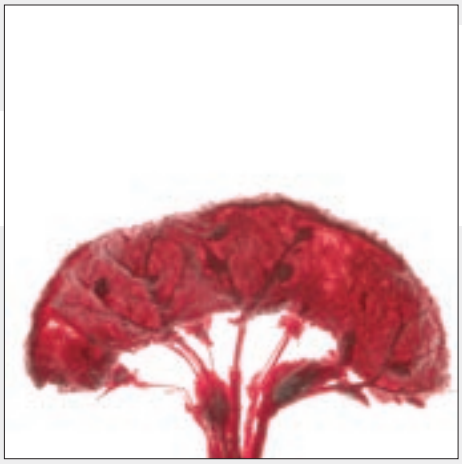
IGB

Fraunhofer Institut
Grenzflächen- und
Bioverfahrenstechnik

Biennial Report 2004 / 2005

2004 2005



Brief profile

Fraunhofer Institute for Interfacial Engineering and Biotechnology
(Fraunhofer-Institut für Grenzflächen- und Bioverfahrenstechnik IGB)
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Director

Prof. Dr. Herwig Brunner
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The Fraunhofer IGB develops and optimizes processes and products in the fields of

Molecular biotechnology for diagnostics, pharma, and fine chemistry:
Research in infectious diseases and drug screening, assay development, biochip technologies (genomics and proteomics), protein expression, fermentation and downstream processing.

Cell diagnostics, autologous transplants, and cell therapy:
Three-dimensional organoid human test systems, biocompatibility testing, 3D autologous transplants, cell sorting and cell therapy, GMP-compliant manufacturing of tissue engineering products.

Functional interfaces for technology and medicine:
Molecularly defined and smart surfaces, ultra-thin layers, biomimetic and biofunctional surfaces, nanobiotechnology, nanoparticles, carbon nanotubes, membranes.

Sustainable bioprocess engineering for industry, urban infrastructure, and the environment:
Reprocessing and conversion of organic raw and waste materials, generation of biogas, wastewater purification and urban water management, production of natural substances (vitamins, neutraceuticals) and energy by microalgae.

In addition to contract R&D, we offer analytical services of reliable and constant quality. The *Deutsche Akkreditierungsstelle Chemie DACH*, an international recognized accreditation body, has certified that analytical methods and test procedures at the Fraunhofer IGB fulfil international quality requirements. In 2003, the Fraunhofer IGB was granted manufacturing authorization for special cell therapy drugs for phase I/II studies and can offer manufacturing capacity in compliance with GMP (Good Manufacturing Practice) guidelines.

Our offerings draw on the outstanding know-how of our staff, presently numbering 140 employees. Over 90 percent are technicians and scientists from the fields of biology, chemistry, physics, and engineering. The interdisciplinary orientation and the integration of the Fraunhofer IGB in excellent research networks ensure scientifically founded results for our customers.

We work with the goal of converting research results into new industrial products and processes. Among other things, our strength lies being able to offer complete solutions from test tube to pilot plant as well as process development and scale-up engineering to industrial dimensions. Among our customers are companies from a variety of industries, local and regional authorities and federal and *Länder* government. The Fraunhofer IGB is also active internationally, especially at a European level.

New technologies for health, the environment and industry

Biennial Report 2004 / 2005

Fraunhofer Institute for
Interfacial Engineering and Biotechnology IGB

Mission Statement

The Fraunhofer-Gesellschaft's philosophy is to emphasize the role of innovation as a kind of motor and transmission belt between basic research and industrial applications. This also holds true for the Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB, resulting in the slogan **"Fraunhofer IGB is helping to create the future"**.

The purpose of this biennial report is to inform our partners in the private and public sectors about our growing technological strength and transforming potential – and of course about our achievements. The year 2004 is marked by the anniversary of ten years' activities under the present leadership. We have overcome the slump in the IT and biotechnology industries, and the confidence and trust placed in us by our commercial partners is manifested by the fact that over 47 percent of our revenues comes directly from industry. In addition, our scientific competence has been affirmed by a substantial number of prizes and awards.

Special emphasis may be given to the fact that our two junior researcher groups could be integrated as independent organizational units, evoking resonance in both the research community and industrial market and proving that our technological achievements are of great interest to industry and may be regarded as the fruits of a successful strategy.

Interfacial engineering technologies – today going by the buzzword "nanotechnology" – have led to quite substantial impacts and acknowledgment in both the scientific community and industry. As a unique selling point, the exploitation of synergies between physical chemistry, polymer chemistry, microbiology and cell biology as realized at the IGB attracts the attention and indeed enthusiasm of our industrial partners. As an example, I would like to cite our success in regioselective functionalization of hollow fiber membranes and our achievements in carbon nanotube technology for medical technology, in collaboration with our internal partner Fraunhofer TEG.

After several years of preparation, our vision of the development and realization of a decentralized urban water and wastewater infrastructure could be set in motion. This is due to support from the Federal Ministry of Education and Research (BMBF) as well as the Baden-Württemberg Ministry of Environmental Affairs and Transportation and partners from industry and communal authorities. For the first time, Fraunhofer IGB is acting as a general contractor responsible for technological as well as financial activities. This is pivotal to coherent project management and undiluted technology transfer.

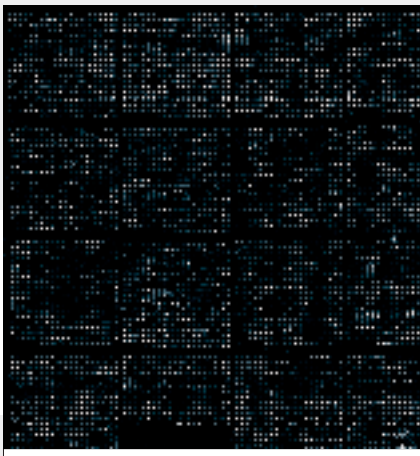
Following approval by the regional commission, our GMP unit for tissue engineering (human cartilage, skin, stem cells) proved very attractive to university hospitals as well as industrial partners, thus promoting our three-dimensional organoid structures for test systems based on human cells and for tissue replacement/autologous transplantation.

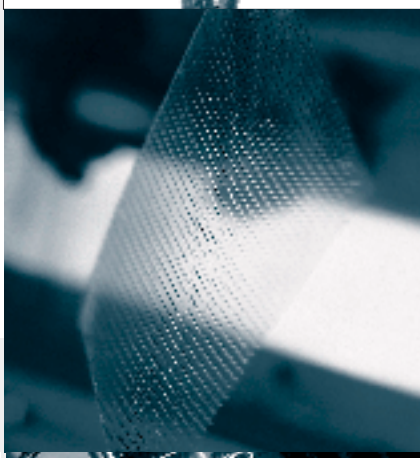
An ever growing number of internal alliances and networks of Fraunhofer institutes enhances our combined efforts according to the value chain, thus creating attractiveness to our customers and offering them one-stop-shop advantages over competitors.

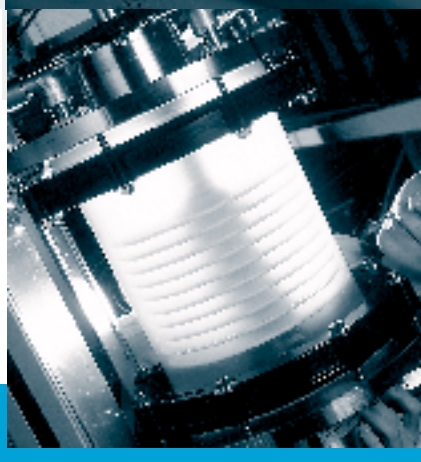
The most valuable token of esteem for our executive team and our staff is acknowledgment by our partners, especially in the form of a continual flow of cooperation projects. It is my pleasure to recognize this and to thank our staff for their enthusiasm and expertise.

Prof. Dr. Herwig Brunner

Content







Research

Development

Services

Profile of the institute

Competencies

Networking

Finances

Research and development (R&D) for the environment, health, and industry

The Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB in Stuttgart develops and optimizes biotechnological processes and products for the environment, health, and technology. In addition to contract R&D we offer our clients services in analytics and advise them on the introduction of novel technologies. Our customers include industrial companies from a variety of sectors as well as municipal, state (*Länder*) and federal authorities.

Application-oriented and interdisciplinary

Our abiding aim is the direct translation of research results into cost-effective and profitable processes and products in industrial practice. We offer our clients the enormous commercial and ecological potential of our technologies, especially environmental technology and biotechnology – and do not shirk the ethical responsibility linked with their use.

More than ever, the success of new products and processes hinges on interdisciplinary and constructive cooperation between science and engineering. At the Fraunhofer IGB, scientists from diverse fields such as chemistry, physics, biology and engineering work together. Small and medium-sized enterprises (SMEs) in particular profit from the multidisciplinary potential of our Institute.

Our strength lies in the provision of complete solutions, from the test tube to pilot plants under industrial conditions, as documented in numerous cases of continual cooperation with our clients.

Competencies and areas of business

The Fraunhofer IGB offers its clients scientific and technological competencies in the following research fields:

- Interfacial engineering and material sciences
- Environmental biotechnology and bioprocess engineering
- Molecular biotechnology
- Cell systems and tissue engineering

Our two junior research groups investigating automated protein screening systems and biomimetic interfaces, respectively, which had been funded by secured knock-on financing over a period of five and a half years, since mid 2004 have augmented our core activities as organizationally independent research units with their own industrial projects.

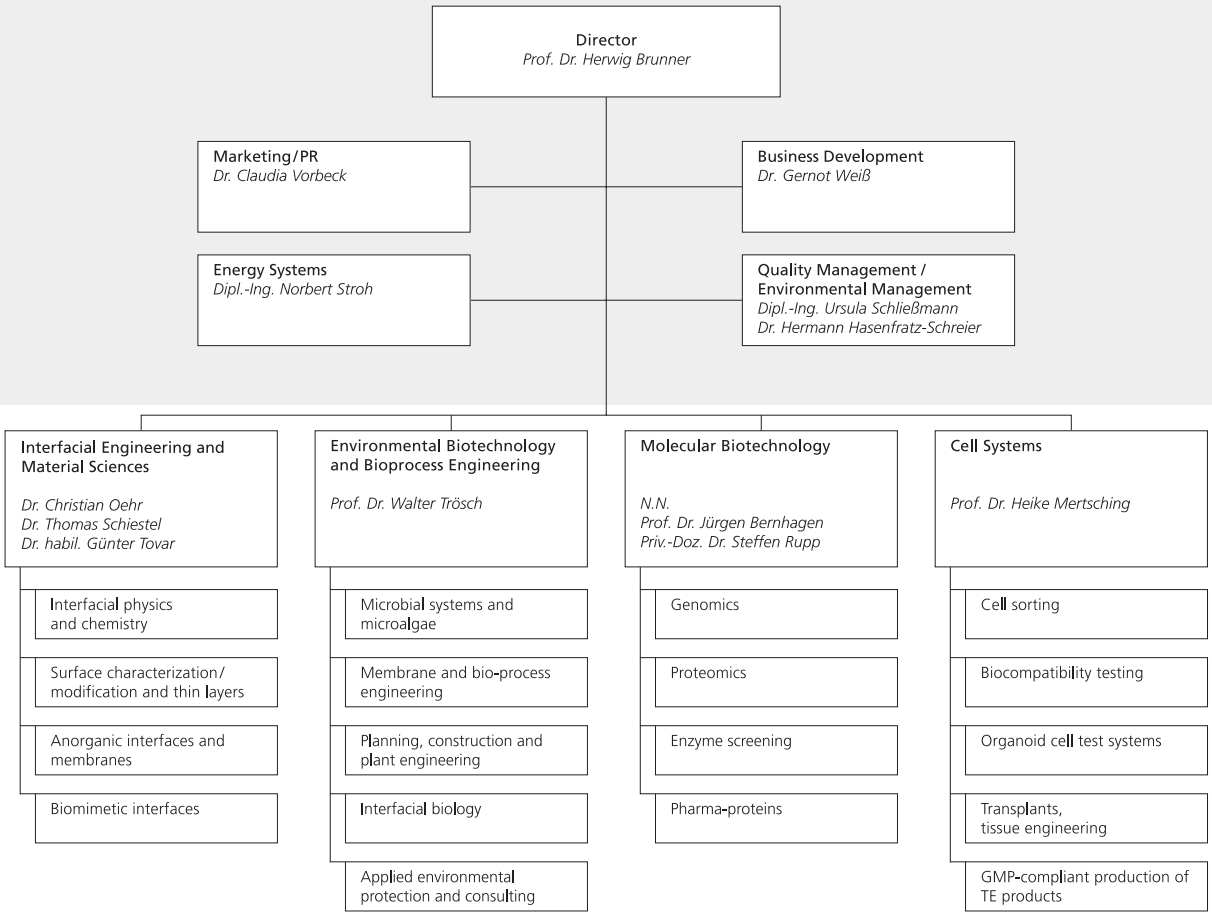
With our know-how we carry out R&D in the following areas of business:

- Molecular biotechnology for diagnostics, pharma, and fine chemistry
- Cell diagnostics, autologous transplants, and cell therapy
- Functional interfaces for technology and medicine
- Sustainable bioprocess engineering for industry, urban infrastructure, and the environment

Several service centers complete the R&D offer of the Fraunhofer IGB (see page 11).

Target industries

- Chemical, pharmaceutical, and cosmetic industries
- Medical technology
- Food and beverage industries
- Textile and leather industries
- Paper and nonwovens industries
- Printing plants
- Metal processing, galvanics
- Automotive industries and their suppliers
- Plant engineering
- Membrane manufacturers
- Air-conditioning industries
- Construction and remediation enterprises
- Local authorities, state (*Länder*), and federal government



What we offer: Research – development – education – consultancy

Our R&D services range from scientific and technical basic research to the development of new applications from laboratory up to pilot plant scale.

On behalf of our customers we develop new products and processes and optimize existing ones, in order, for example, to tap new applications.

At the Fraunhofer IGB we plan and construct pilot plants, carry out testing, and support you transferring them to industrial use.

We offer training for executives, engineers, and scientists through seminars and workshops at Fraunhofer IGB or at the client's premises.

We provide consultancy in the fields of molecular and cell biotechnology, environmental biotechnology and bioengineering, membrane technology and interfacial engineering as well as in the field of hazardous waste disposal.

We carry out patent and market surveys, feasibility studies, and analyses of new processes and products with respect to realization, risks, competitors, and commercial viability.

We offer consultancy in technology planning as well as assistance with patent issues and financing strategies.

Infrastructure

The Fraunhofer IGB provides over 5,000 square meters of laboratories, technical facilities and offices for its 140-strong personnel. In addition, the Fraunhofer IGB is equipped with nationally significant, highly modern central storage facilities for chemicals and hazardous compounds. Our central service for patent research, which has access to international literature and patent databases, is available for internal and external inquiries.

Laboratories and technical facilities

- Plasma installations for cleaning, sterilization, pre-treatment, activation, modification and coating of surfaces
- Electron microscopes (TEM, SEM)
- Probe microscopes (AFM, STM)
- Spectrometers for analysis of surfaces and thin layers
- Plants for the production of membranes and membrane modules
- Membrane testing plants and facilities for membrane application
- Molecular biotechnology and cell culture laboratories up to the biological safety level BL2, and pilot scale production of recombinant proteins
- GMP unit for the production of cell-based therapeutics up to the biological safety level BL2 (cleanrooms, separate quality control area, storage facilities)
- Microarray facility
- Bioreactors of various types and sizes (laboratory, technical and pilot scale)
- Biotechnical pilot plants (applications for environmental and sterile technology)
- Isotope laboratory
- Laboratories dedicated to chemical and biochemical analysis, disposing of a comprehensive range of chromatographic, spectroscopic and electrophoretic equipment

Accreditation

In order to satisfy the requirements and needs of our customers as fully as possible, the Fraunhofer IGB established a quality management system at various of its laboratories. At these reference laboratories, inspectors from an international recognized accreditation body evaluated the technical competence of our staff in executing particular test procedures as well as the measuring and testing equipment itself, and the quality management system introduced.
The Fraunhofer IGB obtained accreditation according to DIN EN ISO/IEC 17025 for the following analytical methods and test procedures:

- High performance liquid chromatography (HPLC)
- Ion chromatography (IC)
- Size exclusion chromotography (SEC)
- Gas chromatography (GC, GC/MS)
- Electron spectroscopy for chemical analysis (ESCA)

The accreditation guarantees the quality of our test methods, which can also be adapted specifically for a customer's needs if no standard methods are available.

GMP unit and manufacturing authorization for cell preparations

The last few years have seen the construction of a GMP unit which satisfies all the conditions for the manufacturing of investigational medicinal products at the Fraunhofer IGB. In 2003, the IGB was granted manufacturing authorization for aseptically produced autologous chondrocyte transplants. The GMP unit is currently used for the collaborative development and manufacturing of clinical test material for cell, gene and tissue engineering therapeutics (see page 18).

Service centers

GMP services:
Manufacturing of cell-based therapeutics, tissue engineering products, and investigational medicinal products according to the EU guidelines of current Good Manufacturing Practice

Special physico-chemical analytical services:
Quality control – Food analysis – Trace analysis – Analysis of residues – Environmental analytics

Biochemical and molecular biological analytics:
Services from protein to gene, DNA- and protein-biochips

Surface analytics:
Characterization of chemical, physical, and morphological properties of surfaces, thin layers, powders, and liquids

Environmental consultancy for companies:
Waste – Hazardous compounds – Wastewater – Environmental management

For detailed information, please request our special Service Brochures (see page 95) or take a look at:
www.igb.fraunhofer.de/www/service

Competencies and contacts

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Steering committee of the institute

The role of an institute's steering committee is to advise the Director and participate in decision-making processes concerning the research and business politics of the institute.

Members in 2004:

Prof. Dr. Herwig Brunner,
Staatl. Gepr. Lebensmittel-Chem. Gabriele Beck-Schwadorf,
Prof. Dr. Jürgen Bernhagen,
Dr. Hans-Georg Eckert (until August 31, 2004),
Ass. Ulrich Laitenberger,
Prof. Dr. Heike Mertsching (since September 16, 2004),
Dr. Christian Oehr,
Priv.-Doz. Dr. Steffen Rupp,
Dr. Thomas Schiestel,
Dr.-Ing. Werner Sternad,
Dr. habil. Günter Tovar,
Dr. Iris Trick,
Prof. Dr. Walter Trösch,
Dr. Ulrike Vettel,
Dr. Uwe Vohrer

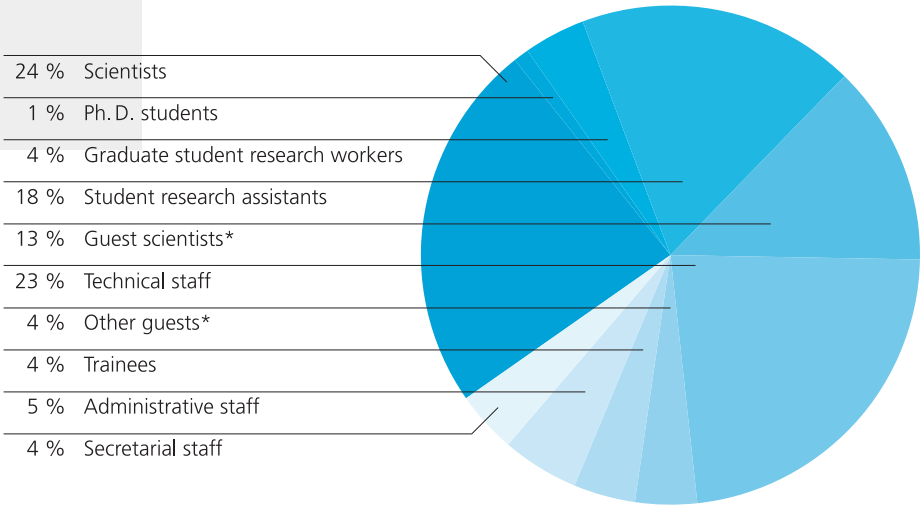
Representative figures

Personnel

At the end of 2004, the Fraunhofer IGB had a staff of 140, with over 90 percent employed in scientific or technical posts. Women made up 47 percent of the total.

Staff members	Number
Scientists	34
Ph. D. students	1
Graduate student research workers	6
Student research assistants	25
Guest scientists*	18
Technical staff	32
Other guests*	6
Trainees	5
Administrative staff	7
Secretarial staff	6
	140

* including IGVT personnel based at the University of Stuttgart



Budget

The financial structure differentiates between the operational budget, including personnel and non-personnel costs as well as corresponding revenues, and the investment budget.

The total budget for 2004 amounted to 9.6 million euros, of which 8.5 million euros were allocated to the operational budget (4.4 million euros on personnel costs, 4.1 million euros on non-personnel costs). 1.1 million euros were dedicated to investment.

Governmental funding covers 24.7 percent of the Institute's operational budget. 66.6 percent of the Institute's revenue is generated by contract research projects acquired directly from industry.

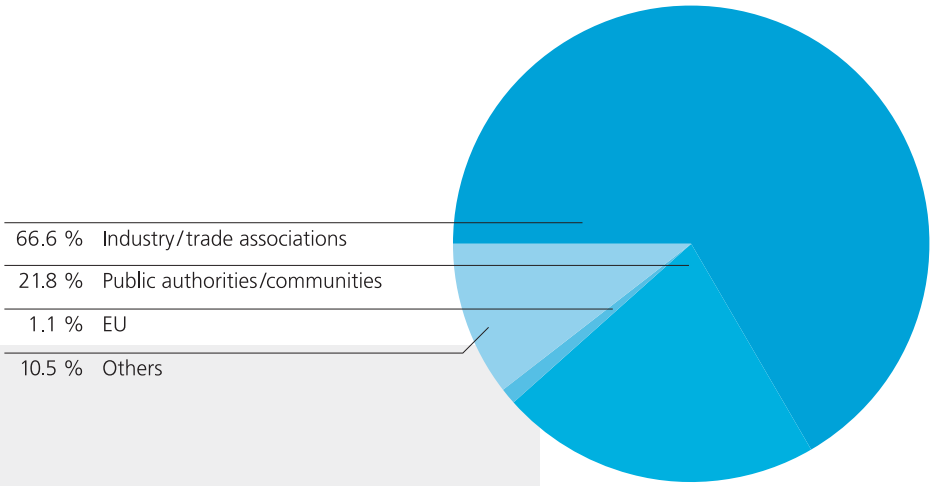


Figure 1: Revenue from contract research.

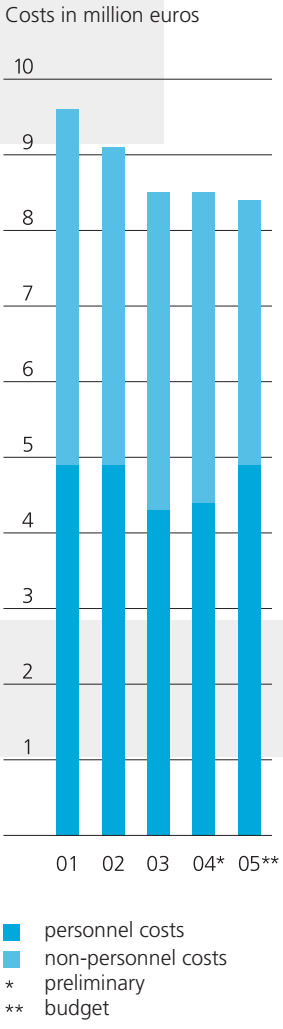


Figure 2: Personnel- and non-personnel costs.

Networking with science, private enterprise and public bodies

The integration of the Fraunhofer IGB in excellent research networks assures future-shaping, breakthrough scientific results for our customers. Long-standing and successful cooperation with various universities and Max Planck institutes in Stuttgart and at other locations in Germany guarantee our scientific credentials. Cooperation with other Fraunhofer institutes supplements our own competences and enables us to exploit synergies in developing new solutions for the needs of industry.

Cooperation with universities

Basic research is a must. Therefore, the Fraunhofer IGB maintains close contacts to neighboring universities. The director of Fraunhofer IGB as well as several heads of department and group managers have "habilitated" as university professors, attained postdoctoral lectureship status or otherwise carried out the duties of a university professor:

- Prof. Dr. Herwig Brunner,
  Institute for Interfacial Engineering, University of Stuttgart
- Prof. Dr. Jürgen Bernhagen,
  University Hospital, RWTH Aachen
- Prof. Dr. Walter Trösch,
  Professor for Biotechnology, University of Hohenheim
- Priv.-Doz. Dr. Steffen Rupp,
  Faculty of Chemistry, University of Stuttgart
- Dr. habil. Günter Tovar,
  Faculty of Chemistry, University of Stuttgart

Institute for Interfacial Engineering (IGVT)

The Institute for Interfacial Engineering (IGVT) is part of the department of "Process Engineering/ Technical Cybernetics" in the Faculty of Mechanical Engineering, at the University of Stuttgart and is under the direction of Prof. Dr. techn. Herwig Brunner. The IGVT is housed in rooms of the Fraunhofer IGB, thus facilitating close and efficient collaboration between both institutes.

IGVT's educational mission is to train a new generation of academics with an engineering and scientific take on biotechnology and biomedicine. This is realized through the study programs "Technical Biology" and "Process Engineering" as well as the graduate courses "Biomedical Process Engineering" and "Bioengineering".

The main research fields of the interdisciplinary team are the molecularly defined design and characterization of surfaces of organic, inorganic, or biological origin as well as of hybrid materials. An additional focus is laid on the development and optimization of interface-dominated processes in membrane technology and biotechnology, including the chemical, biochemical, and molecular biological fundamentals necessary for this.

Chemical and biochemical-nanotechnological methods for surface functionalization are, in detail:

- Synthesis of nanostructured, molecularly imprinted polymeric materials
- Synthesis of polymeric nanoparticles for bioconjugation (e. g. surfmers) by emulsion polymerization
- Nanoparticles for molecular recognition and as carrier systems for proteins
- Synthesis of molecular precursors for surface functionalization
- Self-assembled monolayers for molecular recognition or for anti-fouling surfaces
- Affinity MALDI-TOF mass spectrometry, microcalorimetry
- Development of system components for micro- and nanobiotechnology
- Biofunctionalized and biomimetic materials

In addition, investigations are carried out on pharmaceutically relevant peptides and proteins with respect to their ability to be functionalized on substrate surfaces. Currently, the group's research focus is on the biochemistry of cytokines. These are synthesized biologically in bacterial or eucaryotic cells by recombinant methods and isolated by various state-of-the-art purification procedures. Molecular targets of interest are the cytokine MIF (macrophage migration inhibitory factor), the signalling factor Jab1, amyloid peptides and proteins such as IAPP and Aβ, as well as several receptor and signal proteins. The specific biofunctionalization of technical and biomimetic interfaces with the biomolecules mentioned above aims on one hand towards the development of biosensors and biochips, on the other hand towards the elucidation of protein/protein interactions or binding effects and molecular signal transduction pathways, thus opening up the therapeutic potential of those biomolecules.

Contacts

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Personnel structure of the IGVT

Scientists	9
Ph. D. students	6
Student research assistants	2
Technical staff	3
	20

31.12.2004

Governing Board of the Fraunhofer IGB

The individual Fraunhofer institutes are advised by Governing Boards whose members are drawn from industry, public authorities, and the scientific community.

Members of the Fraunhofer IGB Governing Board in the reporting year 2004 were:

- Dr. Hans-Georg Batz
  ArteBioConsulting
- Prof. Dr. Armin Fiechter
  Sigriswil, Switzerland
- MinR Gerd Heitmann
  Ministry of Economic Affairs of the State of Baden-Württemberg
- Prof. Dr. Dieter Jahn (Chair)
  BASF AG
- MinDirig Dr. Heribert Knorr
  Ministry of Science, Research and the Arts of the State of Baden-Württemberg
- Prof. Dr. Klaus Pfizenmaier
  University of Stuttgart
- Prof. Dr. Ralf Riedel
  Technical University Darmstadt
- Dipl.-Ing. Otmar Schön
  HYDAC Technology GmbH
- MinDirig Dr. Wolfgang Stöffler
  German Federal Ministry of Education and Research
- Prof. Dr. Rolf G. Werner
  Boehringer Ingelheim Pharma KG

Scientific and Technical Council

The Scientific and Technical Council supports and advises the various organs of the Fraunhofer-Gesellschaft in and on scientific and technical matters of fundamental importance. Its members are composed of the institutes' directors as well as one elected scientific-technical representative from each institute.

Members from the Fraunhofer IGB:
- Prof. Dr. H. Brunner (by virtue of his office)
- Dr. U. Vohrer (elected)

From practical work:
Euroderm aims to produce skin transplants at the Fraunhofer IGB

In the future, Leipzig's euroderm GmbH will manufacture its skin transplants in Stuttgart. The management has been searching throughout Germany for suitable clean rooms and production conditions and found them at the Fraunhofer Institute for Interfacial Engineering and Biotechnology in Stuttgart. The validation of the manufacturing process for producing autologous skin transplants EpiDex™ from adult hair root stem cells at the Fraunhofer IGB has now been completed, and an application for manufacturing authorization has been filed to the district administration in Tübingen.

