Fraunhofer
IGB

FRAUNHOFER INSTITUTE FOR INTERFACIAL ENGINEERING AND BIOTECHNOLOGY IGB

ANNUAL REPORT 09|10

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CONTENT

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Dear Sir or Madam,

The 21st century has brought major challenges which – as has been demonstrated by the economic crisis – no individual entity acting alone is able to tackle. Partnerships and networks are therefore of vital importance; with the recognition that working together, more can be achieved in less time, research institutions, too, are increasingly getting out of their ivory towers and seeking meaningful links with industry, academia, politics and society. At the Fraunhofer IGB, 2009 was a year marked by such activity: by the work going on in established networks and by the creation of new ones. Networking has enabled us to greatly strengthen the Institute's business areas and thus ensure its ongoing commercial success.

Integration of the Physical Process Engineering Department (part of the former Fraunhofer Technological Development Group) in early 2009 extended our core competences by the addition of the subject areas mechanical and thermal process engineering. This is of particular benefit for our Environment and Energy business areas. The department grew strongly last year and through many projects has excellent connections to the established departments of the Fraunhofer IGB.

Participation in the Fraunhofer Group for Life Sciences as well as in its Group for Materials is particularly valuable for the Fraunhofer IGB, as a means of expanding our competences in the life sciences and materials science respectively. The Fraunhofer Alliances are also of especial importance for the Fraunhofer IGB, since it is here that solutions are developed along the whole value chain in specific thematic areas. Particular mention should be made of the Water Systems, Energy, Building Innovation, Polymer Surfaces, Nanotechnology, Cleaning Technology and Photocatalysis Alliances, to which the IGB contributes its expertise and through which it extends its competences in joint projects. The Fraunhofer IGB's expertise was, again, highly sought after last year in Fraunhofer internal programs, and led to the Fraunhofer IGB being the most highly networked of the Fraunhofer institutes relative to its size. A highlight of 2009 was the founding of the Fraunhofer Sustainability Network, which the Fraunhofer IGB co-initiated and to which 17 Fraunhofer institutes now belong. The main focus of this network is research into sustainability issues, the sustainability of our own research, and the establishing of sustainable business practices.

The innovative strength of Fraunhofer institutes derives to not a small extent from the symbiotic relationships cultivated with their academic partners. The principal partner of the Fraunhofer IGB in this context is the University of Stuttgart. Here we foster a close relationship in research and teaching that extends beyond our cooperation with the University's Institute for Interfacial Engineering (IGVT). Thus in 2009, our collaboration with the Institute for Cell Biology and Immunology and the Institute for Systems Theory and Automatic Control at the University of Stuttgart, as well as the Max Planck Institute für Metals Research, enabled us to initiate a joint project to investigate biomimetic matrices, with funding from the Fraunhofer-Gesellschaft, the Max Planck Society, the University of Stuttgart and the State of Baden-Württemberg.

The sustainable material and energetic use of renewable resources is a core research topic at the Fraunhofer IGB and saw considerable advances last year. In conjunction with the TU Munich we set up the Fraunhofer BioCat project group at the Straubing Science Center, a working group dedicated to developing catalysts and catalytic processes for a sustainable supply of raw materials and energy on the basis of renewable resources. BioCat is being funded initially by the Bavarian State.

The transformation of processes from research to industrial scale is critically determined by the scaling processes available. In the area of renewable resources, such scaling has previously been possible to a very limited extent. In establishing the Chemical-Biotechnological Process Center CBP at the Leuna chemical industry site we aim to close this gap. Working with partners from research and industry, our goal is to realize the development and scaling of processes to utilize renewable resources up to industrial scale. Funding will come from the State of Sachsen-Anhalt, the federal ministries BMBF, BMELV and BMU as well as InfraLeuna GmbH. The project group in Straubing and the CBP in Leuna will contribute, in particular, to strengthening our business areas Chemistry, the Environment, and Energy.

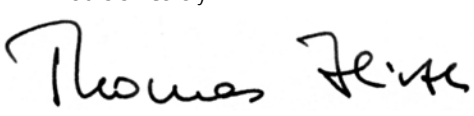
The IGB's Medicine and Pharmaceuticals business areas also benefited strongly from the Institute's networks in the previous year. A grant from the Bavarian State made it possible to set up the "Regenerative Technologies for Oncology" project group at the University of Würzburg's Medical Faculty. Activities will focus on innovative technology development for tailored diagnostics, tumor therapeutics and therapeutic techniques. We were also able to raise funding for an Attract program group specializing in cardiovascular tissue engineering, which is to collaborate closely with the University of Tübingen.

Through aligning our business areas and core competences to fields of social needs such as health, security, the environment, energy and mobility, we were able to hold our ground even in difficult economic times and prepare the Institute well for the challenges to come. Besides continuing to develop our R&D activities, last year was focused in particular on securing a solid and stable financing of the growing Institute budget and ensuring that we meet our projected staffing requirements in terms of numbers, qualifications and experience. At this juncture, I would like to mention in particular the introduction of target agreements to facilitate assessing the performance and development of staff. Credit goes to the employees of the Fraunhofer IGB – and the staff of Stuttgart University's IGVT – for their vital role in the successful performance of both institutes. Moreover, despite the adverse economic climate, we managed to acquire many new customers from industry, and additional public sponsors and foundations as R&D customers.

I hope this annual report will rouse your interest in our R&D activities and would welcome the opportunity to collaborate closely with you in the future. Together with you, we want to use the force of innovation to create a sustainable future for the region, for Germany and for Europe. In doing so, we are inspired by our motto "Ever better together", for we can achieve our goals much more effectively and efficiently through networking.

On this note, I hope you enjoy reading our new Fraunhofer IGB annual report.
I look forward to your comments and to working with you.

Yours sincerely



PROFILE

BRIEF PROFILE

The Fraunhofer IGB develops and optimizes processes and products for the business areas of medicine, pharmacy, chemistry, the environment and energy. In addition to contract R&D we offer our clients services in analytics and advise on the introduction of novel technologies. Our customers come from various industries as well as municipal, state (*Länder*) and federal authorities.

Application-oriented and interdisciplinary

Our overriding goal is the translation of scientific and engineering research results into similarly economically efficient and sustainable processes and products. Our strength lies in offering complete solutions from laboratory scale to pilot plant.

More than ever, the success of new products and processes is dependent on interdisciplinary and constructive cooperation between science and engineering. At the Fraunhofer IGB, some 300 experts in the fields of chemistry, physics, biology and engineering work effectively together. Customers benefit from the synergies and multidisciplinary potential at our institute, which facilitate novel approaches and innovative solutions in areas such as medical engineering, nanotechnology, industrial biotechnology and wastewater treatment.

Competences / Departments

Interfacial Engineering and Materials Science
Molecular Biotechnology
Physical Process Technology
Environmental Biotechnology and Bioprocess Engineering
Cell and Tissue Engineering

Project groups

Chemical-Biotechnological Process Center CBP, Leuna
BioCat Project Group, Straubing
Oncology Project Group, Würzburg

Guiding principles: mission statement and vision

"At the Fraunhofer IGB we carry out application-oriented research according to the principles of good scientific practice and on the basis of our competences and guiding principles in the areas of medicine, pharmacy, chemistry, the environment and energy. With our innovations we contribute to a sustainable development of the economy, the society and the environment."

Ever better together.

ADVISORY BOARD OF THE FRAUNHOFER IGB

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

Members

Dr. Manfred Baier
Roche Diagnostics GmbH

Dr. Gerd Esswein
Freudenberg Forschungsdienste KG

MinDirig Dipl.-Ing. Peter Fuhrmann
Ministry for the Environment of the State of Baden-Württemberg

Dipl.-Ing. Hermann Göhl
Gambro Dialysatoren GmbH

MinDirig Dr. Fritz Holzwarth
German Federal Ministry for the Environment, Nature Conservation and Nuclear Safety

Prof. Dr. Dieter Jahn (Chair)
BASF AG

MinDirig Dr. Heribert Knorr
Ministry of Science, Research and the Arts of the State of Baden-Württemberg

RegDir Dr. Jürgen Ohlhoff
German Federal Ministry of Food, Agriculture and Consumer Protection

Prof. Dr. Klaus Pfizenmaier
Institute for Cell Biology and Immunology,
University of Stuttgart

Prof. Dr. Dr. h. c. Ralf Riedel
Dispersive Solids Division,
Faculty of Materials- and Geo-Sciences,
Technische Universität Darmstadt

Dipl.-Ing. Otmar Schön
HYDAC Technology GmbH

Dr. Jürgen Stebani
Polymaterials AG

Dr. Thomas Stiefel
biosyn Arzneimittel GmbH

MinRat Dr. Joachim Wekerle
Ministry of Economic Affairs of the State of Baden-Württemberg

Prof. Dr. Rolf G. Werner
Boehringer Ingelheim Pharma GmbH & Co. KG

Dr. Günter Wich
Wacker Chemie AG

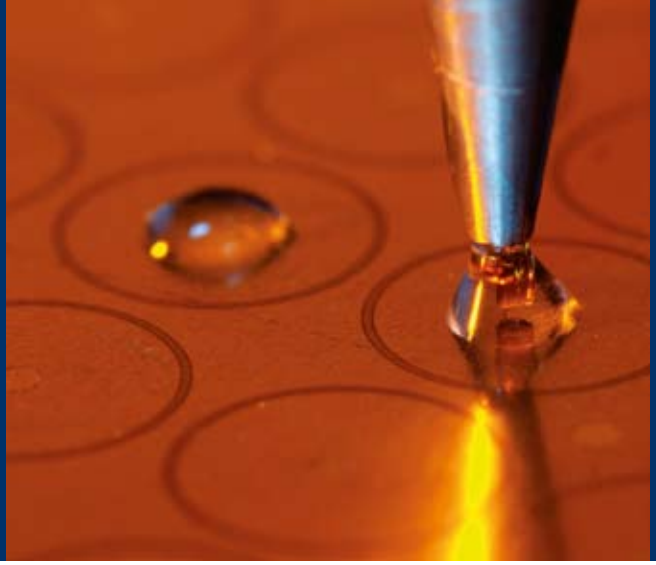
Prof. Dr. Karl-Heinz Wiesmüller
EMC microcollections GmbH

Dr. Wieland Wolf
Dr. Rentschler Holding GmbH & Co. KG

Permanent guests

Prof. Dr. Herwig Brunner
Former IGB Director

Prof. Dr. Uwe Heinrich
Fraunhofer Institute for Toxicology and Experimental Medicine ITEM



SERVICES AND INFRASTRUCTURE

Our contract R&D services range from scientific and technological basic research to the development of new applications from laboratory scale up to pilot plant scale including the design, construction, and testing of industrial plants. We also offer patent and market surveys, feasibility studies and comprehensive consultancy in our specialist areas of expertise. We can train your executives and introduce young people at school or studying to the fascinating world of science and technology.

Infrastructure and laboratory equipment

The Fraunhofer IGB has at its disposal modern laboratories equipped with the latest technology. Our central storage facilities for chemicals and hazardous substances are shared with the other institutes on the Stuttgart Fraunhofer campus.

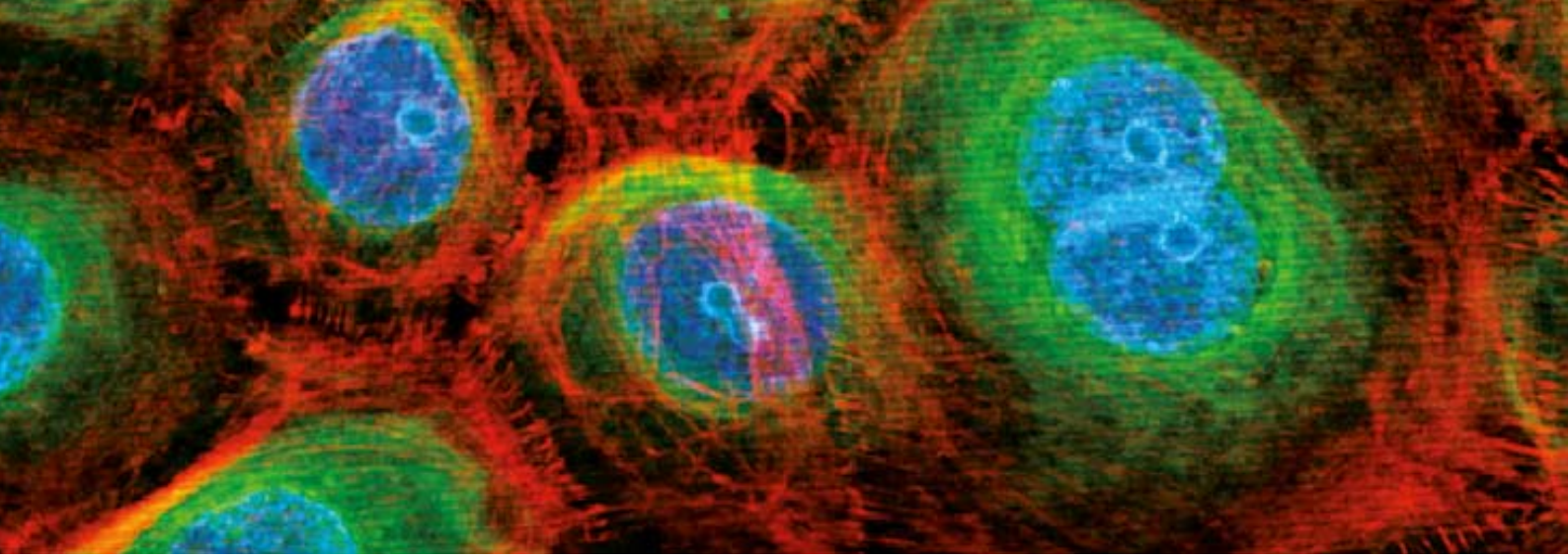
Analytics: Quality management and accreditation

The Fraunhofer IGB has established a quality management system for the analytics in selected reference laboratories, ensuring the highest standards. Accreditation guarantees that our proprietary, in-house test methods are sufficiently validated and that the quality of our tests is assured even where no standard methods are available. The following analytical methods and test procedures are accredited according to DIN EN ISO/IEC 17025:

- High-performance liquid chromatography (HPLC)
- Ion chromatography (IC)
- Size exclusion chromatography (SEC)
- Gas chromatography (GC, GC/MS)
- Atomic emission spectrometry (ICP-OES)
- Electron spectroscopy for chemical analysis (ESCA/XPS)

Accredited biocompatibility and bioavailability testing

Our biocompatibility testing using cell lines and our 3D skin equivalent are accredited according to DIN EN ISO 10993-5. In December 2009, our two-dimensional intestinal assay (Caco2) was first included in the accreditation audit report. It was certified by the competent body, the Deutsche Gesellschaft für Akkreditierung (DGA), as an in-house method for the classification of substances by their transport characteristics at the intestinal barrier, and enables us to certify analysis results.



GMP unit for the manufacture of tissue engineering products

The Fraunhofer IGB has a low-risk (level S2 of the German ordinance on safety in genetic engineering) Good Manufacturing Practice unit for the collaborative development and manufacturing of clinical test material for cell and tissue engineering products (ATMPs).

Good laboratory practice (GLP) test facility

Our GLP test facility (test category 9) "cell-based test systems for the determination of biological parameters" is used in collaborative development projects, e.g. to investigate biological activity of type 1 interferons using the antiviral assay (AVA).

Special services

Physico-chemical analytics:
Quality control, food analysis, trace analysis, analysis of residues, environmental analytics, water analysis

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

Biochemical and molecular biological analytics:
DNA- and protein biochips, RNA and protein expression profiles, protein analysis using MALDI-TOF/TOF mass spectrometry

Cell biology analysis:
Cell sorting and -characterization, single cell preparation/microdissection, quality and sterility control of tissue engineering products

REACH:
Evaluation and testing of chemicals

For detailed information,
please order our special brochures or visit:
www.igb.fraunhofer.de

REPRESENTATIVE FIGURES

Personnel

At the end of 2009, the Fraunhofer IGB had a staff of 245. Some 90 percent were scientific or technical employees. Women made up 53 percent of the total.

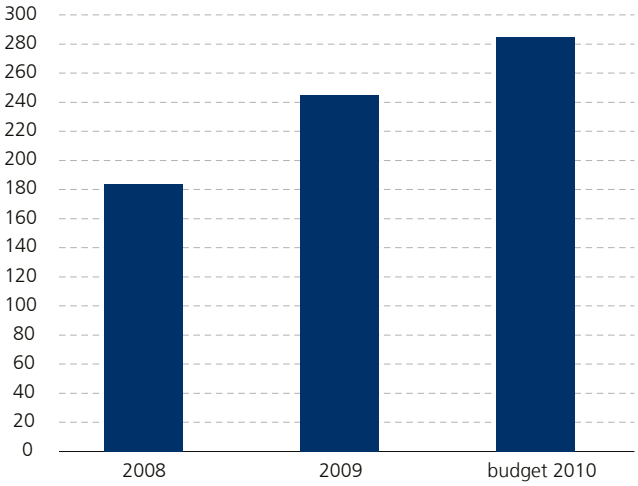
The university institute IGVT counted a staff of 59 effective December 31, 2009, predominantly scientists and Ph.D. students as well as technical staff and student research assistants. Women made up 59 percent of the total.

The Fraunhofer IGB and IGVT staff members come from 26 different nations and work closely together.

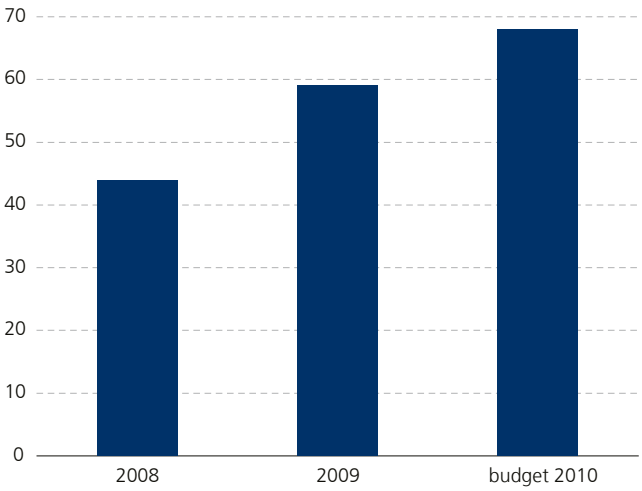
Staff members Fraunhofer IGB	Number
Scientists	60
Technical staff	49
Graduate student research workers	59
Student research assistants	50
Administrative and secretarial staff	19
Trainees	8
Total	**245**

Staff members IGVT	Number
Scientists/Ph.D. students	53
Technical staff	2
Student research assistants	4
Total	**59**

number staff members IGB



number staff members IGVT

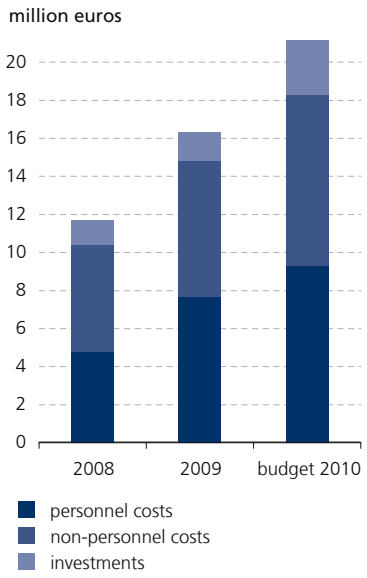


Budget Fraunhofer IGB

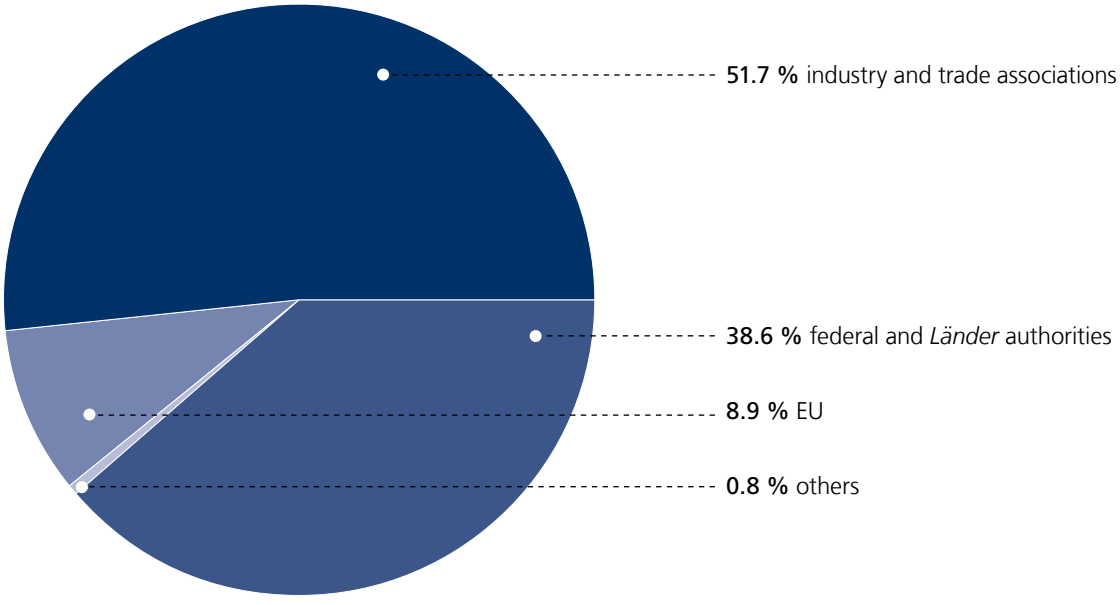
The total budget for 2009 amounted to 16.3 million euros, of which 14.8 million euros was allocated to the operational budget (personnel costs: 7.7 million euros; non-personnel costs: 7.1 million euros). A total of 1.5 million euros was spent on investments.

