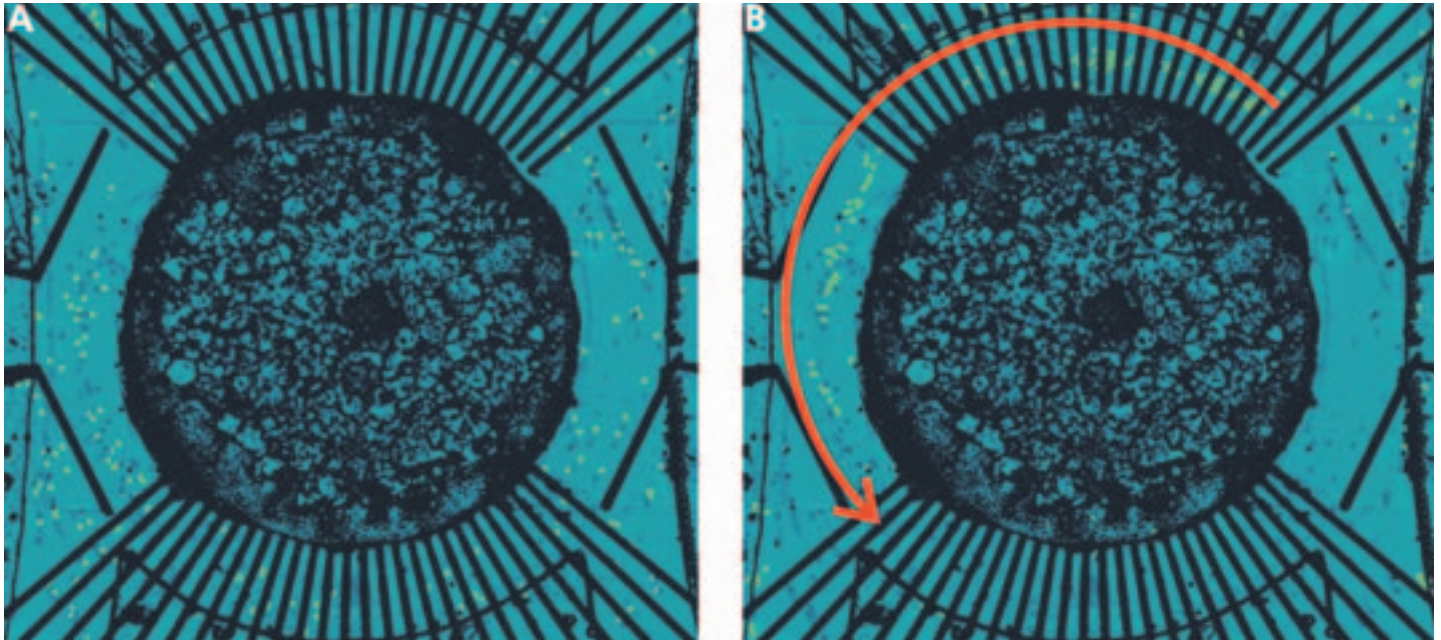


Figure 4: **A** Circular microchannel (diameter: 800 μm) with two areas of radially arranged microelectrodes (width: 10 μm) to use high-frequency electrical fields to pump liquids in micro- and nanochips. A suspension of microparticles (green) was washed into the circular structure. **B** Depending on the geometry of the electrical field, the liquid is pumped clockwise or counterclockwise as visualized by the fluorescent microparticles.

Cell samples from a natural source, e.g. in medicine, typically contain a mixture of different cells which must be identified before any further manipulation. Successful targeted electrofusion or cell programming as described above are only possible if the desired cells can first be identified in a mixture and then selectively sorted. This can be achieved very efficiently by exploiting the fact that different cells react differently to the forces exerted by the electrical field. For instance, if these forces are used to deform cells they react in a specific way depending on the mechanical properties of the respective cell type (Figure 6, p. 112). Such electro-based identification of cells has advantages in that first, it works without the addition of chemical agents, second, it is easy to achieve due to the straight forward production of the microelectrode structures and third, it can be applied in continuous flow systems.

This “electro-stretching” of single cells in lab-on-chip systems represents the modern application of Gilberd’s report cited above about the deformation of a dielectric body in an electrical field. Gilberd managed to make groundbreaking discoveries using extremely simple experiments and accurate observation. Today, lab-on-chip systems with integrated microelectrodes can be employed as relatively simple tools to solve highly complex tasks in biotechnology and medicine.

Project funding

6th Framework Program of the European Commission, Integrated Project “CellPROM – Cell PROgramMING by Nanoscaled Devices”, 2004-2008, No. NM P4 - CT - 20 04 - 50 00 39

Market-oriented strategic preliminary research (MAVO) “Technical use of forisomes”, 2003-2006, 81 22 50

BMBF funding concept “Mikrosystemtechnik2000+”, 2006-2007, 16 SV 22 75

DFG priority program “Nano- und Mikrofluidik: Von der molekularen Bewegung zur kontinuierlichen Strömung” (nano and microfluidics: from molecular motion to continuous flow) (SPP 1164), 2006-2008, JA 17 17 / 1 - 2

Industry cooperation with Evotec Technologies GmbH

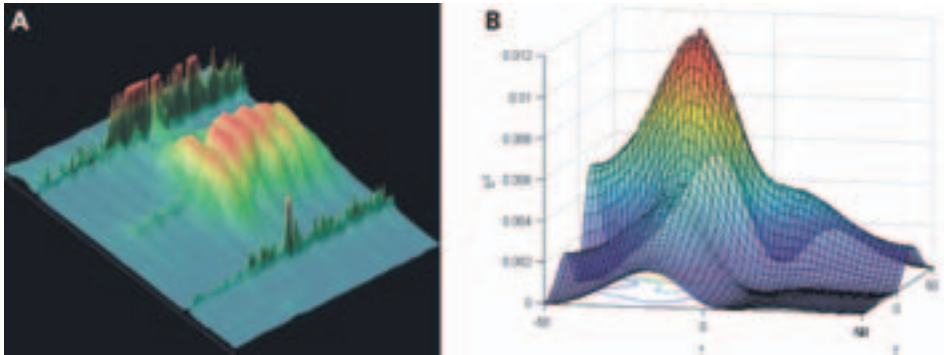


Figure 5: **A** 3-D visualization of 400 nm small nanoparticles accumulating in a structure of parallel microelectrodes (width of the electrodes: 10 μm , frequency: 6 MHz, duration: 400 s). **B** Numerical calculation of the electrical field E distribution in a microelectrode structure.