GMP-compliant manufacturing area

The Fraunhofer IGB runs an enclosed clean room facility about 150 m^2 in size with separate units for production, quality control and storage, which fulfill the GMP requirements. In September 2003, the IGB was granted a manufacturing authorization for autologous chondrocyte transplants in accordance with Article 13 of the German Drug Law.

Contract manufacturing or manufacturing in cooperation

The Fraunhofer IGB offers cooperation partners a validation service for manufacturing processes and the production of investigational medicinal products on a pilot scale, with IGB acting as a contract manufacturer according to the German Drug Law. Alternatively, the Institute offers biotech companies the possibility of producing their products at IGB after grant of an own manufacturing authorization. This form of cooperation exists at present with euroderm.

Fraunhofer IGB had a talk with euroderm's Director Dr. Andreas Emmendörffer.

IGB: Which road led the euroderm company from Leipzig here to Stuttgart?

Emmendörffer: There are several reasons that we arrived here in the STERN bio-region. Firstly, we were looking for a Class B clean room, in which to produce our skin transplants in compliance with GMP guidelines. That wasn't possible in Leipzig and it would have taken too long if we'd wanted to build the necessary infrastructure there ourselves. We looked at various locations throughout Germany, such as Berlin, Freiburg, Würzburg, Stuttgart and Tübingen.

IGB: And what criteria played a role when you chose IGB?

Emmendörffer: It was simply an initial impression that things happen much more quickly and efficiently here than elsewhere. Another decisive factor was that here at IGB, the skin itself is not a new subject, and IGB already has experience with cell cultures and skin cultures, which means that products can be brought onto the market without excessively high additional fixed personnel costs.

IGB: Does this mean that we can meet your requirements accordingly?

Emmendörffer: That was another reason. We need our own manufacturing authorization for our investors. This means that we cannot produce on the basis of the contract manufacturing model. And so besides the question of cost and the

Manufacture of tissue engineering products in compliance with GMP guidelines
In tissue engineering (TE), primary cells are used to regenerate tissues and organs (e.g. cartilage, skin). The manufacture of TE products and of products for cell therapy is regulated by different legal directives and guidelines. The GMP (Good Manufacturing Practices) directives laid down in Article 54 of the German Drug Law in the form of an operative regulation always apply here.

know-how, an important criterion for us was: Where can we obtain our own manufacturing authorization so that we can maintain a degree of control over the process, i. e. that we are the pharmaceutical manufacturer. Fraunhofer IGB was the most flexible in this context.

IGB: What arrangements did you make, and how is knowledge transferred?

Emmendörffer: We concluded a framework contract with Fraunhofer IGB to produce the skin transplants. The validation of the production process, which has now been completed, was carried out on the basis of this contract. We have used these data to apply to the district administration in Tübingen for the manufacturing authorization. It was required that the production and control management had to be performed by Fraunhofer IGB. Accordingly, we fall back on IGB staff for this. From our point of view, the model was conceived so that we also have a contract with the IGB staff at the same time, i. e. they are employed by both Fraunhofer IGB and euroderm, so that there is no loss of information when production is approved.

IGB: How was IGB able to support you in making the application?

Emmendörffer: We received support in all discussions with the district administration. Those people knew that there was prior experience here. This means that there was a basis of trust, making things easier. And on the basis of this experience, we were then able to very quickly go through the SOPs, the corresponding standard operation protocols, with Dr. Anadere (Quality Assurance) for the entire validation. Mr. Schandar, as the Head of Production at IGB, did most of the practical work himself, because he knows how to handle an *in vitro* skin. This saved an enormous amount of time. This means that we received very good support with regard to both the approvals and the validation, which was also performed successfully and without complications thanks to the efforts of Dr. Vettel as Head of Quality Control.

IGB: And as far as equipment is concerned?

Emmendörffer: It was of course also advantageous that we did not have to construct or adapt much concerning the equipment. The system was more or less exactly tailored to our product.

IGB: Is the capacity sufficient? And could the collaboration also proceed?

Emmendörffer: For the next one or two years, we will be aiming to produce between 5 and 20 transplants per month. The system is certainly sufficient for this. If turnover then increases, we will have to consider whether to build a separate production facility. And as far as continued cooperation is concerned: Of course, we are considering joint research projects in order to further develop our products. It is also advantageous for us here that application-orientated research is not an alien concept to IGB. Right from the start, a Fraunhofer institute has in mind the market application and the work is being done accordingly.

IGB: Dr. Emmendörffer, thank you for the interview.

Priv.-Doz. Dr. Andreas Emmendörffer,
born 1959, studied medicine at the Medical University of Hannover. After his admission to the medical practice as a doctor, he entered the field of applied research at the former Fraunhofer Institute for Toxicology and Aerosol Research ITA. In 1990 he gained his doctorate and in 1997 built up *KryoBank*. In 1998 he attained post-doctoral lectureship status. As an experienced Medical Director of the company ZYO BIOTECH GmbH, he joined Modex Therapeutics SA in Leipzig and Lausanne, Switzerland in 2001. Since May 2002, Emmendörffer has been a partner and director of euroderm GmbH in Leipzig.
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euroderm
biotech & aesthetics

The Leipzig-based biotech company researches, develops and produces innovative therapies for treating chronic wounds and also human skin models for *in vitro* testing of pharmaceutical, chemical and cosmetic preparations. Euroderm GmbH was established in 2002 from Modex Therapeutics and now employs 12 people. Switzerland is an important market, because autologous skin transplants are already recognized here as a form of treatment reimbursed by social medical insurance.
www.euroderm-biotech.de

Fraunhofer IGB international

ACOSIC
Freshness indicator for food packagings
If a food is exposed to oxygen in its packaging, it spoils more quickly. Modern film packagings therefore seal the fresh product as airtight as possible and have oxygen-absorbers, referred to as scavengers. These packagings developed by the cooperation project ACOSIC are intended to improve the quality of the food and make it visible to the customer: Color indicators show the increase in oxygen content inside the packaging.

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CRAFT: NOVATEX
In this EU project, Fraunhofer IGB is developing processes for the plasma-supported finishing of textiles. The emphasis here is on hydrophobic finishing, which improves both water repellence and soiling behaviour. Another focus is on optimizing wettability (hydrophilicity), which allows improved printability or optimized dye uptake.

Collective: NANOMED
The aim of this 15-partner project is to develop actuators (artificial muscles) based on bucky paper. The task of IGB is to characterize the carbon nanotubes raw material and to optimize the bucky paper made from these carbon nanotubes (see page 48).

STREP: DESYGN-IT
This 14-partner EU project conducts research into different aspects of carbon nanotubes, from manufacture through to various applications. Here, Fraunhofer IGB works in, among others, the work package "Functionalization of carbon nanotubes". The aim is to investigate the possibilities of plasma technology.

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Marie-Curie Training Network: CanTrain
One of the most prominent tasks in the field of life sciences for the years ahead is the validation of many potential pharmaceutical targets and the identification of therapeutic drugs. In this EU project, young scientists from various countries are being brought together in order to learn the latest methods in drug screening and development, from target identification to its validation and from assay development to drug screening.

CRAFT: Purestream
In this consortium consisting of seven small and medium-sized enterprises (SMEs) and two research institutes, Fraunhofer IGB is developing new types of biosensors for the effective control of production processes in the manufacture of recombinant therapeutics.

Co-operative Research Project: POSBEADD
Fraunhofer IGB is involved in the development of new systems for the targeted application of medicines to combat leiomyomas, benign tumors of the smooth muscles (in this case the uterus). The consortium consists of six SMEs and three research institutes, which are jointly developing these new technologies within 25 months.

USA: Identification of new enzyme activities
A project with the American company GlycoFi to identify highly-specific enzymes for the modification of pharmaceutical therapeutics has been successful completed. This project employed IGB's established metagenomic genetic libraries.

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GlycoFi
Next Generation Biotherapeutics

Fraunhofer World Bank Project

In 2002, the Bavarian State Ministry of Economics, Infrastructure, Transport and Technology and the *Fraunhofer-Gesellschaft* started a project aimed at enabling medium-sized companies to apply for projects tendered by the World Bank or other international banks. Fraunhofer IGB is involved in the organization and coordinates the subject groups "Water/Wastewater/Waste", in which approximately 30 companies (engineering and consultancy offices, suppliers of systems, system components, apparatus and fixtures, sewage works operators) are participants. Fraunhofer IGB analyses and preselects the relevant procurement notices, informs the companies and coordinates the working meetings for planning joint actions. At the present time, projects are ongoing in Hungary, Croatia, Serbia and Montenegro, Egypt, Iran, Russia and China.

Contact
Dr. Dieter Bryniok (see below)

Modern water management in Bosnia-Herzegovina

Together with German, British and Bosnian partners, Fraunhofer IGB is planning to set up two competence centers for water and sewage water management in Bosnia-Herzegovina. A pilot, demonstration and training plant together with the associated infrastructure are to be set up in two communities, at which local technicians, engineers and representatives from the local authorities will receive practical training in all aspects of water management. The emphasis will be on economical, modular and decentralized solutions for the reuse of treated sewage water as service water and for irrigation. Eleven communities have been assessed in a BMBF-financed pilot project. An application for EU support in financing the competence center has now been lodged on behalf of two of these communities.

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Aleksandrovac near Laktaši is one of the selected communities where a regional competence center for water and wastewater management shall be set up.

Figure left: Town hall of Berkovići, the other community for a regional competence center for water and wastewater management.

Brazil: Decentralized water management

In March 2004, IGB's Director Prof. Brunner was for the first time able to welcome the new President of the *Universidade Metodista de Piracicaba* (UNIMEP), Prof. Gustavo Jacques Dias Alvim, to IGB. The German industrial partners involved in the decentralized water management model project commenced in 2004 (see page 70) had the opportunity to introduce themselves at the jointly organized 4th international workshop "*Alternativas em tratamento de agua e esgoto*".

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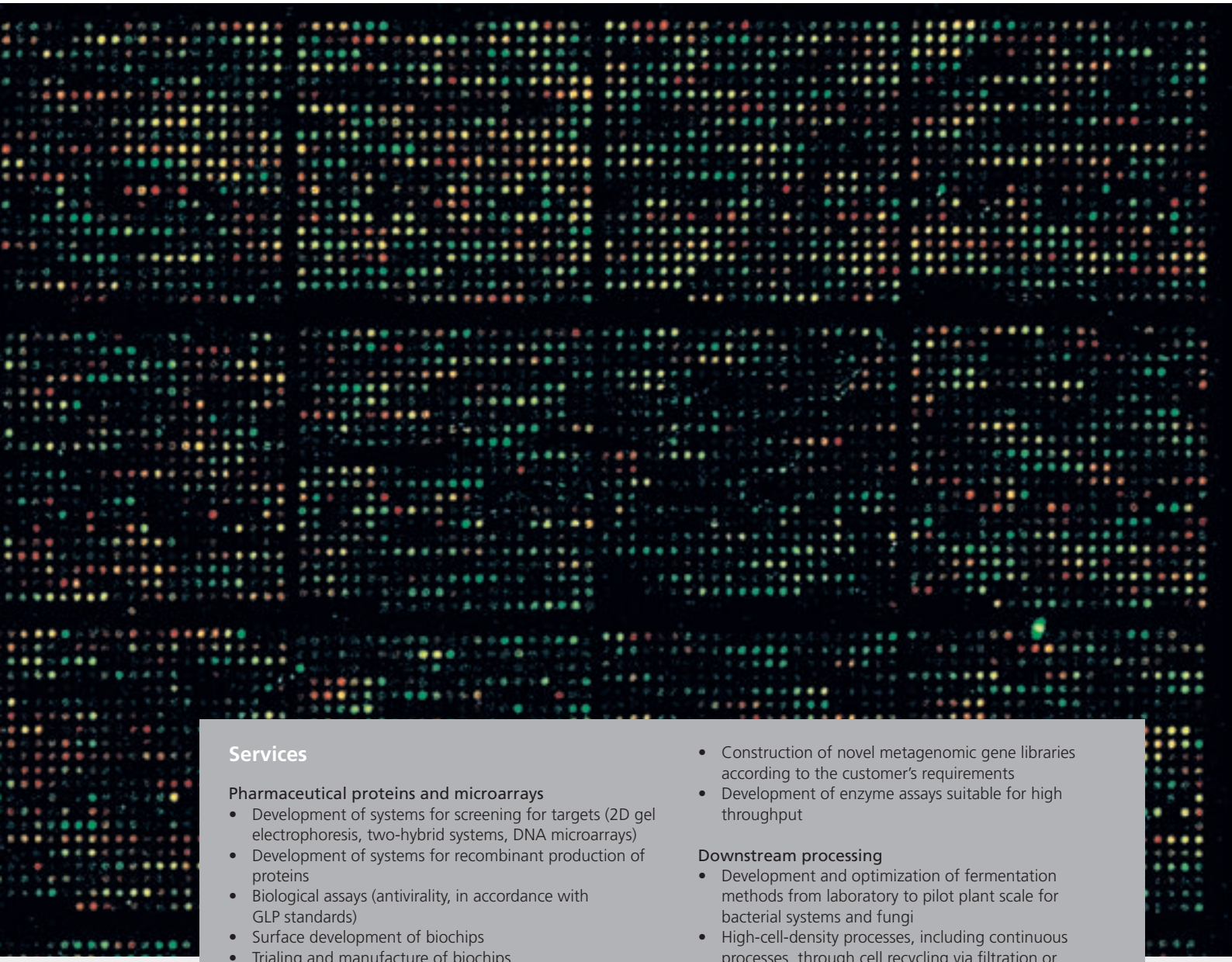
Happy faces at the meeting with the new mayor of Piracicaba, Professor Barjas Negri. From left: Professor Almir de Souza Maia, General Director, Professor Gustavo Alvim, President of UNIMEP, Professor Barjas Negri, Mayor of Piracicaba, Dr. Iris Trick, Fraunhofer IGB, Dr. Christian Wilhelm, Managing Director of Geoterra, Dr.-Ing. Werner Sternad, Fraunhofer IGB, Eduard Seifer and Karl-Heinz Walz, both Managing Directors of MAXX GmbH.

The German-Brazilian cooperation between Fraunhofer IGB and UNIMEP is characterized by a friendly atmosphere. Here, IGB's director Professor Herwig Brunner welcomes Professor Gustavo Jacques Dias Alvim, president of UNIMEP, at the Fraunhofer IGB in Stuttgart.

Figure below: The sewage plant of Široki Brijeg has been built before the war but has never been put into operation.

Selected R&D projects

Molecular biotechnology for diagnostics, pharma, and fine chemistry



Services

Pharmaceutical proteins and microarrays

- Development of systems for screening for targets (2D gel electrophoresis, two-hybrid systems, DNA microarrays)
- Development of systems for recombinant production of proteins
- Biological assays (antivirality, in accordance with GLP standards)
- Surface development of biochips
- Trialing and manufacture of biochips (DNA and protein microarrays)

Enzyme screening

- Exclusive screening of available or novel metagenomic gene libraries for desired enzymatic activities
- Subcloning, sequencing, expression, and characterization of the enzymes identified
- Construction of novel metagenomic gene libraries according to the customer's requirements
- Development of enzyme assays suitable for high throughput

Downstream processing

- Development and optimization of fermentation methods from laboratory to pilot plant scale for bacterial systems and fungi
- High-cell-density processes, including continuous processes, through cell recycling via filtration or immobilization
- Development of techniques for producing, isolating, separating, and purifying biotechnology products and natural compounds
- Scale-up of biotechnology processes
- Contract fermentation up to 300 liters (non-GMP, but with detailed documentation)

Molecular biotechnology has opened up entirely new possibilities in the detection and treatment of diseases. The knowledge gained from genomics and proteomics research can be used to develop specific therapies, or even personalized medicine. Since the therapy will be directed against a highly specific molecular target molecule, it is generally free of side effects to the patient. Modern, high-efficiency screening technologies, however, can be used not only in the search for active ingredients or targets but also, for example, in the identification of new enzyme activities.

The Fraunhofer IGB's research and development in this field is concentrated on the following key topics:

- In the case of target screening the focus is on the development of **new antimycotics**, especially against *Candida albicans.* In addition to **research in infectious diseases and drug screening**, new **screening assays** for drug discovery and development are designed.
- Studies on the development of pharma proteins in inflammatory processes are concentrated on the **cytokine MIF** (macrophage migration inhibitory factor) and its receptors.
- The Fraunhofer IGB has a well established microarray facility that offers assistance for all kinds of microarray applications, including diagnostics or target screening. The **biochip technologies** at the IGB embrace both DNA (genomics/transcriptomics) and proteins (proteomics).
- In the search for as yet unknown **enzymes**, the potential of microorganisms that are difficult if not impossible to cultivate is being mined by means of DNA isolated from environmental samples (metagenomic libraries).
- Moreover, the Fraunhofer IGB provides many years of experience, proven through numerous cooperative projects with industry, in **fermentation**, **downstream processing**, and **scale-up**.

In the field of "Molecular biotechnology for diagnostics, pharma, and fine chemistry" therefore, the Fraunhofer IGB provides new products and processes for the clinician and is developing new cross-sectional technologies – underpinned in each case by its own patents. The unit is also able to offer services, such as analysis in molecular biology and biochemistry, and a microarray and proteomics service.

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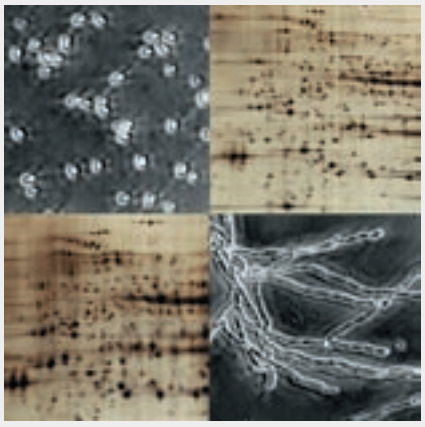

Figure 1: Cell morphology and protein pattern of pathogenic (top) and nonpathogenic (bottom) strains of the yeast *Candida albicans*. Shown for each are the light micrograph of the cells and the associated protein pattern by 2D gel electrophoresis.

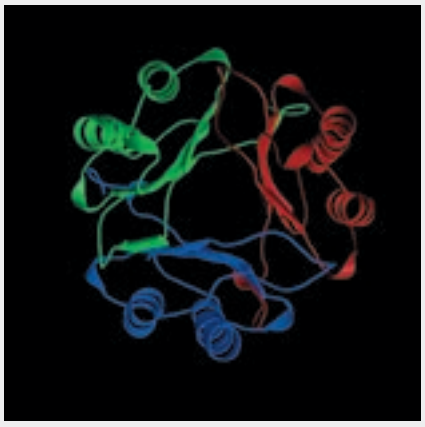

Figure 2: Crystal structure of human MIF at 2.6 Å.

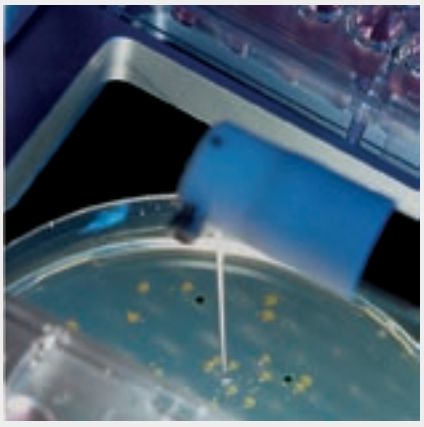

Figure 3: A picking robot transfers cells from colonies to agar plates in ordered gene libraries.

Left-hand page: DNA microarray for genome-wide transcription profiling of a human pathogen, the fungus *Candida albicans*. The chip represents 7,200 different genes. The image shows the signal correspondence between labeled cDNAs of the yeast form (green) and the hyphal form (red). Switching between these two growth forms is essential for the virulence of the fungus.

Cell wall proteome analyses on human-pathogenic microorganisms

A tough nut to crack

In contrast to mammalian cells, microorganisms such as yeasts possess a cell wall. This cell wall consists of a complex network of sugar polymers and surrounds the cell like a shell (Figure 1). This shell is extremely robust and gives the cell high mechanical stability.

In the case of human-pathogenic fungi, such as *Candida albicans*, the cell wall has not only this protective function but also a leading role in attaching the cell to the tissue of the infected host. Attachment to the host tissue represents a central part of infections with *C. albicans* and is therefore essential for the virulence of this fungus. So that *C. albicans* can adhere effectively, the cell wall is additionally equipped with certain proteins, known as adhesins, which interact directly with the surfaces of host cells. Identifying and analyzing such cell wall proteins, however, is often difficult, since many of these proteins are covalently linked to the cell wall and, moreover, are often extensively modified by glycosylation. This makes them hard to analyze via conventional methods of protein biochemistry.
Within the "Genomics, Proteomics, Screening (GPS)" group at the Fraunhofer IGB, therefore, an innovative technique has been developed for fragmenting and solubilizing cell wall proteins in order to analyze them qualitatively as well as quantitatively.

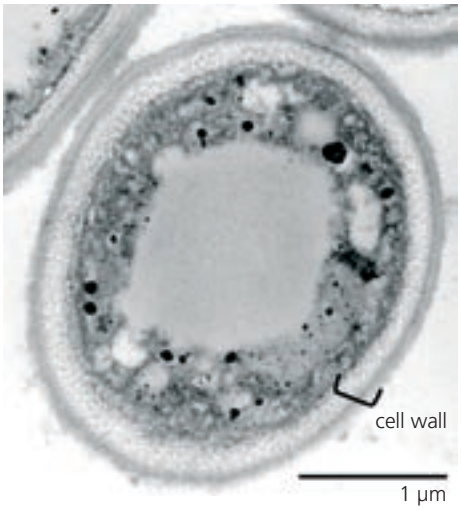

Figure 1: Cross section through a hypha of *Candida albicans*, an invasive growth form of the human-pathogenic yeast (transmission electron microscopy).

The technique

The technical difficulties outlined above make it necessary to adopt a special approach to the qualitative and quantitative analysis of cell wall proteins. To this end, following mechanical disruption, the cell walls are isolated by centrifugation and soluble proteins with nonspecific adhesion are extracted by means of stringent washing steps. Subsequently the cell wall is subjected to a proteolytic digestion. As a result, nonglycosylated domains of the cell wall proteins, which are accessible for enzymes, are solubilized (Figure 2). The resulting peptide mixtures can then be fractionated and analyzed by means of two-dimensional gel electrophoresis and mass spectrometry.
By comparison of the two-dimensional peptide patterns obtained from different growth forms it is thereby possible, for example, to detect the proteins which are expressed exclusively in the hyphal cell wall of *C. albicans* (Figure 3). For subsequent protein identification, the respective spots are isolated and, using mass-spectrometric methods (MALDI-TOF), appropriate mass spectra are generated. The proteins are finally identified by searching databases using these mass spectrometry data.

Proteolytic digestion of hyphal cell walls from *C. albicans*, using the endoproteinase Glu-C, allowed identification, among others, of the chitinase Cht2p and the agglutinin-like cell wall protein Als3p, both of which had already been described, as covalently linked cell wall proteins. In further studies, four different cell wall proteins were identified. On the basis of database analyses,

however, a larger number (> 100) of covalently linked proteins is expected in the cell wall of *C. albicans*. Therefore, the technique will be developed further, concentrating on the identification of surface receptors which are difficult to access or are expressed at low levels.

One technique, many applications

A key advantage of the technique developed at the Fraunhofer IGB is that it can be used independently of the organism under investigation. For a host of different organisms which likewise possess cell walls, such as other fungi, plants, and prokaryotes, for example, there are now new opportunities for carrying out qualitative and quantitative expression analyses of surface receptors at the posttranslational level. Analyzing the surface receptors by conventional methods of protein biochemistry produces only inadequate results.

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Reference

Kai Sohn, Jochen Schwenk, Constantin Urban, Johannes Lechner, Michael Schweikert and Steffen Rupp:
Getting in touch with *Candida albicans*: the cell wall of a fungal pathogen
International Journal of Antimicrobial Agents (in press)

Awards

Hugo Geiger Prize 2004:
New approaches to identifying potential virulence factors in *Candida albicans*.
(Jochen Schwenk)

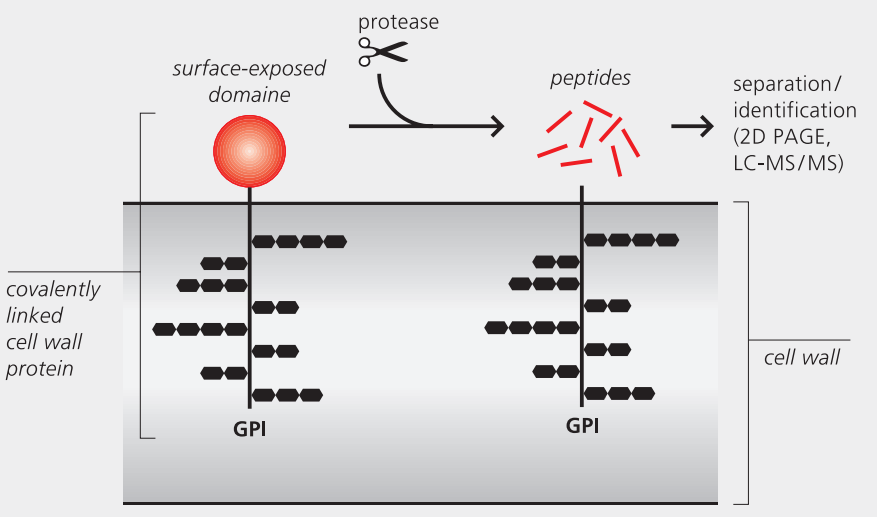

Figure 2: Diagram of the technique for proteolytic fragmentation and solubilization of cell wall proteins.

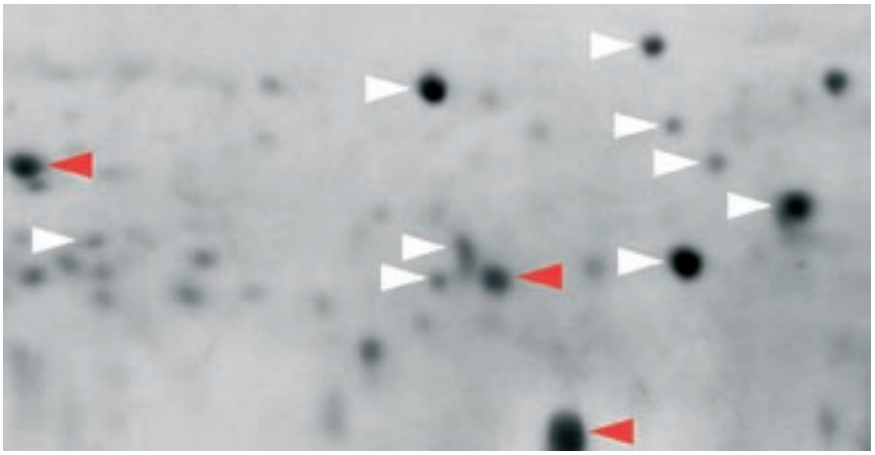

Figure 3: Two-dimensional gel electrophoresis of peptide mixtures after proteolysis of hyphal cell walls in *Candida albicans*. Red arrows mark peptides which are detectable exclusively in hyphal cell walls, while white arrows identify those peptides which can be isolated from cell walls in both yeast and hyphae.

MIF plays a critical role in sepsis

The uncontrolled spread of the toxins from pathogens in the body following a local infection is known as sepsis. Of 6.5 million patients examined in the USA each year, 750,000 suffer from sepsis/SIRS (systemic inflammatory response syndrome), and for one third of these sufferers the outcome is fatal. It is therefore the case that more people die each year from sepsis than from acute heart failure.

Cytokines are important molecular mediators in immune and inflammatory reactions in the body, but if released without regulation lead to a dramatic amplification of septic processes. Macrophage migration inhibitory factor (MIF) is a pleiotropic immune mediator and endocrine factor which possesses a broad site-of-formation and activity spectrum and regulates a multiplicity of inflammatory reactions, plus a number of metabolic reactions. Accordingly, MIF is an important mediator of various human immune and inflammatory diseases. In various animal models, using recombinant MIF, blocking anti-MIF antibodies, and MIF knockout mice, MIF has been found to be a central mediator of Gram-negative and Gram-positive septic shock. In humans as well, the role of MIF in sepsis/SIRS has likewise already become apparent. For instance, a dramatic increase in MIF concentration in the blood plasma is found in particular in the case of sepsis patients with fatal progression of the disease. As a result, there is a high potential for MIF-based therapy and diagnosis.

Development goal

The overall goal of a project at the Fraunhofer IGB on behalf of the company Gambro Dialysatoren GmbH is to develop and optimize new processes and biomedical devices for organ regeneration in acute and chronic inflammatory diseases, on a proof-of-principle basis. Tasks include identifying MIF-binding molecular ligands, characterizing them biochemically, and investigating their binding to specific surfaces, such as hollow fiber membranes. Techniques are therefore being developed which, by removing MIF from the blood, act to regenerate the septic blood plasma to convert it into a noninflammatory or less inflammatory physiological state.