71 percent of the operational budget was financed from IGB's own revenues generated from contract research projects, while governmental funding covered the remaining 29 percent. 51.7 percent of the Institute's revenues came directly from industry.

DEVELOPMENT OF BUDGET



REVENUE FROM CONTRACT RESEARCH



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- Polymeric Interfaces and Materials
- Inorganic Interfaces and Membranes
- Biomimetic Structures and Biomaterials
- Particulate Systems and Formulations
- Carbon-based Materials and Surface Analytics

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- Functional Genomics
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- Enzyme, Strain and Process Development for Biotechnology
- Analytics

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- Oxidative Water Treatment
- Design and System Integration

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- Water Management
- Bio-based Raw Materials
- Bio-energy
- Interfacial Biology

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- Avascular Test Systems
- Vascularized Test Systems
- Cells and Biomaterials
- Bioreactors for Tissue Engineering
- Toxicology and Accreditation
- GMP Production of Cell-based Products

PROJECT GROUPS

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Oncology Project Group, Würzburg
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ATTRACT GROUP

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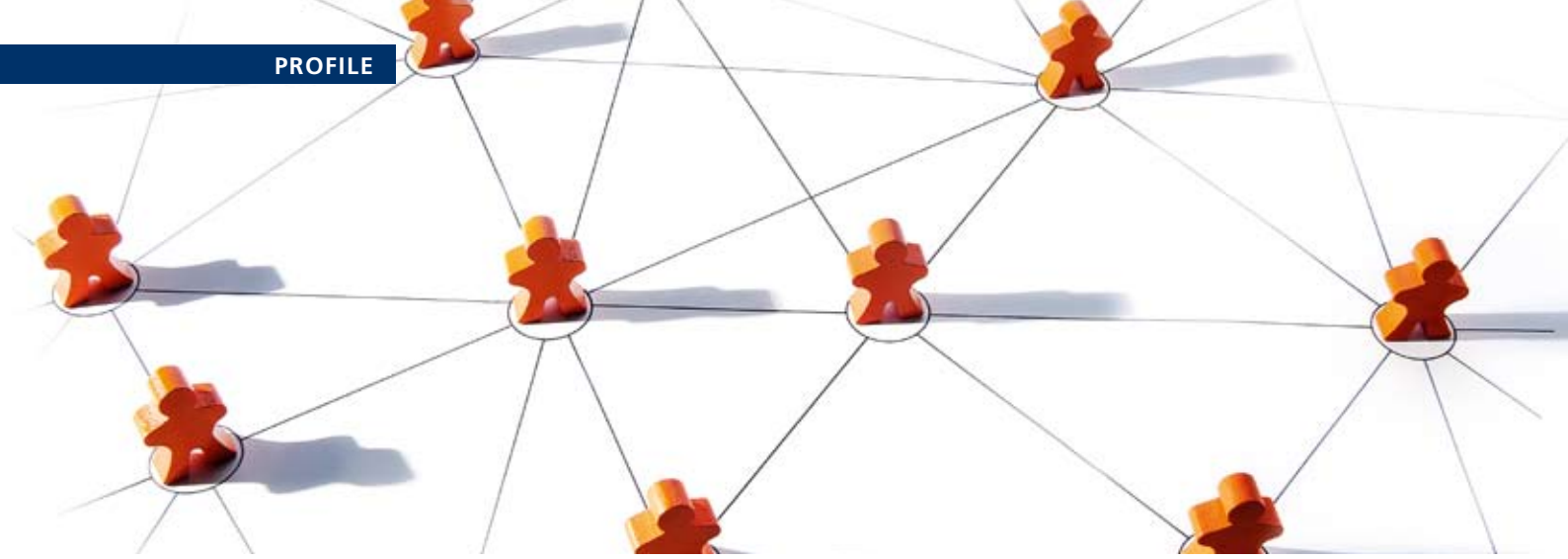

THE FRAUNHOFER IGB'S NETWORKING ACTIVITIES

The Fraunhofer IGB is an active participant in numerous national and international research networks. Cooperative ventures and relations with various universities and non-university research institutes as well as other Fraunhofer institutes complement our own competences and enable us to exploit synergies in developing new solutions for the needs of industry. We are also actively engaged in shaping research policy through championing strategic, economic and sustainable standpoints.

Added value through the "Fraunhofer network plus"

The Fraunhofer IGB is a member of the Fraunhofer Group for Life Sciences. By virtue of its strong competence in materials science, it has also been an approved guest member of the Fraunhofer Group for Materials since 2008. Additionally, we are involved in various Fraunhofer alliances focusing on topics in our business areas and core competences.

An analysis of the research applications for the MAVO and WISA programs, the largest consortia within the Fraunhofer internal funding program, shows that in relation to its size of the institute the Fraunhofer IGB is the most highly networked of all the Fraunhofer institutes. Our networking enables us to promote cross-boundary knowledge and create a breeding ground for innovation.

Networking with universities

Basic research is a must. Therefore the Fraunhofer IGB maintains close contacts with neighboring universities, both through scientific collaboration and Fraunhofer staff engaged in professorial and other teaching duties. We also have project groups working at locations outside Stuttgart.

- **Prof. Dr. Thomas Hirth,**
  Full Professor and Director of the Institute for Interfacial Engineering, University of Stuttgart
- **Priv.-Doz. Dr. Steffen Rupp,**
  Faculty of Chemistry, Biochemistry, University of Stuttgart
- **Prof. Dr. Volker Sieber,**
  Chair for Chemistry of Biogenic Resources, Technische Universität München
- **Priv.-Doz. Dr. Günter Tovar,**
  Faculty of Chemistry, University of Stuttgart
- **Prof. Dr. Walter Trösch,**
  Supernumerary Professor for Biotechnology, University of Hohenheim
- **Prof. Dr. Heike Walles,**
  Chair for Tissue Engineering and Regenerative Medicine, University of Würzburg

EU networks

The EU Working Group for Research and Technological Development Organizations (RTOs) in Baden-Württemberg

Baden-Württemberg is by far the most successful German state in the European Union's 6th framework programme for research and technological development. With 672 million euros of EU funding, the federal state even lies ahead of countries such as Austria and Denmark. A further success factor is the networking activities of Baden-Württemberg's research organizations and universities. Fraunhofer IGB is a member of the EU Working Group for RTOs in Baden-Württemberg which fosters the exchange of expertise at a regional level. A highlight of the working group's activities was the meeting on European research funding in January 2009 at Baden-Württemberg's representation in Brussels, followed by a visit to Mr. Rainer Wieland, MEP (Member of European Parlament).

Fraunhofer EU Network

On October 27-28, 2009, the Fraunhofer institutes located in Stuttgart hosted the bi-annual network meeting of the internal Fraunhofer EU Network. Over 30 participants from 18 institutions made use of the chance to network and share experience on strategic aspects, proposal writing and successful implementation of EU projects.

Fraunhofer International Business Development (IBD) Network

The Fraunhofer IGB is involved in developing the IBD Network, where it is an active member. The network has the goal of linking the international activities of the various Fraunhofer institutes and thus also increasing the visibility of the Fraunhofer brand worldwide. At the Fraunhofer IGB, the current international focus is on water and bioenergy topics in Latin America.

Fraunhofer Sustainability Network

Sustainable development is arguably the most important key political objective of our time. The guiding principle of sustainable development takes equal account of environmental considerations and social and economic aspects, and also includes our intra- and intergenerational responsibilities.

The Fraunhofer Sustainability & Research Working Group founded in 2007 was reorganized as an official network in December 2009. As chairman of the Sustainability Network, Professor Thomas Hirth sets impulses not only for the social, environmental and economic orientation of the IGB, but for the entire Fraunhofer-Gesellschaft.

In the context of its sustainability activities, the Fraunhofer IGB and Fraunhofer UMSICHT took part in the EU conference "Sustainable development – a challenge for European research" in May 2009. The IGB's exhibits on industrial biotechnology and heat storage using zeolites proved very popular with the European visitors from research, business and politics.

THE IGB IN FRAUNHOFER GROUPS AND ALLIANCES

Institutes working in related subject areas cooperate as groups and foster a joint presence on the R&D market. They help to define the Fraunhofer-Gesellschaft's business policy and act to implement the organizational and funding principles of the Fraunhofer model. The Fraunhofer thematic alliances facilitate customer access to the services and research results of the Fraunhofer-Gesellschaft. Common points of contact for the network of institutes active in related fields provide expert advice on complex issues and coordinate the development of appropriate solutions.

Fraunhofer Group for Life Sciences
EMB, IBMT, IGB, IME, ITEM, IVV, IZI
www.lifesciences.fraunhofer.de

The Group for Life Sciences is a key R&D partner to the pharmaceutical and medical engineering industries and to the fast-growing biotech industry. By pooling their complementary areas of expertise, the members are able to offer a broad spectrum of technologies and services. The Group cultivates an international outlook that reflects the globalized nature of this scientific field and the related commercial market, with activities in Europe, East Asia, North America and the MENA region. The Life Sciences Group is active in business areas such as medical translation research and biomedical technology, regenerative medicine, healthy foods, biotechnology, and process, chemical, and herbicide safety, thus bundling numerous IGB key competences.

Fraunhofer Group for Materials
EMI, IAP, IBP, ICT, IFAM, IGB (Guest), IKTS, ISC, ISE, ISI, ITWM (Guest), IWM, IZFP, LBF, WKI
www.vbw.fraunhofer.de

Materials research covers the entire value chain, from the development of new materials and the enhancement of existing ones, to industrial-scale manufacturing technology, characterization of material properties and evaluation of material behavior when employed in components and systems. The Fraunhofer Group for Materials covers the entire range of materials and their composites, including metallic, inorganic/non-metallic, polymeric and renewable materials. The Fraunhofer IGB's strong competence in materials science qualified it to become a guest member of the Group in 2008.

Fraunhofer Building Innovation Alliance
EMI, IAO, IBP, ICT, IFAM, IGB, IMS, IRB, ISC, ISE, IVV, IWM, IZFP, LBF, UMSICHT, WKI
www.bau.fraunhofer.de

The Building Innovation Alliance focuses on questions relating to sustainability and the conservation of resources but also on the aspect of healthy construction and living as well as on issues of product, system, and process optimization. It has particular expertise in the systematic assessment of buildings – from materials to structural elements, from rooms and buildings to complete villages. But the portfolio also covers the chronological assessment of a building comprising its entire life cycle – from drawing board to construction and finally recycling. Fraunhofer IGB contributes to this Alliance with its infrastructure concepts for semi-decentralized energy and water management as well as with its microbiological competences in building-biology.

Fraunhofer Energy Alliance
CSE, IBP, ICT, IFF, IGB, IIS, IISB, IKTS, IOSB/AST, ISC, ISE, ISI, ISIT, IWES, UMSICHT
www.energie.fraunhofer.de

The Fraunhofer Energy Alliance, is a gateway to R&D services in energy technology and economics. Above all small and medium-sized companies, but policy makers and the energy business sector too, benefit from Germany's technology leadership in energy efficiency and renewables. The IGB contributes its knowledge in the exploitation of the material and energy resources contained in raw, residual and waste organic materials (e.g. for biogas production) as well as membrane technology, particularly for gas purification and reforming and fuel cell applications.

Fraunhofer Nanotechnology Alliance
ENAS, IAO, IAP, ICT, IFAM, IFF, IGB, IISB, IKTS, IPA, ISC, ISE, ISI, ITEM, IVV, IWM, IWS, IZFP, LBF
www.nano.fraunhofer.de

The Fraunhofer Nanotechnology Alliance bundles the competences of nearly one third of Fraunhofer institutes, covering almost all aspects of nanotechnology. Activities are focused on three main areas: multifunctional layers e.g. for automotive applications; the design of special nanoparticles as carrier substances for biomedical applications; and the use of carbon nanotubes for actuatoric applications. The two latter applications are key research fields at the IGB. Dr. Günter Tovar is the Alliance's deputy spokesman and chief contact person for nanobiotechnology questions.

Fraunhofer Photocatalysis Alliance
FEP, ICT, IFAM, IGB, IME, ISC, ISE, IST, IWS
www.photokatalyse.fraunhofer.de

Nine Fraunhofer institutes are involved in this Alliance, developing more effective and efficient photocatalysts for applications on glass, ceramics, polymers and metal. Vacuum plasma processes, sol-gel techniques and water-based paints are used to develop self-cleaning layers that break down organic compounds and destroy microorganisms. In order to determine the photocatalytic activity of a new layer, the Photocatalysis Alliance has developed analysis procedures for chemical-physical as well as microbiological evaluation – the latter being IGB's remit within the Alliance.

Fraunhofer Polymer Surfaces Alliance POLO
FEP, IAP, IFAM, IGB, IPA, ISC, IVV
www.polo.fraunhofer.de

The Polymer Surfaces Alliance pools the core competences of seven Fraunhofer institutes in the development of polymer products with functional surfaces, barrier layers or thin films. POLO was among the first Fraunhofer alliances, and products such as anti-microbial polymer surfaces have already been developed and marketed conjointly. Dr. Christian Oehr has been a member of the alliance's management since its inception, and has contributed significantly to its success.

Fraunhofer Cleaning Technology Alliance
FEP, IFAM, IGB, ILT, IPA, IPK, IST, IWS
www.allianz-reinigungstechnik.de

Cleaning technology has steadily gained significance in the past years and regularly arouses the interest of industry with its applications in buildings, in hygienic production and microsystems technology. By founding the Cleaning Technology Alliance, Fraunhofer is able to offer concentrated competence along the whole process chain and a central point for contact, pooling requests and coordinating projects. Fraunhofer IGB contributes its expertise in the plasma purification of surfaces prior to coating processes. Purification success is evaluated by state-of-the art surface analytical methods. The evaluation of microbial contaminations is an additional IGB specialist field.

Fraunhofer Water Systems Alliance (SysWasser)
Full members: IGB, IOSB, ISI, IST, UMSICHT, IKTS, ISE, IPK, ILT
Associate members: IML, ITWM, IVI, IVV, IZFP
www.syswasser.de

Since June 2007, 14 Fraunhofer Institutes have been pooling their expertise in the development of water systems technologies. SysWasser's mission is to develop sustainable solutions for water catchment, infrastructure, and wastewater treatment and adapt them for use in practical applications on a national and international level, taking into consideration relevant social, economic and environmental aspects. Spokesman for the alliance is its founder, Prof. Dr. Walter Trösch. His objective is an integrated, systemic approach linking water with the energy, waste management and agricultural sectors.

HIGHLIGHTS 09

2009 was an extremely successful year for the Fraunhofer IGB, with the quality of our work attested by numerous awards. Three new project groups in Leuna, Straubing and Würzburg as well as the authorization of an Attract research group allow us to deepen and further develop our competences and achievements. At the same time, the Fraunhofer IGB has shown its social commitment in getting high school students interested in the "MINT" subjects (mathematics, IT, natural sciences and technology) and promoting future technologies to the general public.

PRIZES AND AWARDS

The success of the Fraunhofer IGB's research activities was manifested in numerous renowned prizes awarded to staff. For example, the vascularized model of the liver developed by Dr. Johanna Schanz under the supervision of Professor Heike Walles won two awards. The model is viable outside the body for an extended period of time and can be used for drug testing.

Animal welfare research prize

Animal experiments are still the norm in the preclinical phase of drug approval. For her Ph.D. thesis at the Institute for Interfacial Engineering (IGVT) at the University of Stuttgart, Dr. Johanna Schanz developed a model of the liver, which offers potential as an alternative to animal experiments in drug testing. On October 26, 2009 in Berlin, Dr. Schanz, now deputy head of the Cell and Tissue Engineering Department at the Fraunhofer IGB, was awarded the German Federal Ministry of Food, Agriculture and Consumer Protection's research prize for the "promotion of methodical work toward the aim of reducing and replacing animal based research."

1 Prize for human-centered technology

For her diploma and doctoral thesis under the supervision of Professor Heike Walles, Dr. Johanna Schanz developed methods for the reseeding of the blood vessel structures in a biological carrier structure. This technique makes it possible to manufacture complex, vascularized human tissues that can be used as test systems to investigate *in vitro* findings on the potential toxic effects of new active ingredients on humans. Schanz and Walles were awarded the "Prize for human-centered technology" on the occasion of the Fraunhofer-Gesellschaft's annual conference on June 23, 2009. This prize is offered by former Fraunhofer executive board members and institute directors.

Ferchau Innovation Prize

The first place in the Ferchau Innovation Prize 2009 went to a research group led by Professor Walter Trösch, head of the Department of Environmental Biotechnology and Bioprocess Engineering at the Fraunhofer IGB. Trösch is a firm believer in algae when it comes to binding fossil CO_2 and, in collaboration with Dr. Ulrike Schmid-Staiger and Subitec GmbH, has developed a cost-effective reactor platform that enables CO_2

from flue gas plants to be put to good use. A smart side effect is that the algae produce vitamins, fatty acids, and pharmaceutical substances while the remaining biomass provides regenerative energies. The award was made on April 20, 2009, at the Hanover Trade Fair under the motto "Technology for the environment."

2 Hugo Geiger Prize

In his thesis project at the Fraunhofer IGB, biologist Christian Grumaz succeeded in establishing a new method for manufacturing cDNA fragments from biological samples. It allows the creation of global transcription profiles from 10 to 100 picograms of total RNA, and is thus more sensitive than existing methods by a factor of 10,000. The new analysis technique is of particular interest for diagnosis, drug development and basic research. Grumaz was awarded the 3rd Hugo Geiger Prize at the Fraunhofer annual conference on June 23, 2009. This award is given by the Bavarian government for outstanding, application-oriented diploma theses at a Fraunhofer institute.

Prize of the Association of Friends of the University of Stuttgart

The subject of Marc Panas' diploma thesis at the IGVT (in cooperation with the Fraunhofer IGB) was the manufacture and characterization of amino- and carboxy-functionalized planar, nano- or microstructured glass surfaces as well as the investigation of the interactions of primary human keratinocytes with these substrates. The paper was honored by the Association of Friends of the University of Stuttgart in 2009 as an outstanding piece of research conducted in Faculty 4 (Energy Technology, Process Engineering and Biological Engineering).

Poster prizes

The award for best poster went to Petra J. Kluger, Julia Maierle, Heiko Büth, Frank Pretzsch, Esther C. E. Novosel, Christian Wenzel, Christian Brecher and Heike Mertsching for their poster "Development of high-volume producible nano- and microstructured surfaces for studying cell-substrate interaction" at the 3rd International Symposium on Interface Biology of Implants from May 13-15, 2009, in Warnemünde.

Another poster prizewinner was "Development of processes for manufacturing N-acetyl-glucosamine (NAG) with new chitinases" by Karin Moß, Susanne Zibek, Thomas Hirth and Steffen Rupp, which was presented at the DECHEMA lecture and discussion symposium "Biocatalysis: new processes, new products" held from May 18-20, 2009, in Bad Schandau.

NEW PROJECT GROUPS

Fraunhofer institutes play a prominent role in the regional innovation landscape. As an effective bridge between science and industry they facilitate timely technology transfer – also benefiting regional companies. The Fraunhofer IGB has succeeded in securing funding for three new Fraunhofer project groups, a further milestone in extending our own network beyond Baden-Württemberg. The Chemical-Biotechnological Process Center CBP in Leuna will be jointly financed by the Sachsen-Anhalt Ministry of Economics as well as the German Federal Ministries of Education and Research (BMBF), of Food, Agriculture and Consumer Protection (BMELV) and for the Environment, Nature Conservation and Nuclear Safety (BMU). The State of Bavaria has invested considerable sums of money fostering topic-specific Fraunhofer activities in Bavaria as a business and technology location through its hi-tech offensive "BayernFIT – Research, Innovation & Technology". Two of the project groups funded come under the aegis of the Fraunhofer IGB.

1 Chemical-Biotechnological Process Center CBP, Leuna

With the approval of the federal/*Länder* Committee in July 2009, we were able to embark on planning our Chemical Biotechnological Process Center CBP. The CBP in Leuna closes the gap between pilot plant and industrial implementation: by making infrastructure and plant available, it makes it possible for cooperation partners from research and industry to develop and scale up processes to utilize renewable resources in industrial scale. Thus the CBP represents a hitherto unique platform for developing industrial (white) biotechnology up to commercially relevant scale with a direct link to the chemical industry on the one hand, and to Fraunhofer research on the other. It will be built by the Fraunhofer-Gesellschaft and InfraLeuna GmbH in Leuna, with the Fraunhofer IGB as coordinator.