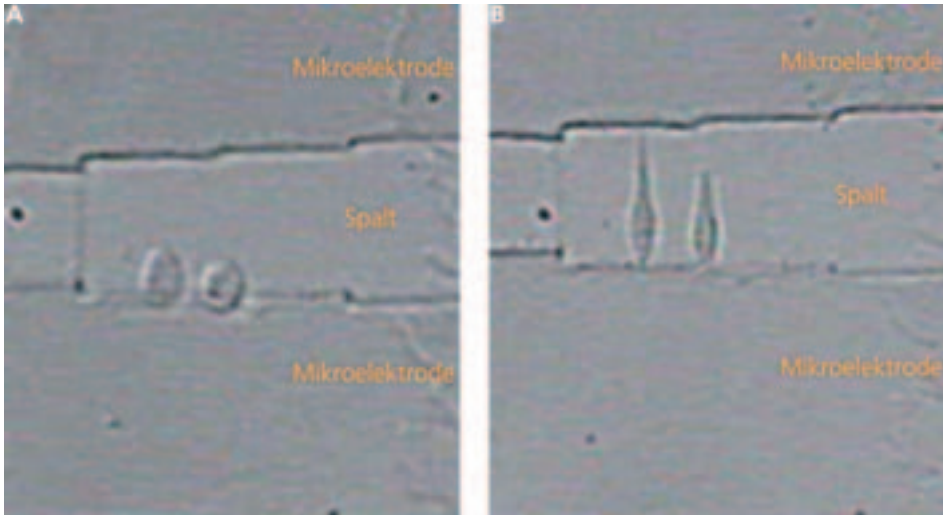


Figure 6: **A** Human lymphocytes were moved dielectrophoretically to the terraced edge of an ITO microelectrode. In the upper part of the image a second microelectrode can be seen that is separated from the attracting electrode by a 20 μm -wide gap. **B** Increased voltage induces a force in the electrical field. Measurement of the resulting deformation of the cells can be automated. The observed mechanical behavior allows conclusions to be made about the cells and the separation of different cell populations.

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Collaborations

Traveling waves

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 Assistant Professor Dr. Andreas Münch, Weierstraß Institute for Applied Analysis und Stochastics, Berlin

Dielectrophoresis

Dr. Martin Wiklund, Biomedical and X-Ray Physics, Department of Applied Physics, Royal Institute of Technology (KTH), Stockholm

Electrofusion

Prof. Dr. med. Richard A. Kroczek, Robert Koch Institute, Berlin

Electro-stretching

Prof. Dr. Josef A. Käs, Department of Physics of Soft Matter (PWM), Institute for Experimental Physics, Faculty of Physics and Geosciences, University Leipzig, Leipzig

Forisomes

Dr. Winfried S. Peters, Institute for General Botany, Department of Biology, Justus Liebig University, Gießen
 Prof. Dr. Andreas Heilmann, Biological Materials and Interfaces, Operation Field Components of Microsystem Technology and Nanotechnologies, Fraunhofer Institute for Construction Material Mechanics (IWM), Halle
 Dr. Michael Knoblauch, Fraunhofer Institute for Molecular Biology and Applied Ecology (IME), Bad Aachen/Schmallenberg
 Prof. Dr. Dirk Prüfer, Institute for Biochemistry and Plant Biotechnology, Department of Biology, Faculty of Mathematics and Natural Sciences, Westphalian Wilhelm University, Münster

Equipment

Lab-on-Chip Technology

- Cytocon 400 technology (Evotec Technologies GmbH) for manipulation of single cells and handling of low numbers of particles in microfluidic chips
- Digital 3-D imaging software for confocal microscopy (Imaris)
- Microfluidics with computer-controlled pump systems
- Excimer laser ablation device (wavelength: 248 nm)
- Transmitted and reflected light microscopy with bright field, phase contrast, fluorescence, polarization and total internal reflection modes (TIRM) as well as computer-controlled object stage and time-lapse option
- Atomic force microscopy (AFM) with simultaneous transmitted and reflected light configuration for bright-field, total internal reflection (TIR), interference reflection (IRM) and fluorescence microscopy
- CAD design (AutoCAD, Solid Works)
- Confocal scanning laser microscope
- Numerical calculation with the finite element method (FlexPDE)
- Optical Tweezers (laser tweezers) with combined UV laser for laser excision
- Osmometry via freezing point

Cell Assay Development

- Computer-based workplace for 3-D imaging
- Contact angle microscope
- Workplace for biochemical functionalization of surfaces and micro-contact printing (μ -CP)
- Confocal laser scanning microscope (CLSM)
- Fluorescence microscope with climate chamber for time-resolved long-term measurements of living cells
- Microscope for multispectral total internal reflection fluorescence (TIRF)
- Transmitted and reflected light microscopes with differential interference contrast, phase contrast, relief contrast, polarization and fluorescence modes
- Laboratory for cultivation of eukaryotic cells

Extremophile Research

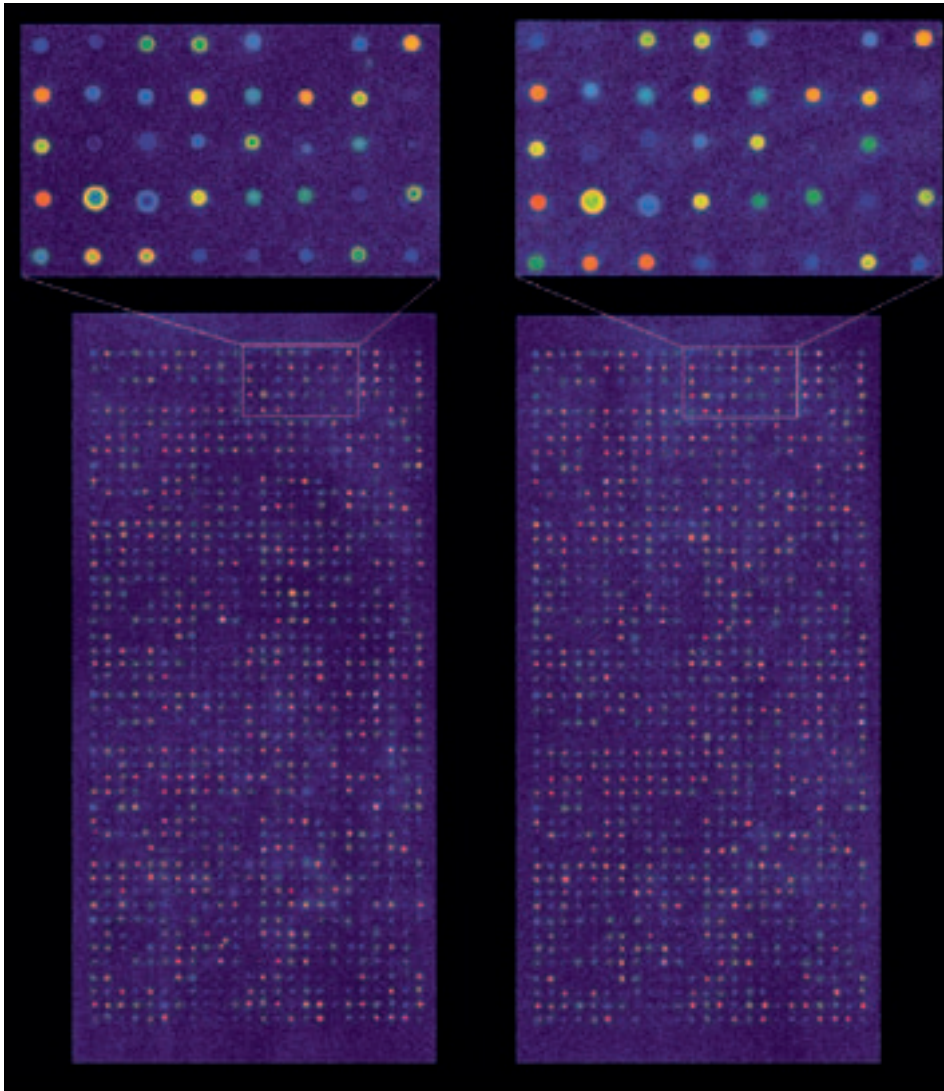
- Upright and inverted light microscopes with differential interference contrast, bright field, dark field and fluorescence modes as well as digital imaging
- Cryomicroscope with digital imaging
- Confocal laser scanning microscope
- Plant cell culture cabinets and rooms ($T = -15$ to $+40^{\circ}\text{C}$, PAR-Light = $0-450 \mu\text{mol m}^{-2} \text{s}^{-1}$ and UV A-B light)
- Laboratory lines for cell disruption; DNA, RNA and protein extraction and purification
- 1-D and 2-D-SDS gel electrophoreses for proteome studies
- S1 genetic engineering laboratories
- PCR thermocyclers
- Controlled rate freezer for cryopreservation