Results

For identifying new MIF-binding ligands, first of all a variety of beads from Gambro, with different forms of modification, have been investigated for their capacity to bind MIF.

Figure 1 shows the results of initial ligand screens. Various beads from Gambro were incubated with physiological solutions, doped with recombinant human MIF (rhuMIF), and mixed by gentle agitation. Unbound MIF was measured by protein assay. In further experiments, a direct detection method (ELISA) was used in order to confirm these initial results. As the figure shows, some of the beads tested adsorb a large fraction of the added rhuMIF. For one bead the affinity is so great that soluble MIF is no longer detectable.

Further ligand screens are being carried out in order to find an optimum ligand. Such a ligand will meet criteria such as maximum binding affinity and a size favorable to the separation system.

Prospects

In its part in the project, the Fraunhofer IGB is centrally involved in the development and establishment of biological assays for monitoring the cytokine response when MIF is removed from the blood (plasma or serum) and for checking the inflammatory status of the blood plasma.
One aim of the studies at the Fraunhofer IGB is to identify and characterize optimum MIF ligands. In a further step, these ligands are to be immobilized on the bead and membrane materials developed by Gambro, which in turn must be optimized not only for ligand immobilization but also for MIF removal. The development, too, of combined ligand strategies, based on endotoxin/LPS removal and MIF removal, are a subject of further-reaching investigations.

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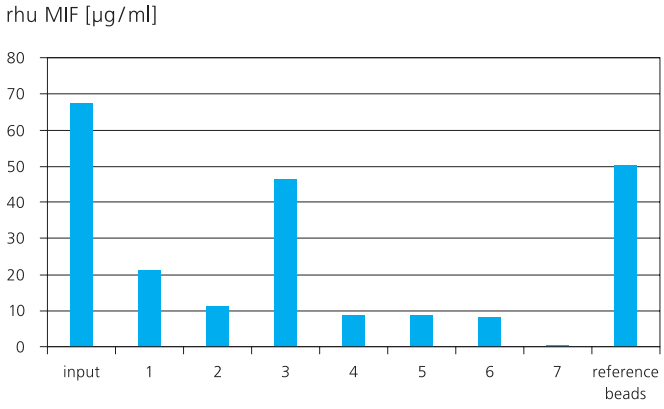

Figure 1: Adsorption of rhuMIF over 15 minutes on beads with different modification (1-7). The control used (reference) comprised S-hexyl-GSH beads.

Microarray technology has become an indispensable tool in medical and applied research. It allows rapid and highly parallelized analysis of a number of parameters, with minimum consumption of material and samples. Using DNA chips, it is possible to routinely monitor the transcription pattern of thousands of genes from tissues or cells on a single chip (Figure 1), offering the reliability and accuracy that are becoming increasingly critical in diagnostic and medical applications. The Fraunhofer IGB's microarray facility hosts a diverse range of chip projects, including technical improvement and bio-medical applications, in both internal (see page 32, Fraunhofer Protein Chips Network) and international cooperative ventures with external companies.

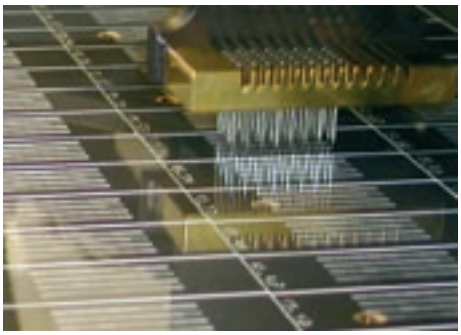

Figure 1: Production of microarrays.

Universal array platforms

In addition to the commonly used direct hybridization of gene-specific probes, at IGB we also use universal array platforms, where "ZIP codes" function as probes instead. These are short oligonucleotides, selected on the basis of equal thermodynamic properties and minimal sequence similarity to the genome under investigation. For each particular investigation, the gene-specific sequences are coupled to the universal set of associated, complementary cZIP codes. Hence the system is highly flexible and can be rapidly adapted to a wide variety of applications. A limiting factor for complex investigations to date has been the lack of availability of a sufficiently large number of suitable ZIP code sequences.
In collaboration with US life sciences leader Applied Biosystems, we are currently carrying out trials with a universal ZIP code array based on a DNA derivative. The enantiomeric L-form of the DNA used here is distinctive in that while it possesses the same physico-chemical properties as the naturally occurring D-form of the DNA, it does not bind to the latter (Figure 2). Thus, because there is no possibility of unspecific binding or cross-reactions occurring, ZIP code sequences can be selected solely on the basis of their thermodynamic properties, making amounts available even in the volume required for very complex investigations. One example of the practical implementation of this system is the transcriptional profiling of different stages of virulence of a human pathogen. In short, the analyses offer both a high degree of specificity and the advantages of a universal platform.

Improved breast cancer diagnostics

The Fraunhofer IGB is currently collaborating with the universities of Stuttgart and Tübingen as well as the Robert-Bosch-Krankenhaus, Stuttgart, in a project sponsored by the *Landesstiftung Baden-Württemberg* to develop a DNA chip for improving breast cancer diagnosis. Containing a set of approximately 800 genes, the chip will allow the compilation of highly informative gene transcription profiles for the classification of mammary carcinomas. It will be used prognostically and concomitantly with therapy in clinical routine diagnosis.
Tests were initially carried out on established breast cancer cell lines which were stimulated by treatment with anti-estrogens or cytokines. The validated chip is being used to investigate tumor samples from patients with a wide variety of clinical histories. With the aid of these initial clinical experiments, the project is also giving rise to bioinformatics techniques enabling the classification of mammary carcinomas.

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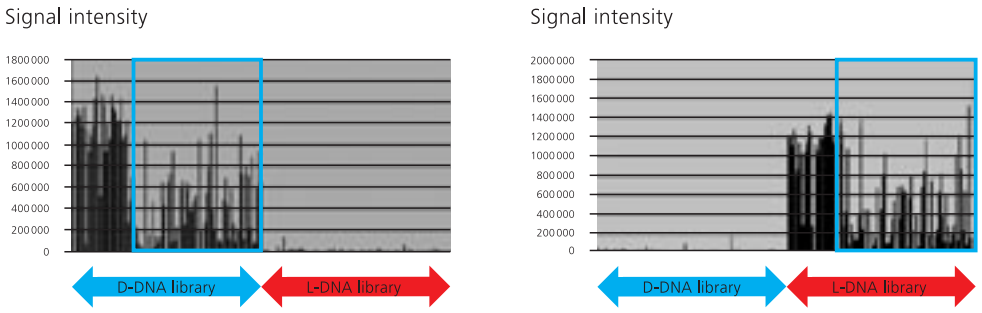

Figure 2: Hybridization of D-DNA and L-DNA libraries. D-DNA binds only with D-DNA, L-DNA only with L-DNA. Under hybridization conditions with low levels of stringency, unspecific binding occurs only within libraries of equal chirality (blue frames).

Fraunhofer Allianz Proteinchips

Proteins, the actors of the cell

Regulated expression of proteins is vital for cells to be able to adapt to their environment or to exert specific functions within an organism. Proteins are therefore among the most important macromolecules in pharmaceutical drug development and in medical diagnosis. The analysis and determination of proteins and their interactions are central topics both in applied research and in basic research. The development of highly sensitive analytical methods with high throughput capacity in the area of mass spectrometry or in connection with protein microarrays is characteristic of the progress in proteomics research and is aiming to satisfy the market requirements.

Fraunhofer Network for Protein Chips

The Fraunhofer IGB is part of the Fraunhofer Protein Chips Network. Here, seven Fraunhofer institutes are combining their know-how and expertise in biological and engineering sciences. Important development goals include:

- New technologies for protein analysis and corresponding analytical equipment with resolutions down to the single molecule
- The protein chips and immobilization techniques required for this
- Equipment for coating, functionalizing, and structuring the protein chips
- Biological model systems, e. g. for pharmaceutical drug development

The coming together of surface and biology

The task of the IGB as part of the Fraunhofer Protein Chips Network is on the one hand to provide tailored surfaces for optimal attachment of the biological components provided. On the other hand, the corresponding sensor proteins are provided. These may be surface antigens or antibodies for the diagnosis of infectious diseases whose diagnosis is difficult or unreliable, such as infections with *Candida albicans* (candidiasis). The alliance benefits here from the experience of the groups headed by Dr. Rupp (Genomics, Proteomics, Screening) and Dr. Tovar (Biomimetic Interfaces) with protein microarrays. Innovative detection methods can be evaluated and optimized at the Fraunhofer IGB by means of conventional detection methods, such as fluorescent or enzymatic labeling of proteins.

Diagnosis of *Candida albicans*

C. albicans is the most frequent causative organism of endogenous fungal infections in humankind, and may lead both to superficial mucosal mycosis and to life-threatening systemic mycosis (sepsis). In order to allow rapid detection of acute infections as for example in the case of sepsis, cell surface proteins of *C. albicans* have been isolated and identified (see page 26). Cell surface proteins are particularly suitable diagnostic markers, since they are freely available for the immune system and therefore can be used for diagnostic tools such as antibody chips. The surface proteins we have isolated react consistently with sera from patients: in other words, these proteins are available to our immune system and possess a high antigenicity.

Nanoparticle biochips for detecting antibodies to *C. albicans*

In comparison to planar biochips, nanoparticle chips have an increased reactive surface. Nanoparticles functionalized with *Candida* antigen, e. g. one of the cell surface proteins isolated, can be applied in microstructured layers to chip surfaces. A protein-stabilizing additive guarantees the retention of the native protein structure and thereby allows the nanoparticle-based protein biochips to be stored. These nanoparticle microarrays, which were developed at the Fraunhofer IGB, bind antibodies which are directed against the *Candida* cell surface protein used (Figure 1) and thus are able to detect an infection with the fungus.

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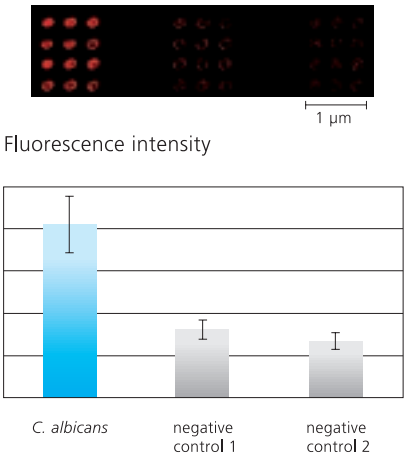
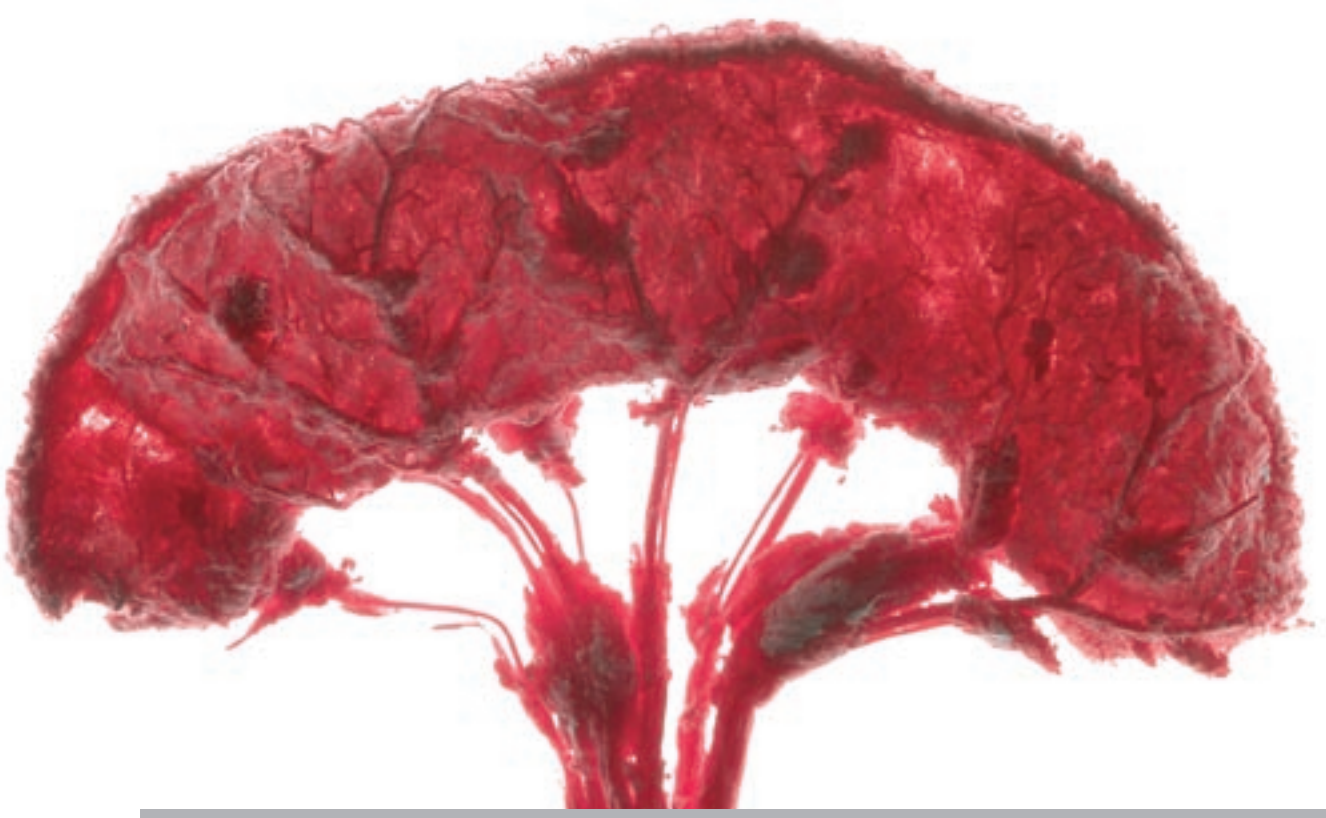


Figure 1: Nanoparticle chip for detecting antibodies to a cell surface protein of *Candida albicans*. If antibodies from the patient's blood bind to the antigen immobilized on the chip, they can be visualized using a second, fluorescently labeled antibody that is directed against the patient's antibodies.

Cell diagnostics, autologous transplants, and cell therapy



Our Services

Custom-made organoid test systems
- Testing of biocompatibility
- Histology
- Primary cell isolation
- Optimization of cell culture conditions
- Molecular and cell biological analysis
- Construction of three-dimensional organ-like tissues
- Pharmacological and toxicological tests
- Genetic modification of primary cells

FACS Service
- Cell sorting analysis of defined populations
- Immunofluorescence measurements of cell surface markers and intracellular markers
- Single- and multi-color analyses
- Cell cycle analysis
- Apoptosis/viability tests
- Cell proliferation test
- Cell sorting according to light scatter of fluorescence parameters
- GFP measurements for analysis and cell sorting
- Kinetic measurements (calcium flux)

Process development for tissue engineering products
- Primary cell isolation
- Optimization of culture conditions
- Cell analyses (marker expression/functionality test)
- Testing of relevant carrier materials/cell matrices
- Construction of three-dimensional cell culture tissue systems
- Establishment and validation of the organoid tissue model
- Proof of biocompatibility
- Pharmacological and toxicological testing

Manufacturing of Investigational Medicinal Products (IMPs) according to current "Good Manufacturing Practices"
- Process development
- Production and quality control of cell and gene therapeutics on a contract manufacturing basis
- Regulatory affairs/documentation
- Quality assurance
- Development and marketing of specialized know-how
- Automation

The discrepancy between necessary transplants and donor organs is increasing steadily. Additionally, there are problems like rejection reactions and lifelong immune suppressions. By means of tissue engineering, damaged, affected or even missing tissues and organs can be replaced by biological compatible and functional implants out of primary cells. Autologous skin and cartilage transplants (from patients' own cells) are already offered, heart valves for example are presently under clinical examination. All concepts have in common the proliferation necessity of capable human cells. After isolation, the relevant primary cells will be increased by cell-culture techniques until sufficient cells are available for the colonization of a matrix structure or even for the cell therapy.

The focus of the technology fields offers the following:

Matrix biology
The matrix structures are mainly coarsely mashed synthetic networks of extracellular matrix components like collagen or fibrine. Thereby, composition and structure of the extracellular matrix used has an essential effect on the function of the arising transplants. Here, at the Fraunhofer IGB we developed a collagen I matrix being admitted for the clinical use and which has already been transplanted within more than 300 patients together with our industrial partner Ars Arthro AG in Esslingen as a cartilage transplant.

3-D organoid test systems
We dispose of a long-lasting know-how in the production of organoid 3D test systems. These are applied in the development of pharmaceuticals and cosmetics – even as an alternative for animal experiments – or for biocompatibility tests. The previous test systems like skin and liver are now completed by vascular structures, so that venous as well as arterial blood vessel conditions can be imitated. Hereby, the standardization of organoid vascularized test systems will be permitted.

Transplants
The Fraunhofer IGB disposes of own GMP-labs for the production of transplants for clinical use. Our trained staff has so far successfully developed a cartilage transplant and will even produce a skin transplant together with the company Euroderm GmbH in Leipzig (see page 18).

Adult stem cells
The focus is oriented in the development of cell-based therapies under use of adult stem cells as well as their organ-specific, functional differentiation (see page 44). The characterization will be done by well-established methods and FACS (see page 42).

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Left-hand page: This vascularized biological matrix with a functional system of blood vessels was isolated from pig intestines. After removal of the porcine cells, a network of arteries, veins, and extremely fine capillaries remains. The collagen matrix can now be populated with primary, organ-specific cells.

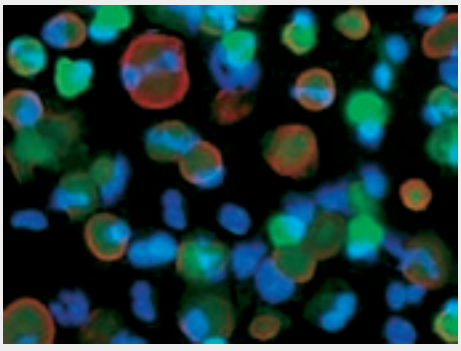

Figure 1: Interactions between matrix and cells can be investigated by fluorescently labeled cells.

Figure 2: Qualified personnel in the GMP manufacturing area.

3D skin model as a test system

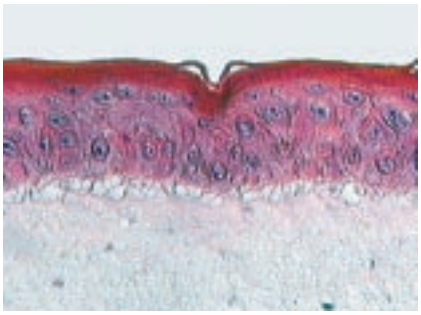

Figure 1: The three-dimensional skin model developed at the Fraunhofer IGB consists of a multi-layered epidermis with an outer corneal layer (*Stratum corneum*).

Since 1985, the Cell and Tissue Engineering Department at the Fraunhofer IGB has been engaged in the isolation and *in vitro* culture of primary cells of different origin. Using a cell matrix component specifically developed for this purpose, the morphogenesis of tissues can be simulated in three-dimensional cell cultures.
Based on this, a three-dimensional skin equivalent was developed with organ-specific characteristics that make it ideally suited for cell and molecular biology research. Another important application is in the evaluation of pharmaceutical, chemical and cosmetic substances, where it can provide an alternative to animal testing.

The skin equivalent is constructed using human keratinocytes and fibroblasts, yielding a good resemblance to natural skin. Keratinocytes are cultivated in special media and differentiate to form a multi-layered epidermis with an outer corneal layer (*Stratum corneum*) (Figure 1). The distinct double-layer construction of the skin equivalent affords the opportunity to investigate different sorts of interaction between the two cell types.

Skin equivalent in wound healing studies

The skin equivalent was initially developed for use in the investigation of skin irritation. Adaptation of the model allows further medical investigations in fields such as dermatology and allergology. For this reason, we developed a model system that allows us to monitor and observe the wound healing process, where keratinocytes and fibroblasts play a central role. Both cell types are acknowledged producers of various cytokines and growth factors involved in wound healing processes. Using a special laser, we created a wound in the artificial skin by mechanical means. Replenishment of the defective region was triggered through stimulation of epidermal keratinocytes. Thus, the course of the *in vitro* wound healing process with our skin equivalent could be clearly determined (Figure 2). We also have the option of using cells from patient material to develop a skin equivalent for analyzing the pathogeneses of skin diseases.

Alternatives to animal experiments

The complexity of our skin model in conjunction with different investigative procedures allows targeted investigation of the many different questions that arise during the testing of chemical, pharmaceutical and cosmetics products. The system can be adapted for immunological, histological and molecular-biological research purposes, such as studies into the penetration and resorption of test material. With this goal in mind, the skin equivalent will be deployed in a new Federal Ministry of Education and Research (BMBF) project to find alternative methods to animal testing. The aim is to reduce the number of animal tests to cutaneous penetration and permeation of contaminants by using a standardized *in vitro* method.

Further future applications of skin models are as alternative and supplementary methods for developing and testing industrial chemicals, pesticides and drugs, with the aim of considerably reducing or even completely replacing tests on animals. To this end, the recently adopted OECD Test Guideline 428 including the relevant Technical Guideline No. 28 is to be extended to include *in vitro* testing of the penetration of contaminants and the permeation of "artificial human skin".

Biocompatible equipment, testing of biocompatibility

The development and evaluation of materials for applications in medicine and medical technology constitute a major research focus at the Fraunhofer IGB. Examples are the development of optimal implant materials from coated polymers and the manufacturing of carrier structures on which biological tissues such as skin and cartilage can be cultivated *in vitro*. The surfaces of the materials involved are defined here in such a way that both optimal cell division and cell differentiation can take place (Figure 3). The basis for the development and investigation of the biological materials is an understanding of the interaction between biological cells and extracellular biological matrix and/or non-biological material.

It is often the case that simple cell culture systems are unable to provide information sufficiently adequate for investigations of the interaction of medical products with whole biological tissues and their various types of cells. Our skin equivalent represents an advanced alternative to these systems. Because its natural three-dimensional structure closely reproduces an *in vivo* situation, even from a histological perspective, the model yields initial insights into the biocompability of materials.

Investigation of tumor therapeutics

In recent years, numerous stimulators and inhibitors of angiogenesis have been identified, isolated and used in tumor therapy. New *in vitro* systems are now needed to further research the effects of these substances. A starting point is the expansion of the full skin model with the addition of human, dermal microvascular endothelial cells and primary malign skin melanoma cells. Thus, both endothelial cell differentiation and angiogenesis can be investigated *in vitro* without the need to add stimulating factors. Experiments to date have already shown that tumor cells trigger increased proliferation and migration of endothelial cells.

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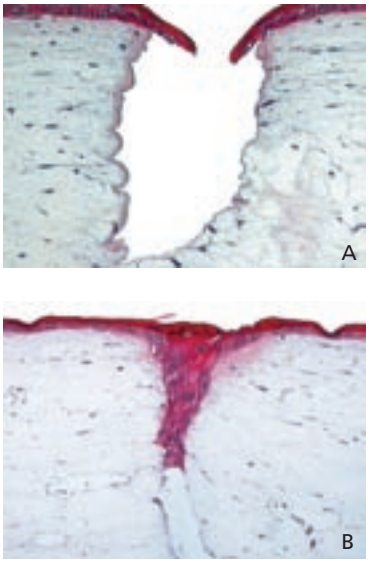

Figure 2: Wound healing on a damaged skin equivalent (histological cross-section, H/E staining, magnified 100-fold).
A: Wound after 3 hours
B: Wound after 72 hours.

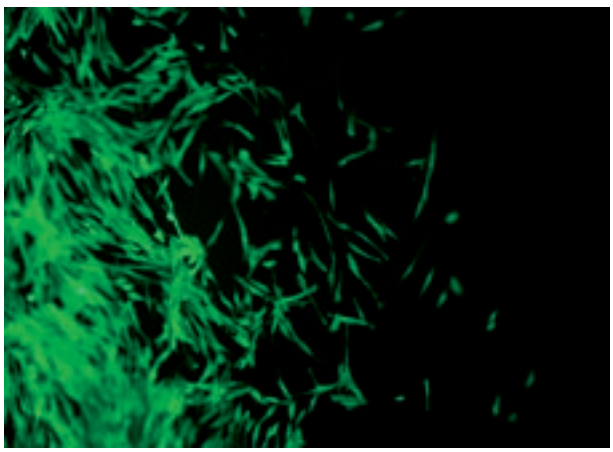

Figure 3: Biocompatibility test: vitally stained cells on a matrix.

3D liver cell models

Three-dimensional liver cell models have already been developed with primary murine and porcine liver cells (hepatocytes) at the Fraunhofer IGB. Cell material derived from pigs has the advantage of being physiologically very similar to human hepatocytes. It is therefore now intended to develop the porcine model further by integrating a vascularized matrix, i. e. one which is permeated by blood vessels. Through this it will be possible for the liver cell model to provide even better information, e. g. in the testing of potential drugs.

Three-dimensional collagen sandwich system retains liver cell function

An established collagen I matrix can be used to cultivate the primary liver cells in a three-dimensional sandwich system. The cells were embedded in this matrix in order to simulate a structure as similar as possible to that *in vivo*. This "sandwich" culture allows the hepatocytes to become organized three-dimensionally and form the cell-cell connections which are vital for them. It is possible in this way to retain the differentiated phenotype and the functionality of mature hepatocytes *in vitro*. One advantage of these organoid cell cultures compared with cell lines or two-dimensional systems is that physiological processes can be approximately compared with the *in vivo* situation.

The two-dimensional "monolayer" cell culture contrasts with the three-dimensional sandwich system in that a complete loss of liver functions, and thus dedifferentiation of the cells, is observed within a few days.

The possibility of three-dimensional structuring and formation of cell-cell and cell-matrix interactions of the hepatocytes thus plays an important part in retaining the shape, polarity and function of the cells.

Aim: Vascularized liver cell model as test system

More efficient processes in pharmaceutical companies for synthesizing potential drugs produce large substance libraries which must be investigated for their specific effects. Time-consuming and technically complicated processes such as *in vitro* tests, animal experiments and phase I-IV studies are necessary for approval as new medicinal product. The best way of assessing the efficacy and toxicity of drugs is from the biological behavior of living cells. Liver cells are particularly suitable for this because they are involved in important biotransformation processes necessary for the body's survival, such as detoxification and metabolic reactions.

The structure of the liver in the body requires for *in vitro* culture a matrix to enable the liver cells to be supplied directly with important nutrients and oxygen without the formation of a gradient. The acellularized and vascularized matrix employed in the cell systems department represents an advantageous support structure in particular for culturing hepatocytes. This structure is permeated by a network of functional vessels and consists mainly of collagens I and III. The hepatocytes are now to be cultivated on this vascularized matrix. This novel perfusion model is intended to make the supply of oxygen and important nutrients to the cells more efficient because the capillary structure means that the diffusion distances are shorter.

Functional characterization

Characterization of the hepatocytes and investigation of their functionality are based on liver-specific parameters such as albumin synthesis, urea synthesis, lidocaine metabolism and ethoxycoumarin metabolism during the culturing time.

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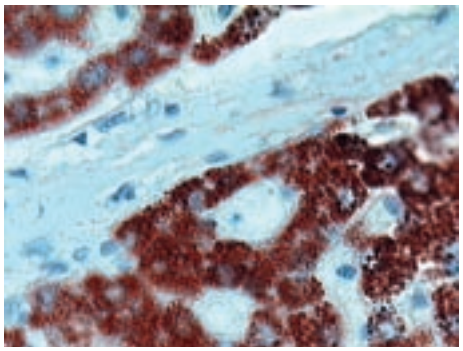


Figure 1: Porcine liver tissue *in vivo*, staining with hepatocyte antibody.

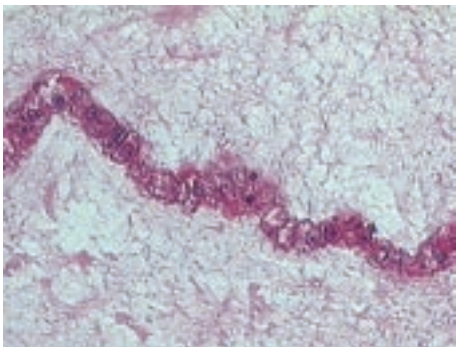


Figure 2: Porcine hepatocytes *in vitro*: Three-dimensional "sandwich" structure with hepatocytes embedded in a collagen matrix, H/E staining.

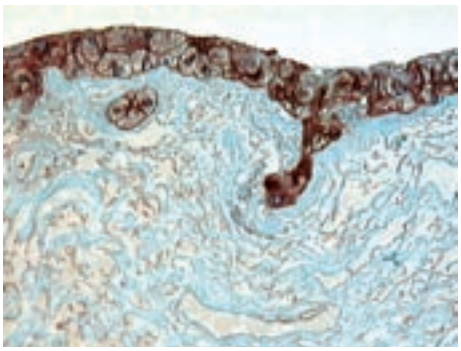


Figure 3: Porcine hepatocytes *in vitro* on a vascularized matrix. Staining with LP34 cytokeratin antibody (5, 6, 18).