The center will provide process capacities up to 10 m^3 plus a wide range of processing, treatment and reconditioning techniques and methods. This versatile "modular biorefinery" will allow the processing of raw materials such as vegetable oils, cellulose, starch and sugar and their conversion into chemical products. The first projects with industrial involvement were already launched in 2009. A new building is currently in planning, and Linde-KCA Dresden is acting as a general contractor for the process plant engineering. Completion is scheduled for the end of 2011.

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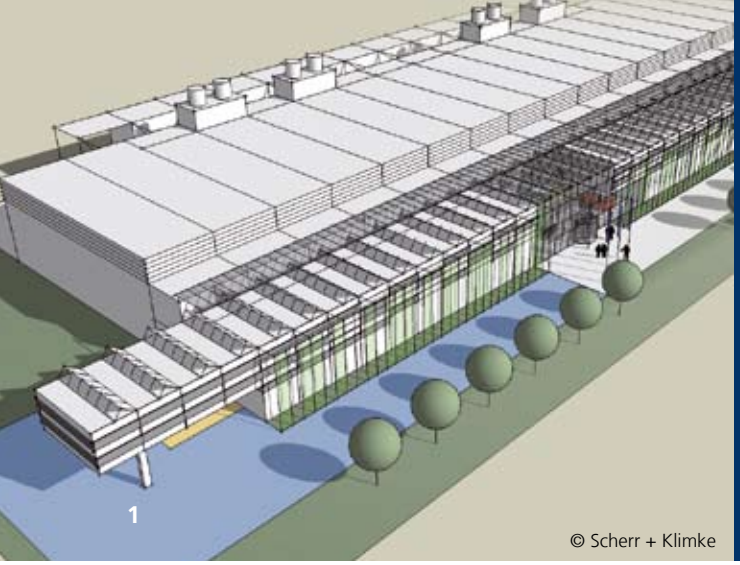

1 © Scherr + Klimke

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2 BioCat Project Group, Straubing

The Fraunhofer project group "Catalytic Processes for a Sustainable Supply of Raw Materials and Energy on the Basis of Renewable Resources" took up its work on August 1, 2009. The group is located at the Straubing Science Center, but is attached to the Fraunhofer IGB in Stuttgart. Headed by Professor Volker Sieber, chair for Chemistry of Biogenic Resources at Munich's Technical University, TU München, the new group's researchers are working closely with several chairs at TUM. Construction work is scheduled to start on a dedicated new building before the end of 2010.

Activities are focused on developing catalytic methods for the conversion of renewable resources into a sustainable raw material and energy supply. The project group's aim is to contribute toward a transition in the chemical industry over to a more extensive use of plant biomass for raw materials. Industrial (white) biotechnology processes play a key role here. The applied research and the technological developments envisaged by the work of the project group are intended to set new impulses for the Bavarian economy in the areas of chemistry, biotechnology and process engineering.

The Bavarian State is making available 5 million euros for BioCat from its "BayernFIT – Research, Innovation & Technology" program, which received budgetary approval from the Bavarian parliament in the summer of 2009. On February 2, 2010, Mr. Grunwald, President of the Government of Lower Bavaria, ceremoniously handed over the official grant approval notification to the Fraunhofer-Gesellschaft, represented by Professor Buller, Senior Vice President Research Planning of the Fraunhofer-Gesellschaft.

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3 Oncology Project Group, Würzburg

The Fraunhofer IGB project group "Regenerative Technologies for Oncology" of the Fraunhofer IGB also officially began its activities on August 1, 2009, at the Medical Faculty of the University of Würzburg. The project group will take on an intermediary role between the numerous university research facilities, the medical faculty including patient care and industry. Innovative technological developments will allow the development of tailored diagnostic products and model tumor therapeutics and therapeutic methods, thus in turn allowing the healthcare system to profit from the new insights as quickly as possible.

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The group's activities centre on an innovation of the Fraunhofer IGB that makes it possible to cultivate human tissue with a functional blood vessel system *in vitro* in a bioreactor system. The Würzburg project group aims to transfer the technologies and techniques involved to the manufacturing of *in vitro* tumor models. If the tumor model can be supplied by blood vessels – as in the body – the system will offer for the first time worldwide the possibility of elucidating the molecular mechanisms of tumor genesis and metastasis. Such tumor models are also ideally suited for the development of cancer diagnostics and drugs.

The State of Bavaria is financing the establishment of the Fraunhofer oncological project group at the University of Würzburg with 3.5 million euros from its "BayernFIT – Research, Innovation & Technology" program. The setting up of the project group goes hand in hand with the appointment of Professor Walles to the newly established chair of Tissue Engineering and Regenerative Medicine at the Medical Faculty of the University of Würzburg on August 15, 2009.

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Attract group: tissue engineering of heart valves

In January 2010, a new Attract group focusing on cardiovascular tissue engineering and regenerative medicine under the direction of stem cell biologist Dr. Katja Schenke-Layland was created at the Faunhofer IGB Department of Cell and Tissue Engineering, headed by Professor Heike Walles. The group has been granted 2.5 million euros over a 5-year period to pursue the development of an optimal tissue-engineered heart valve replacement. Dr. Schenke-Layland completed her Ph.D. at the Friedrich Schiller University Jena where she focused on tissue engineering of alternative cardiovascular tissues, particularly heart valves and blood vessels, and the development of minimal-invasive imaging modalities to monitor structure, composition and function of native and engineered tissues. From 2005-2009, her scientific work at the University of California Los Angeles concentrated on stem cell, matrix and biomaterials research, first in a post-doc capacity, then as Assistant Research Professor. The Attract group at the Fraunhofer IGB is primarily focused on two specific topics: the analysis of cellular and extracellular components of developing heart valves, and the development of new carrier substrates for heart valve tissue engineering. The result of this work will be used to develop an optimal heart valve replacement.

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PROMOTING YOUNG TALENTS | EXHIBITIONS

The Fraunhofer-Gesellschaft is keen to make early contact with the researchers of tomorrow and give them exciting insights into research opportunities. Thus the Fraunhofer IGB is active in both promoting young talents and getting young people interested in research and technology. We do this through events at the Fraunhofer campus in Stuttgart, the Fraunhofer exhibition truck, the Federal Ministry of Education and Research's Science Express, and the Center for New Technologies at the Deutsches Museum in Munich.

Fraunhofer Talent School

At the Fraunhofer Talent School 2009, which took place at the Stuttgart site for the first time, Dr. Kai Sohn, deputy head of Molecular Biotechnology, led the workshop "Who am I, or the amazing journey into the genome." The aim of the workshop is to create a better understanding of the fundamentals of the genetic code, or DNA. For this, DNA is isolated from the participants' saliva samples and characterized molecularly. Every participant gets to take home his or her personal "DNA portrait". Sohn will hold another workshop in 2010 and once again contribute to the success of the Fraunhofer Stuttgart Talent School.
http://talents.izs.fraunhofer.de

Girls' Day at the Fraunhofer center in Stuttgart

In Germany we currently have the best educated cohort of young women of all times, with girls making up 55.7 percent of high-school graduates alone. Despite this, girls still tend to opt heavily in favor of typical female jobs or courses when choosing an apprenticeship or higher studies. Girls' Day – a nationwide event initiated by the Federal Ministry of Education and Research – at the Fraunhofer campus in Stuttgart gives young women an insight into the institutes and the careers available in engineering, IT and the natural sciences. The researchers throw open laboratories and test areas, offices and workshops, using practical examples to demonstrate how interesting their work is. 2009 once again saw well over 100 interested participants in Stuttgart, some of whom visited the "Nature's own chemical plant" and "Here's looking at you, kid" information stations at the Fraunhofer IGB. The next Girls' Day will take place on April 22, 2010.
www.izs.fraunhofer.de/schueler-izs/

BOGY – vocational and academic careers orientation at academic high schools

17 high school students completed their "BOGY" internships at the Fraunhofer IGB in 2009, as part of their vocational and academic careers orientation at Baden-Württemberg academic high schools. They gained insights into the work of scientists and graduate students in different disciplines (engineers, biologists, chemists and physicists) as well as finding out about typical recognized occupations that require formal training (technical assistant, laboratory technician) and about the administration of a research institute. Thus the students were introduced to various working groups of the respective departments and their laboratories, assisted on real projects, became acquainted with methods for identifying particular substances and contributed to the planning and performing of experiments as well as the documentation of the test results.
www.izs.fraunhofer.de/schueler-izs/

Checkpoint Future: open day for university students

On November 23, 2009, some 80 science and engineering students visited the Fraunhofer center in Stuttgart, where they had the chance to find out about the fields of work and opportunities for doing a student research project or diploma project as a student research assistant. They were also able to inform themselves about postgraduate entry-level opportunities as Ph.D. candidates or scientists at the Stuttgart institutes.
www.izs.fraunhofer.de/studierende/

"Expedition Future" science train

From April to November 2009, the science train "Expedition Future" rolled its way through Germany. Composed of twelve futuristically designed cars, the train provided forward-looking information on topics and developments that are just emerging at present – trends in research and technology, which will alter the way we live by 2020. The project is funded by the German Federal Ministry of Education and Research. The Max Planck Society coordinated the train with support from the Fraunhofer-Gesellschaft, the Helmholtz Association of German Research Centers, the Leibniz Association, the Deutsche Forschungsgemeinschaft (German Research Foundation) and a number of universities. In 2010 the Science Express will be underway in China for six months. In the "Convergence of nanoscience and bioscience" car, a Fraunhofer IGB model shows how molecularly imprinted nanoparticles (NANOCYTES®) act as tiny receptors to bind and release the protein insulin.
www.expedition-zukunft.org

Fraunhofer Truck roadshow

Since the 60th anniversary of the Fraunhofer-Gesellschaft in March 2009, the exhibition truck has been touring Fraunhofer institutes, universities, market squares and trade fairs, showcasing how Fraunhofer technologies from the areas of health, the environment, safety, communications and mobility can be incorporated into our daily lives. The truck will continue its travels through the length and breadth of the country until the end of 2010.

In the health section, the Fraunhofer IGB's skin model made from cultivated human cells reveals whether and at what concentration chemicals have a toxic effect. Also on show is a model of the artificial liver which allows investigation of the effect, decomposition and toxicity of active substances in pharmaceuticals. Keeping liver cells alive in the laboratory is difficult: therefore in the IGB's liver model, liver cells are cultivated together with cells from the vascular system and supplied with nutrients in a special bioreactor.

Water is a key focus of our environmental activities. Supplying drinking water is already a big challenge in many parts of the world – thus water management is critical. The Fraunhofer IGB is working on solutions to tap sources of drinking water in an environmentally-friendly way, including investigating the potential offered by moisture in the air. A process has been developed to obtain drinking water from air humidity using solar energy. In the DEUS 21 project, rainwater is purified with state-of-the art filter technology and wastewater treated in bioreactors, at the same time generating biogas as an energy source.
www.fraunhofer.de/veranstaltungen-messen/truck.jsp
www.ebooks.fraunhofer.de/fraunhofer-truck/

Deutsches Museum: nano- and biotechnology at the Center for New Technologies

The mission of the Center for New Technologies (ZNT), which had its opening ceremony at the Deutsches Museum in Munich on November 19, 2009, is to present highly topical issues from science and technology. The Fraunhofer-Gesellschaft is a project partner and has provided scientific and financial support in setting up the ZNT.

The Fraunhofer IGB, for instance, has provided exhibits for the topic "Cells, tissue or entire organisms: the benefits of biotechnology". The title is exemplified by the airlift photobioreactor developed by the Fraunhofer IGB and manufactured by the IGB spin-off Subitec, as well as raw extracts of microalgae and various substrates and products of industrial biotechnology. The topic "Human replacement parts from the test tube: cultivating tissue" is visualized with microscope images and histological cross-sections of human tissue plus a model of the vascularized 3D liver model in the Fraunhofer IGB's bioreactor. "Molecular recognition with nanoparticles" is depicted by a model whose surface bears structures imprinted with a "molecular stamp." The surface structure of these molecularly imprinted polymer nanoparticles can bind specific molecules, allowing uses such as removal of micropollutants from wastewater. The topic "protein chips" shows the new diagnostic applications opened up by the coupling of biological receptor molecules to nanoparticles and printing this hybrid material to render biofunctional microstructures.
www.deutsches-museum.de/ausstellungen/neue-technologien/

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FRAUNHOFER IGB INTERNATIONAL

EU

The 7th Framework Program for Research and Technological Development (FP7) is the main instrument of European research funding and supports the European Union in its aim of becoming the most dynamic and competitive knowledge-based economy in the world. Of interest to the IGB is not only the Cooperation Program with its calls for proposals in the area of Health, Environment, Energy, Nanosciences, Nanotechnologies, Materials & New Production Technologies (NMP) plus the Knowledge-based Bio-economy (KBBE), but also the calls specifically targeted at small and medium-sized enterprises (SME) and their associations.

Research for the benefits of SMEs

Research for the benefits of SMEs supports consortia of innovative small and medium-sized European companies in solving technical problems. Candidate projects must match the business purposes and the innovation needs of SMEs. In the **Light4CleanWater** project the IGB is developing a novel reactor system that converts the toxic pollutants in wastewater into harmless components with the help of multichromatic ultraviolet light. In the **MicroCleanMud** project we are co-developing a microwave-operated system for recovery of drilling mud via extraction and flash-gasification.

Research for the benefits of SME associations

Besides the program supporting research to assist SMEs, there is a parallel program aimed at SME associations. Its goal is to develop technical solutions to common problems facing a large number of SMEs in an industrial sector or in parts of the value chain. The purpose of the EU project **ProEclair** is to establish an efficient and high-quality process for the manufacturing of choux pastry; the IGB is designing a decentralized process for a consortium of European bakers' associations. In the **En-X-Olive** project the IGB is working with Spanish research partners to develop processes to use olive oil production waste for the extraction of anti-oxidants for the cosmetics industry and the recovery of both nutrients for fertilizer production and biogas as a renewable source of energy. With the assistance of European funding, Fraunhofer IGB is boosting the innovativeness and competitiveness of European small and medium-sized enterprises, the drivers of the European economy.

1 Brazil

New biogas utilization project

Funded on the German side by the German Federal Ministry of the Environment, Nature Conservation and Nuclear Safety (BMU), the project "Use of fermentation gases from a municipal sewage works for transportation purposes in the city of Americana, São Paulo state" kicked off successfully, including a high-ranking visit in person from the president of the Fraunhofer-Gesellschaft, Professor Hans-Jörg Bullinger. In Brazil as

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a delegate on an official visit with the German Federal Minister for Research Annette Schavan, Professor Bullinger signed a research cooperation agreement between the Fraunhofer and the renowned IPT institute (Instituto des Pesquisas Tecnológicas) for technological research in São Paulo.

New Fraunhofer contact office

In autumn 2009 Dr. Cornelia Huelsz Müller, Business Development Latin America, took up post in São Paulo in the new Fraunhofer Brazilian contact office. The contact office operates from the premises of the IPT on behalf of the Fraunhofer IGB and two further Fraunhofer institutes (IZM, Munich and IZFP, Dresden), with a focus on tapping the R&D markets for biotechnology, microsystem technology and non-destructive testing technology in Brazil.

Portugal

Following the successful opening of the first Fraunhofer IT research center, FhP-AICOS, at the University of Porto, the Fraunhofer IGB is taking the initiative to extend Fraunhofer activities to research fields in the life sciences within the 7th Framework Program for Research and Technological Development (FP7).

2 Romania

As part of the project "Semi-centralized water- and wastewater management for peri-urban regions in Romania: developing technology to meet requirements in the Timisoara area" funded by the Baden-Württemberg Ministry of the Environment, a pilot plant was taken into operation in the field in September 2009. The plant will be run for several months with communal wastewater, with our Romanian project partner Aquatim carrying out analyses of the wastewater parameters. The IGB is also collaborating with partners from the Timisoara region and colleagues from the Fraunhofer Institute for Manufacturing Engineering and Automation IPA to develop a sustainable concept for the use of renewable energies.

3 France: Cooperation of Fraunhofer and Carnot Institutes

Goal of the German-French research cooperation is to build bilateral collaborations and to develop technologies over the next three years that can be realized as industrial products. The cooperation is being funded in equal parts by Germany's Federal Ministry of Education and Research (BMBF) and France's Agence Nationale de la Recherche. One of the first funded joint projects is between the Fraunhofer IGB and the Carnot Institute CIRIMAT (Centre Interuniversitaire de Recherche et d'Ingénierie des Matériaux). The project "Bio-capabili – Investigation of new anti-bacterial biomaterials based on biomimetic calcium phosphates to prevent bone infections" holds promise for the cultivation of bone tissue using innovative biomaterials. Such materials could be used in surgery, for instance, when new bone material must be grown in order to treat accident victims.

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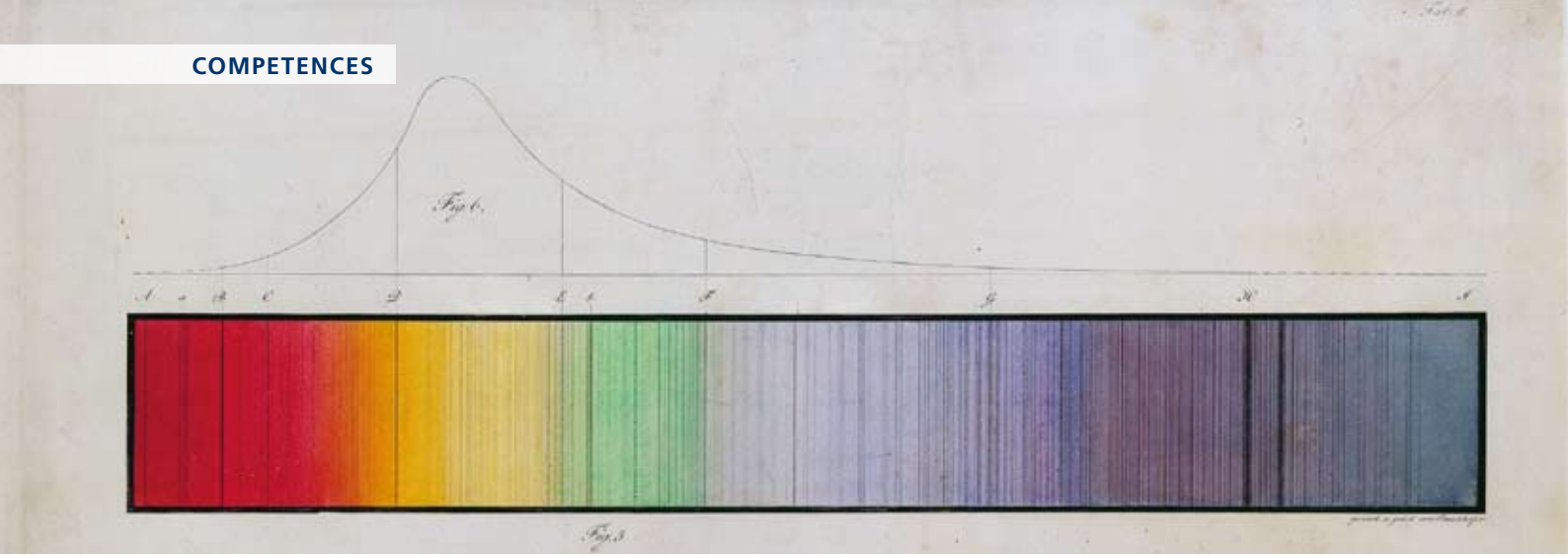


THE FRAUNHOFER-GESELLSCHAFT

Research of practical utility lies at the heart of all activities pursued by the Fraunhofer-Gesellschaft. Founded in 1949, the research organization undertakes applied research that drives economic development and serves the wider benefit of society. Its services are solicited by customers and contractual partners in industry, the service sector and public administration.

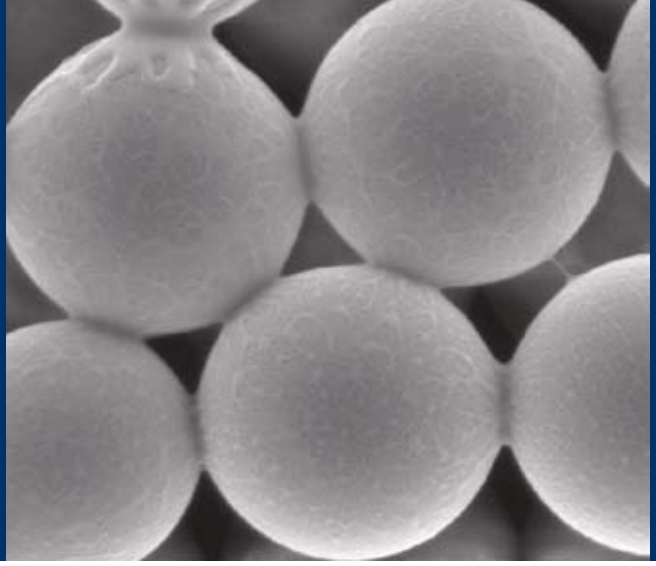
At present, the Fraunhofer-Gesellschaft maintains more than 80 research units in Germany, including 59 Fraunhofer Institutes. The majority of the 17,000 staff are qualified scientists and engineers, who work with an annual research budget of €1.6 billion. Of this sum, more than €1.3 billion is generated through contract research. Two thirds of the Fraunhofer-Gesellschaft's contract research revenue is derived from contracts with industry and from publicly financed research projects. Only one third is contributed by the German federal and *Länder* governments in the form of base funding, enabling the institutes to work ahead on solutions to problems that will not become acutely relevant to industry and society until five or ten years from now.