For further accessible equipment also see the equipment lists of the workgroups "Lab-on-Chip Technology" and "Cell Assay Development"

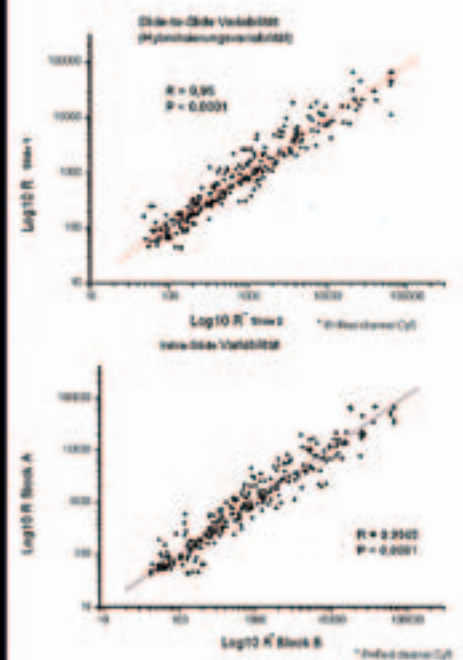
In cooperation with different departments of the Humboldt University Berlin:

- Scanning electron microscope
- Transmission electron microscope

Branch Potsdam-Golm Molecular Bioanalytics & Bioelectronics



Transcriptome analysis of a cell line cultivated as a cancer model. Quality control of the chip production: high reproducibility and low variance within a chip, between different chips and between samples are important factors for successful development from laboratory to product.



Services, results and products of the workgroups

- Biosensors
- Nanobiotechnology
- Microarray & Biochip Technology

Project example: NUCAN – Nucleic Acid Based Nanostructures

Equipment

Today, the most important application area of molecular bioanalytics is in vitro diagnostics, which forms the basis for personalized medicine and will thus become an essential component of modern healthcare. It can reveal significant molecular genotypic or phenotypic features of not only the patient but also, for example, of a pathogen. In addition to more effective and milder treatment for the patient, a number of modern therapeutic approaches would not be possible without in vitro diagnostics. Preventative measures, early diagnosis and therapy optimization all have the potential to improve the patient's quality of life and at the same time relieve the health system.

Until then, many obstacles still have to be overcome, and reliability and accuracy have to be tested for each separate case. The technology is advancing rapidly, and developments in the field of production technology made by the department of Molecular Bioanalytics & Bioelectronics, e.g. for biochips, are helping to draw both small and medium-sized enterprises into this growing market. This is why we are involved in the BioHyTec (biohybrid technologies) association, for which the IBMT provides the biochip competence center. The first and very successful project phase of this association ended in 2006. The network has established itself in biotechnology and created a good basis for technological developments together with the University Potsdam and many regional companies. The companies can now commission the development of their production lines at the IBMT.

The integration of diverse pipetting and spotting robots, which differ in setup and dispensation procedures, in one laboratory provides the necessary high flexibility. Besides the equipment hardware, the controlling software with its user interfaces represents the key to a flexible system. Existing facilities can be extended to include production features and options for quality control management. The work is carried out on a project-spanning level and applied to very different microarrays. The department of Molecular Bioanalytics & Bioelectronics already spots high quality arrays not only onto standard carriers but also directly onto silicon wafers, microtiter plates, membranes and customer-produced carriers. The substances that are spotted comprise the whole range of biologically relevant molecules such as DNA oligomers, PCR products, peptides, antibodies and other proteins, as well as all types of "small molecules" that are used as potential drugs, e.g. for screening. With respect to software, single components of the total system have been completed. Direct equipment control, overall combination of different facilities, production and quality control and the array design are integral elements of our continuous development efforts.

Product orientation is complemented by research: The push towards smaller dimensions ends at the level of single molecules. In medical analytics, e.g. for determining blood parameters, developments are towards ever smaller and smaller sample volumes. This not only has perceptible – in the literal sense – advantages for the patient: in smaller volumes chemical reactions occur more rapidly, they consume less valuable sample material and they can be more easily automated. Ultimately, every chemist dreams of reducing the



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amounts of reagents to such an extent that experiments can be performed with only a few, or ideally single molecules. For many of these kinds of investigations it is necessary to anchor the molecule, but release it after the analysis to make room for the next molecule. For some time such traps have already existed for molecules in a vacuum, but not in aqueous solutions as are essential particularly in biomedical research.

We succeeded in constructing exactly such a molecular trap by using very small and extremely sharp "nanoelectrodes". By applying high voltages, they make it possible to generate strong electrical fields in a very limited volume, and due to their spatial distribution these fields also attract uncharged molecules. Alternating currents in the radio wave range around 1 MHz cause this attraction: while charged particles dissolved in water only oscillate to and from, protein molecules migrate to the tips of the electrodes. Lab-on-chip systems that are based on similar principles and used to characterize and sort living cells were introduced onto the market some years ago. The performance of these systems could be considerably increased by the described possibility of manipulating single molecules alone by electrical signals. This would bring us one step closer to the automated synthesis and analysis of single molecules on such advanced chips.

Apart from the manipulation of single molecules freely suspended in solution, many applications require fixing some or single molecules onto surfaces. For the design of structures, including more complex ones, on the nanometer scale the EU-funded project "Nucleic Acid Based Nanostructures" (NUCAN) brings together nine partners, from seven countries, who are investigating the use of nucleic acids as a construction material (see the following article). However, the year 2006 was characterized by the preparations for moving into the new institute building on the research campus Potsdam-Golm. In new rooms and in the direct vicinity of other institutes of the Fraunhofer-Gesellschaft and Max Planck Society, as well as the University of Potsdam our research will find a creative environment with all the necessary technological resources.

Funding is provided by the Federal Ministry of Education and Research (BMBF) within the framework of the InnoRegio initiative "Biohybrid Technologies" (www.biohytec.de), as well as the State of Brandenburg and the European Union.

Biosensors

Applied Research & Development:

- Development of integrated biosensor and biochip analyzers (microfluidics, detection and analysis software)
- Development of fluorescence detectors
- CCD camera-based microarray reader
- Development of electrochemical and fluorimetric immunoassays and immunosensors (hormones, anesthetics)
- Surface chemistry and immobilization of biomolecules
- Nanoparticle-based immunoassays

Service:

- Protein interaction analysis with label-free biosensor (Biacore T100)
- Characterization of antibodies (affinity, kinetics, thermodynamics)
- Fluorescence spectroscopic and electrochemical characterization of reagents and biomolecules

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Nanobiotechnology

Applied Research & Development:

- High-resolution, lateral structuring of immobilized material (“nanostructures”)
- Establishment of nanotechnology with biomolecules, single molecule anchoring
- PCR on a chip
- DNA-protein interaction analysis
- DNA computing
- Surface analytics (AFM, SNOM, MFM)
- On-chip molecular biology
- Peptide and nucleic acid structures as biochip tools

Technology training:

- Workshop for atomic force microscopy

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Microarray & Biochip Technology

Applied Research & Development:

- Chemical/biochemical coupling of biologically functional molecules to diverse surfaces, e.g. glass and polymer chips, microtiter plates, membranes
- Lateral structuring of immobilized material (biochip design)
- Development of DNA chips
- Development of peptide chips
- Antibody microarrays
- Development of technologies for biochip production
- SNP analysis with dynamic microarray
- Enzyme activity with immobilized substrates
- Chemical array
- Software development
- Bioinformatics/databases

Service:

- Production of test and small-scale production series
- Reports and studies

Technology training:

- Workshop on biochip technology
- Workshop on bioinformatics

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Nanobiotechnology



Figure 1: Technical realization of the concept for generating DNA constructs.