Biological matrices for tissue engineering and transplant development

Collagen I matrix for clinical use

Artificial, purely biological matrices are becoming increasingly important for organoid cell culture, for tissue engineering and for reconstructive surgery. A collagen I matrix prepared from rat tail tendons fulfilling the requirements for tissue engineering has been established at the Fraunhofer IGB for developing three-dimensional organoid test systems. In order to develop a cartilage transplant, which is now in clinical use with great success, this matrix was adapted to meet the quality requirements of Good Manufacturing Practice (GMP) and was approved for clinical use. Consistent quality of the basic matrix is tested on each batch by assays, like photometric, gravimetric, sterility tests, purity/identity tests (electrophoresis/Western blotting), gelation tests and elasticity/viscosity measurements (rheometry) (Figure 1).

It is now intended to use this matrix as basis for the development of further matrices which are specifically adapted to some selected tissues. For this purpose, methods such as HPLC, FPLC, electrophoretic techniques (PAGE, Western blotting), as well as physico-chemical methods, are to be established for analyzing the natural matrices in order to use the results for composing tissue-specific artificial matrices.

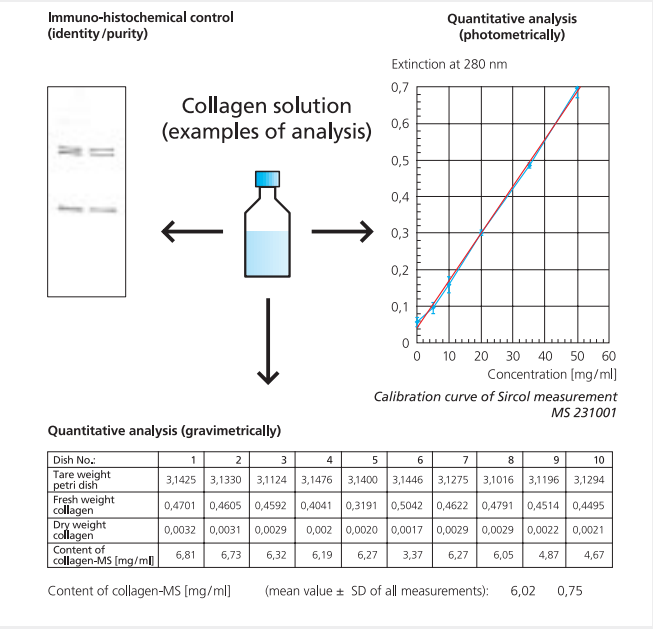
Matrices for reconstructing soft connective tissue

A further type of matrix obtained from porcine intestine by acellularization methods consists of collagen of type I and III. This matrix has been seeded with patients' own connective tissue and muscle cells in layers corresponding to the natural tissue. The resulting tissue patch with an organoid structure has already been successfully tested clinically in attempts at surgical treatment of tracheal defects. It is now intended on the basis of these results to develop a method which makes it possible to provide autologous (patient's own) tissue for reconstruction after surgical procedures such as removal of necrotic tissue, resection of tumors, or in vascular surgery (Figure 2).

Novel possibilities for tissue engineering: the vascularized matrix

In tissue engineering there is a need in particular for metabolically active cells in three-dimensional culture to be supplied with oxygen and nutrients in a way which cannot be ensured by diffusion processes alone. Particularly in the development of artificial multilayer tissue structures employed as test systems or as autologous implants it is necessary to find innovative ways of supplying the cells adequately. A further type of matrix suitable for developing three-dimensional test systems even with highly active cells such as liver cells has been established at the Fraunhofer IGB. To improve the supply to the cells in such systems, the vascular system of the initial matrix is retained, and is thus

Figure 1: Extensive quality controls are necessary for a GMP-compliant matrix production.



Quantitative analysis (gravimetrically)

Dish No.:	1	2	3	4	5	6	7	8	9	10
Tare weight petri dish	3,1425	3,1330	3,1124	3,1476	3,1400	3,1446	3,1275	3,1016	3,1196	3,1294
Fresh weight collagen	0,4701	0,4605	0,4592	0,4041	0,3191	0,5042	0,4622	0,4791	0,4514	0,4495
Dry weight collagen	0,0032	0,0031	0,0029	0,002	0,0020	0,0017	0,0029	0,0029	0,0022	0,0021
Content of collagen-MS [mg/ml]	6,81	6,73	6,32	6,19	6,27	3,37	6,27	6,05	4,87	4,67

Content of collagen-MS [mg/ml] (mean value ± SD of all measurements): 6,02 0,75

available as supply structure, when this matrix is prepared. In the development of implants it is possible for this blood vessel structure to be seeded with appropriate cells (e.g. endothelial cells) and be connected to the patient's circulation during the implantation. It is possible in this way also to implant pieces of tissue which, because of their size, would not become incorporated without an adequate supply from the outset (Figure 3).

The multilayer, organ-like test systems which have been constructed with the vascularized matrix can, when cultivated in small bioreactors, provide data which are very applicable to the *in vivo* situation. The optimal supply resulting from the vascular structures also opens up the possibility of cultivating the artificial tissues over long periods and thus investigating the long-term effects of chemicals or pharmaceuticals (Figure 4).

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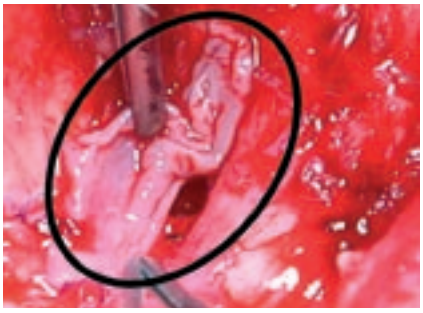

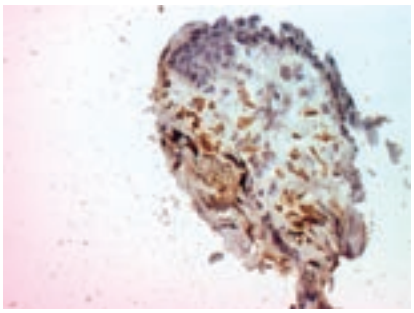

Figure 2: Implantation of an autologous tissue patch into the trachea and histological check three months after the operation.

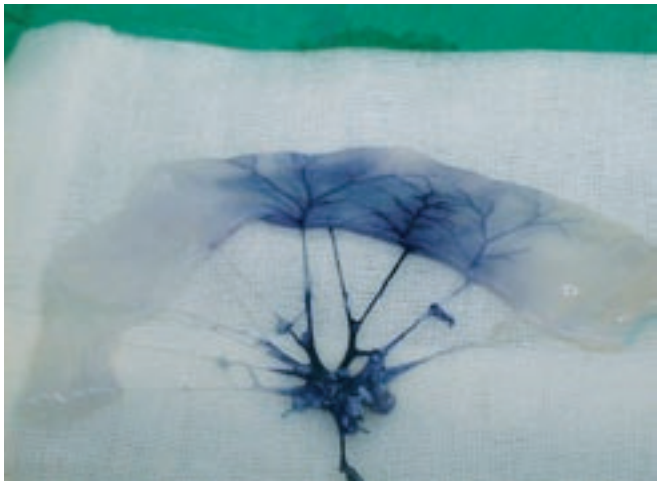

Figure 3: Vascularized matrix permeated by blood vessels. The acellularized vascular structures have been contrasted using a dye.

Figure 4: Vascularized matrix employed in a bioreactor. This has a connection for perfusing the vascular structures from below; medium can be fed in through a second circuit at the side.

FACS service at the Fraunhofer IGB

Advanced FACS technology

The Fraunhofer IGB runs flow cytometry services from a dedicated unit equipped with a FACSVantage SE/DIVA high-performance cell sorter, featuring a water-cooled Enterprise II Laser (simultaneous operation of 488 nm and UV), an air-cooled Helium Neon Laser (635 nm) and numerous detectors. Currently, up to nine parameters (FSC, SSC, six colors, time) can be simultaneously determined. A set of various optical filters allows the use of different fluorochromes.

We also use a FACSCalibur with two air-cooled lasers (488 nm red diode laser) for simultaneous determination of up to seven parameters (FSC, SSC, four colors, time). The unit is part of a facility approved for work with genetically modified organisms up to biosafety level II (according to the German Gene Law).

Figure 1: Certificate issued by DGKL e. V. for interlaboratory immune status test IS3/04.

Flow cytometry in internal and external projects

Conventional *in vitro* culture of primary cells from different tissues and species, the development of three-dimensional cell culture systems, tissue engineering and the production of patient-specific cell therapeutics are all core competencies of the Fraunhofer IGB. Characterization of cells is carried out using classical methods from the fields of molecular biology, histology and immunohistology, which we then supplement with flow cytometric analysis on behalf of both internal and external customers.

The well-established and standardized FACS technique (Fluorescence Activated Cell Sorting) allows enrichment and sorting of relevant cell populations as well as the removal of contaminating cells. Single cell sorting and "index sorting" in 96 well plates or in other user-defined devices are of special interest for clonings, PCR-analysis and MLR-use. Our services include: determination of cell surface and intracellular markers (single or multi-color analysis), kinetical studies (e. g. calcium flux), analysis of cell cycle, apoptosis and cell proliferation, measurements of green fluorescence protein (GFP) and derivatives for determination of transfection efficiency.

Quality control through participation in interlaboratory comparison

The quality of our FACS analysis is regularly assessed by external institutions in the form of round robin tests for flow cytometry.

The test performed by the DGKL e. V. (Reference Institute for Bioanalytics) in Bonn involves the determination of the immunostatus of human test person's blood. Four-color analysis is used to determine six parameters for each of two different blood samples: the absolute number of lymphocytes, the number of whole T-cells, T-helpers, T-suppressors, B-cells and NK-cells as a percentage of lymphocytes.

The $CD34^+$-Enumeration interlaboratory test carried out by INSTAND e.V. in Düsseldorf requires the use of flow cytometric analysis to determine both the absolute amount of $CD34^+$ stem and progenitor cells and also the percentage of $CD34^+$ stem and progenitor cells of all leukocytes in human test person's blood. If all round robin tests are passed, a certificate is issued, valid for one year, attesting the accuracy of our FACS analysis.

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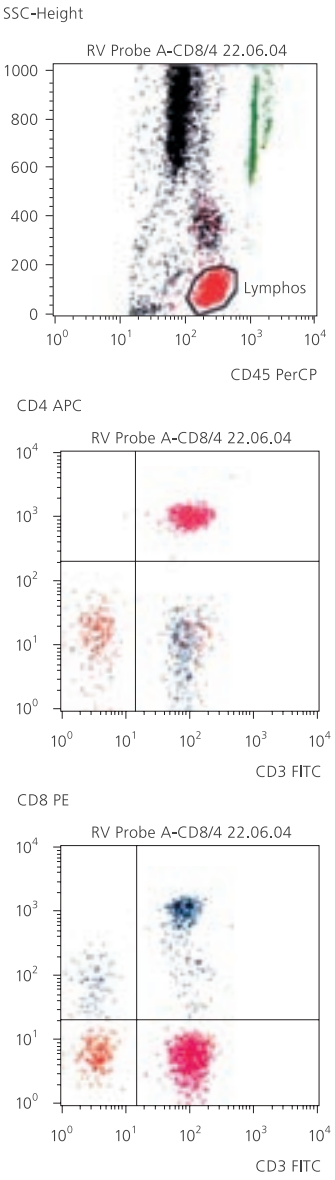
FACS service at the Fraunhofer IGB

- Immunofluorescence measurements of cell surface and intracellular markers
- Single- and multi-color analysis
- Cell cycle analysis
- Apoptosis detection, viability and proliferation testing (e. g. for testing biocompatibility)
- Cell sorting according to light scatter or fluorescence parameters
- GFP analysis for determination of transfection efficiency or establishment of stable clones
- Kinetic measurements (calcium flux)
- Side population analysis (Hoechst efflux)

Additional services on request:
- Single cell sorting
- Measurement of activation (e. g. of thrombocytes)
- Allergy diagnostics (activation of basophils)
- Determination of residual leukocytes in blood preparations such as erythrocyte or thrombocyte concentrates
- Establishing additional methods



Region Statistics

File: RV Probe A-CD8/4 22.06.04 Tube: CD3/CD8/CD45/CD4
Acquisition Date: 22-Jun-04 Gate: G5

Region	Events	% Gated	%Total
Lymphos	3833	43,40	14,90
T-helpers	1822	20,63	7,08
CTL	1168	13,22	4,54
Beads	5000	56,61	19,44

Quadrant Statistics

File: RV Probe A-CD8/4 22.06.04 Tube: CD3/CD8/CD45/CD4
Acquisition Date: 22-Jun-04 Gate: G1
Quad Location: 14,205

Quad	Events	% Gated	%Total
UL	1	0,03	0,00
UR	1829	47,72	7,11
LL	807	21,05	3,14
LR	1196	31,20	4,65

Quadrant Statistics

File: RV Probe A-CD8/4 22.06.04 Tube: CD3/CD8/CD45/CD4
Acquisition Date: 22-Jun-04 Gate: G1
Quad Location: 15,21

Quad	Events	% Gated	%Total
UL	221	5,77	0,86
UR	979	25,54	3,81
LL	588	15,34	2,29
LR	2045	53,35	7,95

Figure 2: Determination of T-cell subpopulations using four-color analysis.

Figure 3: Sorting and separation of specific tissue and organ cell populations using FACSVantage equipment.

Organ repair with adult stem cells

Diseased organs are at present still treated by giving medicines. However, growing knowledge derived from research in cell biology is opening up new prospects for the treatment of diseases with biologically active cellular transplants. These transplants have an effect after being administered once, and act over a longer period than conventional medicines; in addition, they stimulate the self-repair potential of the malfunctioning organ. One type of cell in which great hopes are placed in relation to the development of cell transplants are "stem cells". Besides the totipotent embryonic stem cell there are a number of other types of stem cells which can be detected in widely differing organs and have already started their characteristic mode of differentiation: adult stem cells.

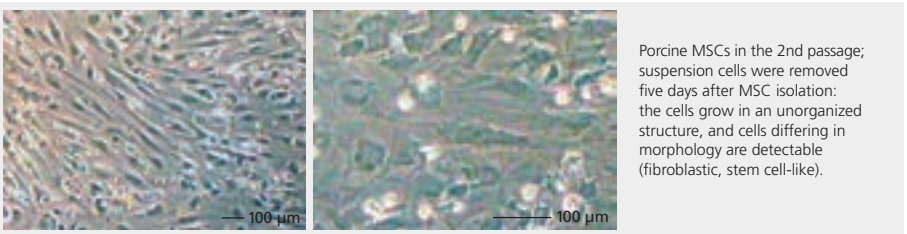
Standardized isolation and cultivation of stem cells

Many research groups have shown in recent years that a particular type of stem cell, the mesenchymal stem cell (MSC) which is mainly found in bone marrow, can be employed on use of particular additives and suitable conditions for regenerating bone, cartilage and ligaments. In addition, MSCs can differentiate into fatty tissue. Freshly isolated MSCs represent a very heterogeneous population which is why they can develop into a wide variety of cell types. The extent to which this pluripotency may have adverse effects on certain therapeutic purposes is unclear at present. The initial work on the cells in our laboratory therefore aimed at investigating various MSC subpopulations for an unambiguously controllable differentiation. These subpopulations were obtained from porcine bone marrow by being sorted via a particular surface antigen (SH2; SH3/4) in a flow cytometer or through magnetic columns (MACS system). An alternative investigation was of the influence of non-adherent suspension cells of the bone marrow on adherent MSCs.

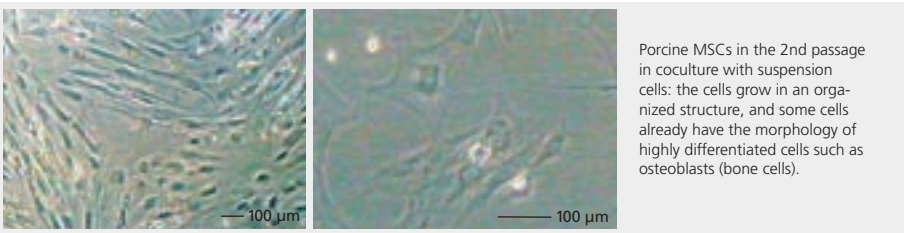
It was shown that the bone marrow cells adhering first tended to have an osteoblastic (bone cell-like) morphology if they were not cultivated further with suspension cells. By contrast, the adherent MSCs retained an undifferentiated fibroblastic (connective tissue cell-like) morphology if they were cultivated in coculture with suspension cells (Figure 1). This shows the MSCs are influenced by the surrounding cells. This is possibly mediated by paracrine mechanisms.

Examination of a number of bone marrow isolates for their range of surface molecules, which is conventionally used for characterization of MSCs in many research laboratories, showed that MSCs frequently do not have the quantity of SH2, SH3 or Thy1 antigens described in the literature. Despite this, these cells are able simultaneously to follow all the differentiation pathways known for them, and develop into bone, cartilage or fat cells (Figure 2).

These initial results indicate that the methods generally used at present for isolating MSCs do not function equally reliable, but nevertheless the MSC differentiation pathways can be induced. It appears that MSCs depend more on



Porcine MSCs in the 2nd passage; suspension cells were removed five days after MSC isolation: the cells grow in an unorganized structure, and cells differing in morphology are detectable (fibroblastic, stem cell-like).



Porcine MSCs in the 2nd passage in coculture with suspension cells: the cells grow in an organized structure, and some cells already have the morphology of highly differentiated cells such as osteoblasts (bone cells).

Figure 1: Differentiating effect of bone marrow suspension cells on adherent mesenchymal stem cells (MSCs).

their environment than on their development status, which is reflected by their surface molecules.

Uses and prospects

The discovery of principles leading to obtaining autologous adult stem cells more efficiently and selectively and to their specific differentiation will open up new possibilities for tissue engineering and cell therapy.

We hope, through better standardization of adult stem cell isolation and cultivation, combined with new methods, cultivation geometries and materials, to simplify the application of tissue engineering products and cell therapeutic agents for the clinician. We also regard well-characterized adult stem cells as being useful as model systems: medicines and factors developed for the regeneration of organs can be investigated for their efficacy in these test models at an early date.

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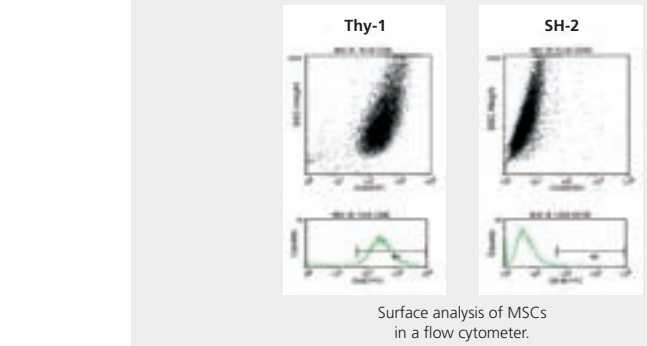

Surface analysis of MSCs in a flow cytometer.

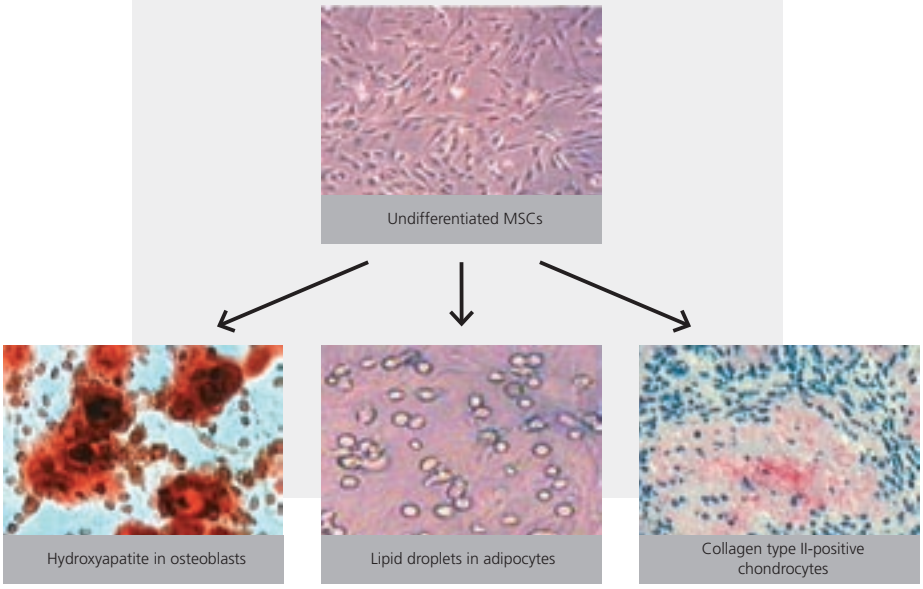

Figure 2: Thy-1-positive and SH-2-negative mesenchymal stem cells (MSCs) differentiate to chondrocytes (cartilage cells), adipocytes (fat cells) and osteoblasts (bone cells).

Functional interfaces for technology and medicine

Interfaces of materials are the surfaces where the materials interact with their environment. Interfaces play a supporting part in, for example, the development of materials of construction and components in the automotive sector as well as in medical technology. For many materials the surface properties required are often quite different from those which are intrinsic for the bulk material. For instance, many plastics are often not wettable and are difficult to bond adhesively, or, in contact with biological media, lead to uncontrolled protein adsorption.
To modify their properties, the interfaces are first characterized in detail, using special, surface-sensitive methods, and then, in a second step, are functionally modified with different modification and coating techniques – using plasma technology or supramolecular chemistry, for example. Among the accomplishments which characterize the work of the Fraunhofer IGB in this field are recent achievements in nanotechnology, and in particular in nanobiotechnology, characterizing and modifying surfaces at molecular or atomic level. It is on this basis that we at the Fraunhofer IGB are developing specific solutions for individual challenges.

Services

- Surface analysis and characterization
- (Bio)functionalization of surfaces
- Synthesis of nanoparticles with tailored surfaces
- Development of inorganic membranes
- Development of membrane modules
- Process development

Figure: A fluoropolymer film given a hydrophilic microstructure by a plasma method using a mask. In this way, polymeric films and membranes can also be functionalized specifically with a carboxyl or amino group microstructure. They are then suitable for use as selective binding surfaces for biochips in diagnostics and medicine.

- **Ultrathin layers**
  With thicknesses of less than 100 nanometers, our ultrathin layers ensure desirable functions such as wetting (defined adjustment of surface tension), the adhesion of assemblies of different materials, adsorption properties, and compatibility or functionality in contact with biological systems.

- **Molecularly defined and smart surfaces**
  Molecularly defined surfaces are required in the production, for example, of biochips or sensors or in heterogeneous biocatalysis. At the Fraunhofer IGB, surfaces are provided with chemical functions in a targeted manner. In other cases, surfaces are required to alter their properties as and when required: for example, to be switchable from wetting (hydrophilic) to water-repellent (hydrophobic).

- **Biomimetic and biofunctional interfaces, nanobiotechnology**
  Interactions at the interface between biological and technical systems play a decisive part in medical technology and biotechnology. At the Fraunhofer IGB we are producing materials which are biocompatible, bioactive or bioinert, by virtue of a defined molecular architecture of interfaces. Biomimetic surfaces are characteristic for nanostructured functional materials which allow molecular recognition reactions at their surface, such as in chips or sensors, for example.

- **Nanoparticles, carbon nanotubes**
  Nanoparticles having a diameter in the range of 50 to 300 nanometers are produced by the Fraunhofer IGB from organic and inorganic materials. Here as well, attention is focused on the design of the surface: equipped with specific functionalization, such as with a therapeutic protein, they form drug delivery and controlled release systems or, with their molecularly defined surfaces, they allow new solutions in separation technology.
  Together with the Fraunhofer TEG, the Fraunhofer IGB is optimizing fleece made of carbon nanotubes, referred to as bucky paper, as actuators for the construction of artificial muscles or as substrate for tissue engineering purposes.

- **Inorganic membranes**
  The ceramic hollow fiber membranes and capillary membranes developed at the IGB, in comparison with other geometries, possess the greatest packaging density in terms of separation area to volume. These membranes are especially suitable for high-temperature applications such as gas separation or membrane reactors.

- **Interface analysis**
  The IGB has at its disposal a wide spectrum of interface analysis methods with the latest equipment, allowing structures and chemical compositions to be analyzed in nanoscale dimensions. We are also able to take on analytical work under order, for the purpose of solving your interface problems. Please request further information (page 95).

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Figure 1: Fluorescent nanoparticles on the micrometer scale on a chip, viewed using a fluorescence scanner.

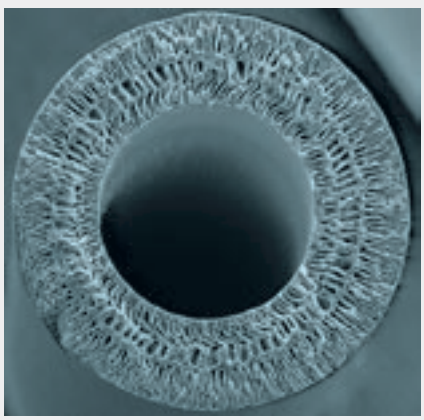


Figure 2: Ceramic hollow fibers for microfiltration.

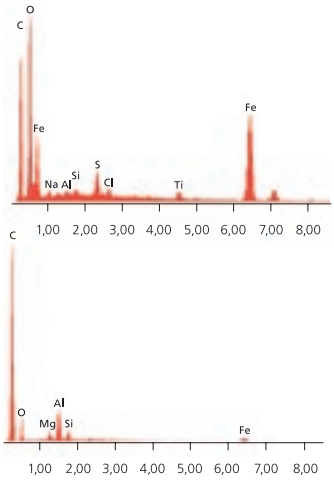


Figure 3: EDX spectra before and after the removal of iron catalysts.

Material with exceptional properties

Soon after the initial discovery of carbon nanotubes (CNTs) by Sumio Iijima in 1991, it was realized that they possess exceptional properties. Their high current-carrying capacity, estimated at 1 billion ampere per square centimeter, makes them interesting for electrical applications; high field emission at low activation voltages (1-3 V) opens the way to a new generation of flat screens. Their tensile strength is 13 times greater compared to Kevlar and 21 times compared to the best steel – at low weight. Thermal conductivity is twice as high that of pure diamond while thermal stability at approx. 750 °C in air and up to 2,800 °C in vacuum is higher than for other materials known to date.
A further property, that of expansion under the application of low voltage (1-5 V) predestines the CNTs for use as artificial muscles.

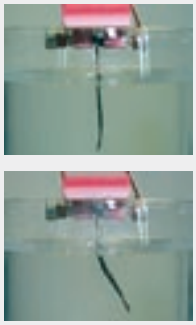
Aim and approach

The Fraunhofer IGB has been researching the properties of carbon nanotubes for over four years. The chief focus has been on the optimization of the electromechanical properties of so-called "bucky papers" (single-walled nanotube sheets or mats) for use as electrochemical actuators.

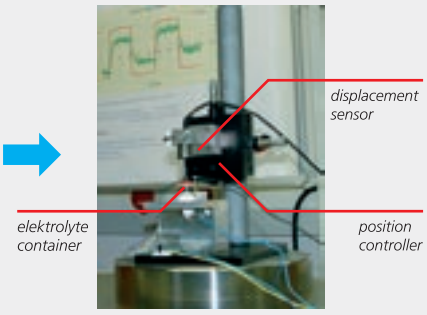
This research, carried out in close cooperation with the Fraunhofer TEG, will now be continued in an EU project (Collective), with the aim of developing "artificial muscles for applications in medical technology" (Figure 1). The project involves significant contributions both from partners in industry and the Fraunhofer ISC. The most important goal is to examine the extent to which multi-wall carbon nanotubes (MWNT), which are cheaper and available in larger volumes, can be used as actuators compared with the single-wall carbon nanotubes (SWNT) used up to now.
A second EU project (STREP) flanks these activities. In this project, the main contribution of the Fraunhofer IGB is to investigate the chemical functionalization of nanotubes using plasma technology. The remit is to examine the extent to which functionalization directly affects the electromechanical properties of the nanotubes, and how secondary effects such as better dispersibility can be influenced.

Application center

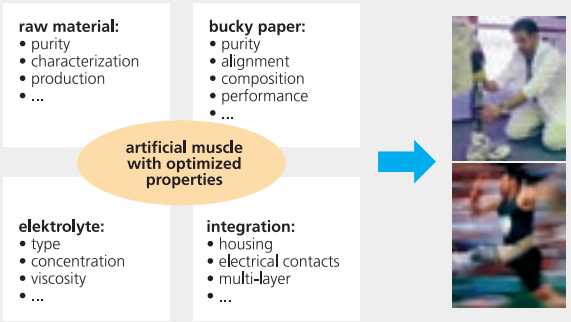
With the Fraunhofer-Gesellschaft providing financial support, an application laboratory was set up at the Fraunhofer Campus in Stuttgart. The laboratory, jointly operated by the Fraunhofer TEG and Fraunhofer IGB, serves demonstra-



First demonstration of the electromechanical properties of carbon nanotube sheets (*bucky paper)* by Baughman 1999.