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

With its clearly defined mission of application-oriented research and its focus on key technologies of relevance to the future, the Fraunhofer-Gesellschaft plays a prominent role in the German and European innovation process. Applied research has a knock-on effect that extends beyond the direct benefits perceived by the customer: Through their research and development work, the Fraunhofer Institutes help to reinforce the competitive strength of the economy in their local region, and throughout Germany and Europe. They do so by promoting innovation, strengthening the technological base, improving the acceptance of new technologies, and helping to train the urgently needed future generation of scientists and engineers.

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

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



INTERFACIAL ENGINEERING AND MATERIALS SCIENCE

The main activities of the Interfacial Engineering and Material Science Department are focused on the deposition of thin and ultra-thin films as well as on preparation of functional nanomaterials. To this end we have established various methods for the deposition of films and particles from the gas phase as well as from the liquid phase. Regarding bulk materials to be treated we are focused on polymers, but in addition we also handle some inorganic substrates. Besides the quality of the products, the material and energy efficiency of the techniques are a chief concern. Emphasis is also laid on the scale-up potential of the processes developed.

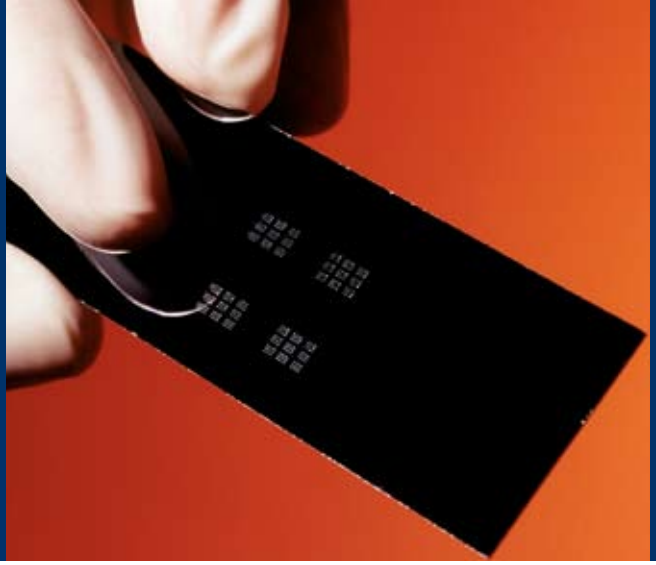
Established preparation methods are:

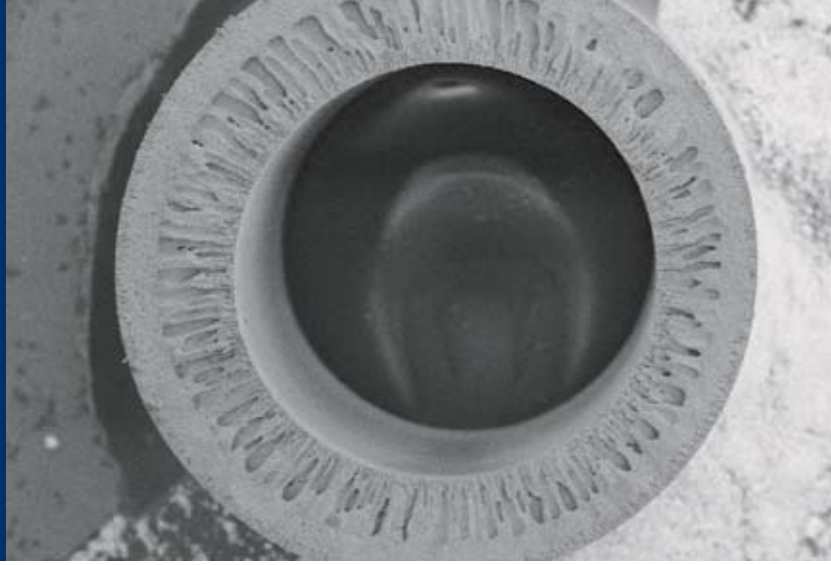
- Deposition of thin films by chemical and physical vapor deposition (PVD, CVD e.g. plasma processing, evaporation and sputtering)
- Manufacturing of nano-particles via several polymerization methods
- Production of separation membranes by sol-gel processes and consecutive annealing
- Deposition of thin layers by layer-by-layer (LbL) techniques as well as by self-assembly monolayers (SAM)
- Deposition of thin films via spin-coating
- Generation of nano-fibers by electro-spinning

To achieve reliable processes, every step of the process development has to be controlled. In addition the products have to be characterized in detail. For this purpose a multitude of analytical tools is available and can partly be used also for *in-situ* monitoring of processes (process diagnostics). Due to the fact that the majority of our products are characterized by nanometer dimensions (ultra-thin films and nano-particles), we use several methods to deliver information, with resolution down to the nanometic scale.

The following characterization and diagnostic methods are used for process development as well as for the solution of product-specific problems assigned by our clients:

- Determination of interfacial energy with different types of tensiometers.
- Estimation of topography and geometric patterning of surfaces on the nanometer scale by different (AFM) probe modes as well as by scanning electron microscopy and digital optical microscopy.
- Micro-caloric measurements of adsorption properties, specific surface area via BET measurements and estimation of film thicknesses with ellipsometry.
- Chemical composition with respect to functional groups is analyzed via IR spectroscopy in ATR mode, IR microscopy, confocal Raman and fluorescence spectroscopy as well as MALDI-TOF-SIMS; the chemical composition of elements is measured by ESCA and EDX.





- For plasma process diagnostics, probe measurements as well as optical and mass spectrometric methods are available.
- Application-relevant properties such as the separation and permeation properties of thin films (membranes, barriers and corrosion protection) as well as the specific separation capabilities of molecular imprinted nanoparticles or the dispersibility of modified carbon nanotubes are examined in customized apparatuses.

Thanks to the combination of preparation methods and analytical tools we are well prepared to successfully handle the development challenges of our clients across the IGB's portfolio – whether in medicine, pharmacy, chemistry, the environment or energy.

Infrastructure and laboratory equipment

- Plasma reactors for cleaning, sterilization, pretreatment, activation, modification and coating of surfaces
- Equipment for sputtering and parylene coating
- Electron (SEM) and probe (AFM) microscopes
- Spectrometers for the analysis of surfaces and thin layers
- Chemical-nanotechnical laboratories for the synthesis and preparation of nano-structured (bio)-materials and surfaces
- Plants for the production and testing of membranes

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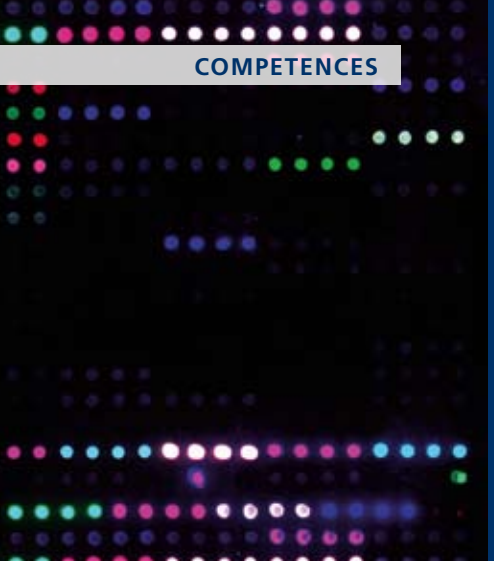


MOLECULAR BIOTECHNOLOGY

The Department of Molecular Biotechnology (MBT) focuses on the identification and analysis of the structure and mode of action of enzymatic, cellular and microbial systems. This know-how is transferred into applications for the chemical and pharmaceutical industries: from target identification and validation to lead compound development for the pharmaceutical industry and to the development of processes for sustainable production of chemicals (biorefinery).

The department's main areas of expertise are:

Methodical development for genome-wide analyses, including:

- Multiple microarray platforms for DNA and protein-microarrays (Microgrid II Arrayer and Axon GenePix® 4300A Scanner for up to 15,000 probes per slide, GMS417 Arrayer and GMS 418 Scanner for up to 300 probes per slide)
- Universal nucleic acid analysis using next-generation sequencing and qRT-PCR (LightCycler 480)
- Proteomics using MS technologies (nano-LC-MALDI-TOF/TOF, HPLC-ESI-MS/MS)

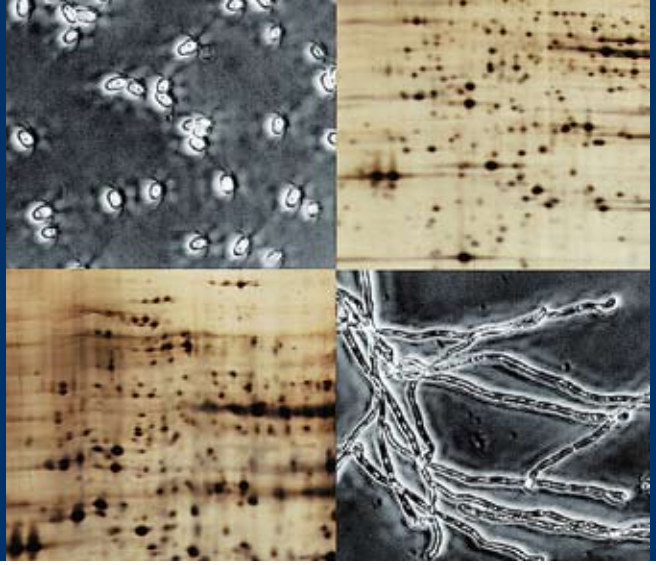
The development of highly sensitive and specific diagnostic assays using:

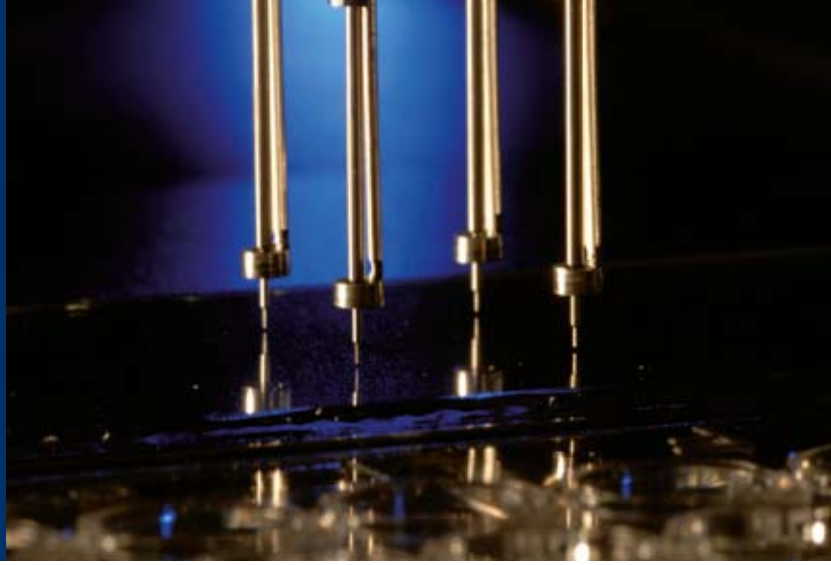
- Cell-based assays for determination of biological parameters (e.g. anti-viral assay, pyrogen detection assay, GLP certified)
- Universal microarray platform (microbiologic diagnostics, tumor diagnostics)

A certified analytical lab (GC-MS/MS, LC-MS/MS, GPC, IC, ICP-AES, ICP-MS) is able to determine a multitude of chemical molecules (metabolites, ions, etc.).

We use this technological repertoire for functional genome analysis especially in infection biology as well as for diagnostics (detection of microbial pathogens or tumor markers) and compound screening. In addition, these technologies are used to develop microbial strains and cell lines for industrial and pharmaceutical biotechnology.

Microbial strains and cell lines for industrial and pharmaceutical biotechnology are developed using recombinant technologies developed in-house. For the development of optimized fermentation procedures we rely on a multitude of microbial strains or cell lines. In addition, equipment for fermentation in suspension or with adherent cell lines is available up to 10 liters non-GLP. Downstream processing is available for the respective products.





For the development of fermentation processes in industrial biotechnology we possess the necessary equipment for up-stream processing (attritors, etc.), multi-fermenter-systems and several laboratory-scale. Upscaling ranging from 30-300 liters is possible in cooperation with other Fraunhofer IGB departments using batch, fed-batch or continuous processes, including the required downstream processing for the respective products.

Within the Fraunhofer IGB, we are able to develop highly efficient processes for the production of pharmaproteins as well as fine chemicals covering the entire value chain from development of production strains to purification of the product.

Using these competences, MBT, in cooperation with other departments of the IGB, is active in the business fields of medicine, pharmacy, chemistry and environment.

Infrastructure and laboratory equipment

- Molecular biotechnology laboratories up to biology safety level BL2
- Microarray facility
- Quantitative real time PCR
- Proteomics facility with MALDI-TOF/TOF-MS
- Laboratories dedicated to chemical and biochemical analysis, disposing of a comprehensive range of chromatographic, spectroscopic and electrophoretic equipment

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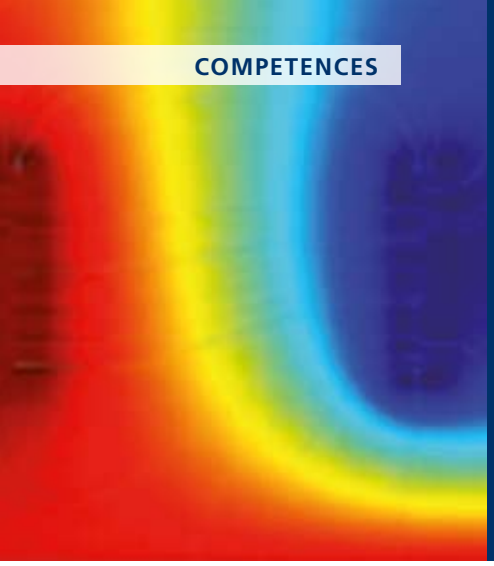
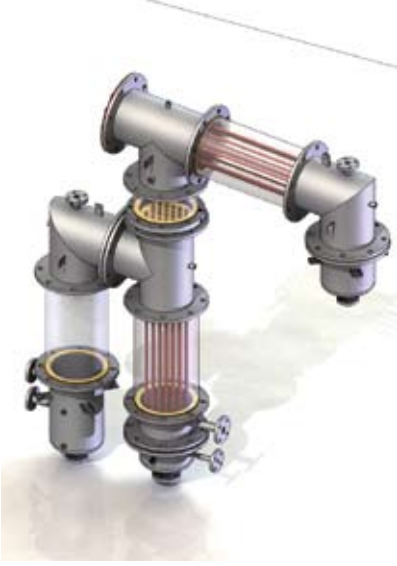




PHYSICAL PROCESS TECHNOLOGY

The Department of Physical Process Technology (PT) is involved in developing processes and process components based on physical principles, and our work encompasses industrial treatment, production and recycling processes. A main objective of our projects is to achieve sustainable solutions for materials treatment and energy management.

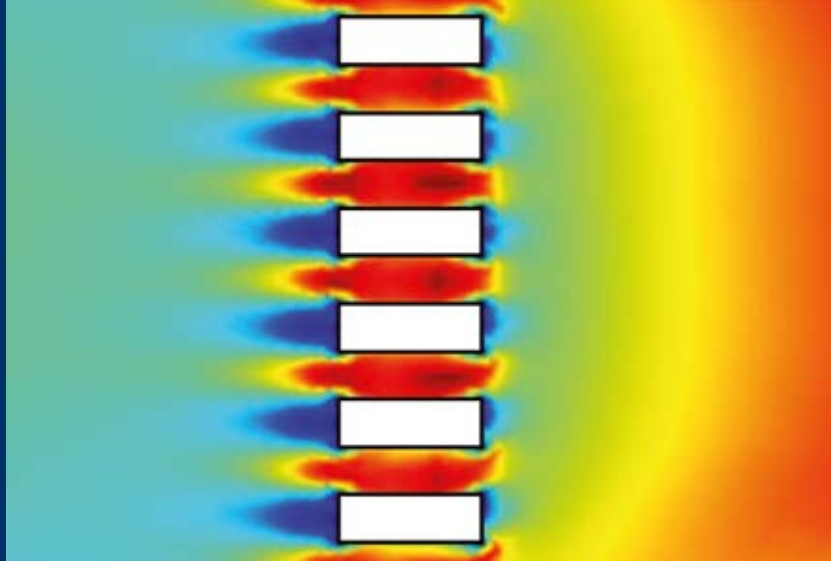
The current thematic fields the department is focusing on are:

- Heat and sorption systems
- Drying and extraction
- Nutrients recycling and plant nutrients management
- Electro-physical processes
- Oxidative water treatment
- Design and system integration
- High frequency technology in process engineering

The PT department is staffed by scientists from various engineering (e.g. process, chemical, civil, high-frequency and thermodynamic) and other (e.g. food chemistry) disciplines, who work together in multi-disciplinary project teams. This may also involve collaboration with specialists from other IBG departments, such as microbiologists and bioengineers, leveraging synergies in expertise.

Our development work on processes and process components is characterized by the continuity of our applied research work, from laboratory-scale characterization and analytics, to software modeling, to design and system integration in real industrial applications.

To design our technological concepts, we use the latest 3-D CAD design software, which is directly linked by data interface to various numeric modeling software products. For standard modeling we use COMSOL-MultiPhysics (FemLab) for the flexible execution of basic tasks, ANSYS for theoretical pre-studies of multi-phase processes such as the behavior of solid particles in a fluid flow, and CST-Microwave Studio for the calculation of high frequency electromagnetic fields in cavities and the design of antennas for efficient and proper radiation.



From the knowledge thus gained, we can go on to realize demonstration prototypes using the many resources at our disposal – workshops, laboratories and pilot plant stations, as well as a network of highly qualified industrial partners and suppliers.

Design and simulation software

- SolidWorks 2008 SP4.0
- CST Microwave Studio 2009
- ANSYS Version 11.0: Multiphysics™ and CFX®
- COMSOL MultiPhysics® Version 3.5
- Design-Expert 7 Workstation
- Mechanical Desktop 2004 DX (AutoCAD 2004)

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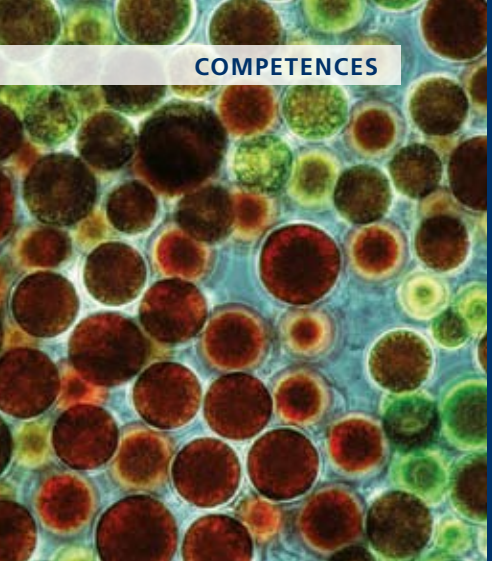

ENVIRONMENTAL BIOTECHNOLOGY AND BIOPROCESS ENGINEERING

The core competence of the Environmental Biotechnology and Bioprocess Engineering Department is the development of sustainable processes for bulk chemical production or energy generation using organic raw, residual and waste materials. The resulting carbon-based substances are used either as bulks for fine chemicals and polymers or simply for renewable energy production. We offer complete processing – from microbiological fundamentals such as growth- and degradation kinetics to the planning, design, construction and test operation of technical demonstration plants. Intelligently combining the unit operations of engineering with bioprocesses, plus our expertise in the targeted colonization and depletion of surface microorganisms give us unique selling points.

Departmental competences at a glance:

- Both classic and "continuous" high-throughput screening methods for autochthonic production strains as high potentials for sustainable processes
- Batch-, fed-batch and continuous operation fermentations, with partial or total cell retention (filtration or im mobilization)
- Psychrophilic, mesophilic and thermophilic bioprocesses
- Anaerobic digestion technology
- Cultivation of microalgae in flat-panel airlift photobioreactors
- Antimicrobial surfaces, target material for biocatalysts immobilization
- Modeling of processes and simulation of process lines
- Scale-up studies and scale-down experimental set-ups to solve problems during technical operation
- Mobile pilot plants in m^3-scale to generate basic engineering data for reliable planning of technical plants
- Downstream processing technologies such as membrane-based filtration processes, liquid-liquid extraction, extraction with supercritical media, protein separation
- Holistic models for energy, waste and water management

The Department of Environmental Biotechnology and Bioprocess Engineering is thus in a position to take part in solving socio-political challenges such as the greenhouse effect, energy supply and freshwater shortage. By offering sustainable technology options, the Department can help industry, communities and policymakers design a balanced future.