Initial situation

Arranging and establishing relationships in very small dimensions, i.e. at the molecular scale, is the domain of nanotechnology. Nature has long occupied this domain and created perfect highly complex biomolecular structures, which ensure maximum efficiency within the cell. Nanotechnology tries to exploit Nature's example. Biomacromolecules are not only used for their original function but also as structural components in completely different ways. For example, nanometer-scaled tools can be produced for applications in very different areas, such as pharmaceutical research, bioanalytics or microelectronics.

Tasks

Nucleic acids serve as a basis for the construction because these heterogeneous molecules can be produced biotechnologically in almost any length. The unique characteristic of base pairing, which can also be achieved with artificial nucleic acids, e.g. peptidic nucleic acids (PNA), is used for directional targeting within the long strand. If the long strand can be positioned and forced into a geometrically constricted configuration, this can result in a universal backbone with nanometer-scaled spatial resolution. A particular advantage of nucleic acids is their enzymatic processivity: Ideally the backbone structures can be cloned in bacteria with the final goal of an "electronic circuit from the bioreactor". This basic task is tackled within the project "Nucleic Acid Based Nanostructures - NUCAN" by nine partners from seven European countries and applied as an example in thematic fields mentioned above.

Realization

The technical realization of the concept is proceeding along two paths: The first path follows up the self-assembly process of complementary nucleic acid fragments, as well as the synthesis of nucleic acids in conjunction with other nano-scaled entities (proteins, nanoparticles, carbon nanotubes). Such conjugates then take on functions resulting from their spatial relationship, e.g. molecular recognition of complex patterns via different binding molecules. This path also addresses the production of nucleic acids, both synthetic (PNA) and long DNA molecules by enzymatic synthesis. The second path focuses on surface contacts. Nanoelectrodes or glass surfaces serve as anchor points for the production of stable compounds with the maximum spatial resolution and the minimum number of molecules.

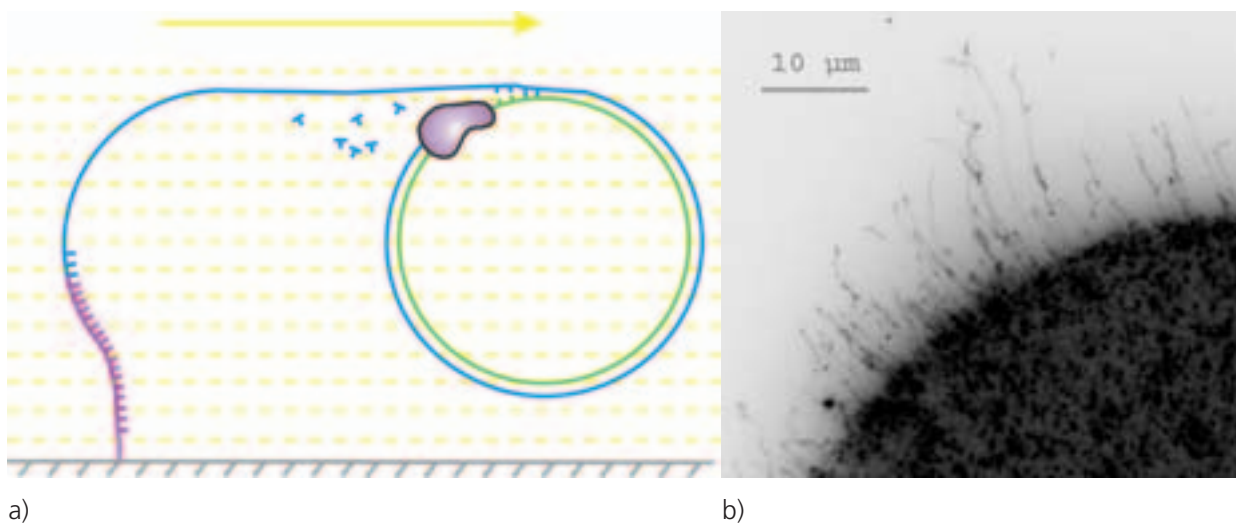


Figure 2: Growth of long single-stranded DNA threads on a surface. The principle of rolling circle amplification initiated at an immobilized starter sequence (purple). The F29 DNA polymerase synthesizes a single strand on the circular template (green). Fluorescence image of a spot (diameter 150 μm) in which the starter sequence was covalently immobilized on a glass surface. The threads of DNA growing laterally from the spot are distinctly visible.

Results

The three-year project reached its mid-point in 2006. The components are now available and are being analyzed in different application areas. One example is the growth of DNA molecules on solid surfaces. Short DNA strands are coupled at one end to a glass surface and subsequently elongated to long thread-like molecules by an enzymatic reaction (rolling circle amplification). These threads are aligned in parallel in a fluidic system. Specifically synthesized proteins bind at certain sequence motifs that are regularly repeated on the DNA. At the moment these proteins are fluorescently labeled in order to optimize the procedure. In a further step, the parallel DNA strands are crosslinked and further proteins with more complex functions can then be coupled to this "nanogrid".

Project partners

Partners in the EU-funded project, which is coordinated by the IBMT, are the University of Bologna, University of Copenhagen, University of Dortmund, Institute for Physical High Technology in Jena, University of Newcastle, Karolinska Institute in Stockholm, Nuclear Research Center (CEA) Saclay/Paris as well as the SMEs Nanotec Electrónica, Madrid and Alphacontec, Berlin.



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Equipment

Biosensors

- Bioaffinity analysis with label-free detection technologies
- Biacore T100
- S1 genetic engineering laboratory equipment (cell culture, yeast laboratory, PCR, electrophoresis, gel imager, centrifuges, etc.)
- UV-Vis spectrophotometer
- Bioluminescence
- FT-IR spectrometer
- Fluorescence MTP reader
- Fluorescence polarization
- Electrochemical workstation (impedance spectroscopy, amperometry, etc.)
- Optical measurements (e.g. power measurement, spectral analysis)

Nanobiotechnology

- Laser scanning microscope (LSM, 350-633 nm)
- Fluorescence correlation spectroscopy (Zeiss "Confocor", coupled with LSM)
- Scanning probe microscopy (AFM, SNOM)
- Optical microscopy (phase contrast, DIC, dark field) with single photon sensitivity, frame rates up to 500 Hz
- S1 genetic engineering laboratory equipment (cell culture, yeast laboratory, PCR, electrophoresis, gel imager, centrifuges, etc.)
- Sub-nanosecond light sources
- Electronics: Oscilloscopes, spectrum, impedance and vector network analyzers from DC to above 20 GHz; signal and vector generators from DC to 8 GHz, up to 25 W
- Software for three-dimensional electric field calculations
- Software for electronic circuit simulation

Microarray & Biochip Technology

- Biochip arrayer for the production of DNA and Biochips (different arrayers available, contact and non-contact)
- Biochip scanner: Applied Precision "Arrayworx"
- Own development "FLOW" for simultaneous kinetic flow measurements
- Laser scanning microscope (LSM, 350-633 nm)
- Scanning probe microscopy (AFM, SNOM)
- Plasma purification
- Spin coating
- Sputtering