First available experimental setup for the measurement of the actuation forces vertical to the sheet plane. Fraunhofer TEG/Fraunhofer IGB 2002.



Challenges for the improvement of the electromechanical properties of carbon nanotube sheets for industrial applications.

Development of carbon nanotube actors for use in medical technology (Fraunhofer-Gesellschaft together with European partners).

Figure 1: Stages in the development of commercially viable "artificial muscles".

tion purposes for industrial customers and project partners, as well as merging most of the two institutes' CNT research activities. The laboratory facilities are divided into the "Measurement Technique" section, where physical, mechanical and electrical tests will be performed, and the "Macroscopization" section primarily dedicated to the production of bucky papers from raw materials. Macroscopic devices will also be developed here.

Results

The production of bucky papers from multi-wall carbon nanotubes was for a long time considered virtually impossible, due to the fact that the filtration process for MWNT did not yield a fleece-like structure similar to that of the single-wall nanotubes, leaving the resultant product brittle and fragile. One reason is that the raw material consists of many different macroscopic shapes and forms, as illustrated by the SEM (scanning electron microscope) images in Figure 2. Through optimizing the dispersion and purification parameters, we successfully achieved the production of bucky papers from raw MWNT material. EDX spectroscopy may be used to verify the removal of the iron required as a catalyst in the manufacturing process (Figure 3).

Outlook

The postulated properties of carbon nanotubes have given rise to a huge interest in a commercially suitable actuator. We have shown that it is feasible to produce bucky papers from the less expensive MWNT material. Further optimization and characterization of this material is the object of our current research. In the near future, it is planned to test bucky papers for biocompatibility and toxicity. This can be carried out using the cell lines and organoid test systems available at the Fraunhofer IGB "Cell Systems" department. Figure 4 shows first results with primary humanoid fibroblasts which exhibit improved colonization and proliferation on the surface of specially treated bucky paper.

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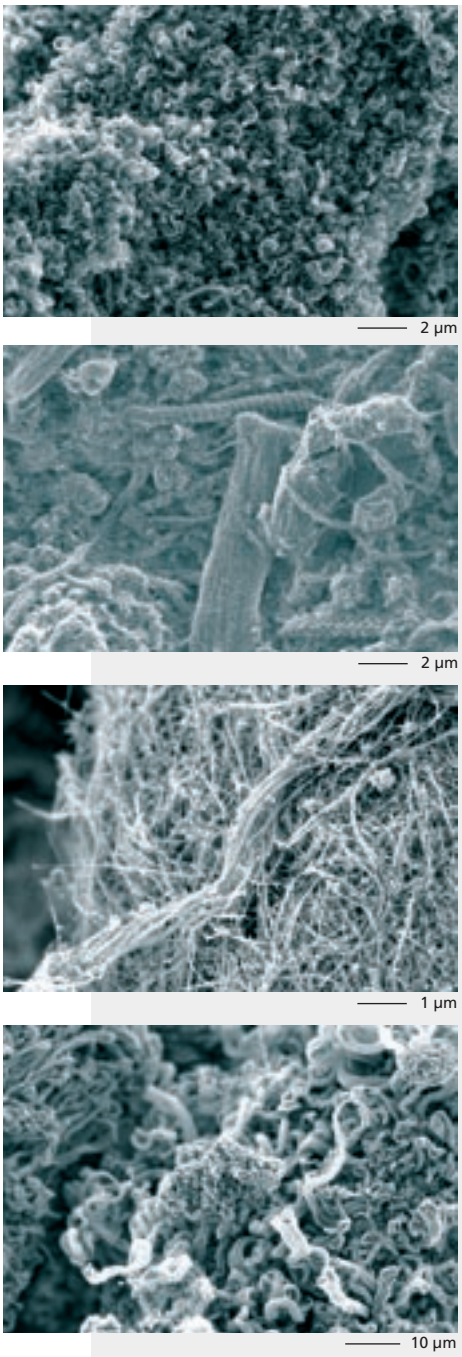

Figure 2: Scanning electron microscopy images of different raw materials composed of multi-wall carbon nanotubes (MWNT). The images clearly show the differences in quality in terms of their macroscopic structure.

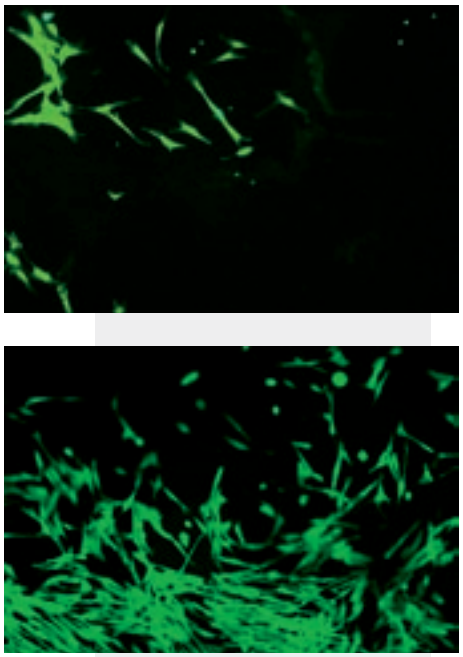

Figure 4: Fluorescence-labeled humanoid fibroblasts on bucky paper before and after specific pre-treatment of the paper. The pre-treatment results in improved cell adhesion and proliferation.

Innovative hollow fiber membranes for extracorporeal blood purification

In the USA alone, 500,000 people each year suffer septic shock as a result of blood poisoning, usually caused by endotoxins of Gram-negative bacteria. Effective blood purification could considerably reduce the high mortality rate of 40 percent.

Purifying blood is a complex operation

Systems known as therapeutic apheresis systems cleanse the blood which is passed extracorporeally through an adsorber system. This process removes substances which play a key role in the incidence of the disease, such as the endotoxins in the case of septic shock. The apheresis systems presently used in clinical practice usually use only the plasma fraction of the extracorporeal bloodstream, since the cellular constituents of the blood would be activated by the adsorber surface. It is therefore necessary to insert a plasma separation unit upstream of the actual blood cleansing unit, in order to separate off blood cells. This procedure is expensive in terms of apparatus and must be monitored by trained care staff. There are on the market a number of hemoperfusion systems which are easier to operate, in which the unfractionated blood perfuses the adsorber matrix directly. These systems, however, possess low hemocompatibility, and this severely restricts the acceptance of this technique.

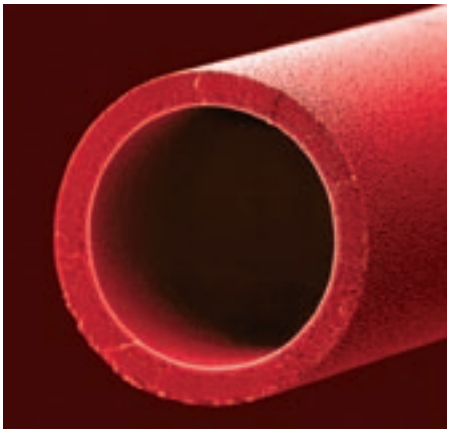

Figure 1: The polymeric hollow fiber has an external diameter of 0.4 millimeters. Blood cells flow on the inside, while plasma escapes through its pores and is cleansed of toxins.

Objective: Blood purification in one step

In a project assisted by the German Ministry of Education and Research, as part of the nanobiotechnology support program, the Fraunhofer IGB, together with the company Gambro Dialysatoren GmbH, is developing innovative hollow fiber membranes for blood purification (Figure 1). These membranes interact with liquid media, and constituents dissolved in them, both by way of size exclusion – for the retention of blood cells – and by way of regioselective affinity adsorption. For use in plasma apheresis, the surface of the membrane in the lumen is to be made blood cell compatible. The internal surface of the membrane, and the outside, however, are to be chemically modified so that here the endotoxins present in the blood plasma are adsorbed preferentially (Figure 2). The hollow fiber filtration modules manufactured from such membranes combine size-selective separation with chemical selectivity (restricted access membranes) and hence enable more efficient blood purification in a single step.

Filtration module: Size exclusion combined with regioselective affinity adsorption

A filtration module of this kind is composed of a bundle of hollow fiber membranes. Because of the highly porous structure within a small space, a very large surface area (around 500 m^2) is available for interaction with the blood. Using the dry plasma glow discharge process developed at the Institute, only the interior nanoscale porous membrane structure and the outer membrane surface, but not the lumen, are equipped – specifically and regioselectively – with a chemical functionality. Coupled with this functional treatment, then, in a downstream wet-chemical treatment step, are the adsorber substances which bind the endotoxins (Figure 3). The modified pores of the membrane are so small that sensitive blood cells are unable to pass through them, and hence cannot come into contact with the chemically active surface. Investigations to date indicate that a membrane module constructed in this way "fishes" toxins out of the blood

selectively and rapidly (Figure 4). The composition of the blood is not changed during this procedure.

Further advantages

The combination of two separation principles in one membrane geometry offers a higher efficiency than with granular systems (microbead columns): the interaction of the species to be extracted is not determined by the comparatively slow diffusion into the microchannels of microparticles but can instead be controlled by means of a pressure gradient, which strongly favors interaction with the inner pore surface treated for chemical affinity.

Applications

The workability, demonstrated here, of a regio-selectively modified hollow fiber membrane for purifying blood from endotoxins should be seen only as an example of further applications of a new type of membrane. With a similar membrane but with a different chemical treatment it would also be possible to remove from the blood harmful blood lipids (LDL cholesterol) or proteins which cause autoimmune diseases. The potential applications are not limited to medical therapy. The regioselectively modified membranes can be used as chemical nanoreactors wherever the task at hand is to separate a low molecular mass chemical structure from a stream of material efficiently by means of specific binding, without affecting chemically equivalent structures of higher molecular mass.

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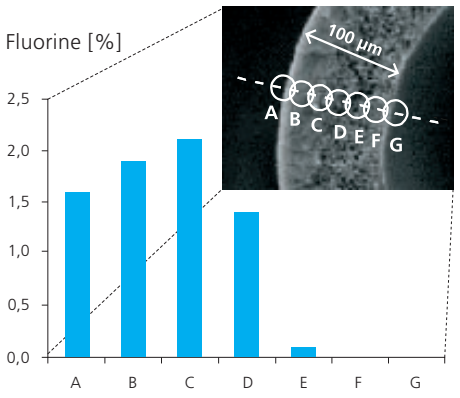

Figure 3: Distribution of chemical functionality over the cross section of a hollow fiber following derivatization of the surface-bound amino groups with pentafluorophenylalanine, analysis by ESCA.

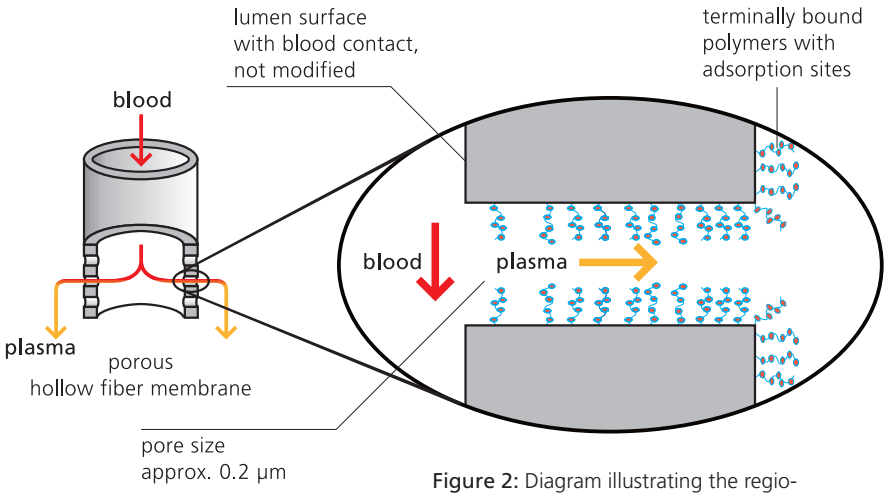

Figure 2: Diagram illustrating the regio-selective modification of the pore surface of hollow fiber membranes by a plasma technique.

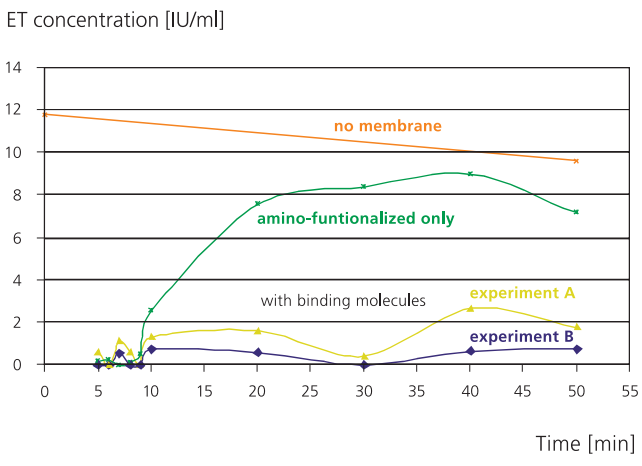

Figure 4: Adsorption of *E. coli* endotoxin (ET) from heparinized blood plasma on hollow fiber membrane modules equipped regioselectively with binding molecules.

Preparation of fluorocarbon domains by plasma technology

Properties of fluorocarbons

Characteristics of fluorocarbon polymers include their high chemical stability and very low surface tension. Contact angles of water on these polymers are in the region of 90° for Teflon®, but depending on chemical composition and surface roughness may even attain 120° (smooth surfaces) or more than 150° (textured surfaces). Moreover, they are often oleophobic (oil-repellent), and this is why, for example, Teflon® is used as a coating for kitchen utensils. Fluorocarbon compounds are also used in textile finishing: they are able to provide protection in a variety of ways – repelling dirt and water, for example – and to enhance the appearance of the textiles. A further field of use lies in medical technology, since many fluorocarbons are biocompatible.

In industrial sectors, the functionalized surfaces are usually generated wet-chemically. An alternative route is the functionalization by means of plasma processes: monomer gas is introduced into a plasma reactor in which a discharge produces free radicals and the surface is activated. Thus a direct chemical reaction of the gas species with the substrate can take place on the surface. These processes involve the use of smaller quantities of chemicals, and direct attachment of the functionalized layers to the base material.

In the past year, there has been plenty of activity at the Fraunhofer IGB in the field of plasma polymerization with fluorocarbons. Major attention is currently focused on the plasma-mediated production of domain structures as part of the German Education and Research Ministry's project "Nanofunctionalization of interfaces for data, textile, construction, medical, aerospace and biotechnology".

Nanofunctionalization produces domains

In conventional surface-covering coating processes, the new properties of the surface are determined by the choice of coating material. If, however, domains are formed, rather than impervious layers, surfaces are obtained whose properties are a combination of those of substrate material and plasma covering polymer – in some cases, indeed, entirely new properties arise. Areas of application for this innovative technology are primarily, those of tribology (friction reduction), biology, and medical technology.

In this new process of nanofunctionalization, plasma polymer is deposited with film thicknesses of less than 5 nm (ultrathin layers). The coverage of the layer can be varied from zero to one hundred percent through the variation of the operating parameters. The low layer thickness ensures that the mechanical, magnetic, optical and further properties of the substrate material are retained, while on the nanometer scale the surfaces acquire the properties of the functional groups. The process takes place in a pulsed glow discharge at radio frequency (13.56 MHz) and different layer coverages can be achieved by altering a single parameter.

Controlled adjustment of surface energy

This results in different surface energies, which decrease as the level of coverage with fluorocarbon polymer increases. The parameter generally measured is the specific surface energy per unit area (surface tension). This includes polar and disperse components, which can be determined by means of contact angle measurements. An increase in

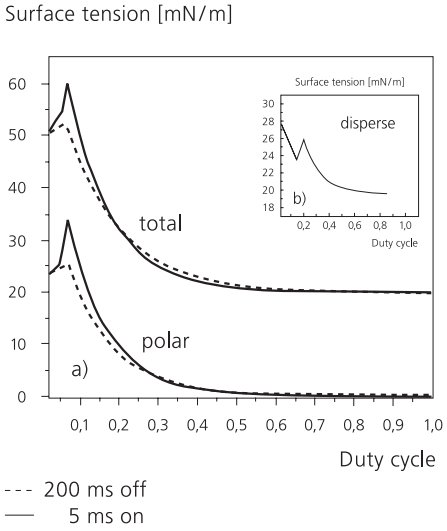

Figure 1: The ratio of pulse on time to pulse duration (on time plus off time), referred to as the duty cycle, influences the surface energy of a plasma-treated material. Depicted here is the change in the polar (a) and disperse (b) surface energy components as a function of the duty cycle with constant pulse off time (200 ms) or constant pulse on time (5 ms).

the surface tension results in better wetting of the surface with the test liquid, while a reduction in surface tension leads conversely to repellent behavior.

By varying the pulse on and off times as depicted in Figure 1 for silicon, it can be seen that above a certain ratio of pulse on time to pulse duration (duty cycle = $t_{on}/(t_{on}+t_{off})$), the polar surface energy initially increases, followed by a sharp decrease of all surface energies. This results in water contact angles (water possesses predominantly strong polar components) of 40° to 110°. In other words, initially wetting (hydrophilic behavior with low contact angle) is observed through to beading of water droplets (hydrophobic behavior with high contact angle). 1-bromonaphthalene, a purely disperse medium, wets in the range from 34° up to a maximum of 72°. The effect is attributed to a surface coverage in the nanometer range, as can be seen on the scanning force micrograph (Figure 2): the domains, as can be seen in part C of the figure, possess a height of less than 5 nm.

Advantages

This approach to the controlled adjustment of surface energy via layer coverage is highly promising, since the process is readily controllable and the modification of the surface is restricted to a minimum coating thickness. Moreover, the chemical composition remains confined to the elements fluorine, carbon, hydrogen, and those of which the base material is composed.

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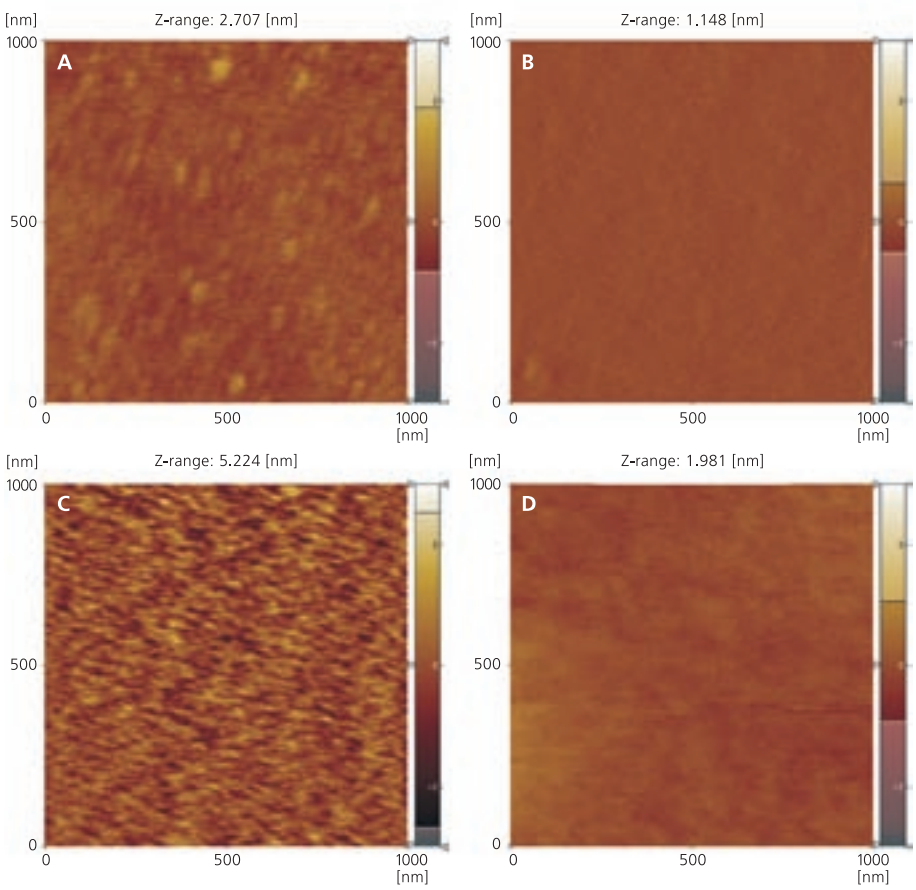
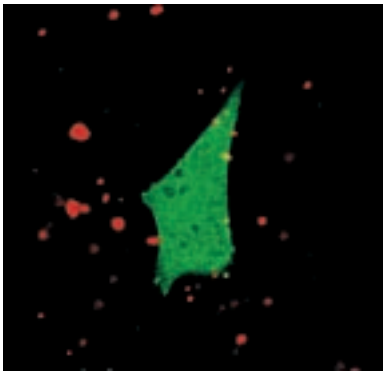
Figure 2: Scanning force microscope measurement of the surface of different plasma-treated silicon wafers. The effect of plasma functionalization is shown for different duty cycles.

A: untreated,
B: etched surface,
C: domain structures,
D: impervious layer.



Biomimetic nanoparticles

Figure 1: Nanocytes® particles (red), carrying an anti-tumor agent, bind to the surface of a model cancer cell (green). Where the particles interact with the cell they appear yellowish green. The silica particles used have a diameter of 1 µm to 4 µm.



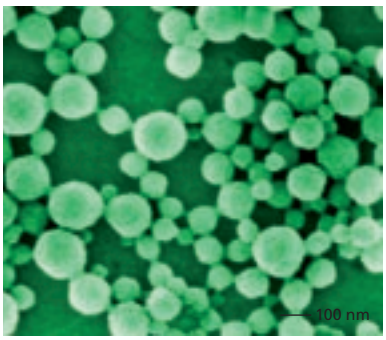


Figure 2: Scanning electron micrograph of molecularly imprinted polymer nanoparticles. Using the lock and key principle, these synthetic particles have the ability to recognize biomolecules.

The diverse properties of biological cells are inspiring nanotechnology to ever-new applications. Thus, in accordance with principles of nature, "biomimetic surfaces" are being designed, composed of amphiphilic molecules and nanoparticles. The resulting surfaces consist of supramolecular structures whose properties derive from the structural interplay of nanoscale building blocks. This allows molecular recognition reactions on the lock and key principle on planar surfaces or in colloidal suspensions, and these reactions form the basis for sensor systems or therapeutic systems in biomedicine or biotechnology. In the purification of product mixtures in pharmaceutical and biotechnology applications, too, macromolecular supports are needed for selective binding of impurities or major products.

Both for therapeutics and for the field of biological separation technology, the "Biomimetic Surfaces" group offers a variety of systems:

Nanocytes® – cellmimetic nanoparticles

Acting, so to speak, as cellular foreign secretaries, cytokines and other signal proteins regulate the interactions of cells with their environment. In R&D practice, membrane proteins in particular are choosy about their immediate chemical surroundings: in many cases they possess complex structures and develop their biological activity only in particular steric conformations and arrangements.

At the Fraunhofer IGB, therefore, hybrid biological-synthetic particles have been developed which simulate the circumstances prevailing on cell surfaces. The surface of these cellmimetic nanoparticles binds proteins in a way which fully retains their biological properties in the natural state on the cell membrane (Figure 1). The basis for these systems, called Nanocytes®, is formed by chemically tailored nanoparticles. The surface of the minute particles can be modified according to application, so that a whole host of different biomolecules can be coupled to them.

These hybrid particles give researchers at the IGB a versatile, modular system which can be used as a new kind of tool in research in the areas of cell biology or immunology, and in diagnostic systems.

Synthetic receptors from molecularly imprinted nanoparticles

A key task in biotechnology operations and other industrial operations is the specific separation of biomolecules or of unwanted by-products. Nanoparticles with a molecular imprint are outstandingly suitable as a solution to these issues (Figure 2). Operating on the lock and key principle, the nanoparticles perform specific recognition of biomolecules, such as amino acids, peptides, and proteins, and also low molecular mass compounds, such as nicotine. At the Fraunhofer IGB, specific receptor nanoparticles of this kind are prepared by miniemulsion polymerization, with typical particle sizes in the range from 100 to 300 nm (Figure 3). The technique of molecular imprinting of nanoparticles, applied and patented by the IGB, offers the advantage over conventional bulk systems of a single-stage synthesis with a quantitative yield and a defined particles morphology.

Surfmer particles get to grips with proteins

Nanoscale spherical polymer particles are equipped with reactive "pincers" for proteins. Surfmer particles, as they

are known, are prepared by co-polymerizing a polymerizable surfactant with commercial monomers. The Fraunhofer IGB surfmer technique allows rapid, single-stage production of particles with which proteins and peptides can be immobilized specifically (Figure 4). They can therefore be used as a replacement for existing multi-stage processes. Surfmer nanoparticles are prepared at the IGB with diameters from 80 to 200 nm. In this way systems are generated which, with their very large specific surface area, decisively enhance the molecular binding properties of the particles.

Bio-loaded polymer particles as biodegradable supports

Polymer particles loaded with biomolecules find multifaceted application in modern medicine, particularly in connection with the administration of active agents. By enclosing active ingredients in polymer particles it is possible to customize and control the time during which the active agents are released. In preparing polymer nanoparticles of this kind, the Fraunhofer IGB uses not only commercially available polymers which are biocompatible, biodegradable, and approved by the FDA, but also polymers synthesized at the Institute itself and having different molecular weights (Figure 5). By selection of suitable polymer systems, these "bio-loaded" nanoparticles are tailored to the individual applications. For more complex applications it is possible for suitable nanoparticles to be functionalized additionally on the surface.

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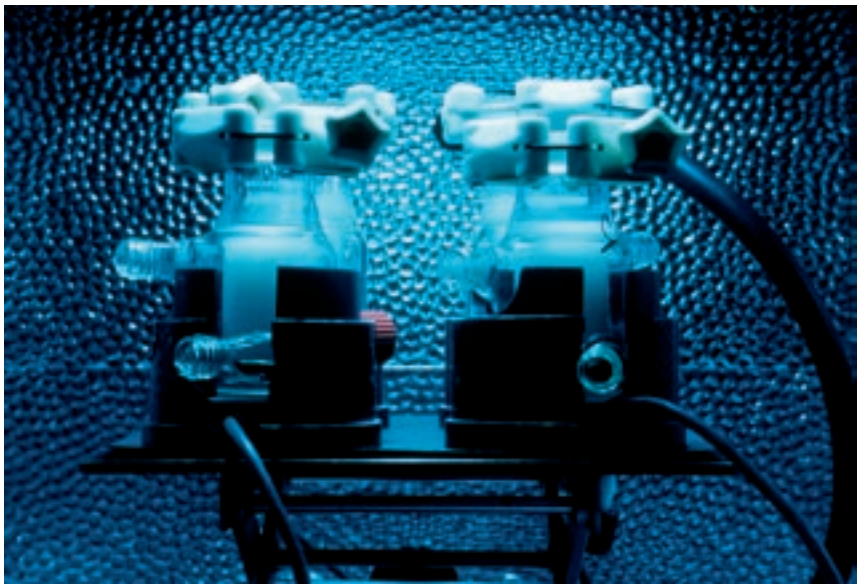


Figure 3: Miniaturized glass reactors for UV polymerizations allow a parallelized search for optimum compositions and process parameters for nanoparticle production.

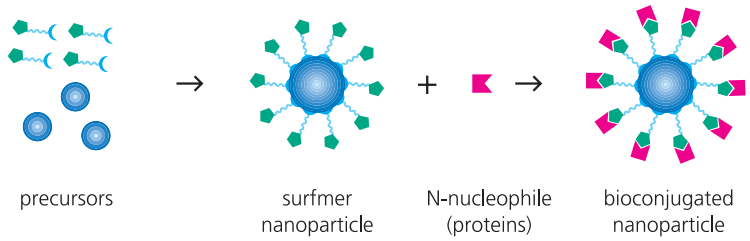


Figure 4: Active ester surfmers enable for the preparation of nanoparticles for bioconjugation in a single-step reaction.

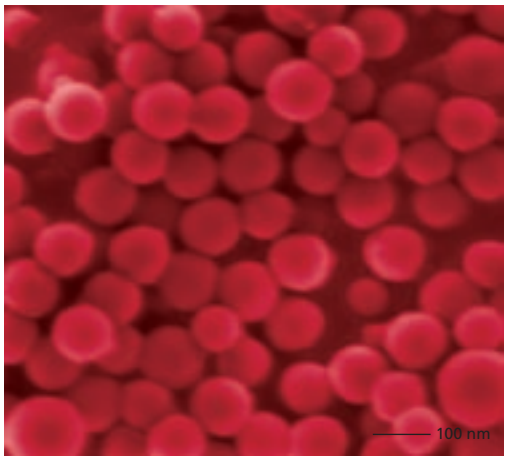


Figure 5: Scanning electron micrograph of biodegradable nanoparticles. These particles can be used for long-term controlled release of active agents in the body.