With the combined competence of other IGB departments, the Department of Environmental Biotechnology and Bioprocess Engineering serves the needs of the chemical, energy and environmental sectors.

Infrastructure and laboratory equipment

- Bioreactors of various types and sizes (laboratory, pilot and technical scale)
- Mobile membrane bioreactors for wastewater treatment
- Pilot plants (applications for environmental and sterile technology)
- Rotation disk filtration units (different membrane surfaces and different pore sizes)
- Extraction units with supercritical fluids
- Electrodialysis

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CELL AND TISSUE ENGINEERING

The core competences of the Cell and Tissue Engineering Department are the establishment of

(I) processes for culturing primary cells from different tissues and species

(II) procedures for the development of three-dimensional organ-like cell cultures for testing or reconstruction purposes

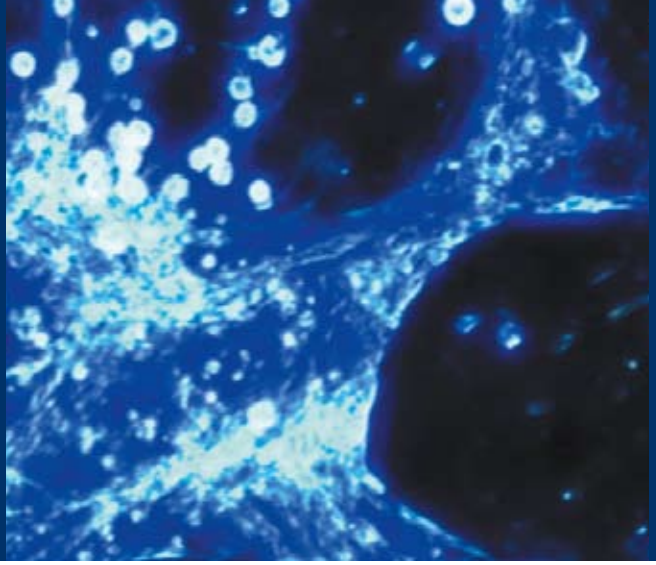
(III) methods for non-invasive cell and tissue characterization by means of Raman spectroscopy.

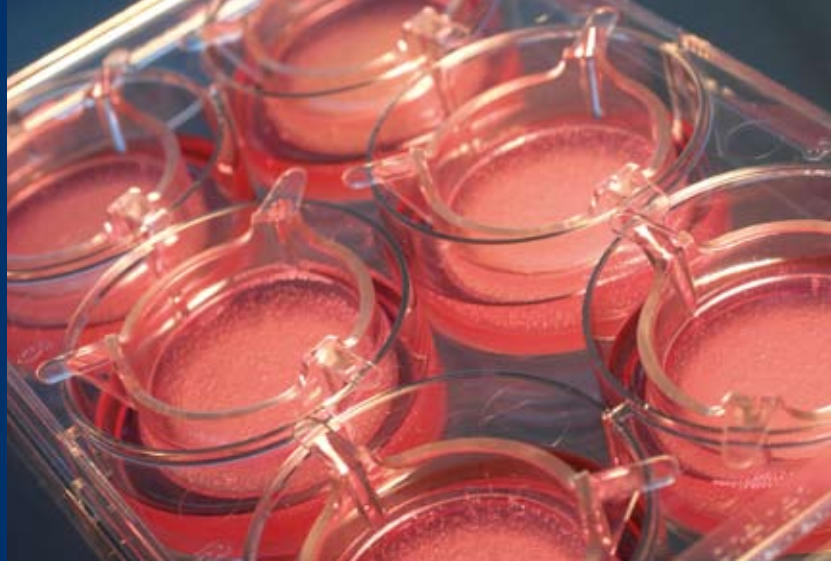
We develop biocompatible micro- and nano-structured material surfaces for the effective isolation and culture of primary cells and for optimal cell type-specific cultivation, in particular of adult stem cells. With these products, we are helping to solve complex challenges in the areas of regenerative medicine, tissue engineering and the development of cell-based assays for toxicology.

A two-layered human 3D skin equivalent has been patented (EP1290145B1) and certified for the testing of the biocompatibility of medicinal devices (DIN ISO 10993-5). The skin model can be extended by further cell types, for example melanocytes or tumor cells. It is also suitable as a preliminary stage to animal testing in investigations of the penetration and the distribution of test substances, as required by the European Union chemicals regulation REACH. The model's scope extends to investigation of differentiation, cell death, and also tumor initiation and graduation. In addition, in 2009 our two-dimensional intestinal testing system based on colon carcinoma cells (2D CaCo-2 model) was approved for use as an in-house method by the German Association for Accreditation (DGA). The model enables rapid classification of the permeability of potential candidate drugs and other substances at the intestinal barrier, and assessment of their bioavailability when administered orally.

A vascularized matrix (BioVaSc) was developed to generate complex organ structures and its cultivation established in specific bioreactors. With the help of these vascularized test systems, absorption, distribution, metabolism, excretion and toxicity (ADMET) of substances or medicinal products can be investigated. These criteria are critical in the characterization of the pharmacokinetic and toxicological properties of active substances. Currently established vascularized systems are a human liver, intestine and trachea model.

Additionally, we offer process development and prototype production of autologous transplants in the context of the EU Directive on Advanced Therapy Medicinal Products (ATMPs). The first step involves establishing and verifying the specific manufacturing process for a particular ATMP, which is then adapted to regulatory demands. The final step is applying for authorization to conduct clinical trials (Manufacturing Authorization for Investigational Medicinal Products). We manufac-





ture autologous transplants in our GMP unit, which was modernized in 2008. At present, we possess manufacturing authorization for an autologous cartilage transplant, an autologous stem cell formulation and an autologous blood vessel transplant for bypass surgery.

Services offered

Cell culture technology of primary human cells and of specific cell culture media:

- *In vitro* testing of biocompatibility according to DIN ISO 10993-5

Cell biology analysis:

- Molecular biological, histological and immunohistological methods
- Flow cytometry (FACS), including sorting
- Modern digital image processing techniques such as micro-dissection und Raman spectroscopy

Establishing of various 3D tissue models:

- Accredited for REACH testing
- Alternatives to animal testing in cosmetics R&D
- ADMET testing for substance and drug screening
- Target screening for new therapeutics and infection biology

Process development, manufacturing, and testing of cell and gene therapeutics as investigational medicinal products (phase I/II clinical studies)

Infrastructure and laboratory equipment

- Cell culture laboratories up to biological safety level BL2 conforming to safety levels S1 and S2 of the GenTSV (German ordinance on safety in genetic engineering/of the German GenTSV Genetic Engineering Safety Regulations) with state-of-the-art equipment, e.g. inverse fluorescence microscope, FACS, Raman-AFM, microdissection instrumentation
- GMP production unit (cleanrooms, separate quality control area, storage facilities) up to biological safety level BL2 (conforming to safety level S2 GenTSV)

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INSTITUTE FOR INTERFACIAL ENGINEERING

The Institute for Interfacial Engineering (IGVT) under direction of Professor Thomas Hirth belongs to the Faculty of Energy Technology, Process Engineering and Biological Engineering of the University of Stuttgart (Faculty 4). At year end the Institute had a staff of 59 and an annual budget of around 1.85 million euros. Most of the Institute's activities are currently carried out on the premises of the Fraunhofer IGB. Additionally, the IGVT runs also laboratories and pilot plant facilities at Stuttgart University's multipurpose branch at Allmandring 5b. The Institute's working groups have at their disposal sophisticated laboratory and pilot plant facilities with equipment for chemical, physical-chemical, physical, biochemical, cell biological and biotechnological research.

The close cooperation with the various IGB groups facilitates a continuity of the projects from basic research to application, in the form of IGVT research funding
received from the German Research Foundation (DFG), the German Federal Ministry of Education and Research (BMBF), the DBU, the European Union, the state of Baden-Württemberg, various foundations and industry. At the IGVT, academic fundamental research is combined with application-oriented approaches, incorporating ideas from practice.

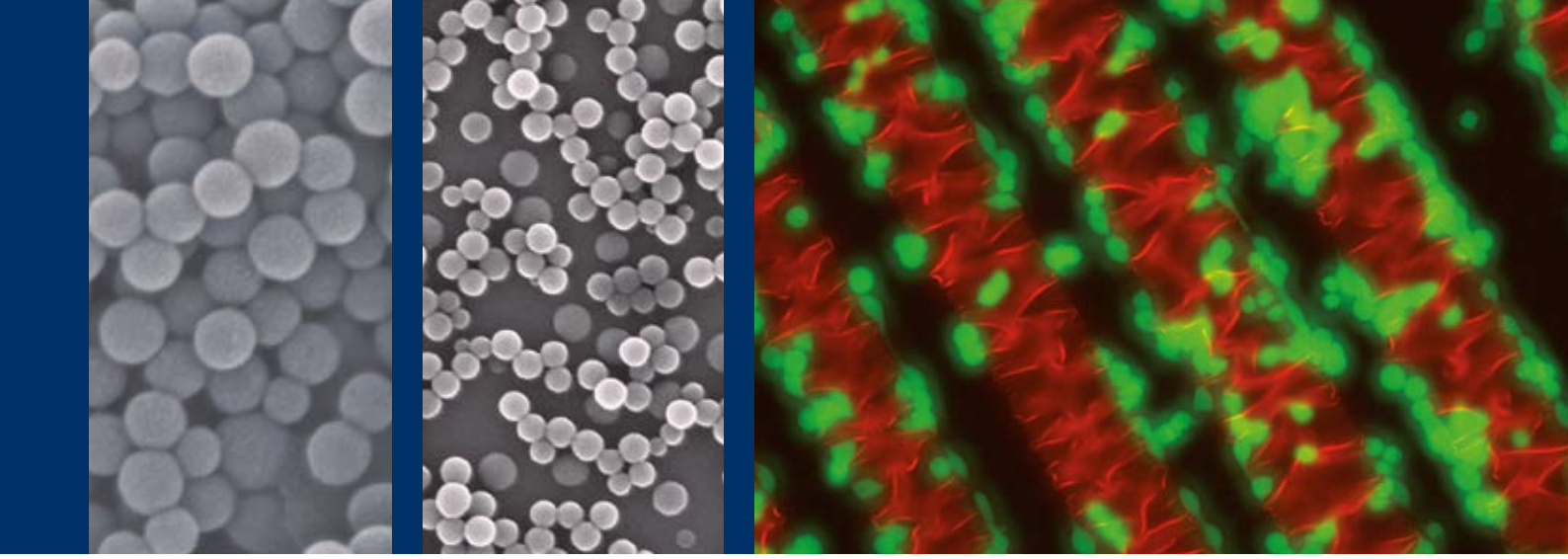
Research and teaching

The IGVT's mission is the characterization, design and functionalization of surfaces of organic, inorganic and biological origin as well as of nano-, bio- and hybrid materials and their interaction. Further activities include the simulation and process engineering of interfacially driven processes in membrane technology and biotechnology, including their chemical, physical-chemical, biochemical, molecular and cell biological fundamentals.

The IGVT's teaching activities are focused on the fields of interfacial process engineering, nanotechnology, and industrial biotechnology. Qualifying courses are also offered in other interdisciplinary fields. Students predominate from courses in process engineering, technical biology, the WASTE master study program, applied materials science, chemistry, technical cybernetics, and mechanical engineering.

Biological Interfacial Engineering

- Host-pathogen interactions
- Interactions between microorganisms and surfaces
- Microarray technology for diagnostics and biomedical research
- Screening for enzymes and microorganisms, as well as process development for industrial (white) biotechnology



Chemical Interfacial Engineering

- Molecular recognition
- Nano- and microstructured (bio)functional surfaces
- Core-shell nano- and microparticles, with a focus on biomimetic shells
- Biomimetic functional layers for medical and bio-technological applications
- Biomaterials
- Radical formation and reaction of mixtures of two-materials in energetic fields

Medical Interfacial Engineering

- Organoid human test systems as a substitute for animal experiments
- Generation of vascularized tissue
- Toxicity studies using organoid tissue models
- Autologous transplants and cell therapies
- Tissue-specific bioreactor development

Physical Interfacial Engineering

- Plasma diagnostics, interface characterization and physical-chemical model building
- Surface functionalization and coating for biological and medical applications, packaging technology and energy technology
- Process development for the dispersion of nanotubes and nanoparticles in liquids and polymers
- Electrochemically stimulated crystallization in precipitation reactions
- Adsorption/desorption processes for heat storage and dehumidification
- Particle suspensions and emulsions in electric fields

Environmental Interfacial Engineering

- Development of novel membranes and membrane processes for water treatment
- Development of dynamic membrane processes for cell retention and water hygienization
- Specific adsorbers for elimination of micro-pollutants from water and exhaust air flows
- Membranes for gas separation and fuel cells
- Producing valuable products from microalgae in photobioreactors
- Recycling of inorganic nutrients as crystals
- Characterization of products dried with superheated steam

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MEDICINE

Prof. Dr. Heike Walles

The Business Area Medicine at the Fraunhofer IGB is founded on the pillars of regenerative medicine, infection biology, diagnostics and optimization of established medical devices.

The focus of regenerative therapies is on the development of autologous transplants (ATMPs). The Fraunhofer IGB maps the complete value-added chain to a GMP conform manufacture of ATMPs and assumes the role of the mediator, particularly for small and medium-size enterprises – from the outset to preclinical tests. To increase the chances of regenerative medicine in public health, we are developing a GMP conform plant for the standardized, fully-automatic manufacture of skin by means of an *in vitro* process in a joint research project financed by the Fraunhofer-Zukunftsstiftung (Fraunhofer Future Foundation).

Contrary to initial expectations that treatment of infectious diseases with antibiotics would be a story of ever increasing success, they still pose a growing threat to public health worldwide. In industrial nations both bacterial and fungal infectious diseases are again on the increase. New scientific strategies to combat infections or avoid sepsis are therefore essential. Based on its own patents, the Fraunhofer IGB has developed various array technologies and transcriptome analysis methods, and is therefore in a position to research efficiently into host-pathogen interaction. On this basis we want to develop new diagnostics as well as active agents and treatment strategies.

A further key issue, thanks to the interdisciplinary orientation of the Fraunhofer IGB, is the optimization of surface properties of established medical devices such as stents and contact lenses, particularly by means of plasma processes. New applications are created through the utilization of biochemically functionalized nanoparticles to mark cancer tissue for surgery.

1

PATHOGENOMICS – BASIS FOR COMBATING INVASIVE FUNGAL INFECTIONS

Dr. rer. nat. Ekkehard Hiller, Priv.-Doz. Dr. rer. nat. Steffen Rupp

Systemic mycoses, invasive fungal infections, are severe infections – particularly in haematological-oncological diseases, neutropenia, AIDS, in patients after major surgical interventions or during chemotherapy or also in preterm neonates. They can often have a fatal outcome as only limited diagnostic and therapeutic options exist for effective treatment.

Target structures of an antimycotic therapy

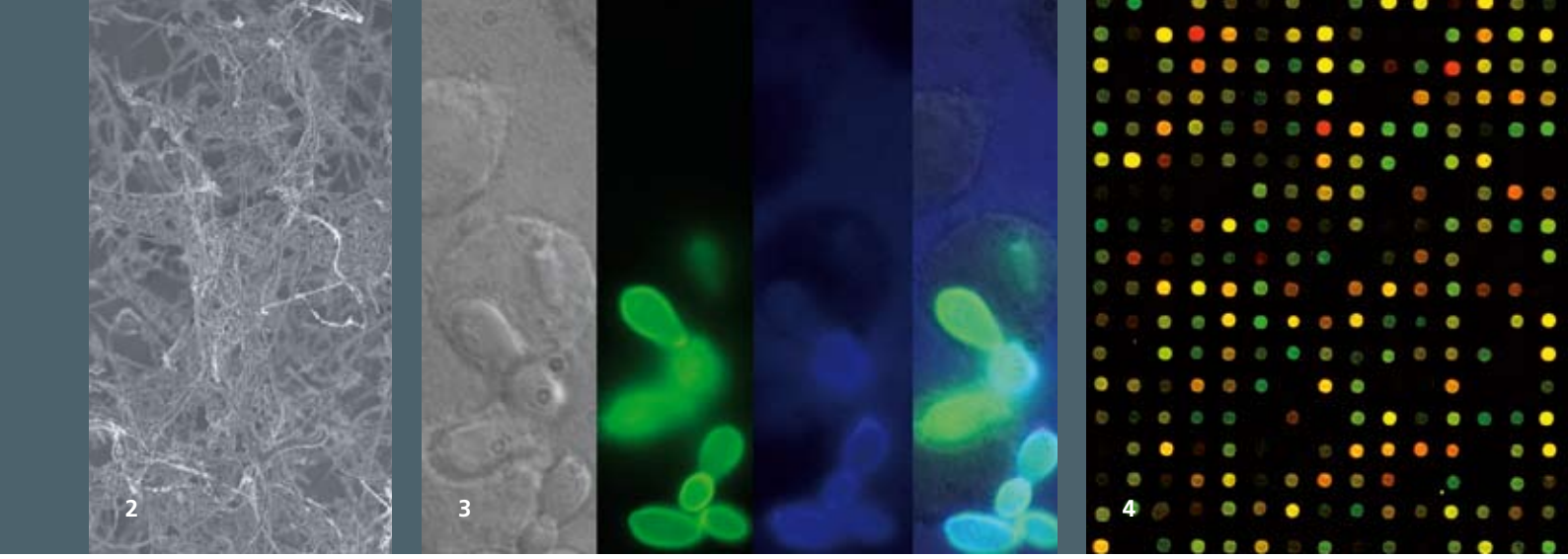
For the development of new antifungal substances an understanding of the fungal cell wall is of particular importance. This structure, which does not occur in human cells, bears essential functions for the interactions of the pathogen with the host and is thus central for the fungal virulence. Both the cell wall itself and the factors which are required for its adaptation to different environments (adhesins, enzymes for assembly and degradation of the cell wall, and many other factors) are thus preferred targets for antimycotic substances.

Projects

At the Institute for Interfacial Engineering (IGVT) of the University of Stuttgart we cooperate closely with the Fraunhofer IGB on several projects funded by the German Research Foundation (DFG) and the Federal Ministry of Education and Research (BMBF) to further clarify the processes which are relevant for the virulence of different fungi. These studies are predominantly concerned with the human pathogenic fungi *Candida albicans* (Fig. 1) and *Candida glabrata*, which occur as the most frequent pathogens causing systemic mycoses. In this context, the cell wall, which is important for interaction with the host, including its proteins are analyzed to identify appropriate target structures for combating the respective organisms. Additionally, the objective of our work is to analyze the cellular processes occurring during the formation of biofilms (Fig. 2) and the adhesion to the host cells. The results obtained here are directly utilized in associated projects with research partners and used for example for drug screening assays, which are funded in the scope of the ERA-NET PathoGenoMics program by the BMBF.

Influence of the cell wall on immunogenicity

In order to analyze the influence of cell wall structures on infection processes, we use tissue models to simulate adhesion and invasion processes *in vitro*. Genes or proteins, which can be relevant for the infection process in *C. albicans* were identified by genome-wide transcription profiles and proteomics [1, 2, 3]. According to these results we analyze the effect of potentially infection-relevant proteins, which are involved in cell wall organization, by generation of appropriate deletion mutants in *C. albicans*. These mutants are also used in *in-vitro* experiments for example with macrophages in order to investigate the interaction with the host's immune system (Fig. 3). Differences in the numbers of individual *Candida* strains phagocytized by the macrophages can be used to identify the structures utilized by the fungus to hide itself from the immune system. Investigations on *in-vivo* models are performed by our project partners (see info box).



Deletion study identifies virulence genes

In order to identify virulence associated genes of *C. glabrata*, we use comprehensive gene deletion studies. For this purpose, genes which code for known signal transduction pathways, membrane-bound sensors, transporters and transcription factors were identified with the aid of comparative genome analysis and subsequently deleted. In this manner, approximately 700 deletion mutants were generated. We analyze the function of the deleted genes with the aid of biological assays for cell wall stability, adhesion and stress tolerance in order to be able to draw conclusions as to their function during infection. To date 39 mutations which result in altered reactions to various stress factors have been identified. We were able to demonstrate the influence of one of these genes, whose potential function previously was only based on sequence homology, on cell wall composition and adhesion behavior by experimental evidence.

Strains with reduced virulence are further characterized by means of genome-wide transcription profiles (Fig. 4). In this manner, we were able, for example, to reveal differences in the signal transduction pathways used to convey cell wall damages in *C. glabrata* compared to the very closely related, but not pathogenic, yeast *Saccharomyces cerevisiae*. The results obtained from this allow conclusions on the pathogenicity mechanisms and possible targets for combating human pathogenic fungi.