Research Group: Biohybrid Functional (Supramolecular) Systems

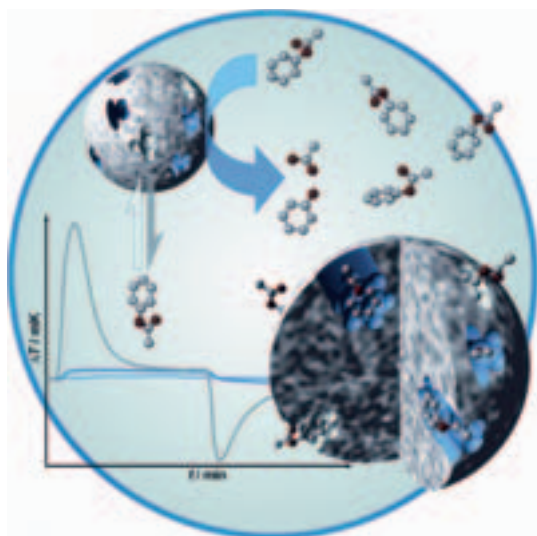


Figure 1: A bi-functional MIP: Analysis of binding and catalysis by a flow calorimeter.

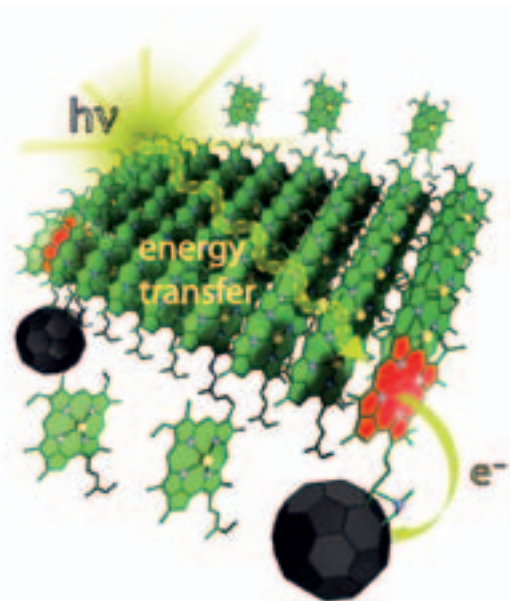


Figure 2: Organization and functional principle of an artificial supramolecular antenna/RC unit (schematic view).

The research group “Biohybrid Functional (Supramolecular) Systems” at the Fraunhofer IBMT in Potsdam-Golm works within the field of nanobiotechnology at the interface between materials sciences and bioanalytical chemistry. The application of state-of-the-art nanomaterials for solving problems in bioanalytical chemistry is of particular interest. The research is focused on two main subjects being connected by the concept of molecular self-assembly.

One subject deals with the development of “Biohybrid Redox Systems” to provide novel solutions for a functional interlink between biological recognition elements and electrochemical signal transducers. This includes the optimization of immobilization procedures for redox enzymes as recognition element for biomarkers on electrode surfaces yielding protein-embedded redox sites which directly exchange electrons with the sensor electrode without free diffusing redox mediators (third-generation biosensors). Research is directed towards the development of reagentless amperometric biosensors compris-

ing all components required for the biological recognition, biocatalytic reaction, and the signal transduction, all of which are stationary arranged in specifically designed sensor architectures. The development of gentle immobilization strategies enables the controlled and specific deposition of complex sensor layouts solely on the surface of electrodes. This implies the application of electrochemically induced deposition schemes using conducting polymers, electrodeposition polymers, and redox-modified electrodeposition polymers. An additional approach is based on engineering metal sites in redox proteins which allow for investigating the relation between activity and electrochemical as well as spectroscopic features of the new protein complex. These new biological components shall be applied in electrochemical devices with the emphasis to study biological redox processes such as electrocatalysis on nanoscale.

The second subject focuses on the development of “Bioanalogue Recognition Elements”. The project aims at the development of robust molecular recognition elements or biomimetic catalysts by molecular imprinting of synthetic polymer matrices. Newly generated tailor-made functional monomers and molecular imprinting protocols yield polymerizable functional monomers which associate strongly and reversibly with a template molecule. The resulting self-assemblies which are stabilized by polymerisation with extensive crosslinking lead to the formation of specific binders or catalytic sites for the template or an analogue molecule. The network polymers (MIPs) rebind the template molecule with very high affinity and specificity. Additionally, these MIPs are readily synthesized and relatively stable which has spurred the applications in the fields of separation sciences, analytical chemistry, chiral technologies, therapeutics, and catalysis. However, due to some inherent problems associated with the conventional imprinting procedure, the number of applications is still rather limited. These problems are being

addressed by a bottom-up approach taking into account, for example, hierarchical templated synthesis and surface energy.

Furthermore, the research group is engaged in electrochemical energy production and nanosciences as both create an unusual opportunity for advances in basic material research for solar energy. Currently, new nanostructured architectures with smart materials are investigated to create, for example, an energy gradient for the use in solar energy conversion. Novel approaches to a system assembly of nanoscale components benefit from mimicking the self-assembly, self-adjustment, and self-repair features of biological systems, including fault tolerance. Progress in the aforementioned areas is additionally supported by a variety of research activities on (carbon)nanotubes, photochemistry, and basic (spectro)electrochemistry.

The group is funded by the BMBF grant no. 0311993; mentoring Prof. Dr. F. W. Scheller.

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Research and Development:

- Development of molecularly imprinted polymers (MIPs) for separation (decontamination) and analytical purpose
- Synthesis of chemical receptors and fullerene based nanoparticles
- Synthesis of conducting polymers and redox-active hydrogels (pH- and temperature responsive)
- Development of amperometric biosensors
- Surface modification of different materials and immobilization of biomolecules

Service:

- Chemical/biochemical binding studies and enzyme kinetics by isothermal titration calorimetry (ITC, VP-ITC Microcal)
- Flow Chip Calorimetry, Flow through calorimetry
- Several electrochemical methods (normal and pulsed)
- Scanning electrochemical microscope (SECM)
- Impedance Spectroscopy
- Spectroelectrochemistry
- HPLC (analytical and preparative, light scattering detector), Carbohydrate analysis





“Central Research Infrastructure for molecular Pathology” CRIP



Figure 1: Formalin-fixed paraffin-embedded human tissue samples (Photo: Michael Hummel).

Background

After sequencing of the human genome, big pharmaceutical companies are widely applying high-throughput technologies to investigate in biomarkers, in targeted and personalized medicine. Their work critically depends on large biorepositories – so-called “biobanks” – containing human biospecimens and data from healthy and diseased donors. Academic researchers also claim¹ that biobanks must be “designed to support the needs of systems biology approaches to human diseases, drug discovery, and public health”. To secure statistically relevant findings, both academic and industrial biomedical research require large case numbers which are often not available at a single hospital.

Allowing for investigation of localized diseases – such as cancer – or the organ-specific manifestations of systemic diseases, human tissue samples are of special importance for research. On the other hand, human tissue is an irreproducible, invaluable “not for sale” resource which is and will further be collected and stored for patient’s sake – i.e. for diagnosis or surgery – at remote clinics and Institutes of Pathol-

ogy, with aliquots preserved for potential further diagnosis and therapy. Therefore, in our view to join these clinical tissue sample repositories is legally and logistically not feasible and ethically forbidden. So for research issues, they can only and have to be joined virtually by networking, harmonizing and standardizing them.