Functional nanoparticles in use

Nanoparticles enable high-grade chemical and biochemical functionalities to be provided at a high density of integration. For that purpose the nanoparticles can always be suspended in the form of a colloidal solution, and yet their integration into nanoscale or microscale layers provides composite materials having an optimized profile of properties.

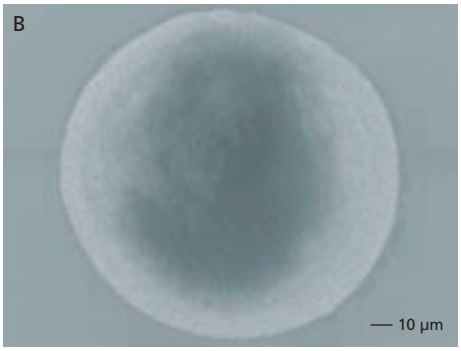
Functional nanoparticles in biochip technology

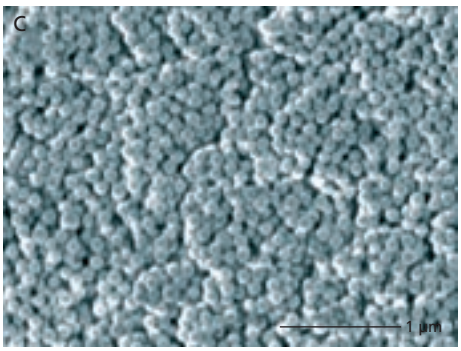
For biology, the miniaturization of biological detection reactions has opened up the gateway to chip technology: A large number of biomolecules can be immobilized in specific locations on glass or silicon surfaces and then subjected simultaneously to a variety of tests. This allows comprehensive insights into complex biomedical interactions with a very small amount of sample material. Accordingly, in the wake of the DNA chips which are now well established in everyday laboratory practice, protein biochips are in the spotlight of current research and development as promising tools for diagnostic purposes: the use of specific capture molecules, anchored on the surface of the chip, allows rapid and easy detection of disease-specific antigens or antibodies. The increasingly important field of proteomics research would also profit enormously from progress in protein chip technology. The "Biomimetic Surfaces" group at the Fraunhofer IGB is therefore working intensively on developing 3D nanostructures and microstructures made up of functionalized nanoparticles for producing biochips with morphologically and chemically optimized surfaces (Figure 1).

Nanoparticulate 3D structures increase the reactive surface

Because of the small size of their building blocks, single or multiple layers of nanoparticles possess a very much larger surface area than the footprint they occupy. Accordingly they offer a three-dimensional reaction space for the attachment of analyte molecules. The use of functional nanoparticles has the advantage, moreover, that the surface of the particles, and hence also the surface of the resulting 3D layer, can be custom-tailored with molecular definition. These layers are applied in microstructured form and so create microstructures each having an adapted coupling chemistry for the bioactive immobilization of highly selective capture proteins. Protein-stabilizing additives ensure that the native protein structure is retained and give the nanoparticle-based protein biochips good storage properties. These biochips are suitable for analysis by mass spectrometry or fluorescence detection (Figure 2), for example.

Figure 1:
A: Nanoparticle microarray on a silicon chip.
B: Scanning electron micrograph of a nanoparticle spot (Ø 150 µm) on a chip, generated using a pin and ring spotting robot.
C: Scanning electron micrograph of the three-dimensional affinity layer comprising functionalized nanoparticles.





Nanoparticle composite membranes permit selective separation

The specific separation of individual components from a mixture is a challenge encountered again and again in separation technology. With their large specific surface area, functional nanoparticles are effective selectors in composite membranes. A composite membrane of this kind with integrated molecularly imprinted polymer nanoparticles provides a high density of specific molecular recognition sites, with which the substance to be separated is initially retained while the mixture flows through the membrane (Figure 3). Whether in quasi continuous operation or by batch methods, the substances thus initially retained by the membrane are subsequently recovered with a separate flow, by means of corresponding process steps. The very high specific surface area of this system, amounting to about 80 m^2 per g of particles, enables high separation performances to be achieved even in the case of layers which are microscopically thin (Figure 4). By modeling the overall process of separation, completion is achieved not only in the controlled production but also in the theoretical principles underlying the development of custom-tailored separation membranes.

3D nano-micro-structures on a porous support as optimized biochips

The hierarchical structures described here, which possess three-dimensional nanoscale and molecular definition and follow laterally microscopic patterns, can also be applied to porous supports and so open up further dimensions for the supply of sample solutions, for washing operations, and for sample analysis.

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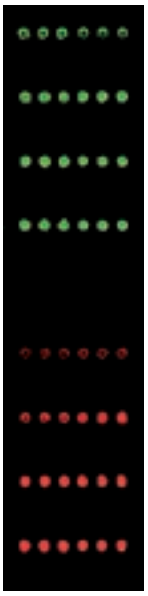


Figure 2: Fluorescence scan of a nanoparticle microarray after incubation with fluorescently-labeled analytes. The amount of particles transferred per spot increases from top to bottom, with a corresponding increase in the amount of bound analyte and hence in the fluorescence signal.

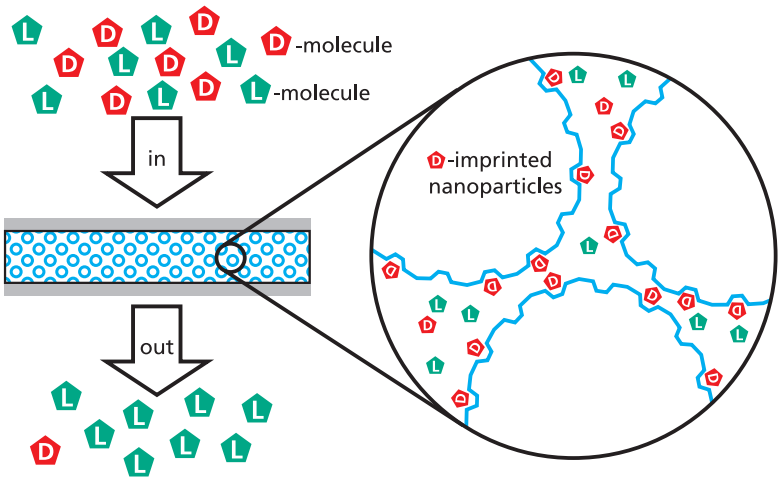


Figure 3: Schematic construction and functioning of a composite membrane with molecularly imprinted polymer particles.

Figure 4: Stainless steel module with integrated composite membrane for actual use in separation.

Initial situation

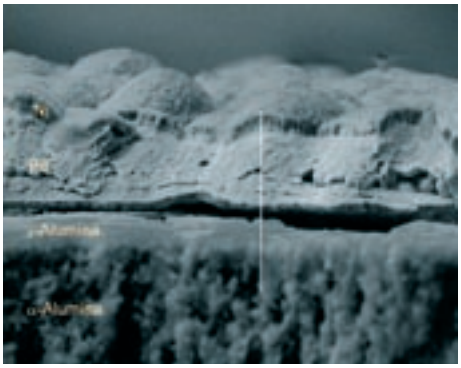
The demand for high-purity oxygen and hydrogen as reactants in petrochemical refinement and as an energy source for fuel cell applications is permanently increasing. Due to their high effectiveness and selectivity, membrane technologies possess a high potential for the purification of such gases. Especially in the case of high process temperatures, inorganic membranes are the only alternative. The Fraunhofer IGB has developed inorganic hollow fiber membranes that combine the specific material properties of inorganic membranes with an effective specific membrane area. In comparison with conventional geometries (disk, tube or multi-channel), such membranes possess the highest packing density (membrane area to volume) and offer very low material consumption.

Manufacturing of ceramic hollow fibers

The Fraunhofer IGB has developed an efficient process for the continuous production of ceramic capillary and hollow fiber membranes. Ceramic capillaries with outer diameters ranging from 0.5 to 3 mm and wall thicknesses ranging from 0.05 to 1 mm are manufactured using a spinning process. It is possible to produce both dense and porous capillaries with pore sizes between 0.2 and 1 mm and porosities of 25 and 70 percent.

Palladium membranes for hydrogen purification

Porous hollow fiber Al_2O_3 membranes are mechanically stable and can be used at high temperatures, thus lending themselves as ideal carrier structures for metallic gas separation membranes. In a first step, α-Al_2O_3-capillaries are coated with palladium-doped boehmite nanoparticles. Afterwards, a palladium layer is deposited using an electroless plating process. The layer thickness can be controlled in the lower micron size range. In addition, further metallic layers can be deposited (Figure 1) on the palladium-doped surface, whereby the thickness of the individual metallic layers determines the composition of the resulting alloys after sintering. The separation performance of such capillaries was demonstrated in separation experiments with hydrogen and nitrogen. At a temperature of 430 °C, a constant hydrogen flow of more than 10 $m^3 \cdot m^{-2} \cdot h^{-1} \cdot bar^{-1}$ was achieved over a period of over 800 hours, with a typical separation factor $\alpha(H_2/N_2)$ of over 1,000 (Figure 2).
Thus the use of very thin metal membranes, which is very interesting for commercial reasons, can be technically realized. Gas-tight modules with membrane areas of up to 0.1 m^2 could be produced using ceramic sealing mass. Figure 3 shows such a module where the outside of the capillaries is coated with palladium.



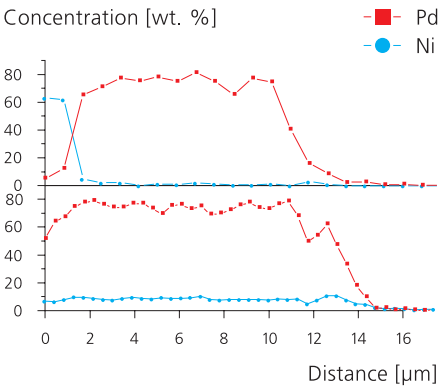


Figure 1: Metallic-ceramic composite membrane. The palladium-nickel coating is deposited on the ceramic carrier structure using an electroless plating process.
Left: Electron micrograph image.
Right: Measurement of element distribution by EDX, before (above) and after (below) thermal treatment for alloying.

Perovskite membranes for oxygen separation

Dense perovskite hollow fibers were developed for the purpose of oxygen separation. Perovskites are mixed ion-conducting oxides with a high electron and oxygen conductivity. The hollow fibers are won from porous green fibers using a controlled sintering procedure (Figure 4). At 850 °C, the fibers show a high oxygen permeability in the order of 1 $m^3 \cdot m^{-2} \cdot h^{-1} \cdot bar^{-1}$ and a good selectivity $\alpha(O_2/N_2 > 1{,}000)$. At present, we are concentrating our research efforts on designing modules and identifying suitable sealing materials.

Applications and outlook

The performance of the hollow fiber membranes developed allows use in applications such as gas separation in the petrochemical industry, in fuel cells technology or as membrane reactors in the chemical industry. The *in situ* reforming of fossil fuels or of bioalcohols and the subsequent use of carbon monoxide for hydrogen production based on the water-gas shift reaction are key technologies for mobile fuel cell systems. The use of ceramic hollow fiber membranes is under investigation for various process steps and is expected to benefit such technologies.

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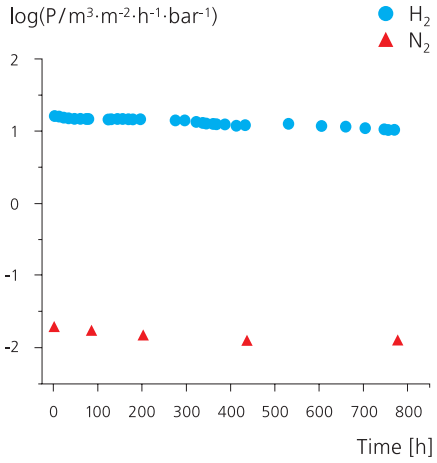
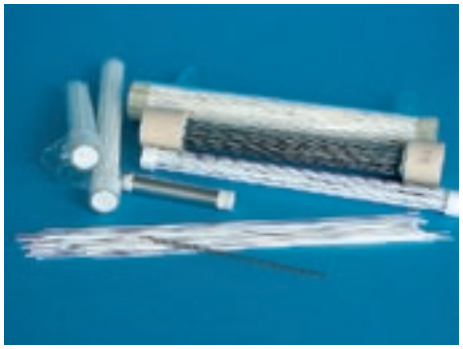


Figure 2: Hydrogen permeability and selectivity of Pd-coated Al_2O_3 capillaries at 430 °C.

Figure 3: Various ceramic hollow fiber modules with separation surfaces of up to 0.1 m^2.



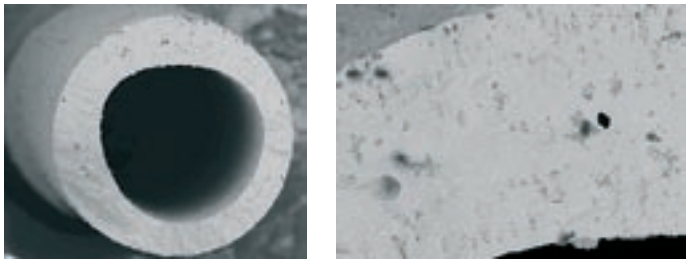


Figure 4 : Typical geometry of a perovskite hollow fiber. Outer diameter 900 µm, inner diameter 600 µm, length 30 cm.

Sustainable biotechnology for industry, urban infrastructure, and the environment

Services

- Production of bulk and fine chemicals and energy from raw, residual, and waste materials, industrial-scale implementation with process-optimized bioreactors
- Modern methods of wastewater treatment, development of modular reactor systems, trialing facilities (semi-industrial)
- Cost-efficient optimization of existing treatment plants by systemic analysis and specific design
- Specific design of membrane bioreactors for sludge treatment (rotating disk filters)
- Development of microbial systems for breaking down environmental and health hazard substances
- Development of processes for using biological breakdown performance to treat groundwater and air
- Assessment of environmental impact and biodegradability of organic chemicals and their by-products
- Aerobic and anaerobic degradation tests

In nature, energy and materials are utilized in accordance with the principles of the circular economy: waste as such does not exist; instead, microorganisms break down organic residues into molecules which can be utilized again by other organisms. Taking this as its pattern, the Fraunhofer IGB offers R&D services for future-proof sustainable production and for disposal on the same basis:

- **Physical recycling and energy recovery from organic raw, residual and waste materials**

  Biological processes can be used, in a way which is beneficial both environmentally and economically, for recovering value from organic raw materials and residues, with a focus on reaction with anaerobic microorganisms. The best-known form of this is the recovery of biogas, from sewage sludge or biowaste, for example, or from other renewable raw materials. However, physical recycling also includes the recovery of inorganic materials such as ammonia and phosphate, as a substitute for synthetic fertilizers.

- **Wastewater treatment and sustainable urban water management**

  Important drivers for the field of water management are coming as a result of the adaptation of municipal treatment plants to the requirements of the EU Drinking Water and Waste Water Directive, which is to be implemented by 2005. Knowledge gained in relation to the elimination of persistent substances from groundwater has now become a basis for the elimination of drugs and endocrine disruptors from wastewater. For the industrial producers of wastewater, increasing pressure is being brought to bear in particular through the introduction of stricter environmental guidelines. As well as offering a broad spectrum of services for treatment plant operators, the Fraunhofer IGB also offers innovative solutions for municipal water management with eye to the future in new towns and city districts in need of overhaul, or if the existing urban infrastructure can no longer accommodate new challenges (climate change, demographic change) or is too expensive to renovate. DEUS 21, a water management concept, is particularly suitable, too, for states with an extensive hinterland and for newly industrializing countries – anywhere, in fact, where there is as yet none of the conventional water infrastructure with its comprehensive sewer network and central treatment plant.

- **Production of natural substances, such as those from microalgae**

  Algae produce vitamins and polyunsaturated fatty acids, dyes and drug ingredients; moreover, their residual biomass can be used as a source of energy. All they need for growth is sunlight, minerals, carbon dioxide, and water. Raw materials from algae are therefore a sustainable alternative to fossil products. The Fraunhofer IGB has developed a special bioreactor for the economic cultivation of microalgae, which is now growing a variety of algae as suppliers of valuable materials. These materials are then worked up, for example, to give proteins, enzymes or nutraceuticals, on a scale ranging from anything to milligrams through to tons.

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Figure 1: Two-stage high-performance plant for sewage sludge digestion, at Leonberg, Germany.

Figure 2: Aeration tank of a treatment plant. The Fraunhofer IGB optimizes and expands existing wastewater treatment plants using systematic analysis and specific measurements.

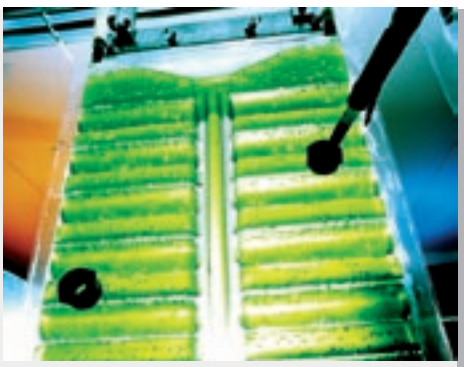

Figure 3: Innovative photobioreactor for economic cultivation of microalgae. A controlled flow system provides the algae with optimum light, causing them to grow with a high cell density.

Left-hand page: Rotating disk filter for low-energy and hence cost-effective filtration of wastewater, such as in municipal wastewater treatment.

Optimization of wastewater treatment plants: safe compliance with nitrogen discharge limits

Baseline

Since the beginning of the last decade of the last century, the quality of German watercourses has improved markedly as a result of the introduction of statutory discharge limits for nitrogen and phosphorus. The EC's Urban Waste Water Directive (91/271/EEC) saw a further tightening of the discharge limits for nitrogen for treatment plants in size class 5 (> 100,000 population equivalents, pe), and entered German national law in the form of the Wastewater ordinance. Consequently, the treatment plants affected must now discharge less than 13 (formerly 18) mg/l of N_{inorg}. Many plants are finding it difficult to comply reliably with this limit, having not been originally designed to do so.

Principles of biological nitrogen removal

In the nitrification stage of the sewage treatment plant, nitrifying microorganisms (*Nitrosomonas* and *Nitrobacter*) oxidize ammonium via nitrite to nitrate. This process needs dissolved oxygen in sufficient concentration. Because of the slow growth of the nitrifying organisms, it is necessary to ensure that the aerobic sludge age is sufficient, so that the bacteria can establish in the plant. The growth rate of the nitrifiers is heavily temperature-dependent, and so at low temperatures nitrification is more difficult to implement. Figure 1 shows the changing level of ammonium nitrogen in the discharge from a sewage treatment plant as a function of the temperature in the aeration tank.

The majority of heterotrophic microorganisms are capable, under what are called anoxic conditions, of utilizing nitrate or nitrite, instead of oxygen, as a terminal electron acceptor. For energy production, a carbon source is needed at the same time, as a hydrogen or electron donor. In denitrification, elemental gaseous nitrogen is produced from nitrate or nitrite, and escapes into the atmosphere. A number of processes have become established here, such as downstream, upstream, simultaneous or intermittent denitrification (DN).

Parameters affecting nitrogen elimination

Effect of dissolved oxygen

If dissolved oxygen is present in the DN zone it is first consumed before denitrification can take place. The input of approximately 3 mg of dissolved oxygen prevents denitrification of 1 mg of nitrate nitrogen.

The sources of oxygen input are, on the one hand, the influents to the DN zone and, on the other, the agitated surface. An overview of the quantities of oxygen introduced via the individual sources is given by Table 1, based on the example of a sewage treatment plant with a population equivalent (pe) of approximately 160,000.

Winter inflow (pO_2 = 10.5 mg/l)	→	220.5 kg/d
Summer inflow (pO_2 = 1.2 mg/l)	→	25.2 kg/d
Returned sludge (pO_2 = 2.7 mg/l, RV = 1)	→	56.7 kg/d
Circulation water (pO_2 = 3.7 mg/l, RV = 1)	→	77.7 kg/d
Agitated surface (20 °C, 1490 m^2)	→	590.3 kg/d
Agitated surface (10 °C, 1490 m^2)	→	727.4 kg/d

Table 1: Oxygen input into the denitrification zone. Example for plant with 160,000 population equivalents, average inflow 21,000 m^3/d.

Effect of hydraulic residence time in the DN zone

For technical reasons associated with the reaction, the hydraulic residence time in the DN zone has a great influence on the possible nitrate conversion. Particularly with upstream denitrification and with high return ratios of the circulation water or recycled sludge, this can result in reduced nitrate conversion. This situation has been investigated experimentally in a pilot plant. The result is depicted in Figure 2. As can be seen, nitrate conversion falls sharply with short hydraulic residence times.

Effect of circulation water flow

A treatment works with an expansion size of approximately 160,000 pe would be unable to comply with the

discharge limit of 13 mg/l for total inorganic nitrogen with the necessary security. Through investigation and a special program of measurements, we found that the cause of this lay in the control of the circulation water. This was coupled with the incoming volume flow and with the nitrate concentration in the discharge from the DN zone. In the case of relatively high incoming volume flows and/or relatively high nitrate concentrations in the DN zone discharge, the circulation volume flow was reduced. When, subsequent to the investigations, this control strategy was altered, there was not a single exceedance of the discharge limits, which were in fact visibly reduced.

Avoiding back-contamination by digestion water

Two years ago, in cooperation with the Fraunhofer IGB, the *Abwasserzweckverband Heidelberg* (Municipal Association for Sewage Treatment), started the operation of a high-performance digestion facility as the first stage in sludge digestion. At the present time, in a pilot plant consisting of a 3.5 m³ high-performance digestion stage with rotating disk filter and air stripping of the filtrate, the Fraunhofer IGB is investigating the possibility of reducing the back-contamination of the plant with nitrogen from the digestion water, economically. The overall expectation is that it will be possible largely to prevent the ammonium contamination of the plant, and so to reduce the incoming nitrogen load by at least 20 percent.

Outlook

By carefully evaluating the performance capacity of a sewage treatment plant and optimizing its operation accordingly, it will be possible in some cases, even without extensive building work, to comply with the 13 mg/l requirement in the future.

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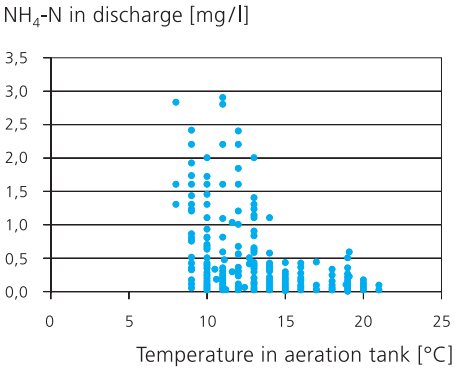


Figure 1: Levels of ammonium nitrogen in the discharge from a treatment plant as a function of the temperature in the aeration tank.

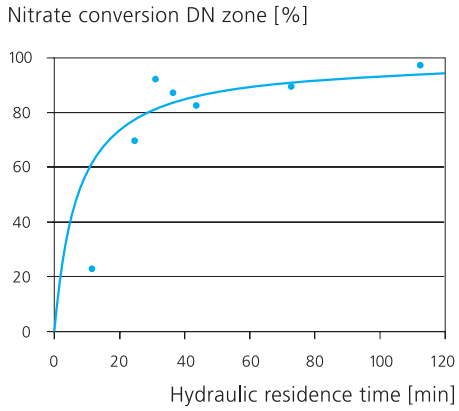
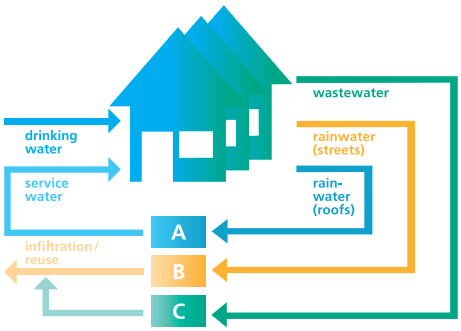


Figure 2: Effect of hydraulic residence time on nitrate conversion in the denitrification (DN) zone.



A roof-rainwater treatment

B treatment of rainwater (streets, public areas) or of weakly polluted wastewater (grey water)

C sustainable wastewater treatment

Figure 1: Diagram of water circulation in the new "Am Römerweg" settlement in Knittlingen.

Background

The majority of centralized sewerage systems in Germany have grown historically, but have a series of minuses. On the one hand, the long, subterranean sewers are very expensive both to build and to maintain; on the other hand, the transport medium they use is water, a product not just valuable but, indeed, vital. Wastewater treatment is made more difficult as well by its dilution with rainwater: in the event of torrential rain, untreated wastewater frequently enters the rivers along with the rainwater.

New, innovative solutions are therefore sought by the Fraunhofer IGB, working together with the Fraunhofer ISI (Institute for Systems and Innovation Research, Karlsruhe) and the Institute of Environmental Engineering (ISA) at the RWTH Aachen University as part of the project entitled DEUS 21 (Decentralized Urban Infrastructure Systems). On the newly built "Am Römerweg" estate in the Knittlingen district of Pforzheim, Germany, a form of municipal water management that is unique in the country to date is being realized for an initial number of about 350 citizens. This is a new design of semi-decentralized urban water and wastewater management, first providing quality-assured rainwater utilization and secondly employing modern wastewater treatment technology with recovery of substances of value.

Rainwater utilization

The project has a number of components (Figure 1). Rainwater from roof expanses and residential roads is collected, stored underground, processed in accordance with the provisions of the German Drinking Water Ordinance, and supplied as utility water via a separate supply circuit. It can be used for bathing and showering, flushing the WC, watering the garden, and in washing machines and dishwashers.

Although roof-collected rainwater, in terms of organic soiling, is almost up to drinking water standard, its salt content is almost the same as that of fully demineralized (deionized) water. Within a household, this quality of water leads to considerable economic advantages, considering the limescale damage affecting all of the systems which require water to be heated. Limescale removers, fabric softeners, and the like could become a thing of the past.

Wastewater transport and treatment

The collection and transportation of domestic wastewater is accomplished by means of a vacuum sewerage system, requiring substantially smaller pipe diameters than conventional sewers. Residents have the option of taking the vacuum system right inside their houses, which allows the installation of water-saving vacuum toilets. A kitchen waste disposal unit can be installed as well, in which case the comminuted kitchen waste is taken off together with the wastewater, with no need for a separate can for biodegradable refuse.

Water treatment installations are being erected on a section of ground at the edge of the building area, on which it is also planned to accommodate the rainwater processing and vacuum station. Since the residential area is only gradually being built, the plan is to build up these installations progressively while further optimizing the wastewater treatment procedure.

First of all, the incoming wastewater is separated using a rotating disk filter (microfiltration unit; see forthcoming paper in the current Biennial Report relating to the membrane bioreactor

plant at Heidelberg-Neurott) into a viscous concentrate stream and a solids-free filtrate stream. The concentrate stream is digested in a high-performance anaerobic stage with integrated microfiltration, producing biogas which is utilized as a regenerative energy source. Since the microfiltration procedure uncouples the solids residence time from the hydraulic residence time, the anaerobic degradation, which follows first-order kinetics, can be maximized.

From the digestion filtrate water, the nutrients that are present in relatively high concentration therein are recovered: in an MAP (magnesium ammonium phosphate) precipitation procedure, the N/P fertilizer Struvit is produced, while in an ammonia stripping operation ammonium salt is formed which can be used as a nitrogen fertilizer. The remaining organic load in the filtrate water after the anaerobic unit and the recycling stations is passed to the filtrate stream after the primary filtration.

This filtrate stream is cleaned either by means of a membrane-supported aerobic technique (nitrification/C degradation) with upstream denitrification, or by means of anaerobic methane digestion, from whose discharge the nutrients nitrogen and phosphorus are recovered. In any case, as a result of the downstream microfiltration, the discharge from the treatment plant is free from bacteria, the pollutant load of the discharge has been reduced to the degree required in the discharge of large-scale treatment plants, and the amount of organic trace substances (drugs/endocrine disruptors)
in the discharge is substantially reduced compared to that from large-scale plants. This reduction is likewise the result of employing the filtration technology.

Current situation and outlook

The ceremonial beginning of the development works on the site of the new community was the groundbreaking on June 8, 2004. Since then the infrastructure has been put in place (Figure 2), and in parallel with this some plots have been sold: these sales have been more successful so far in that part of the site in which the research project is being implemented than in the remaining part. Initial administrative steps have already been successfully carried out, and in August 2004 the permit required under water law was granted.

The results of this research project are of interest not least from an international standpoint. The water problems that are coming to a head worldwide can be solved only by means of innovative decentralized supply and disposal systems. The concept developed is also suitable for those developing and newly industrializing countries that are affected by water shortage and do not have a sewage infrastructure yet, since it obviates the construction of complex, expensive drainage systems for the central collection of wastewater.

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Figure 2: As part of the development work the wastewater infrastructure in the new settlement is being erected.