1 *Electron microscopic image of Candida albicans.*
2 *Scanning electron microscopic image of a C. albicans biofilm.*
3 *Fluorescence microscopy of the phagocytosis of C. albicans by macrophages (green: C. albicans cells, blue: non-phagocytized C. albicans cells).*
4 *Spot pattern of a microarray for the transcriptional analysis of C. glabrata.*

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[3] Hiller, E. et al (2007) Eukaryot Cell 6(11): 2056-65

Partners

www.spp1160.hki-jena.de
www.pathogenomics-era.net/1stJointCall

Funding

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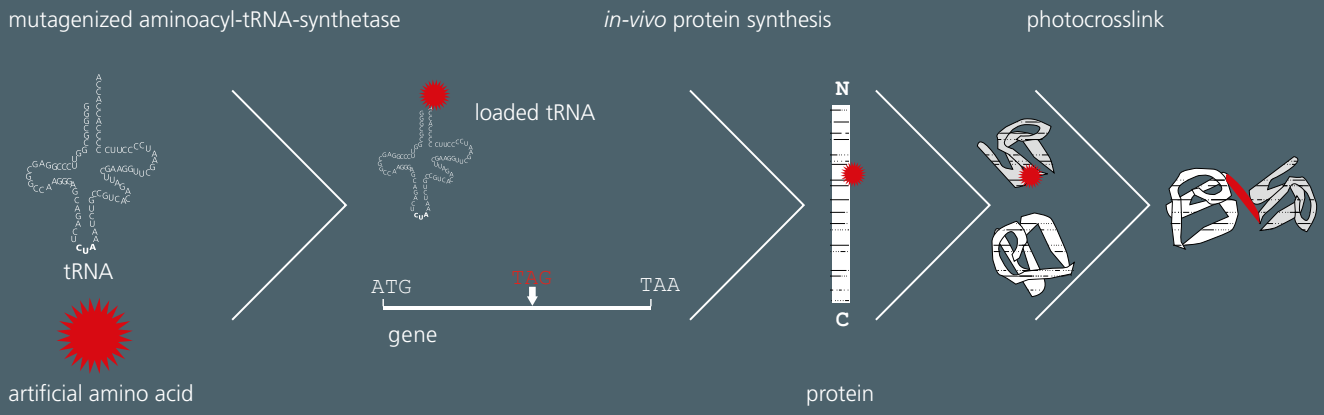


1

SYNTHETIC PROTEINS FOR THE ANALYSIS OF BIOMOLECULAR INTERACTIONS *IN VIVO*

Dipl.-Biol. Michael Berg, Dr. rer. nat. Kai Sohn

Proteins are macromolecules, which as a rule are formed from 20 canonical amino acids via peptide bonds in the cell. In this context, the unique amino acid sequence of each individual protein defines its biological function and its physico-chemical characteristics. Proteins are of scientific and economic importance, for example highly specific enzymes with defined catalytic properties for the synthesis of complex compounds or therapeutically applicable active substances. Currently, proteins are generated by standard recombinant technologies.

One of the most recent and promising approaches for the biosynthesis of proteins with novel physico-chemical characteristics is provided by the rapidly developing field of synthetic biology. In this context, the underlying principle allows the generation of recombinant organisms using standardized components as well as engineering principles. In addition to standard, natural amino acids, these synthetic organisms can also site-specifically incorporate artificial amino acids with novel properties into the peptide sequence *in vivo*. These newly added functional groups can either improve the physiological function of the protein or provide the protein with unique biochemical properties that go far beyond the natural spectrum, such as cross-linking capability, photoactivation, or the possibility of selective, posttranslational modifications.

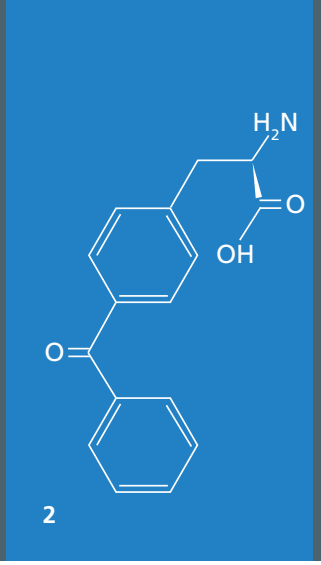
At present more than 200 artificial amino acids can be chemically synthesized; more than 30 of them have already been incorporated into proteins *in vivo*. However, their actual application and utilization still is in its infancy.

Developmental objective

The objective of the Fraunhofer IGB is to generate synthetic proteins based on the site-specific incorporation of artificial amino acids such as azidophenylalanine or benzoylphenylalanine *in vivo* (Figs. 2 and 4). Using these proteins it should then be possible to study biomolecular interactions, such as protein-DNA and protein-protein interactions, in eukaryotes under physiological conditions *in vivo*. For the implementation of this technology at the Fraunhofer IGB we make use of the Gal4p transcription factor in *Saccharomyces cerevisiae* as a model system in order to localize DNA binding sites genome-wide and to identify potential protein-protein interactions.

Principle

Frequently, the interactions of a protein with its environment are not stable, but only transitory. The association between the interaction partners can, for example, dissociate as soon as the biological systems being examined are disintegrated for analysis. For this reason it is essential for the analysis of protein-protein interactions that the respective biomolecular interactions are covalently linked. In this context the time of fixation should be arbitrary and specific for the interaction.



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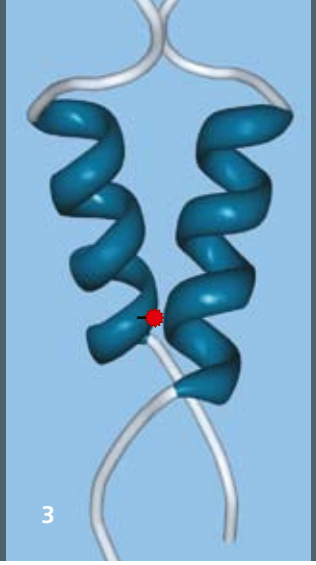
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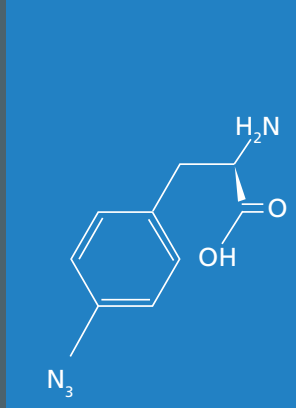

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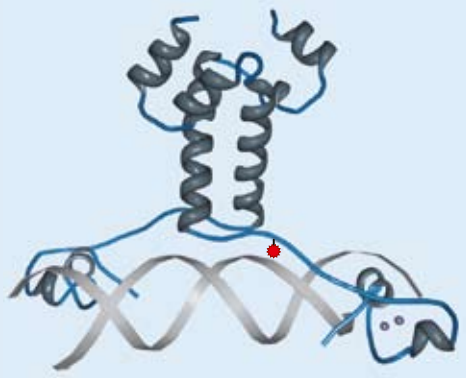
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To meet this requirement, we make use of an expanded genetic code (Fig. 1). In this context, instead of a natural amino acid an artificial amino acid will be incorporated into the interaction domain of the transcription factor Gal4p *in vivo* at a defined position during biosynthesis (Figs. 3 and 5). For this purpose, azidophenylalanine and benzoylphenylalanine, which are derived from the natural amino acid phenylalanine, are used as artificial amino acids. The additional side groups of these amino acids can then be photoactivated by UV light to form covalent links to the respective interaction partners. These protein complexes, which are very tightly bound to one another, can then be isolated, subsequently enriched, and identified by means of mass spectrometry.

Perspective

The technology for the generation of "synthetic" proteins for the analysis of biomolecular interactions has the potential to be universally applied and thus will contribute to a better understanding of complex regulatory networks in the development of diseases or to clarify metabolic pathways.

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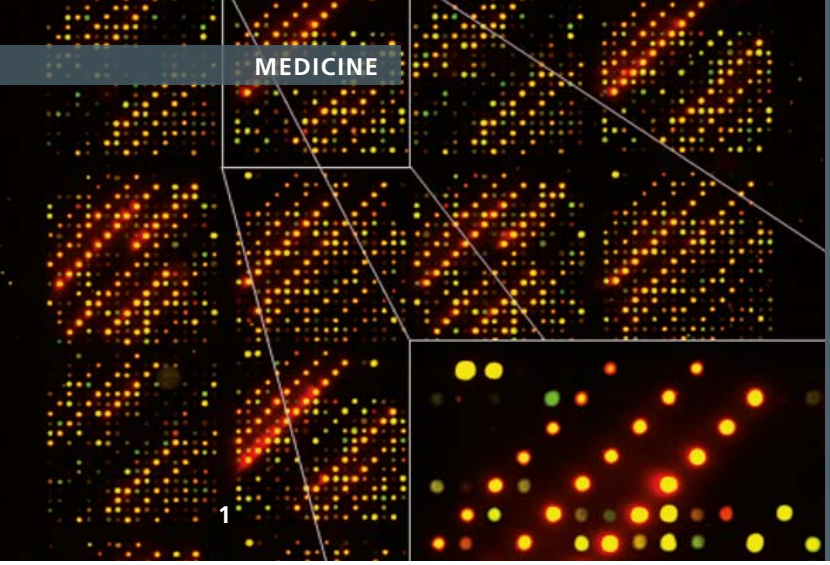
1 *Principle of the expanded genetic code in S. cerevisiae.*
2 *Structure of the artificial amino acid benzoylphenylalanine.*
3 *3D crystal structure of the protein interaction domains of the Gal4p transcription factor.*
4 *Structure of azidophenylalanine.*
5 *3D crystal structure of the DNA interaction domains of Gal4p.*



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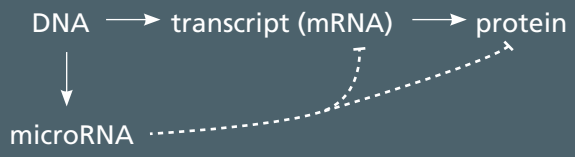


2

DEVELOPMENT OF A UNIVERSAL MICROARRAY PLATFORM FOR IMPROVED DIAGNOSIS OF CANCER

Dipl.-Biol. (t.o.) Sonja Weishaupt, Dr. rer. nat. Nicole Hauser

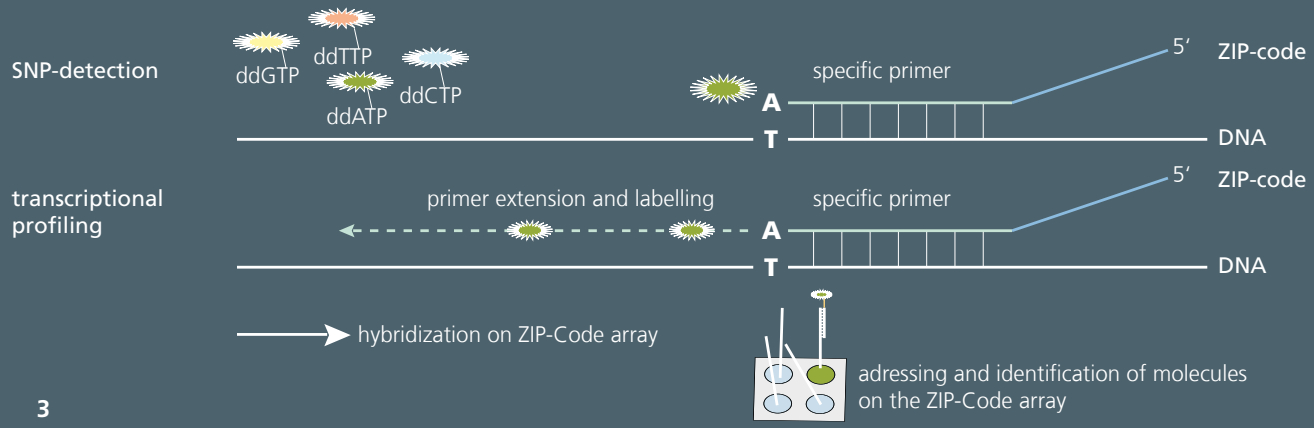
Cancers are the second most frequent cause of death in industrialized countries. The number of new cases increases annually. In order to be able to treat the patients as rapidly and as successfully as possible, a precise diagnosis is of decisive importance. In routine clinical diagnostics, the classical immunophenotypical and histopathological methods are primarily used. However, these standard methods are normally too imprecise for an exact classification of the excised tissue. In order to achieve a precise diagnosis, the tumor must be classified at the molecular level. Microarray technology is an appropriate procedure, which provides the possibility of highly parallel molecular examination.

Diagnostic arrays at Fraunhofer IGB

At the Fraunhofer IGB we develop diagnostic microarrays for various fields of disease such as infections or cancers. In this context, various molecular biological methods, for example, gene expression analyses or genotyping are used. One of our foci is in the development of diagnostic arrays for extremely frequent or heterogeneous cancers. In different projects with the Robert Bosch Hospital, Stuttgart, and the NanoCinna Ltd. Company we were able to establish gene-expression microarrays, which function on the basis of selected specific tumor marker genes, for the classification of breast cancer, the most frequent type of cancer worldwide in women.

Universal array platform for the analysis of several regulatory levels

A precise classification is particularly essential for very heterogeneous cancer. The complexity of such cancer types requires an extension of the standard diagnostic tools in order to be able to determine the molecular cause of the tumor more exactly. With the aid of microarray technology it is possible to investigate cells on different regulatory levels, for example on the genomic (DNA) and on the transcriptional (RNA) levels (Fig. 2) simultaneously. These parallel analyses of DNA, mRNA and microRNA allow, for example, a more specific classification of the tumor and can thus provide decisive information for therapeutic success. At Fraunhofer IGB we realize the parallel detection of genomic and transcriptional nucleic acids with the aid of a universal ZIP-code microarray. The ZIP-code is an artificially generated nucleic acid sequence which exhibits no homology to the DNA in the investigated cancer cells. It is attached to specific sequences, which contain sectors relevant for tumor classification, as a kind of anchor. The specific sequences bind to the target cell DNA or RNA, respectively, in the sample and allow their enrichment and labeling. Via the ZIP-code part, the thus-labeled DNA or RNA, respectively, can be bound to the array at defined positions of complementary immobilized sequences (complementary ZIP-codes) and identified (Fig. 3).



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Tumor classification using ZIP-code arrays

In a cooperative project between the Fraunhofer IGB and the German Cancer Research Centre (DKFZ), Heidelberg, we were able to successfully establish the parallel detection of several parameters for breast cancer classification on a universal ZIP-code-based array platform. For this breast cancer ZIP-code array, the focus is on the preparation of gene expression and SNP (single nucleotide polymorphism) detection.

In cooperation with the DKFZ and the Institute for Pathology at the University of Lübeck, we are currently developing a ZIP-code array for the classification of aggressive non-Hodgkin's lymphoma. Without treatment the aggressive non-Hodgkin's Lymphoma, known colloquially as lymph node cancer, results in rapid death, but can be healed if properly diagnosed. As a result of their very large number of manifestation forms, non-Hodgkin's lymphomas are among the most difficult cancers to classify. To date no scientific-medical uniform classification exists for them. To be better able to analyze the complexity of this cancer, we additionally integrate molecular parameters such as SNP status, microRNA and transcriptional profiling in our array. This extended combination allows a detailed molecular diagnosis of non-Hodgkin's lymphomas, which serves as the basis for a targeted individual therapy of the patient.

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Robert Bosch Hospital, Stuttgart

German Cancer Research Centre (DKFZ), Heidelberg

NanoCinna Ltd., Teheran

Funding

Parts of this work were supported by the State Foundation of Baden-Württemberg in the scope of a graduate fellowship for Ms Sonja Weishaupt.

1 *Diagnostic breast cancer array for the preparation of gene expression profiles.*

2 *Information flow in the cell.*

3 *Principle of the universal ZIP-code microarray using the parallel SNP detection for genotyping and transcriptional profiling in gene expression analysis as an example (modified according to Hauser et al. 2006).*

1

2

BIOMATERIAL DEVELOPMENTS – HYDROGELS FOR THE DEVELOPMENT OF BIOMIMETIC SOFT TISSUE

Dr. rer. nat. Daniela Pufky-Heinrich

Demographic development poses enormous challenges for health research in the areas of diagnostics and therapy worldwide. Therefore, medical practice today demands the use of biocompatible, high-performance materials as biomaterials. In this context, the spectrum of their applications extends from injection systems to catheters, wound dressings and temporary implants up to permanent implants and organ replacement. Biomaterials for applications in soft tissue such as skin, blood vessels, connective or supportive tissue are to simulate or substitute for flexurally soft natural structures. For this purpose hydrogel polymers are predominantly used. In these artificially configured hydrogels, reactive polymer units are linked to form a three-dimensional network. At present, both bio-based and synthetic polymers are used to manufacture artificial matrices for *in-vitro* tissue substitution. However, there is a great need for the development of intelligent biomaterials which imitate the mechanical and biological properties of natural systems equally well.

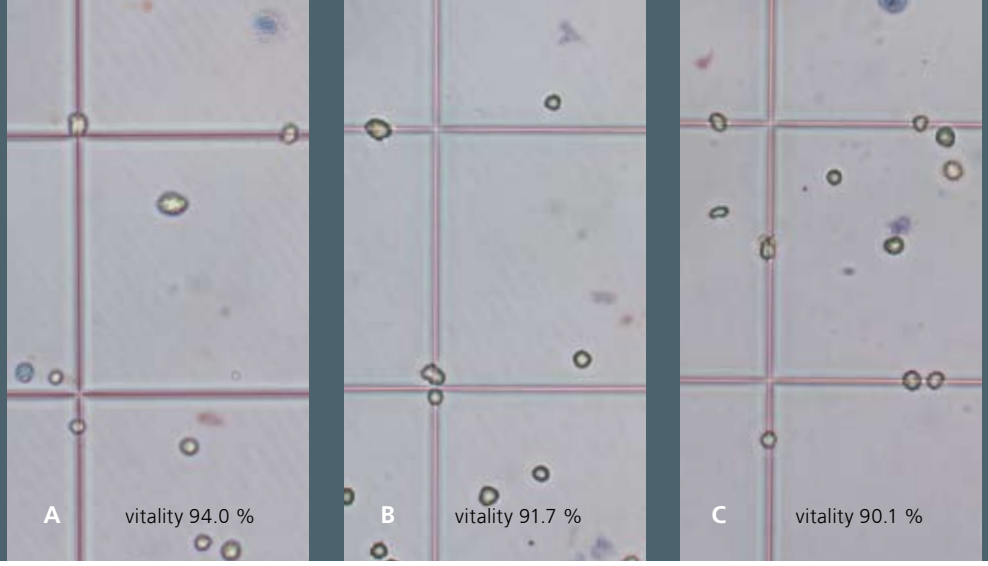
Elastic polymers for configuration of three-dimensional layers

In interdisciplinary development approaches, which combine research from the fields of polymer and synthetic chemistry, materials sciences and biology, biomaterials for specific applications are being developed tailor-made at the Fraunhofer IGB. The development of materials with high elasticity and the capability of elastic recovery is at the focus of different research projects. For example, functionalized polymer units based on polyethylene glycol are synthesized and three-dimensional hydrogel layers are formed from them (Fig. 1). In this context, we use photo-polymerization techniques and methods of click chemistry. By adjusting the hydrophilicity and the degree of cross-linking we can thus selectively produce custom-tailored, cross-linked polymer layers for corresponding application. In addition to the elastic functionality, the cell adhesion properties of the synthetic gel systems play an important role. Thus, we have derived biofunctional polymeric structural units based on gelatines (Fig. 2) and elastin in order to be able to generate appropriate hybrid systems, which unite both the mechanical and the biological aspects.

In situ gelling gel systems

In situ gelling hydrogel systems are used to enclose cells homogenously in a polymer matrix. This methodology is of particular interest for developing analogues for soft tissue, for example artificial skin systems. In this context, our developments include the preparation of pH and temperature induced gel systems, e.g. via N-isopropylacrylamide or sulphonamide or cell-compatible highly reactive polymer components for generating chemically cross-linked hydrogel structures. In the adaptation of the polymer matrices we orient ourselves both on bioinert and biodegradable systems.

The biodegradable polymer units which we have developed were selectively developed for the preparation of pure synthetic hydrogelling systems. The biocompatibility of the established reactive thiol-ene system based on polyethylene glycol for the encapsulation of human cells could be proven by vitality tests with primary fibroblasts (Fig. 3).



Applications and perspective

Innovative novel biomaterials are especially developed for use as medical-technical products. In this context the applications of the synthetic three-dimensional hydrogel systems extend from *in-vitro* test systems up to artificially fabricated implants. Systematic investigations of the cell material interactions also allow to design cell-specific framework structures for the creation of carrier structures for cell cultivation.