At the eve of a pan-European Biobanking and Biomolecular Resources Research Infrastructure (BBMRI)², Germany had not overcome the fragmentation of her numerous tissue banks representing outstanding expertise in pathology at more than 30 university hospitals until 2006. In October 2006 the RZPD Deutsches Ressourcenzentrum für Genomforschung GmbH launched the “Central Research Infrastructure for molecular Pathology” (CRIP). CRIP has been transferred to Fraunhofer IBMT in summer 2007 and is seen as a pilot project for BBMRI.

Project

CRIP (<http://www.crip.fraunhofer.de>) interlinks human tissue banks and serves researchers to access clinical material and data. The FFPE³ and frozen tissue samples remain stored at the cooperating institutes. An integrative database renders them accessible by an intelligent web-based search tool. It is open for free to registered scientists from academia and industry as well enabling them to check how many cases might be available for a special research problem. As a search result, researchers may download a pool of anonymized data and decide upon the feasibility of the project they had in mind. In other words: CRIP displays statistical information on anonymized research data and specimens available in the partners’ institutes. If a project is to be initiated, CRIP provides the researcher (and now for a handling fee) with the contact details and project proposals of the partner institute(s) who contributed data to his or her search result, and is ready to support project agreement and management. Project procurement is free of charge for institutions contributing to CRIP. Unless already available, CRIP partners will annotate biospecimens selected for a certain project with additional clinical data as required.

CRIP partners disclose their internal sample preservation SOPs and have agreed in writing to obey common SOPs for prospective common projects. Thus CRIP advances the standardization of sample preservation at the partners’ institutes which will be further boosted by IBMT’s expertise in cryotechnology. CRIP has standardized the imported data sets and aligned them

¹ www.bioresource-med.at

² www.biobanks.eu

³ formalin fixed paraffin embedded

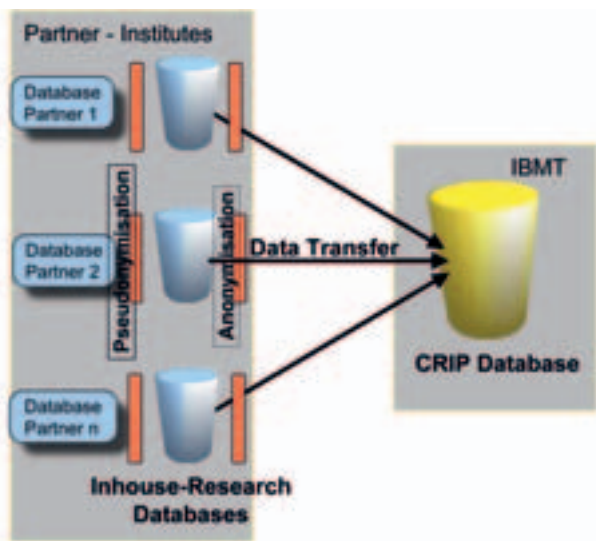


Figure 2: CRIP Data Flow.

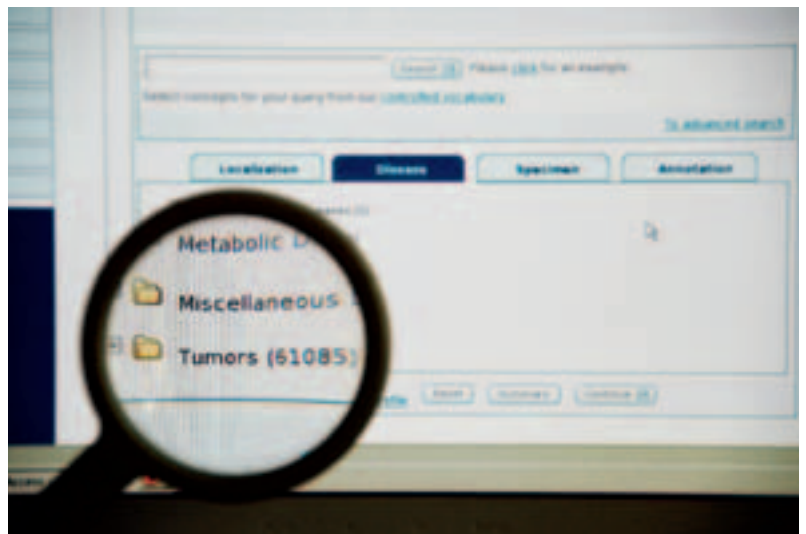


Figure 3: CRIP Search Tool (Photo: Theresa Ippen).

with the NGFN core parameters⁴ and the "Minimum data set for tissues and isolated cells" of the OECD⁵. CRIP works in full compliance with ethical and legal standards and is overseen by an independent interdisciplinary Advisory Board. The "Berliner Beauftragter für Datenschutz und Informationsfreiheit" has appreciated CRIP as a model concept in his annual report 2006⁶.

Partners

CRIP's initial database partners are the Charité Universitätsmedizin Berlin, Europe's largest university hospital, and the Medical University of Graz holding Europe's largest tissue bank. Further partners join CRIP in 2007 to complement its disease and biospecimen spectrum.

CRIP was initiated in 2004 and funded since 2005 by the former Förderverein Humangenomforschung und Biotechnologie e.V.. The CRIP concept has been developed in close cooperation with leading German and Austrian pathologists and representatives of seven pharmaceutical companies⁷. These companies, as well as BMBF, awarded CRIP additional funding in 2006 and 2007.

Outlook

The greater the extent to which human tissue samples are standardized and annotated with data from the patients' clinical records, the more outcome and value they may generate in research projects on the onset and course of disease and on therapy monitoring. However, annotating tissue samples in a quality-controlled manner is costly and time-consuming. It cannot be performed at once for complete tissue banks. CRIP provides a concept and infrastructure to annotate existing repositories project by project and will further support this process by IT expertise on text mining, etc. Thus, CRIP develops the tissue repositories of local hospitals towards a central research infrastructure which is unique in Germany and Austria.



Standardizing data and SOPs, CRIP might serve as a model concept for any networking of biobanks and a pilot project for a pan-European research infrastructure.