Modern decentralized wastewater treatment as exemplified by the membrane bioreactor (MBR) plant Heidelberg-Neurott

Parameter	3 year pilot study	After completion of research project
	[mg/l]	[mg/l]
COD	75	60
BOD_{5d}	15	15
NH_4-N	10	10
Total N	18	13
Total P	-	1

COD: chemical oxygen demand
BOD_{5d}: biological oxygen demand after 5 days

Table 1: Effluent limitations of the MBR plant Heidelberg-Neurott

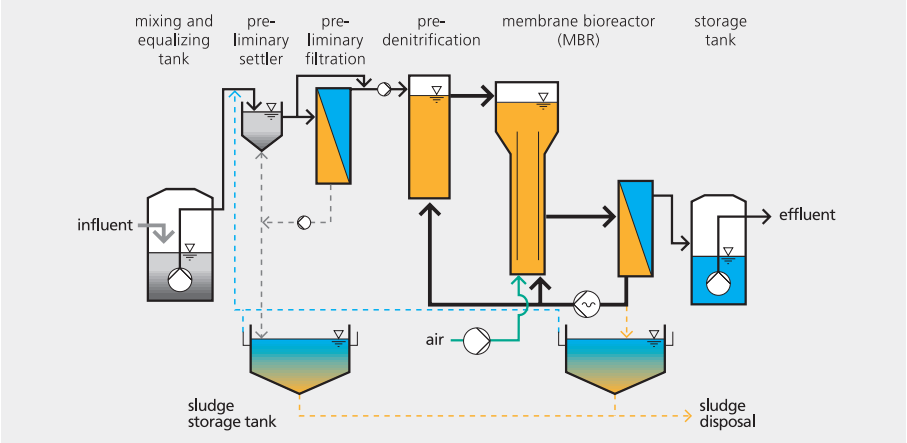

Figure 1: Process flow chart for the planned Heidelberg-Neurott MBR plant. Preliminary filtration and sedimentation form part of the mechanical pre-clarification process. During biological purification, mainly nitrogen (denitrification) and carbon (MBR) are broken down. The activated sludge stage of the bioreactor (nitrification) is combined with a membrane filtration stage for the separation of the activated sludge from purified effluent.

"Decentralized Urban Infrastructure System (DEUS 21)" is a project supported by the German Federal Ministry of Education and Research (BMBF) with the aim of developing and testing of a new concept for semi-decentralized water and wastewater management in collaboration with other German research institutes and industrial partners. The Fraunhofer IGB is planning to build a modern MBR plant in Heidelberg-Neurott of approximately 100 population equivalents. The plant, where wastewater and rainwater will be separated is intended to showcase the effectiveness and profitability of the concept.

Initial situation

The small village of Neurott, situated in a rural area south of Heidelberg, has a population of 60 and is made up of farms and an inn with approximately 30 population equivalents. The daily total average wastewater flow amounts to 6.6 cubic meters. In the summer, tourist trade can easily push the volume of wastewater up to 9.9 cubic meters per day.
At present, domestic wastewater is collected in septic tanks, whose contents have to be disposed of on a regular basis. The local environmental agency has made it incumbent on the *Abwasserzweckverband Heidelberg* (Municipal Association for Sewage Treatment) to take remedial measures to improve environmental situation.

Effluent limitations

The effluent limitations imposed by the local environmental agency are accordingly strict. These are listed in Table 1, which shows the differing values for operations during the pilot study and after completion of the research project. The quality requirements for effluent discharge into the nearby Leimbach stream correspond to the limits for class 5 wastewater treatment plants, i. e. > 100,000 population equivalents or even stricter.

Process design of the pilot plant

Figure 1 depicts the concept proposed by the Fraunhofer IGB for the decentralized treatment of domestic wastewater from Neurott. The untreated wastewater is pumped from a mixing and equalizing tank into a preliminary settler. Preliminary sedimentation is only necessary if the preliminary filtration function is temporarily out of order. Preliminary filtration serves to separate the raw wastewater into a solid-free and carbon-poor filtrate that is channeled into the biological purification stage (denitrification and membrane bioreactor) for further treatment and a particle-rich bleed that is collected and transported as primary sludge into the digester of Heidelberg's central wastewater treatment plant. In the event of a lack of carbon for the biological removal of nitrogen, part of the raw wastewater can be pumped directly from the primary settler into the denitrification reactor.

The biological removal of nitrogen is carried out by the process of pre-denitrification. Here, the pre-clarified waste-

water together with the cycling sludge, i.e. returned activated sludge from the MBR, is pumped into a mixed tank where microorganisms convert nitrate to elementary nitrogen. The next treatment stage is nitrification, which takes place in an aerobic bioreactor, followed by membrane filtration to achieve separation of the activated sludge (membrane bioreactor).
The treated effluent is periodically pumped into the Leimbach stream from a collecting well while the secondary sludge is collected in a tank for further treatment at Heidelberg's central wastewater treatment plant.

Dimensioning

With regard to dimensioning of the individual plant components, the Fraunhofer IGB possesses substantial expertise. The challenge at Heidelberg-Neurott lies in the uncertainties concerning the quality and quantity of the raw wastewater.
The hydraulic dimensioning was carried out on the basis of a number of scenarios combining utilizable storage volume and varying plant capacity. It should be noted that, unlike conventional wastewater treatment plants, the performance of MBR plants does not depend on the characteristics of the sludge, but on the throughput of the filters.
Extensive investigations preliminary to the dimensioning of the biological purification stages have confirmed the relative robustness of the process. A relieving factor is that the highest capacities are required during the warm time of the year, when biological activity reaches its peak.

Commercial application of the rotating disk filter

Preliminary filtration and the membrane bioreactor both use the rotating disk filter developed at the Fraunhofer IGB. The latter is a dynamic membrane filter, whose functional principle is illustrated in Figure 2. It is composed of a cylindrical housing containing a stack of ceramic membrane disks on a rotating hollow shaft. Through application of a pressure gradient, sludge is filtrated from the outside (influent side) to the inside of the membrane disk, with the result that a covering layer develops on the outside of the membrane. This surface layer is controlled by the centrifugal force field generated.
The rotating disk filter, which is manufactured under license by the company Gebrüder Bellmer. is being applied on a large scale for the first time in Heidelberg-Neurott.

Status of the project 2004

Preparations for proper wastewater disposal in the village are under way with the construction of a pressure sewer system with a total of 7 pumping stations. The detailed planning of the plant in conjunction with the two companies, Eisenmann (plant engineering) and Gebrüder Bellmer (wastewater equipment and technology) as well as the Heidelberg Sewage Treatment Association should be completed at the beginning of 2005. Construction of the plant in the former equipment store of the local fire brigade (Figure 3) is scheduled for the second quarter of 2005.

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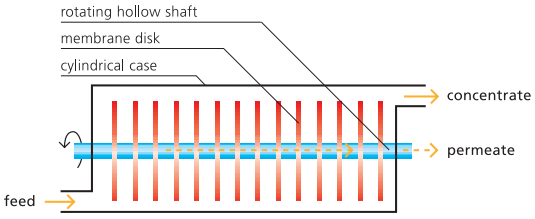

Figure 2: The rotating disk filter developed at the Fraunhofer IGB for use in preliminary filtration as well as in membrane bioreactors.

Figure 3: The MBR plant will be constructed here in 2005, in the former equipment house of the local fire brigade.

Decentralized wastewater treatment: adaptation of processes to subtropical countries

Initial situation

South American countries have an enormous need of well functioning wastewater purification systems, particularly in the densely populated regions, in view of the environmental problems. The statutory framework is in many cases already in place; but the implementation is missing, which in the majority of cases founders at financial hurdles. Consequently, at the present time, just 10 percent of wastewater in the major South-American cities goes for treatment. This results in enormous pollution of lakes and rivers, and limitations on water supply in respect to qualitative and/or quantitative factors (Figure 1). As an alternative to large, expensive, centralized treatment plants, decentralized solutions are being considered in many cases.

Piracicaba, a city with a population of 320,000 in São Paulo State, Brazil, has at any rate 35 percent connection to wastewater treatment systems. The city is pursuing ambitious plans, and aims by 2007 to have all its inhabitants hooked up to treatment plants. Because of its geographical situation, a central treatment plant for the entire city is out of the question. The municipal concerns responsible for water supply and disposal decided in years gone by to erect a large number of relatively small treatment plants in the urban area. In the majority of cases they adopted conventional decentralized solutions, which were developed more for the rural region (Figure 2). That decision has now resulted in a number of problems, the solutions to which are being sought in cooperation with the Fraunhofer IGB. Evaluating the treatment plants, with corresponding measurement programs, represents the first step in a cooperative venture between the Brazilian and the German partners in a project assisted financially by the German Ministry for Education and Research (BMBF).

Decentralized wastewater treatment for densely populated urban structures

With future treatment plants, new concepts are to be followed, which effectively treat wastewater to remove organic substances in closed systems, coupled with energy recovery and/or recycling of nutrients like phosphorus and nitrogen.

The statutory provisions governing treatment plant discharges in Brazil are relatively stringent, particularly as regards emissions of pathogenic organisms. In order to avoid aerosols and odors, the plants are to be closed systems and must include further treatment of the outlet of the plant so that, in a sustainable water management concept, the treated wastewater can be used as service water. Great importance is attached to processes which operate with low sludge levels, in order to minimize or, ideally, avoid disposal problems. The Fraunhofer IGB has already begun with investigations in Germany and has established the necessary contacts on site.

Model project

In Piracicaba, gradually, small, self-contained neighborhoods are being set up, which require connection to a treatment plant. Decentralized solutions are particularly well suited to this kind of situation. A number of plants are to go into operation, initially, on the site occupied by a university to show how digestion of organic wastes works in the developed process as well as effective treatment of the wastewaters, while also taking account of possibilities for appropriate rainwater management.

Also under discussion as a site for a model treatment plant is a district of the city that is earmarked for high tourist expansion. At present there are 600

people living there, with plans for about 1,800 inhabitants in the future. The treatment plant is to be erected on the site of a historic sugar factory, which directly borders the residential and recreation area.

The utilization of water, heat and energy looks to be a good possibility, with minimal expense, and will convince both users and visitors to the plant as a whole of the benefits of innovative processes.

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Financial support

The project entitled "Decentralized water supply and disposal in conjunction with energy recovery and recycling, taking account of hygiene aspects, for the Piracicaba (Brazil) region" is being financially supported by the German Ministry of Education and Research (subvention code 02WD0507).
German industrial partners involved are the companies MAXX of Rangendingen and GeoTerra of Aachen.
The Brazilian project coordinator is the Universidade Metodista de Piracicaba (UNIMEP).

Figure 1: The water quality in Piracicaba is to be significantly improved, by treating the wastewater in modern, compact decentralized treatment plants before it enters the river.

Figure 2: View of a wastewater lagoon established as decentralized treatment plant. Disadvantages of this processes are particularly for urban structures, the large amount of space, and the occasional odor pollution caused by overloading.

Wastewater management in Ecuador

Figure 1: Chicken breeding in floor management. Up to 25,000 chickens are held in this shed. On one chicken farm there are up to 500,000 chickens in 20 sheds.

Figure 2: Dr. Oscar Silva, head of pig breeding for the whole company, and the Fraunhofer team (Claudia Rittner, Dr. Dieter Bryniok, Dr. Werner Sternad) at a pig farm.

Initial situation

The Fraunhofer IGB was tasked by the International Finance Corporation (IFC), a subsidiary of the World Bank that supplies credit to private companies, with assisting the major producer of poultry and pork products in Ecuador in developing its wastewater management and waste management regime at selected production sites.
The company operates a total of 95 production sites, which are distributed over wide areas of the country. Following new environmental legislation, industry in Ecuador has until 2008 to ensure that wastewaters from industrial production, before being discharged into surface water bodies, comply with limits which meet international standards and are comparable with the EU directives. Unlike Western Europe, however, Ecuador largely lacks a public wastewater infrastructure. Enterprises in Ecuador are therefore, basically, direct dischargers and must observe the corresponding guidelines. There are similarly stringent requirements affecting the disposal of solid waste.
The company has set itself the objective of meeting the new statutory requirements as early as 2006. The management of the company is able to draw on extensive experience in quality management and in the introduction of hygiene standards which not only meet international levels but may even have a template function.
The job of the Fraunhofer IGB was to present sound proposals for wastewater and waste management for selective production sites. Following a situation analysis, various technical means were to be indicated, and compared, the most favorable variants selected on the basis of cost-benefit estimations, and an action plan drafted.

Implementation

In preparation for a tour of inspection, a questionnaire developed by the Fraunhofer IGB about the key framework data was answered by environmental officers at the company's headquarters in Quito, Ecuador. The inspection tour itself, lasting a week, visited a reproduction farm for poultry, a hatchery, a poultry farm, three poultry slaughterhouses, a reproduction farm for pigs, a pig farm, a pork slaughterhouse, two sausage factories, with slaughtering of cattle and pigs, and a production factory for shrimps and tilapia. Following the visit, additional information was requested from the head office by e-mail and telephone.

Result

Even during the inspection tour, at a number of production sites immediate concrete measures were proposed to improve the existing situation. Longer-term measures were mooted in a concluding discussion after the tour, and set out at length in a final report. The measures proposed relate to company-wide installations, such as septic tanks and open lagoons, for example, which are widely used for wastewater treatment, or the disposal of animal corpses, but particularly solutions for the individual sites. Here, in most cases, an anaerobic wastewater treatment with biogas production was recommended. In some cases it is possible here to draw on existing and well-functioning facilities such as rendering plants, flotation plants for mechanical wastewater treatment, simple biological treatment plants such as biofilters, or else optimization programs aimed at reducing water consumption. None of the existing wastewater treatment facilities, however, is able at present to comply with the limits laid down in the new Ecuadorian environmental legislation. Even some new wastewater treatment plants already

being offered would not be suitable for such compliance, following analysis by the project team.
In the absence of sufficient data, plausible estimates had to be used in drawing up the proposed processes. Precise plant designs or cost calculations could not be carried out for that reason, however. On this basis, the action plan envisages a first step involving a measurement program for determining the key wastewater parameters.

In a follow-on project, already with the IFC as a tender, the tasks will be to compare, across the whole company, digestion and composting for the treatment of organic industrial waste, taking into account the energy requirement, the possible saving in terms of greenhouse gas emissions, the trading of emissions rights, and logistical aspects.

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Figure 3: Open lagoon for the treatment of wastewater from a pig farm. These installations have considerable drawbacks, such as the emission of odors, ammonia and methane. The solids in the wastewater, moreover, can easily clog the lagoons, leading to short circuit flows. Additionally, aerobic installations of this kind are breeding grounds for mosquitoes, and contribute considerably to the spread of yellow fever and dengue fever.

Figure 4: Simple biofilter unit for the treatment of wastewater from a sausage factory.

Eicosapentaenoic acid (EPA) from algae

The essential dietary component eicosapentaenoic acid

Eicosapentaenoic acid (20:5, EPA) belongs to the omega-3 fatty acid class. These are highly unsaturated fatty acids with specific positioning of the first double bond. Many organisms cannot synthesize omega-3 fatty acids, and they are essential. In humans also, they have to be supplied during childhood development.
The omega-3 fatty acids act as precursors for important tissue hormones. A deficiency of omega-3 fatty acids leads to an increased risk of diseases of civilization such as cardiac infarction and stroke [1]. In addition, antioxidant and hence cancer-protective effects of the omega-3 fatty acids are under discussion. The main source of EPA in the diet is fish oil from marine cold-water fish. A low fish intake leads to an undersupply in broad parts of the population.
The industrial production of the omega-3 fatty acids also relies on fish oils. The disadvantages of this, how-ever, are the flavor which is experienced as unpleasant and the accumulation of toxic heavy metals, especially mercury, from the environment [2]. Hence there is an intensive search for other sources for the industrial production of EPA.

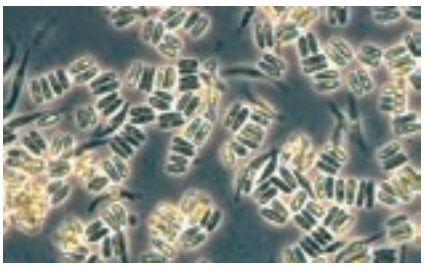

Figure 1: Micrograph of *Phaeodactylum tricornutum* (magnification 400 x).

Phaeodactylum as EPA producer

The marine microalga *Phaeodactylum tricornutum* UTEX 640 combines all the important criteria for an industrially utilizable EPA producer: rapid growth, high EPA content, lack of substances with antagonistic action such as docosahexaenoic acid (22:6, DHA) and purely photo-autotrophic production, with only sunlight as energy source and carbon dioxide as carbon source.

Phaeodactylum tricornutum is cultivated in a photobioreactor [3], the Flat Panel Airlift (FPA) reactor, specially developed at the Fraunhofer IGB. The FPA reactor is characterized by an optimal light supply on account of specially designed flow control. Its production from two deep-drawn PVC half-shells guarantees low production costs.

Under laboratory conditions, all relevant operating parameters and in particular components of the medium were studied in detail. Urea as the nitrogen source, a mean aeration rate of 0.66 vvm (volume per volume per minute) and a relatively low carbon dioxide concentration of 1.25 percent (v/v) were found to be optimal. By means of this operating mode adapted to the organism, productivity levels of 2.35 grams dry substance per liter per day were already achieved at 1,000 $\mu E \cdot m^{-2} \cdot sec^{-1}$ (E = Einstein, corresponds to half sunlight strength). The biomass concentration in the reactor rises to 26 grams dry substance per liter. At average light intensities, up to 10.6 percent of the incident light energy is converted into biomass. This is 35 percent of the theoretically possible maximum value.

Outdoor EPA production

From the beginning of May until the end of October, ten production reactors were operated in parallel outdoors (Institute Site, Stuttgart). The modular construction mode enables separate control of each individual reactor, as a result of which the process control could be rapidly and efficiently adapted to outdoor conditions. In mid-year, with a North-South orientation (reactor flat sides facing North and South) and 80 cm distance between the individual reactors, productivity levels of 530 mg dry substance per liter per day were achieved. In June, with good weather conditions, these values were just under 40 percent higher, and reached 730 mg per liter per day.

In the laboratory and outdoors, the EPA content is constant at 5 percent of the total dry biomass. This results in EPA productivity levels of the order of 27 mg EPA per liter per day as an annual average. An EPA content of 30 percent of the total fatty acids facilitates the purification process.

Outlook

High growth rates, a high EPA content and low capital costs for the reactor provide the preconditions for the industrial photo-autotrophic production of omega-3 fatty acids using microalgae.

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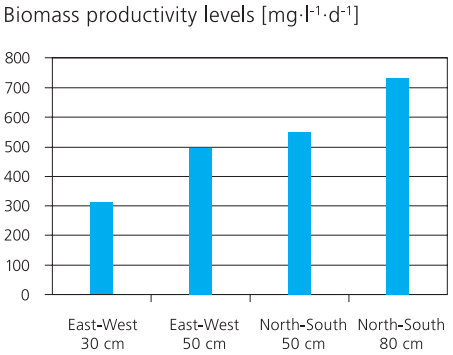

Figure 2: Biomass productivity levels of *Phaeodactylum tricornutum* in June under outdoor conditions with different reactor orientations and distances.

Figure 3: Outdoor production plant with ten FPA reactors on the Institute Site in Stuttgart.

Figure 4: FPA reactors at the outdoor production plant on the Institute Site in Stuttgart.

Patents and licenses

In the year under review the Fraunhofer IGB filed 121 patents; 66 are applied for in Europe and oversea countries. In 2004, eleven inventions have been applied for and 16 patents were granted.

Examples of patents granted in 2004:

Peptides as agonists and / or inhibitors of amyloid formation and / or cytotoxicity and their use against Alzheimer's disease, type II diabetes mellitus and spongiform encephalopathy
EP 0 885 904 B1 granted 2004-03-24
Certain peptide molecules can be used as the basic structures (template molecules) for inhibiting and analyzing amyloid formation and cytotoxicity in amyloid illnesses. These peptides have an effect on the molecules which are responsible for the amyloid illnesses (for their part amyloid-forming peptides and proteins). The peptides are thus either inhibitors themselves or agonists of amyloid formation and cytotoxicity or can serve as a template for identifying and producing further inhibitors and agonists and can be used as molecular tools during analysis.

Metal-containing ribonucleotide polypeptides
US 6,770,455 granted 2004-08-03
The present invention relates to metal-containing ribonucleotide polypeptides (RNP) and a process for their production, their use as medicaments containing ribonucleotide polypeptides or their molecular-biological equivalent structures and / or parts and / or derivates.

Reactor module with capillary membranes
EP 1 297 106 B1 granted 2004-11-10
US 6,821,762 granted 2004-11-23
The present invention relates to a reactor module for use in artificial organs and contains ceramic hollow fibers on which cells are immobilized.

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Further patents for licensing:

Superpotent calcitonin analogs having greatly increased hypocalcemic action *in vivo*
US 6,265,534 granted 2001-07-24
DE 19736457 granted 2001-08-23
US 6,617,423 granted 2003-09-09

Superpotent calcitonin analogs have greatly increased hypocalcemic action *in vivo*. These calcitonins and calcitonin derivates are employed for the therapy of, for example osteoporosis, Paget's disease or hypercalcemia. The calcitonins and calcitonin derivates are distinguished by a bridging of the amino acids present in the positions 17 and 21. By means of suitable choice of the amino acids present in these positions an 18-membered or 19-membered ring is produced.
The first US-patent (6,265,534) describes that this ring leads to an increased conformational stability and to an increased activity of the modified calcitonin. A particularly suitable hCt (human calcitonin analog) is a cyclo^{17,21}-[Asp^{17}, Orn^{21}]-hCt having a 19-membered ring structure between the lactam-bridged Asp^{17} and Orn^{21}.
The other US-patent (6,617,423) describes that a particulary suitable hCt (human Ct) analog is the cyclo^{17,21}-[Asp^{17}, Orn^{21}]-hCt according to the invention having a 19-membered ring structure between the lactam-bridged Asp^{17} and Orn^{21}.

New human recombinant interferon-gamma
DE 4036856 granted 1992-05-27
EP 0652903 granted 1998-03-04
CA 2,096,532 granted 2002-12-31
JP 3219274 granted 2001-10-15

The invention concerns a new mutant of gamma-interferon. This new polypeptide contains 134 amino acids. Amino acids 1 to 132 are the same as those of natural gamma-interferon. The first amino acid, methionine, in the zero position is also present, as has been demonstrated by protein sequencing. The amino acid in position 133 is leucine instead of glutamine. The invention also concerns DNA sequences and plasmid DNA (DSM 6238) coding for this new polypeptide. The invention further concerns the use of the polypeptide as a drug as well as its use as a fine-chemical reagent for *in vitro* experiments.

Thermostable variants of human interferon-gamma
DE 19535853 granted 1999-04-01
US 6,046,03 granted 2000-04-04
EP 0851926 granted 2003-07-30

The invention provides new variants of recombinant human interferon-gamma (rhIFN-gamma), vectors and host cells for their production, and therapeutic methods employing them. The variants are characterized by the substitution of one or more pairs of amino acids selected from Glu^{8}-Ser^{70}, Ala^{18}-His^{112}, Lys^{81} Leu^{121}, and Gln^{49}-Leu^{96} by pairs of Cys residues, and optionally by the deletion of one to ten amino acid residues from the C-terminus of the native IFN-gamma sequence. The variants of the invention exhibit greater thermal stability and no loss of biological activity as compared to native-sequence rhIFN-gamma.

Contact licenses

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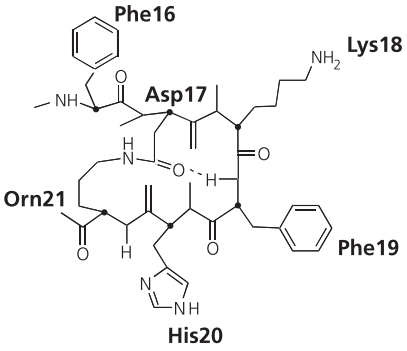


Figure 1: Structure of calcitonin analog CC19.

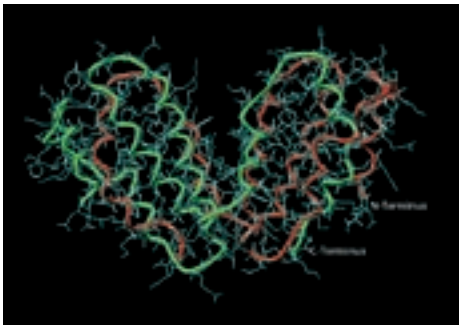
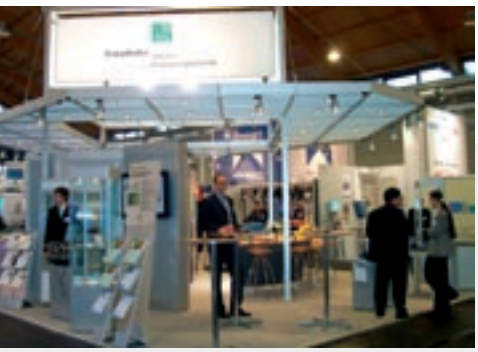
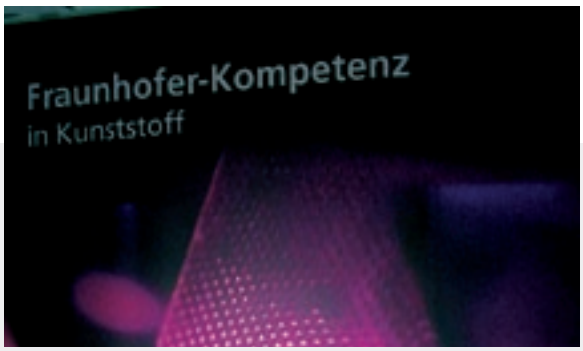


Figure 2: Dimeric structure of human interferon-gamma.

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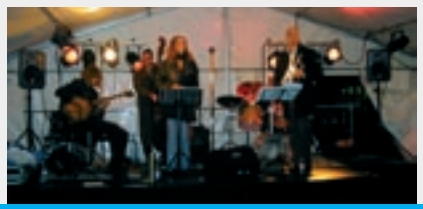

Events

Trade fairs

Awards

Names, dates, events 2004/2005

Cooperations

Outlook 2005

Publications

Jochen Schwenk receives the Hugo Geiger Prize 2004 at the annual conference of the Fraunhofer-Gesellschaft in Dresden.

Hugo Geiger Prize – promoting talented young scientists

The Bavarian government instituted this prize five years ago, on the occasion of the 50th anniversary of the Fraunhofer-Gesellschaft. It is named for former Bavarian secretary of state Hugo Geiger – patron of the inaugural assembly of the Fraunhofer-Gesellschaft on March 26, 1949. The Hugo Geiger Prize is awarded for outstanding, application-oriented doctoral theses or dissertations in the field of life sciences. The prizewinning papers are selected on the basis of scientific quality, industrial or economic relevance, novelty, and an interdisciplinary approach. The work must be directly related to a Fraunhofer institute or have been written at a one. This year, the first-placed winner will receive 3,000 euros in prize money, second place 2,000 euros and third place 1,500 euros.

Hugo Geiger Prize 2004: Jochen Schwenk identifies cell wall proteins of yeast

At the Fraunhofer IGB Jochen Schwenk has been studying new approaches for the identification of potential virulence factors in *Candida albicans*, a fungus that can cause life-threatening infections in patients with a weak immune system. Currently available antimycotic drugs produce many unwanted side effects. To enable biological scientists to develop a specific pharmacological treatment, they need to know more about the action mechanisms of the fungal pathogen. Hyphae, the thread-like growth form of the fungus, enable it to enter organs and to destroy them. However, the first contact between the fungus and the target cell is through attachment or adhesion, and is controlled by certain proteins. The proteins that provide the adhesion are – just like the proteins involved in hyphae formation – promising molecular targets for specific medicines. In his thesis Jochen Schwenk investigated exactly these proteins and was awarded the second 2004 Hugo Geiger Prize for his work.
The proteins that provide the adhesion are located in the cell wall of the fungus cells. Schwenk has developed a two-stage process that allows these proteins to be isolated from the cell wall and subsequently to be analyzed. Thus, he identified a total of 14 different cell wall proteins, including a previously unknown one (see page 26).

Research award 2005 of the German Society for Mycology

Priv.-Doz. Dr. Steffen Rupp received the 2005 Research award of the German Society for Mycology. The research award is endowed with 5,000 euros and represents the highest award for scientific achievements in medical mycology. The award is bestowed for excellence in scientific research and encourages interdisciplinary communication between natural and medical sciences.

Girls' Day 2004

The fourth national Girls' Day sponsored by the German Federal Ministry of Education and Research (BMBF) once again offered schoolgirls aged 13 and over an insight into he working world of science and research. Around 100 schoolgirls from high schools in and around Stuttgart visited laboratories and testing departments at the Fraunhofer campus,

Interested schoolgirls are introduced to the world of a working laboratory.

performed experiments and questioned scientists about their professions.
In the molecular biology laboratory of Dr. Christiane Buta, the schoolgirls were able to see the building blocks of life, DNA, with the aid of gel electrophoresis. IGB scientist Dr. Nicole Hauser gave an introduction to biochip technology and explained how they function, using the example of DNA chips. For the first time the schoolgirls were able to get to know something about environmental biotechnology at IGB: Gabriele Bott guided them through the technical aspects of biology with bioreactors for wastewater treatment and sewage sludge fermentation.