1 *Cross-linked poly-(ethylene glycol-co-pentaerythritol) for the preparation of three-dimensional hydrogel layers.*
2 *Hydrogel made from gelatine-based hybrid material.*
3 *Cell biological assessment of the biocompatibility of established polymer components for in situ gelling hydrogels: light-microscopic images of primary fibroblasts after incubation with solutions made of A) reactive thiol and B) reactive ene-macromer compared to C) positive control (gel neutralization solution).*

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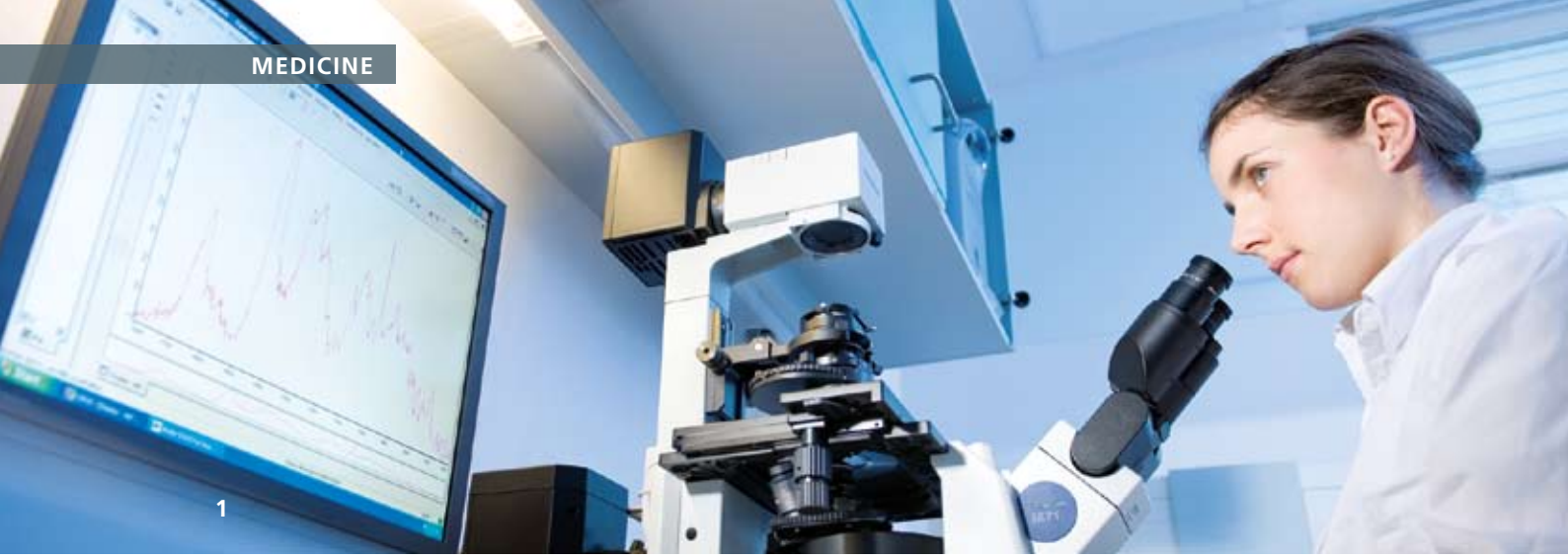

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BIORAMAN – THE APPLICATION OF RAMAN SPECTROSCOPY FOR STERILITY AND QUALITY CONTROL IN TISSUE ENGINEERING

Dr. rer. nat. Steffen Koch

Raman spectroscopy is a laser-based optical technology for the characterization of synthetic materials as well as for the determination of biological materials. With regard to the biological use of this vibrational spectroscopic method the main advantage is the easy handling of sample preparation, the possibility of measurements directly in fluids and the marker-free and non-destructive analysis of cells and microorganisms.

In cooperation with two other Fraunhofer institutes, we are developing a procedure, a measurement system and a fluidic cell which form a system for the positioning of single biological particles coupled with automated Raman spectroscopic analysis. Thus the system will enable the touch-free and non-destructive determination of sterility in, for example, the manufacturing of transplants. In addition, the procedure can also be used for non-contact and non-invasive measurements in the quality control of different cell types.

Raman spectroscopy

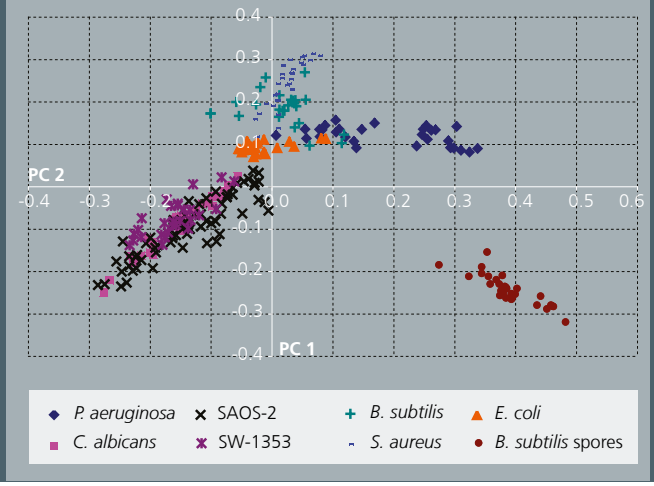
The Raman effect, named after its discoverer C. V. Raman, and for which he was awarded the Nobel Prize in 1930, is based on the observation of inelastic scattered light in a sample. The sample is irradiated by monochromatic (laser) light; the inelastic scattered light which is red-shifted against the excitation can be detected as a spectrum. Different bands are observable in the spectral information, which correspond to the chemical composition of the sample and thus constitute a chemical fingerprint.

Data processing in biological applications

The high variability of cells (mammalian cell lines, microorganisms and spores) used in biological applications necessitate a large number of measurements in order to set up equipment appropriately and to establish a reference database for discriminating microorganisms and mammalian cells. Therefore a data processing and analysis tool for large volumes of data becomes expedient. At the Fraunhofer IGB we meet this challenge with principal component analysis (PCA), an analytical tool used to identify systematic differences in large volumes of data and to reduce these data volumes. PCA reveals similarities of spectral data by explaining the variance of the data.

Sterility control

A prerequisite for sterility analysis in tissue engineering is the detection of contaminants directly in the cell culture media, for example in the supernatants of biopsies. For the investigation of possible contaminants six different microorganisms were tested, including four types of bacteria, a kind of bacterial spore, and the fungus *C. albicans*. The investigation was carried out by detecting and differentiating between mammalian cells and microorganisms, as well as between the organisms and other particles in the cell culture supernatant such as cell debris. These particles are very difficult to discriminate, especially from bacteria, by microscopy and image analysis. In contrast, using Raman spectroscopy it is possible to dis-



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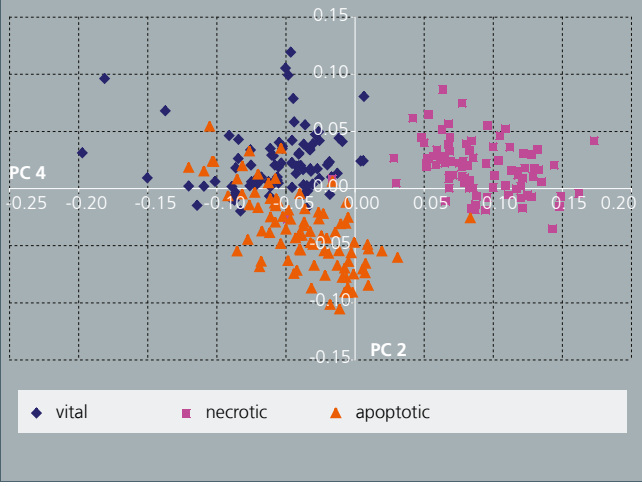

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criminate well between cells, microorganisms and particles recovered from the supernatant. Beyond this, the method offers potential for discriminating and identifying different microorganisms.

Cellular analysis and cell viability

Key criteria for quality control of cells in tissue engineering include determination of cell viability, status of cellular differentiation, and the identification of different cell types. With this approach important parameters can be estimated for the manufacturing of tissue engineering products. Spectroscopic methods allow the categorization of a huge variety of cell types. Thus the purity of the cell type in use can be controlled. Besides this, controlling of cell viability is another important aspect of quality control. Here we were able to identify spectral regions for discriminating between viable, necrotic and apoptotic cells.

Outlook

We are currently working on the automation of measuring processes such as image analysis, automated start-up and measuring of relevant particles. In addition, work is also in progress on the quantification of the spectroscopic data; using a Support Vector Machine (SVM) (a computer-assisted mathematical technique for pattern recognition) first results yield a good classification of the different organisms.

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Fraunhofer Institute for Biomedical Engineering IBMT, St. Ingbert

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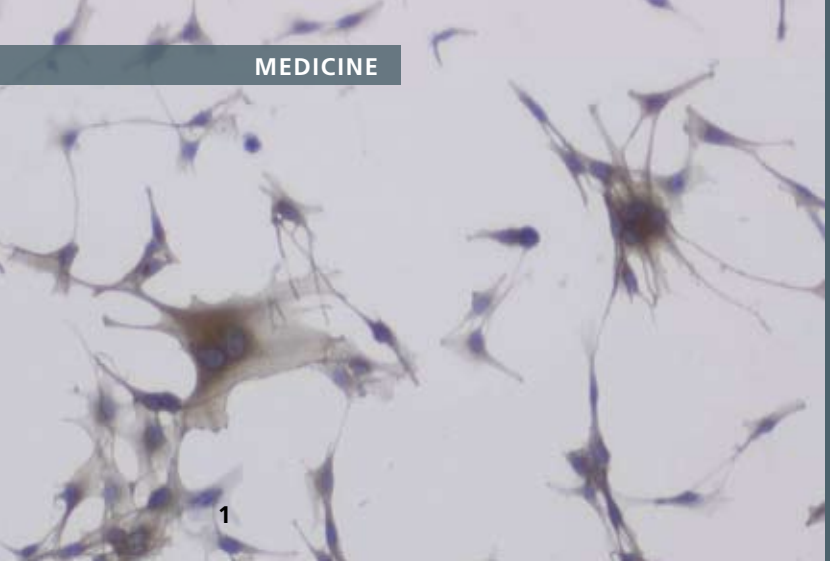
We would like to thank the Fraunhofer-Gesellschaft for funding our work under the MAVO (Market-driven Prospective Research) Program with the project title "Online quality control for accelerated drug development and individualized therapy by means of Raman spectroscopy imaging."

1 *Bioraman at Fraunhofer IGB.*

2 *PCA for the discrimination of microorganisms and cells. In each case, 25-30 spectra of the different organisms were measured. Clusters for bacteria, spores, cell lines and C. albicans are clearly recognizable. Explained variances for PC 1 and PC 2 are 28 % and 21 % respectively.*

3 *PCA for the determination of vital (blue), necrotic (pink) and apoptotic (orange) SAOS-2 cells. The explained variances for PC 2 and PC 4 are 17 % and 5 % respectively.*



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GMP MANUFACTURING OF A MELANOCYTE GRAFT

Dr. rer. nat. Iz Anadere

Vitiligo is a chronic disorder involving the partial depigmentation of the skin. The cause can be attributed to the degeneration or malfunctioning of melanocytes (the cells producing the skin pigment melanin). Knowledge about the ultimate cause of this disease is, at present, still very incomplete. First, normal melanin synthesis ceases. This phase is possibly reversible. In the further course of the disease depigmented skin patches appear, mostly at the extremities. With a lack of the necessary skin protection against UV-radiation, the risk of vitiligo patients for developing cancer is increased in the melanocyte-free areas.

Treatment with a melanocyte graft

Vitiligo has not been considered curable to date. A new therapeutic approach for the treatment of vitiligo is now available in the form of melanocyte grafts. Assuming that patients are no longer affected by depigmentation-causing conditions such as sunburn and acute stress or by other serious illnesses, implantation of autologous (patient-own) melanocytes into the affected skin areas offers good chances of healing.

Manufacturing of the graft

Melanocyte grafts (Fig. 1) involve a cell implant to reseed the diseased, pigment-free skin areas, promoting repigmentation of the skin and activating the melanocyte growth. The melanocytes are first isolated from a skin biopsy of the patient and then cultivated over several weeks in the GMP unit at the Fraunhofer IGB (Fig. 2). Finally, the cells are harvested and transported at a defined cell concentration as a suspension to the operation site. There, the melanocytes are transplanted into the pigment-free skin areas of the patient. A manufacturing authorization has already been applied for with the responsible local authority, which will allow the use of autologous melanocyte transplants in clinical studies.

GMP manufacturing unit at the Fraunhofer IGB

We develop GMP manufacturing processes for autologous transplants in regenerative medicine and clinical trials, apply for manufacturing authorization and manufacture cell-based therapeutics on a pilot scale in our certified GMP manufacturing unit (according to the German Drug Law). In 2008, the Fraunhofer IGB's GMP unit was extended from 150 to 215 square meters, completely newly designed and renovated, and reaudited by the local authorities (Regierungspräsidium Tübingen). In the past four years we have been awarded three additional proprietary manufacturing authorizations. Our customers are biotech and pharmaceutical companies as well as hospitals and medical centers worldwide.

Services at a glance

- Process development of autologous transplants
- Manufacturing of cell- and matrix-based transplants
- Production and quality control of cell-based investigational medicinal products (IMPs) for phase I/II clinical studies
- Regulatory affairs/documentation
- Quality management

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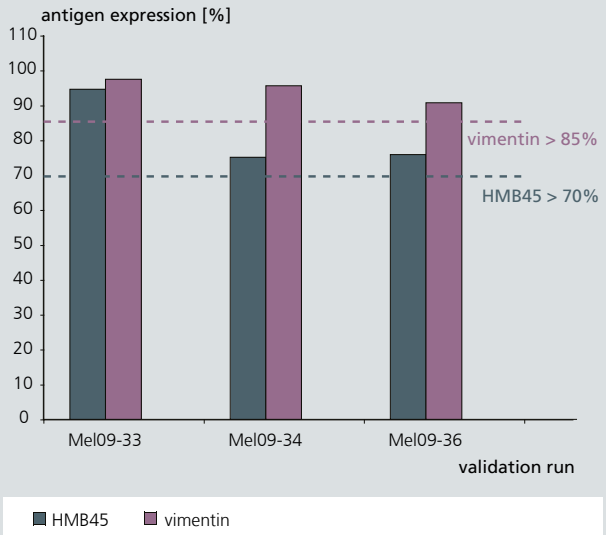
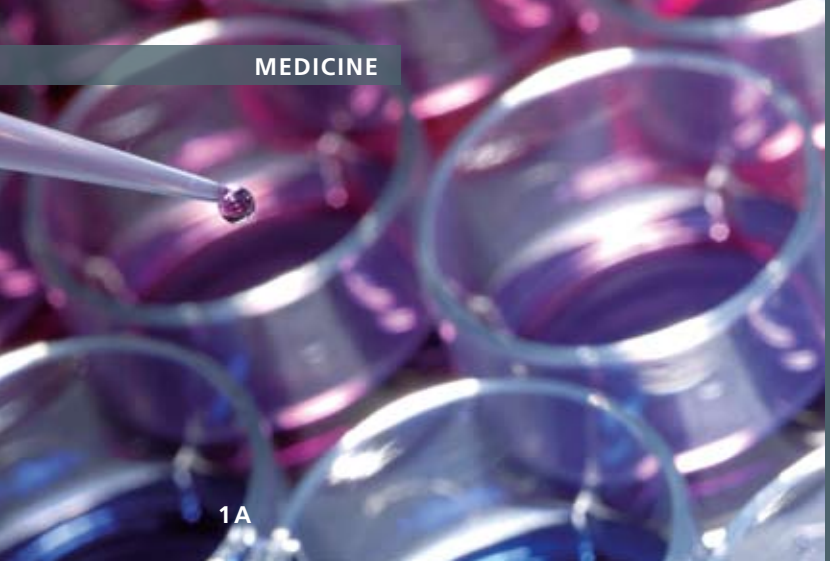
Detection of the identity of melanocytes: expression of HMB45 and vimentin (intracellular analysis by flow cytometry)



1 *Histological staining of melanocytes (with HMB45).*

2 *GMP-compliant manufacturing – consistent manufacturing processes, trained personnel and ultra-modern cleanroom technology guarantee the safety and quality of our products.*



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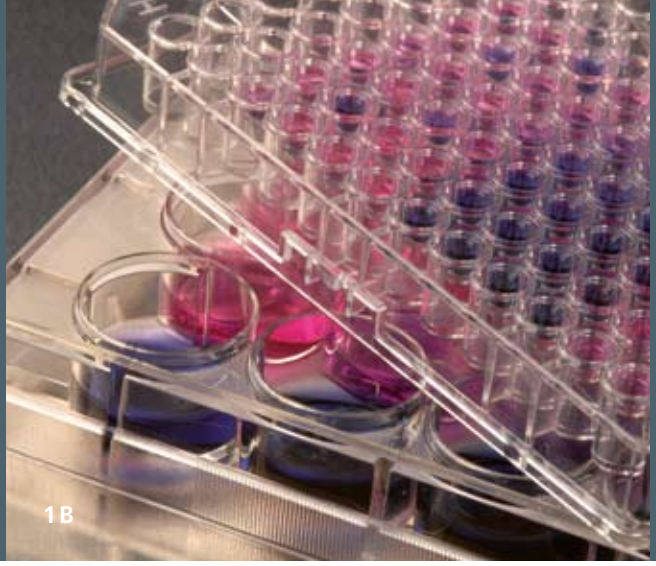


1B

INNATE IMMUNE SYSTEM IN THE MICROTITER PLATE

Dr. rer. nat. Anke Burger-Kentischer, Dr. rer. nat. Ina Abele

Pyrogenic, fever-inducing remnants of bacteria, viruses or fungi can cause sepsis after entering the human bloodstream. Sepsis is one of the most severe complications associated with intensive care, and is characterized by a sum of life-threatening symptoms caused by conserved microbial or viral remnants, known as "pathogen-associated molecular patterns" (PAMPs). These remnants can be isolated chemical structures, cell wall components or even entire microorganisms. PAMPs are recognized by so-called "pattern recognition receptors" (PRRs), receptors of the innate human immune system which then activate the cellular production of fever-inducing signal molecules. Successful treatment of sepsis patients depends on fast and reliable classification of the original pathogen. This is only possible to a limited extent today.

PAMPs can be observed not only in clinics but also as potential contaminates in medical engineering production processes. In order to prevent the transmission of pyrogenic residues into the bloodstream, surgical instruments, medical equipment and products must be declared pyrogen-free. This requires new, efficient analysis methods which recognize a large number of PAMPs inexpensively and quickly.

Cell-based test system for the detection of pyrogenic residues and differentiation of microorganisms

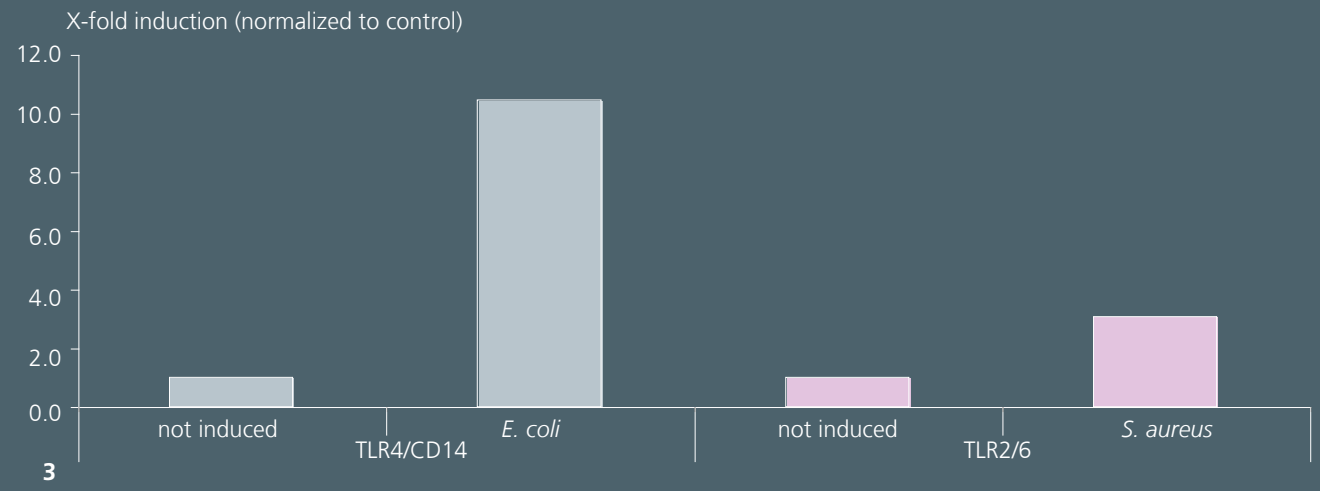
At the Fraunhofer IGB we have developed a new, cell-based test system that allows PAMPs to be identified and differentiated via their natural pattern recognition receptors such as toll-like receptors (TLRs), NOD-like receptors (NLRs), RIG-like receptors (RLRs) or dectins coupled to a reporter gene assay. The test system replicates the innate human immune system and can, uniquely, selectively recognize and identify PAMPs.