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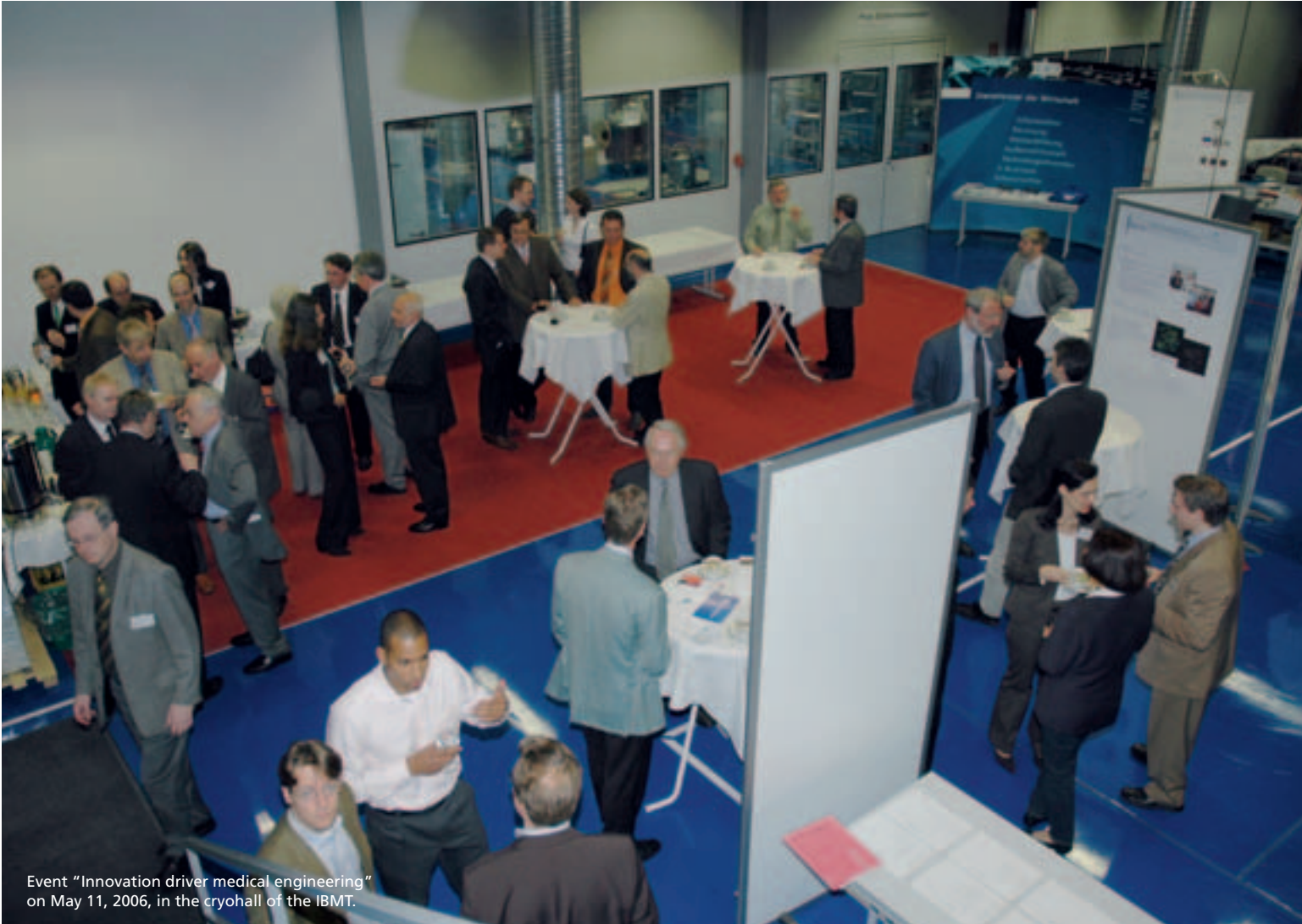
⁴ <http://www.science.ngfn.de/509.htm>

⁵ <http://www.oecd.org/dataoecd/7/13/38777417.pdf>

⁶ <http://www.datenschutz-berlin.de/informat/dateien/jb/jb06.pdf>

⁷ ALTANA Pharma AG, Bayer HealthCare AG, Boehringer Ingelheim Austria GmbH, Merck KGaA, Roche Diagnostics GmbH, Sanofi-Aventis Deutschland GmbH, Schering AG

Biomedical Competence Centers



Event "Innovation driver medical engineering" on May 11, 2006, in the cryohall of the IBMT.

Services, results and products of the workgroups

- MEDICS – European Center of Competence for Biomedical Microdevices
- MOTIV – Medical Technological Competence Center for Miniaturized Monitoring and Intervention Systems
- CC-Nanochem – National Competence Center for Chemical Nanotechnology
- Nano2Life – European Network of Excellence in Nanobiotechnology

Project example: Technology consulting by experts

Equipment

Dominated by the USA, Europe and Japan, the global market for biomedical technology amounts to around 180 billion € annually, and is characterized by stability with constant growth rates. Despite this apparent attractiveness, the market for biomedical technology is extremely complex and difficult. Research and development in particular must overcome immense challenges in a tense field determined by continuous improvement in medical care accompanied by increasing savings in costs, low production volumes with high quality standards, long development times facing an increasing pace of innovation, cumbersome approval procedures and extensive interdisciplinary demands.

Micro, nano, optical and biotechnologies are often described as the key technologies of the 21st century due to their enormous possibilities, and they show great potential to meet such complex demands. Consequently, the application of these technologies has advanced considerably over recent years: Capsule endoscopy in small intestine diagnostics, the use of nanoparticles for treating patients in tumor therapy, as well as the wider use of active implants for the treatment of epilepsy or Parkinson's disease during rehabilitation are only a few examples impressively demonstrating this.

The use of new technologies alone does not guarantee the development and production of successful products and applications in biomedical technology. Rather, it is necessary to continuously assess the usefulness and risks, which can only be accomplished by an interdisciplinary team of experts.

The workgroup "Biomedical Competence Centers" at the Fraunhofer IBMT specializes in novel technologies in the application areas of biomedical technology. It supports small and medium-sized companies, industry, public customers, as well as banks and investors

in finding solutions for numerous problems.

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Biomedical Competence Centers

- Micro, nano, optical and biotechnologies for biomedical applications
- Technology consulting
- Feasibility studies and concept assessment
- Technology, patent and market enquiries
- Finding industrial and scientific partners
- Application, funding and coordination of R&D projects
- Independent project management
- Support with business start-up
- Support with approval procedures (MPG, MDD, FDA)
- Internet information services
- Workshops and training programs

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Project example: Technology consulting by experts

Initial situation

The important role of the workgroup "Biomedical Competence Centers" and the Fraunhofer IBMT within the field of biomedical technology is underpinned by their being appointed as the European and national competence centers for the following:

- Coordination of the European Center of Competence for Biomedical Microdevices "MEDICS" as assigned by the European Union (www.medics-network.com).
- Coordination of the National Medical Engineering Competence Center "MOTIV" – Miniaturized Monitoring and Intervention Systems as assigned by the Federal Ministry of Education and Research (www.motiv-medtech.de).
- Taking charge of nanobiotechnology competence within the National Competence Center for Chemical Nanotechnology "CC-NanoChem" (www.cc-nanochem.de).

Services

Technology consulting – Ask the experts

The multidisciplinary core team of the workgroup "Biomedical Competence Centers" at the Fraunhofer IBMT comprises biologists, bionics experts, medical technology engineers and economists. Moreover, we have access to an international network of experts in different technology and application areas.

The workgroup offers services supporting Research & Development of biomedical devices and applications.

In addition to project applications, independent project management, brokerage of project partners and support with approval procedures, technology consulting represents a particularly important field of expertise of the workgroup. Technology consulting includes feasibility and market studies, concept assessment and concept consulting as well as technical and patent enquiries.

The following case study exemplifies the procedures and process of a consulting project at the Fraunhofer IBMT.

Case study of technology consulting for an industrial customer

The goal of this technology consulting project is to support an industrial customer in assessing a novel production technology and in identifying potential application areas within biomedical technology.

The first contact with the industrial customer is mediated by a partner within the international network of the workgroup "Biomedical Competence Centers".

Month 1:

Establishing contact between the customer and staff of workgroup "Biomedical Competence Centers" at the Fraunhofer IBMT. First meeting at the customer's location to discuss the challenges and objectives as well as possibilities for support by the Fraunhofer IBMT.

Month 2:

Submission of an offer to the customer, which includes the components: design of a consulting concept, conducting interviews with experts, producing a results report, as well as final presentation with discussion of the results and further steps at the customer's location.



Month 3:
The industrial customer places their commission, the Fraunhofer IBMT accepts it.