Stuttgart Summer of Science

The *Wissenschaftssommer*, the climax of the "Year of Technology" 2004 was held in Stuttgart. Some 110,000 interested parties from Stuttgart and the surrounding region attended lectures, the film festival, the Students' Parliament or the numerous exhibitions to discuss with researchers subjects from the fields of technology, mobility and communication. Fraunhofer IGB participated in a science exhibition and displayed individual elements and modules of new tubular fuel cells. Thanks to their compact design, they are particularly well suited for use as mini-fuel cells or smaller mobile applications, such as auxiliary power units (APU), for powering mopeds or for supplying mobile phones and portable music players. The Summer of Science is organized annually by *Wissenschaft im Dialog (WiD)*, an initiative of the *Stifterverband für die Deutsche Wissenschaft* with the support of the BMBF.

The Long Night of Science

The Summer of Science 2004 was launched by the "Long Night of Science" on 25th September 2004, in which numerous research institutes in Stuttgart showed interested visitors the main areas of their research work between 6 p.m. and midnight. The long night at the Fraunhofer Campus in Stuttgart was a complete success: Thousands of visitors were given a guided tour of the testing departments, technical equipment and laboratories. IGB unveiled new concepts of modern water management and red-dyed algae for the sustained production of valuable substances.

nanoTruck: A journey to the nano-cosmos

The nanoTruck – also a joint project of BMBF and WiD – is a roadshow vehicle with an integrated exhibition that visits events at schools, universities and research institutes and is present at trade fairs, congresses and conferences. Having arrived on site, the truck transforms itself into a mobile world of experiences. Numerous exhibits give a clear and fascinating insight into the world of nanotechnology. Here, Fraunhofer IGB illustrates examples of its own nano-research: Carbon nanotubes (see page 48) and also cytokine-functionalized nanoparticles (see page 54). The nanoTruck has been so successful that its tour has been extended to the end of 2006.
www.nanotruck.net

Numerous visitors came to the "Long Night of Science" at the Fraunhofer campus in Stuttgart.

EU premiere of the nanoTruck in May 2004 in Brussels.

As black as coal and full of surprises: Carbon atoms in carbon nanotubes form a rolled-up mesh of hexagons.

Trade fairs and events

Trade fairs and exhibitions

MEDTEC 2004
International Exhibition for Medical Device Industry
Participation of the Fraunhofer Life Sciences Alliance VLS
March 9-11, 2004, Stuttgart

TechnoPharm 2004
International Trade Fair for Life Science Process Technologies
Pharma, Food, Cosmetics
March 16-18, 2004, Nuremberg

Hannover Fair 2004
Technology – Innovation – Automation
Participation of the Fraunhofer Network for Photocatalysis
April 19-24, 2004, Hannover

Cooperation Forum
Technologies for Stem Cells
May 19, 2004, Munich

International Conference of the Burda Academy of the Third Millenium
Health Care Conference
July 7-8, 2004, Heidelberg

Water Middle East 2004
International Exhibition and Conference for Water Technology
September 13-15, 2004, Manama, Bahrain

Abfalltage 2004 Baden-Württemberg
Integrative Strategien für eine nachhaltige Abfallwirtschaft
September 22-23, 2004, Stuttgart

K 2004
International Trade Fair for Plastics and Rubbers
Participation of the Fraunhofer Polymer Surfaces Alliance (POLO)
October 20-27, 2004, Düsseldorf

parts2clean 2004
International Trade Fair for Industrial Parts Cleaning and Drying
Participation of the Fraunhofer Network for Cleaning Technology
October 26-28, 2004, Friedrichshafen

Medica 2004
World Forum Medicine – International Fair with Congress
Participation of the Fraunhofer Network for Protein Chips
November 24-27, 2004, Düsseldorf

Events at or with participation of the Fraunhofer IGB

Intensive Seminar: The Basics of Nanotechnology "Optimization of surfaces and materials using nanotechnology"
January 29-30, 2004, Würzburg
April 1-2, 2004, Cologne
June 24-25, 2004, Stuttgart
September 21-22, 2004, Dresden

9th Meeting for Municipal Waste and Wastewater Treatment
April 1, 2004, Fraunhofer Institutes Center, Stuttgart

Girls' Day 2004
Future Day for Girls
April 22, 2005, Fraunhofer Institutes Center, Stuttgart

ESBES5
European Symposium on Biochemical Engineering Science
of the European Federation of Biotechnology and the University of Stuttgart
September 8-11, 2004, Stuttgart

Lange Nacht der Wissenschaften (Long Night of Science)
September 25, 2004, Stuttgart

Wissenschaftssommer (Summer of Science)
Organized by the German Federal Ministry of Education and Research (BMBF), Wissenschaft im Dialog (WiD) and the Deutscher Verband Technisch-Wissenschaftlicher Vereine
September 25 - October 1, 2004, Stuttgart

BioStar 2004
Congress on Regenerative Biology
November 4-6, 2004, Stuttgart

Trade fairs and exhibitions 2005/2006

MEDTEC 2005
International Exhibition for Medical Device Industry
Participation of the Fraunhofer Life Sciences Alliance VLS
February 15-17, 2005, Stuttgart

Forum Life Science 2005
International Conference and Exhibition
February 16-17, 2005, Munich

Congress Industrielle Oberflächentechnik CIO 2005
Participation of the Fraunhofer Network for Photocatalysis
February 22-23, 2005, Braunschweig

NanoTech 2005
International Nanotechnology Exhibition & Conference
Participation of the Fraunhofer Life Sciences Alliance VLS and the Fraunhofer Nanotechnology Alliance
February 23-25, 2005, Tokyo, Japan

Hannover Fair 2005
Technology – Innovation – Automation
Participation of the Fraunhofer Energy Alliance
April 11-15, 2005, Hannover

IFAT 2005
14th International Trade Fair for Water, Sewage, Refuse and Recycling
April 25-29, 2005, Munich

Bio Expo 2005
4th International Bio Expo Japan
Participation of the Fraunhofer Life Sciences Alliance VLS
May 18-20, 2005, Tokyo, Japan

International Environmental Exhibition 2005
Iran Green Week
June 8-12, 2005, Teheran, Iran

Bio 2005
Annual International Convention
Participation of the Fraunhofer Life Sciences Alliance VLS
June 19-22, 2005, Philadelphia, USA

Biotechnica 2005
Biotech meets Business
14th International Trade Fair for Biotechnology
Participation of the Fraunhofer Life Sciences Alliance VLS
October 18-20, 2005, Hannover

parts2clean 2005
International Trade Fair for Industrial Parts Cleaning and Drying
Participation of the Fraunhofer Network for Cleaning Technology
October 18-20, 2005, Essen

Water Middle East 2005
International Exhibition and Conference for Water Technology
November 14-16, 2005, Manama, Bahrain

ACHEMA 2006
28th International Exhibition-Congress on Chemical Engineering, Environmental Protection and Biotechnology
Participation of the Fraunhofer Life Sciences Alliance VLS
May 15-20, 2006, Frankfurt/Main

Events at or with participation of the Fraunhofer IGB 2005

Intensive Seminar: The Basics of Nanotechnology "Optimization of surfaces and materials using nanotechnology"
January 11-12, 2005, Passau
April 5-6, 2005, Würzburg
June 28-29, 2005, Dresden
September 20-21, 2005, Stuttgart

10th Meeting for Municipal Waste and Wastewater Treatment
April 14, 2005, Fraunhofer Institutes Center, Stuttgart

Girls' Day 2005
Future Day for Girls
April 28, 2005, Fraunhofer Institutes Center, Stuttgart

Symposium
New Trends in Regenerative Medicine
June 9-10, 2005, Fraunhofer Institutes Center, Stuttgart

AK Plasma 2005
Autumn Meeting and Workshop
Plasma Surface Technology
November 7-8, 2005, Fraunhofer Institutes Center, Stuttgart

Details may be subject to alterations.

Get further information here:
www.igb.fraunhofer.de

05

Scientific cooperations

With Fraunhofer institutes

Fraunhofer Life Sciences Alliance, in cooperation with the Fraunhofer Institute for Biomedical Engineering IBMT, St. Ingbert, the Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Schmallenberg, and the Fraunhofer Institute for Toxicology and Experimental Medicine ITEM, Hannover
www.lifesciences.fraunhofer.de

Fraunhofer Energy Alliance, in cooperation with the Fraunhofer Institutes AST (Anwendungszentrum Systemtechnik, Ilmenau), IBP, ICT, IFF (Factory Operation and Automation IFF, Magdeburg), IISB (Integrated Systems and Device Technology, Erlangen), IKTS (Ceramic Technologies and Sintered Materials, Dresden), ISE, ISI and IUSE (UMSICHT)
www.energie.fraunhofer.de

Fraunhofer Nanotechnology Alliance (NANO), in cooperation with the Fraunhofer Institutes IAP (Applied Polymer Research, Golm), ICT, IFAM (Manufacturing Engineering and Applied Materials Research, Bremen), IFF (Factory Operation and Automation, Magdeburg), IISB (Integrated Systems and Device Technology, Erlangen), IKTS (Ceramic Technologies and Sintered Materials, Dresden), IOF (Applied Optics and Precision Engineering, Jena), IPA (Manufacturing Engineering and Automation, Stuttgart), ISC (Silicate Research, Würzburg), ISE, IWM (Mechanics of Materials, Freiburg), IWS (Material and Beam Technology, Dresden), IZFP (Non-Destructive Testing, Saarbrücken), IZM, LBF (Structural Durability and System Reliability, Darmstadt), IUSE (UMSICHT)
www.nano.fraunhofer.de

Fraunhofer Polymer Surfaces Alliance (POLO), in cooperation with the Fraunhofer Institutes FEP (Electron and Plasma Technology, Dresden), IAP (Applied Polymer Research, Golm), IFAM (Manufacturing Engineering and Applied Materials Research, Bremen), IPA (Manufacturing Engineering and Automation, Stuttgart), ISC (Silicate Research, Würzburg) and IVV
www.polo.fraunhofer.de

Fraunhofer Network for Photocatalysis, in cooperation with the Fraunhofer Institutes ICT, FEP (Electron and Plasma Technology, Dresden), IME (Molecular Biology and Applied Ecology, Schmallenberg), ISC (Silicate Research, Würzburg), ISE and IST (Thin Films and Surface Engineering, Braunschweig)
www.photokatalyse.fraunhofer.de

Fraunhofer Network for Protein Chips, in cooperation with the Fraunhofer Institutes ILT (Laser Technology, Aachen), IME (Molecular Biology and Applied Ecology, Schmallenberg), IOF (Applied Optics and Precision Engineering, Jena), IPM, IST (Thin Films and Surface Engineering, Braunschweig) and IWS (Material and Beam Technology, Dresden)
www.proteinchips.fraunhofer.de

Fraunhofer Network for Cleaning Technology, in cooperation with the Fraunhofer Institutes ICT, FEP (Electron and Plasma Technology, Dresden), IFF (Factory Operation and Automation, Magdeburg), ILT (Laser Technology, Aachen), IPK (Production Systems and Design Techology, Berlin), IPA (Manufacturing Engineering and Automation, Stuttgart), IST (Thin Films and Surface Engineering, Braunschweig), IVV and IWS (Material and Beam Technology, Dresden)
www.allianz-reinigungstechnik.de

Fraunhofer Institute for Building Physics IBP, Stuttgart

Fraunhofer Institute for Chemical Technology ICT, Pfinztal

Fraunhofer Institute for Material Flow and Logistics IML, Dortmund

Fraunhofer Institute for Physical Measurement Techniques IPM, Freiburg

Fraunhofer Institute for Solar Energy Systems ISE, Freiburg

Fraunhofer Institute for Systems and Innovation Research ISI, Karlsruhe

Fraunhofer Institute for Environmental, Safety and Energy Technology IUSE (UMSICHT), Oberhausen

Fraunhofer Institute for Process Engineering and Packaging IVV, Freising

Fraunhofer Institute for Reliability and Microintegration IZM, Berlin

Fraunhofer Technology Development Group TEG, Stuttgart

With universities

Charles University, Prague, Czech Republic

Eindhoven University of Technology, The Netherlands

Escola de Engenharia de Piracicaba (EEP), Brazil

Escola Superior de Agricultura "Luiz de Queiroz" (ESALQ), Brazil

Hacettepe University, Ankara, Turkey

Katholieke Universiteit Leuven, Belgium

Ludwig Institute for Cancer Research, Stockholm, Sweden

Lund University, Lund, Sweden

Medical School of Hannover

National Institute of Laser, Plasma and Radiation Physics, Magurele-Bucharest, Romania

RWTH University, Aachen

School of Veterinary Medicine of Hannover

Stanford University, USA

Technical University of Darmstadt

Universidade Metodista de Piracicaba (UNIMEP), Brazil

University of Gießen

University of Greifswald

University of Hannover

University of Hohenheim

University of Kiel

University of Münster

University of Nürnberg-Erlangen

University of Paderborn

University of Stuttgart

University of Tübingen

University of Vienna, Austria

University of Würzburg

University of Amsterdam, The Netherlands

University of Bari, Italy

University of Kent, UK

University of Milano-Bicocca, Italy

University of Toulouse, France

With research organizations

ACA Institute for Applied Chemistry, Berlin-Adlershof e. V.

ARC (Austrian Research Center) Seibersdorf Research GmbH, Austria

Dalian Institute of Chemical Physics, Dalian, China

European Molecular Biology Laboratory EMBL, Heidelberg

Federal Institute for Materials Research and Testing (BAM), Berlin

German Cancer Research Center (DKFZ), Heidelberg

German Center of Excellence on Biomaterials and Organ Replacement, Stuttgart-Tübingen

IFREMER, Nantes, France

Institute of Low Temperature Plasma Physics, Greifswald

Institute for Textile Chemistry and Chemical Fibers ITCF, Denkendorf

Institute of Textile Technology and Process Engineering ITV, Denkendorf

Max Planck Institute of Biochemistry, Martinsried

Max Planck Institute of Colloids and Interfaces, Golm

Committee memberships

Max Planck Institute for Metals Research, Stuttgart

Max Planck Institute of Molecular Physiology, Dortmund

Max Planck Institute for Polymer Research, Mainz

Max Planck Institute for Solid State Research, Stuttgart

NMI Natural and Medical Sciences Institute, Reutlingen

UFZ Centre for Environmental Research, Leipzig

Whitehead Institute for Biomedical Research, Cambridge, MA, USA

CSEM Centre Suisse d'Electronique et de Microtechnique SA, Neuchâtel, Switzerland

With hospitals

Blutspendezentrale, Katharinenhospital, Stuttgart

Charité, Berlin

Katharinenhospital, Stuttgart

Klinikum Ludwigsburg

Marienhospital, Stuttgart

Olgahospital, Stuttgart

Robert-Bosch-Krankenhaus, Stuttgart

Universitätsklinik, Düsseldorf

Universitätsklinik, München

Universitätsklinik, Tübingen

Universitätsklinik of the RWTH Aachen

Bayern Kapital Risikobeteiligungsgesellschaft,
Investment Board Biotechnology

BIOPRO Baden-Württemberg GmbH,
Supervisory Board (Representative)

BioRegio STERN Management GmbH, Stuttgart,
Scientific Advisory Board

BioRegio Stuttgart/Neckar-Alb, Bioprofile,
Evaluation Committee, Chairman

BMBF Federal Ministry of Education and Research,
BioChance, Dezentrale Wasserver- und -entsorgungssysteme, Nachhaltige Bioproduktion, Tissue Engineering, Technical Experts

Bonner Runde – Expertenrunde der Hochschulverwaltungen und Forschungseinrichtungen zu überregionalen Fragen des Arbeits- und Umweltschutzes der Arbeitsgemeinschaft Sicherheitstechnik/Angewandter Umweltschutz of the University of Bonn,
Member

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Expert Committee "Grundlagen der Stoffproduktion" in the Working Committee "Biotechnology", Vice Chairman;
Expert Group "Membrantechnik", Member;
Working Committee "Medizinische Biotechnologie", Member;
Working Committee "Umweltbiotechnologie", Member

Deutsche Gesellschaft für Hygiene und Mikrobiologie DGHM,
Expert Group "Eukaryontische Krankheitserreger", Member

DFG German Research Foundation,
Evaluator for biotechnology and molecular biology,
Senatskommission für Grundsatzfragen der Gentechnik

DIN Deutsches Institut für Normung e. V.,
Working Committee "Wärme-Brutschränke", Member

EU COST Action 527:
Plasma Polymers and Related Materials,
Management Committee, Vice Chairman

European Academics Science Advisory Council EASAC,
Biotechnology Strategy Group, Member

European Union EU,
Expert Evaluator for FP 6

Fraunhofer Nanotechnology Alliance (NANO),
Second Speaker, Steering Committee, Member

Fraunhofer Polymer Surfaces Alliance (POLO),
Steering Committee

GBM Society for Biochemistry and Molecular Biology,
Expert Group Cytokines

»Gensensorik« Alliance, University of Bremen,
Supervisory Board

German Bunsen Society for Physical Chemistry,
Member

Gesellschaft Deutscher Chemiker (GDCh),
Member

GVC Gesellschaft für Verfahrenstechnik und Chemie-Ingenieurwesen,
Committee Interfaces

Kolloid Gesellschaft e. V.,
Member

Life Science Center, Esslingen,
Advisory Board

Ninth International Conference on Plasma Surface Engineering PSE 2004,
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NMI Natural and Medical Sciences Institute at the University of Tuebingen,
Kuratorium der Stiftung für Naturwissenschaftliche und Medizinische Forschung,
Supervisory Board, Vice Chairman

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Board Speaker

Plasma Processes and Polymers,
WILEY-VCH, Weinheim,
Editor in Chief

Research group Plasmaoberflächentechnologie,
Common Board of AWT, DVG, DGO, DGM, DGPT, DVS und VDI-W, Coordination Board, Member;
Expert Group Polymers and Plasma, Chairman

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Vakuum in Forschung und Praxis, WILEY-VCH, Weinheim,
Editorial Board

VDI Association of German Engineers,
Technical Committee "Qualitätssicherung bei der Vakuumbeschichtung von Kunststoffen", Member

Vereinigung für Allgemeine und Angewandte Mikrobiologie e. V. (VAAM),
Council "Umweltmikrobiologie", Member

Verein zur Förderung der Biotechnologie, Tübingen,
Member

Lectures and seminars

Brunner, H.
"Management von Forschung und Entwicklung in der Biotechnologie",
University of Stuttgart

Brunner, H.
"Einführung in die Verfahrenstechnik",
University of Stuttgart

Brunner, H.
"Moderne industrielle Bioverfahren",
University of Hohenheim

Brunner, H., Lehmann, M.
"Management of Research and Development in Biotechnology",
MSc Study Program WASTE,
University of Stuttgart

Brunner, H., Mertsching, H., Tovar, G.,
"Biomedizinische Verfahrenstechnik",
University of Stuttgart

Brunner, H., Oehr, C., Tovar, G.
"Membran- und Grenzflächenverfahrenstechnik in der Biomedizin und Biotechnologie",
University of Stuttgart

Mertsching, H.
"Aspekte der Regenerationsbiologie und -medizin",
University of Tübingen

Rupp, S.
Biochemical practical course
University of Stuttgart

Rupp, S.
Practical course biochemistry for biology and chemistry students,
University of Stuttgart

Rupp, S.
"Moderne Methoden in der Biochemie",
University of Stuttgart

Sternad, W.
"Automatisierungstechnik",
University of Hohenheim

Trösch, W.
"Umweltbiotechnologie und Nachhaltigkeit",
University of Hohenheim

Trösch, W.
"Wasser-, Abwasser- und Abfallbehandlung",
University of Hohenheim

Postdoctoral, Ph.D., diploma and master theses, student research studies

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Jingcheng, L.
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University of Stuttgart

Liu, D.
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University of Stuttgart

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University of Stuttgart

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University of Stuttgart

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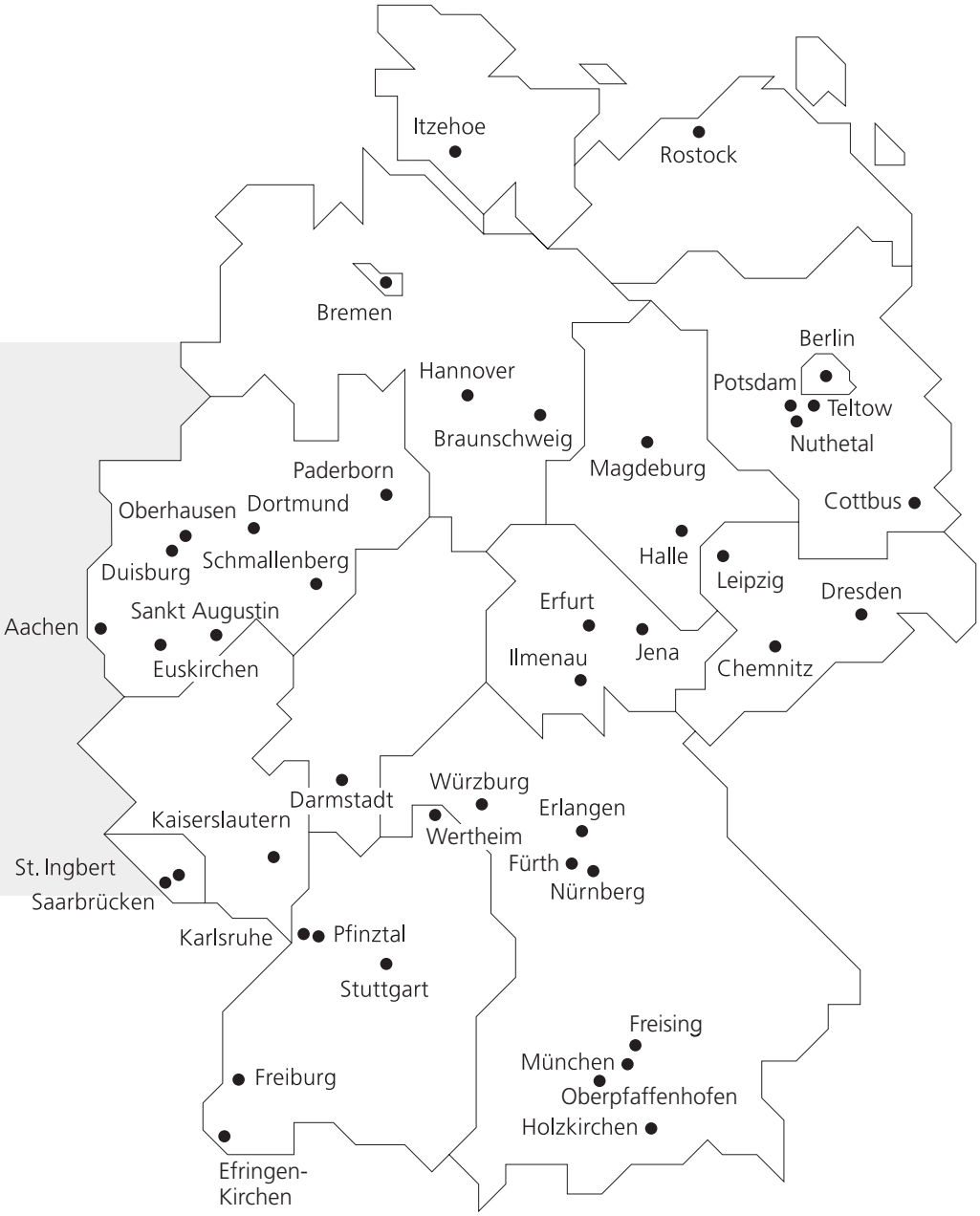

Locations of the research facilities in Germany.

Editorial notes

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All other photographs and figures

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By train
At Stuttgart main station take city rail (*S-Bahn*) lines 1 (towards Herrenberg), 2 or 3 (towards the airport/Filderstadt), all departing from platform 101 at the lower level of the station. Get off at "Universität" and take the "Wohngebiet Schranne/Endelbang/Nobelstraße" exit. Follow the "Fraunhofer-Gesellschaft" signs. The walking distance is about 800 m. Alternatively, at "Universität" station you can also take the bus nos 84 or 92 to "Nobelstraße". From Stuttgart main station you will need a total of about 20 minutes, including walking time of about 10 minutes.

By air
At Stuttgart airport take city rail (*S-Bahn*) lines 2 or 3 towards "Stuttgart-Vaihingen/Hauptbahnhof". Get off at "Universität", then continue on foot, or take the bus as described above. Taking a taxi from the airport, the distance is about 16 km and travel time is approximately 20 minutes.

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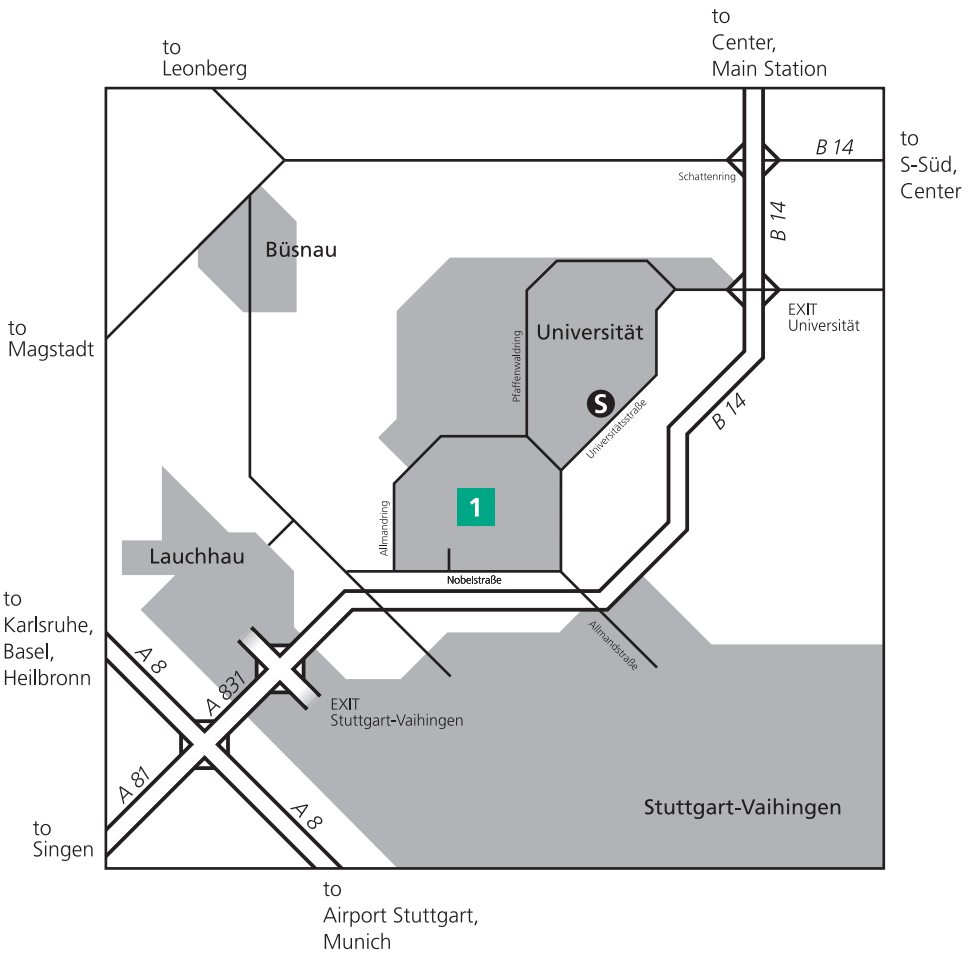

2004
2005

The Fraunhofer IGB has developed a sludge fermentation process, whereby integrated microfiltration enhances the decomposition of the sludge, and ammonium is recovered from the filtered sludge water. A pilot plant – consisting of a bioreactor, rotating disk filter and ammonia stripping plant – came online in 2004 as the second stage of a high-performance digestion of the Heidelberg Municipal Association for Sewage Treatment (*Abwasserzweckverband*).

This vascularized biological matrix with a functional blood vessel network was isolated from pig intestines. After removal of the porcine cells, a network of arteries, veins, and extremely fine capillaries remains. The collagen matrix can be populated with primary, organ-specific cells. The vascularized matrix improves the supply of nutrients both in three-dimensional organoid test systems and in transplants.

Nanoparticle microarray on silicon chip. Proteins are bound to the nanoparticle via specific linking molecules. The protein chip can thus be used for proteome research or diagnostics, e. g. for the detection of disease-specific antigens or antibodies. The Fraunhofer IGB models and functionalizes diverse nanoparticles and spots them as microstructures onto carriers such as glass or silicon. The chips can then be analyzed with state-of-the art optical screening systems.