Month 3-5:
Work on the industry commission. The technology under investigation is introduced with a short presentation, which is prepared in cooperation with the customer, and subsequently discussed with selected experts from different disciplines. A total of 24 expert interviews are conducted where the following points are discussed and recorded in writing:

- Assessment of the strengths and weaknesses and working out the unique features of the technology.
- Discussion of possible application areas and their potential. More than 20 application areas in biomedical technology are examined as well as potential non-biomedical technology spin-offs are developed.

- Definition of important industry suppliers and downstream customers.
- Discussion of possible access routes to the respective industry branches and downstream customers.

The contents of the expert interviews are subsequently backed up by background research and additional literature. The final report concisely presents all the results and background research of the technology consultation as well as presenting recommendations for further steps.

Month 5:
Handing over of the final report.

Month 7:
Presentation of the results at the customer's location with subsequent discussion of the results, the necessary measures as well as the further steps and cooperation.

Month 9:
Receipt of a consecutive commission from the industrial customer.

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Equipment



Biomedical Competence Centers

Facilities and staff of the workgroup "Biomedical Competence Centers" at Fraunhofer IBMT.

- Interdisciplinary team of experts from biomedical engineering, bionics, biology, micro- & nanotechnology and economic engineering
- European Competence Center MEDICS – Biomedical Microdevices
- National Competence Center MOTIV – Miniaturized Monitoring and Intervention Systems
- National Competence Center CC-NanoChem – Chemical Nanotechnology
- European Network of Excellence Nano2Life – Nanobiotechnology
- Biomedical database
- Biomedical Internet search engine
- International network of suppliers and users

Facts and Statistics



IBMT at the joint stand of the Fraunhofer-Gesellschaft at the MEDICA 2006 in Duesseldorf.

Names, Dates, Events

- National/international guests: scientists, research fellows and guest lecturers
- Exhibition and event list

Scientific Publications

- Diplomas, masters, bachelors and PhD theses
- Publications and talks 2006
- Patents

National/international guests: scientists, research fellows and guest lecturers

Visiting scientists 2006

Isabella Guido	Stiftung der Deutschen Wirtschaft
Markus Küppers	RWTH Aachen
Rita M. Malpique	Universität Lissabon
Sven Martin	JenLab, Jena
Juan Martinez	Leonardo da Vinci-Programm der EU
Dr. Igor Morgenstern	Universität Rostock
Uta Siebert	RWTH Aachen
Aisada Uchugonova	DAAD
Henrik W. Wagner	Justus-Liebig-Universität Gießen
Dr. Pavel Zinin	Universität of Hawaii, USA

Guest lecturers 2006

Dr. Wataru Watanabe	National Institut of Advanced Industrial Science & Technology (AIST), Japan
Prof. Dr. Albert van den Berg	University of Twente, Niederlande

Exhibition and event list

Nano2Life Business Day on NanoMed 2006
16.02.2006, Berlin

NanoMed 2006 – 5th International Workshop on Biomedical
Applications of Nanotechnology
16.–17.02.2006, Berlin

MEDTEC 2006 – Fair and Conference
07.–09.03.2006, Stuttgart
Coordination Fraunhofer Gemeinschaftsstand
<http://www.medtecshow.de/>

MOTIV/ZPT-Unternehmertag »Innovationsmotor Medizintechnik: Anwendungen über die Medizin hinaus«
11.05.2006, Sulzbach

20. Treffpunkt Medizintechnik, Telemedizin und
medizinische Informatik
15.06.2006, Berlin

Workshop on Advanced Multiphoton and Fluorescence
Lifetime Imaging Techniques
19.–21.06.2006, St. Ingbert

Lange Nacht der Wissenschaften 2006
30.06.2006, Fraunhofer IBMT/AMBT, Institut für Biologie,
Humboldt-Universität zu Berlin, Berlin

Health Care Forum Saar »Perspektiven der Krankenhausversorgung«
04.10.2006, Saarbrücken

Kompetenzzentren für die Medizintechnik – eine Erfolgsgeschichte
23.10.2006, Aachen

MEDICA 2006 – Weltforum der Medizin, Internationale
Fachmesse mit Kongress
15.–18.11.2006, Düsseldorf, Halle 10 Stand F05
<http://www.medica.de>

NanoTech 2006
14.–16.11.2006, Montreux

Diplomas, masters, bachelors, and PhD theses

Name	University	Qualification
Feili, Dara	Universität des Saarlandes, Physik und Mechatronik	Promotion
Fournelle, Marc	Universität des Saarlandes, Physik	Diplom
Geismann, Claudia	Universität zu Lübeck, Biologie	Master
Hanft, Marius	HAW Hamburg, Physik/Biophysik	Master
Kim, Sohee	Universität des Saarlandes, Mechatronik	Promotion
Lehmann, André	FH Wildau, Biosystemtechnik	Bachelor
Lobeda, Peter	FH Wildau, Biosystemtechnik	Bachelor
Maaß, Kirsten	FH Saarbrücken, Mechatronik	Diplom
Mietchen, Daniel	Universität des Saarlandes, Physik und Mechatronik	Promotion
Mundakapadam, Shirin	RWTH Aachen, Biomedizinische Technik	Master
Olbert, Marion	FH Remagen, Biomedizinische Technik	Diplom
Petschnik, Anna	Universität zu Lübeck, Biologie	Master
Rickmann, Christiane	FH Jena, Medizintechnik	Diplom
Steffen, Jenny	Universität Potsdam, Molekularbiologie	Promotion
Steinmetz, Oliver	Universität des Saarlandes, Mechatronik	Promotion
Tagliareni, Fabio	Universität des Saarlandes, Mechatronik	Promotion
Yildirim, Mehmet	HTW Saarbrücken, Elektrotechnik	Diplom

1. Articles in Journal (print or online), peer-reviewed

Department Microsystems/Laser Medicine

BECKER, W., BERGMANN, A., HAUSTEIN, E., PETRASEK, Z., SCHWILLE, P., BISKUP, C., KELBAUSKAS, L., BENNDORF, K., KLÖCKNER, N., ANHUT, T., RIEMANN, I., KÖNIG, K.: „Fluorescence Lifetime Images and Correlation Spectra obtained by Multidimensional Time-correlated Single Photon Counting. *Microscopy Research and Technique*”. 69, 186-195 (2006)

CSAKI, A., GARWE, F., STEINBRÜCK, A., MAUBACH, G., FESTAG, G., WEISE, A., RIEMANN, I., KÖNIG, K., FRITZSCHE, W.: „A Parallel Approach for Sub-wavelength Molecular Surgery using Gene-specific Positioned Metal Nanoparticles as Laser Light Antennas”, (eingereicht)

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EHLERS, A., RIEMANN, I., STARK, M., KÖNIG, K.: „Multiphoton Fluorescence Lifetime Imaging of Human Hair”. *Microscopy Research and Technique*, (in Druck)

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Department Ultrasound

WIKLUND, M., GÜNTHER, C., LEMOR, R. M., JÄGER, M., FUHR, G. R., HERTZ, H. M.: „Ultrasonic standing Wave Manipulation Technology integrated into a Dielectrophoretic Chip”. *Lab Chip*, DOI: 10.1039/b612064b, Germany (2006)

ZININ, P. V., WEISS, E.C., ANASTASIADIS, P., LEMOR, R. M.: “Mechanical Properties of HeLa Cells at Different Stages of Cell Cycle by Time-resolved Acoustic Microscope”. *The Journal of the Acoustical Society of America*, 120(5) 3230 (2006)

Department Medical Engineering & Neuroprosthesis

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Imprint

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Print and Layout:

O/D Druck. Logistik. Datenservice.

Johannes-Gutenberg-Strasse

66564 Ottweiler