For this assay, various receptors or receptor complexes were stably transfected together with a reporter gene and expressed in NIH3T3 fibroblasts. Receptor activation by a pyrogen leads via a signaling cascade to activation of the respective transcription factors (e.g. NF-κB), which induces the expression of the reporter gene (e.g. the secreted alkaline phosphatase, SEAP, or a fluorescent protein such as green fluorescent protein, GFP) (Fig. 1). Pyrogens present in the analyte thus can be detected directly via expression of the reporter gene, both qualitatively and quantitatively (Fig. 2).

The testing of different, specific receptor combinations facilitates the identification of a wide range of microorganisms, for instance Gram-negative bacteria such as *E. coli* using the receptor combination TRL4/CD14. Gram-positive bacteria such as *S. aureus* can be detected with the receptor combination TLR2/TLR6 (Fig. 3).

Applications

Pyrogens can be present on medical equipment, implants and injectable drugs, as well as on surgical instruments. Our test system can be applied in medical engineering for the detection of pyrogenic residues, complementing or replacing existing tests such as LAL (Limulus amebocyte lysate) and



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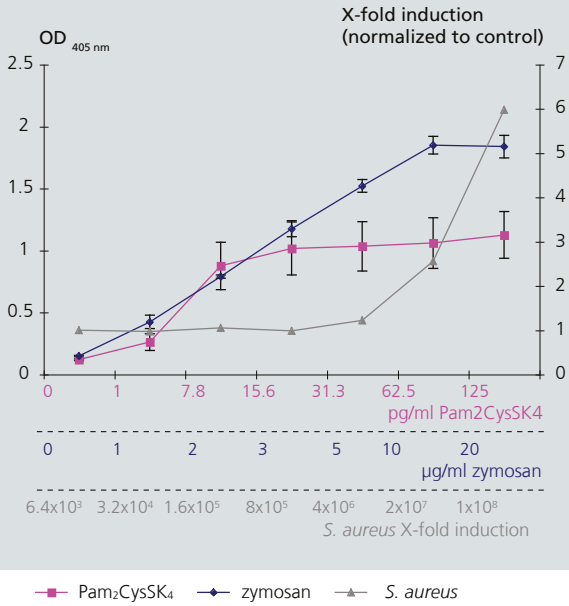
IPT (*in vitro* pyrogen test). The test system is also suited for detection of pyrogens and microorganisms in food production, as well as in the manufacturing of medicines and intravenous fluids by the pharmaceuticals sector.

The test system replicates the innate immune system via individual receptors or receptor pairs (PRRs) directly in the microtiter plate and can thus be used for screening new TLR antagonists or chemotherapeutics but also as a quality control system in medical engineering. The novel assay is also ideal for improved detection and classification of sepsis-causing pathogens in medical diagnostics (Fig. 3). Through the inclusion of additional known PRRs, the test system can be extended to fully replicate the innate immune system and used to investigate a variety of topics.



2 Detection of PAMPs with the TLR2/6 test system

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Funding

Part of this work was financed by the Fraunhofer-Gesellschaft through its MEF program (Research program for small and medium-sized enterprises), in the form of the project "Cell-based test system for identification and differentiation of microorganisms."

1 *Cell-based assay for the detection of pyrogens (A and B).*

2 *Detection of PAMPs, e.g. chemical structures (synthetic lipopeptide Pam_2CysSK_4), cell wall components (zymosan from S. cerevisiae) or entire microorganisms (S. aureus), using the TLR2/6 test system.*

3 *Differentiation of the most frequent sepsis-causing bacteria after heat inactivation: NIH3T3 SEAP TLR4/CD14 cell line after induction with the Gram-negative bacteria E. coli and NIH3T3 SEAP TLR2/6 cell line after induction with the Gram-positive bacteria S. aureus ($2x10^7$/ml).*

PHARMACY

Priv.-Doz. Dr. Steffen Rupp

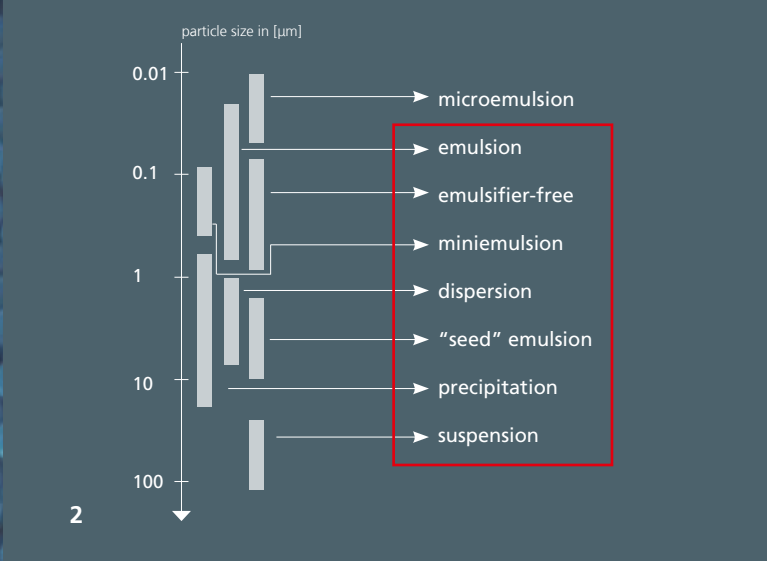
The current challenges of the pharmaceutical industry include the accurate diagnosis of diseases and their personalized therapy, the development of new active agents and the enhancement of the effectiveness of new drugs through improved formulations. The Business Area Pharmacy at the Fraunhofer IGB is developing solutions for drug screening, pharmaceutical biotechnology, pharmaceutical chemistry and drug release and formulation.

We identify new drugs by means of the targeted use of cell-based assays, for instance, for immunomodulatory substances of antiinfectives. Structure-activity correlations are performed on active hits. Potential active compounds are characterized *in vitro* by using organotypic complex 3D primary cell models (skin, intestine, lungs, liver) for effectiveness, absorption, distribution in the organ model, metabolization and toxicity – corresponding to studies of clinical phase I. This research is completed by molecular methods such as gene expression and proteome analysis as well as by histology and confocal Raman spectroscopy. The aim is to recognize toxic side-effects of potential active agents and their metabolites at an early, preclinical stage.

In the field of pharmaceutical biotechnology we are developing processes to manufacture pharmaceutical proteins: from the development of expression vectors and strain development in microorganisms and mammalian cells to the optimization of fermentation processes and the purification of the pharmaceuticals – also by means of molecular imprinted nanoparticles (NanoMIPs). We are able to supply you with proteins produced in compliance with GMP (Good Manufacturing Practice) for clinical testing through cooperation within Fraunhofer. For the formulation of active agents we work on nanoparticular structures which deliver drugs directly to the target location and then release them in a controlled manner.

In addition, we develop cell-based therapeutics and produce test samples according to GMP guidelines. Our quality control identifies potential contaminants (microorganisms, viruses) in a non-destructive way using spectroscopic, cell-based or molecular methods according to the guidelines of Good Laboratory Practice (GLP) or Good Manufacturing Practice (GMP).

1



2

ENCAPSULATION AND CONTROLLED RELEASE – PARTICLE-BASED FORMULATION

Dr. rer. nat. Carmen Gruber-Traub, Priv.-Doz. Dr. rer. nat. Günter Tovar

The carriers, polymer core-shell nanoparticles and microparticles, control the release of the encapsulated effect substances or active substances (controlled release) and can be used for new formulation concepts in pharmacy, medicinal products, in cosmetics, in plant protection and in food technology. Combining particles with protein active substances makes it possible, for example, to experimentally monitor new active substance concepts. In addition to the possibility of protecting sensitive effect substances against biodegradation, particulate carrier systems can also mediate release of encapsulated substances. At the Fraunhofer IGB we have already successfully encapsulated different therapeutically relevant compounds such as proteins (cytokines, growth factors, etc.) in such nanoparticulate or microparticulate carriers, respectively. By means of established biological assays we were able to demonstrate that the thus-bound active substances again showed their original bioactivity after release.

Techniques of particle preparation

At Fraunhofer IGB customer-specific nanoparticles and microparticles in the range of 200 nm - 10 µm, depending on the problem, are prepared from commercially available or tailor-made polymers. In this context, different polymerization techniques such as miniemulsion polymerization or the emulsifier-free emulsion polymerization are used. By varying the particle size, the load factor, the molecular weight and the ratios of the hydrophilic and hydrophobic monomer units, we can influence the release kinetics of the encapsulated substances in an individually adapted manner.

Thus, releases over very long periods of three to four months (Ultralong Drug Release, ULDR) can be realized. In this context, biodegradable compounds are of particular interest because they are completely metabolized or degraded after their use in the body or in the environment.

The technologies for particle preparation which have become established at the institute have been recently supplemented by the innovative Büchi Nano Spray Drier B-90. Particles in the range from 300 nm - 5 µm can be prepared with the spray drier. The electrostatic particle separator ensures yields of up to 90 % for sample quantities in the milligram range. Customary methods achieve yields of only 60 to 70 %. In this manner, experimental work with extremely small substance quantities for feasibility studies is possible.

Tailor-made polymers

Commercially available biodegradable, linear polyesters often do not provide adequate properties for a controlled active substance release. Consequently, new polymer matrix systems – biodegradable and biocompatible block copolymers – with improved properties and different molecular weights are developed at Fraunhofer IGB. We then adapt these nanoparticles to the individual applications according to customer preferences and customer specification by selecting appropriate polymer systems. In this context, the functional groups which make up the biodegradable polymers determine the physical and chemical properties such as the release and degradation rates.

3

Surface modification – efficient formulation concepts

The surface of the polymer particles can additionally be functionalized for complex applications, and as a consequence efficient formulation concepts can be realized. We modify particles prepared at the Fraunhofer IGB, for example, on their surfaces via free carboxyl groups using established coupling methods to achieve targeted active substance transport in the body (Drug Targeting). By means of carbodiimide and crosslinkers, biomolecules such as antibodies are successfully bound to the surface – without loss of activity. In addition to biodegradable nanoparticles, we also develop biological-synthetic nanoparticles which simulate the conditions on cell surfaces (NANOCYTES®).

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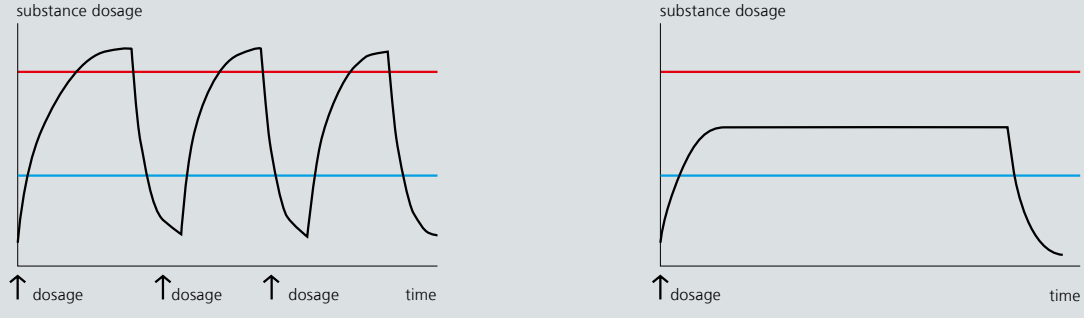
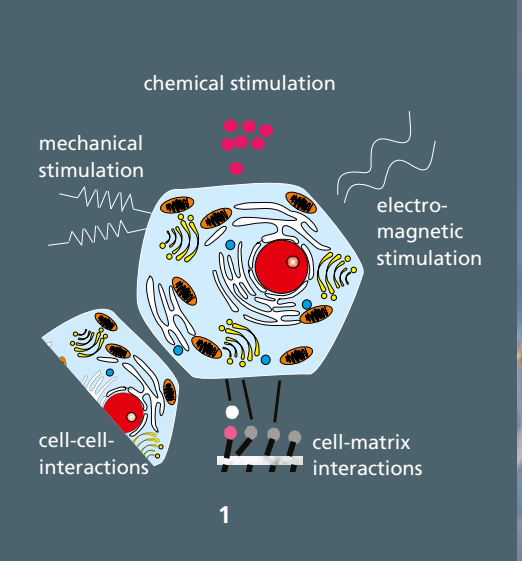
Scope of services

- Performance of feasibility studies
- Development of nanoencapsulated and microencapsulated effect or active substances
- Synthesis of polymers and block copolymers
- Polymer characterization
- Bioconjugation of nanoparticles
- Bioanalysis

1 *Scanning electron microscopic image of biodegradable nanoparticles. With these particles active substances can be released in the body for a long period of time.*
2 *Particle preparation techniques and their typical particle sizes. The technologies in the red frame are established at Fraunhofer IGB.*
3 *Image of the particle size distribution of microparticles using light microscopy.*

Active substance dosage in the traditional manner (left) and in a controlled manner with drug delivery systems (right)





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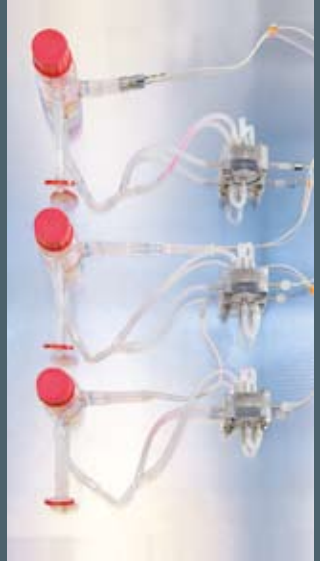

APPLICATION-ORIENTED BIOREACTOR DEVELOPMENT FOR TISSUE ENGINEERING

Dr.-Ing. Jan Hansmann

Basic cellular activities are governed by extrinsic signals sent from the microenvironment where cells reside. Cellular function can further be influenced by other cell-specific external stimulation. This fundamental mechanism of action has to be considered when interpreting data derived from *in vitro* test systems using modifiable cell culture parameters or for the pre-implantation quality control of autologous, *in vitro* generated grafts. The key to obtain reproducible culture conditions that mimic the physiological environment is developing well-defined, controllable bioreactor systems.

Parameter for bioreactor design

A critical element in the design of an adequate bioreactor unit for a specific cell, tissue type or objective (e.g. cell expansion versus differentiation) is identifying the essential and determining stimuli for each individual system. This can be challenging when there are a high number of potential impulse targets (Fig. 1). The Fraunhofer IGB has at its disposal a number of different cultivation systems for manufacturing tissue of different origin which can be used both for research purposes and for applications in regenerative medicine (Fig. 2).

Improved handling of peripheral incubators

In order to improve the operability of typically very complex bioreactor systems, the Fraunhofer IGB has developed more user-friendly peripheral devices. Figure 3 depicts an incubator that is used in the laboratory for *in vitro* graft culture according to GMP guidelines, which was particularly designed for the use with bioreactors.

Reactor design using systems biology

Systems biological methods can also be used in reactor design. This involves the system-theoretical investigation of processes within the cells that lead to specific cell reactions. An example is the description of the relation between a given stimulation and the expression of surface markers, which in turn point to a defined cell status. Analysis of the processes thus mapped out allows the selection of the cultivation conditions required for bioreactor design, e.g. with the specific goal of expanding mesenchymal stem cells with uniform properties. Mesenchymal stem cells are cells that can be found in a variety of adult tissues that possess the potential to differentiate into various tissue-specific cell types such as bones and cartilage cells; however, a limiting factor is that these cells exist only in low numbers within the tissues and must be reproduced in sufficient quantities before they can be successfully used for regenerative medicine applications.

3

Bioreactor for expansion and differentiation of mesenchymal stem cells

In close collaboration with the Center Systems Biology (CSB) at the University of Stuttgart and the Max Planck Institute for Metals Research, Stuttgart, we are currently conducting a research project that aims to isolate mesenchymal stem cells from patient material (biopsies), expand these cells and eventually differentiate them into osteoblasts (bone-forming cells) *in vitro*. For this purpose, we expose the cells to defined biochemical and biomechanical signals within a dynamical bioreactor system. Mechanical stress can be applied by controlled pump systems. The implementation of the knowledge generated by bench-scale testing is then realized in a bioreactor system that allows the biochemical and mechanical stimulation of the mesenchymal stem cells. The bioreactor system will be specifically developed at the Fraunhofer IGB for the expansion of this type of adult stem cells with uniform properties and/or to promote controlled, reproducible differentiation into mature osteoblasts of high purity according to GMP guidelines.

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Project partners

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Center Systems Biology CSB, University of Stuttgart
Max Planck Institute for Metals Research, Stuttgart

Funding

We would like to thank the Federal Ministry of Education and Research (BMBF) for funding the project "Systems biology for the tissue engineering of mesenchymal stem cells: integration of new experimental methods and mathematical models," Grant No. (FKZ) 0315506D.

1 *Signals that mediate cell maintenance.*
2 *Various bioreactor systems at the Fraunhofer IGB.*
3 *Incubator developed for in vitro graft culture.*

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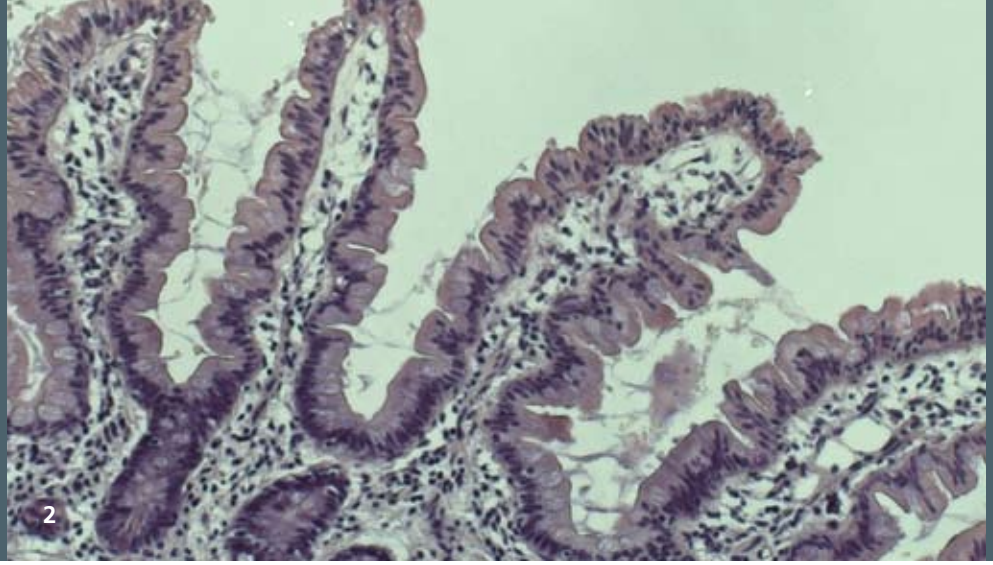


2

ANALYSIS OF THE ABSORPTION PROCESSES THROUGH THE INTESTINAL BARRIER *IN VITRO*

Dr. rer. nat. Jacqueline Pusch

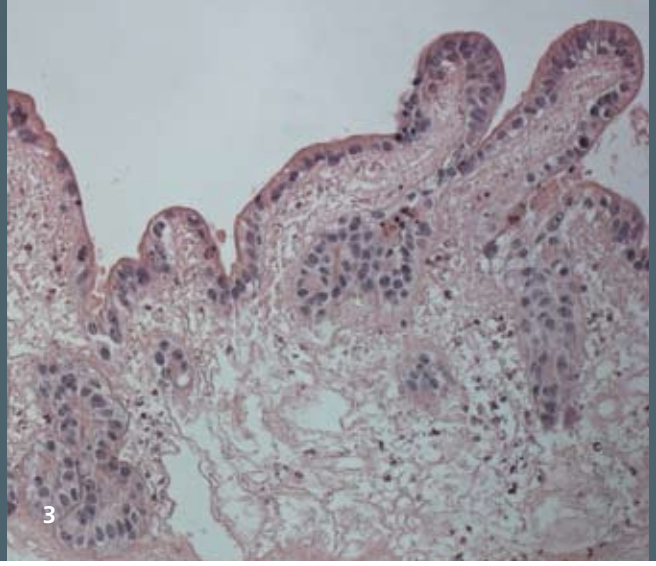
Before oral drugs can enter the circulation and reach their target site, they first have to pass the epithelial cells of the small intestine. Besides the liver, the intestine therefore represents one of the largest barriers to the bioavailability of these orally administered substances. For this reason, in-depth knowledge of the pharmacological characteristics of new drug candidates is a prerequisite for evaluating their efficacy and possible toxic side effects in the early stage of drug development. Due to species-specific differences between animals and humans, it is not possible to extrapolate all the data yielded from animal experiments to human organisms. Ethical aspects also make it necessary to establish appropriate alternative methods for substituting and refining animal experiments. Therefore our aim at the Fraunhofer IGB is to develop various cell-based *in vitro* models, which can be used to analyze intestinal absorption mechanisms and evaluate possible toxic side effects in different substance classes.

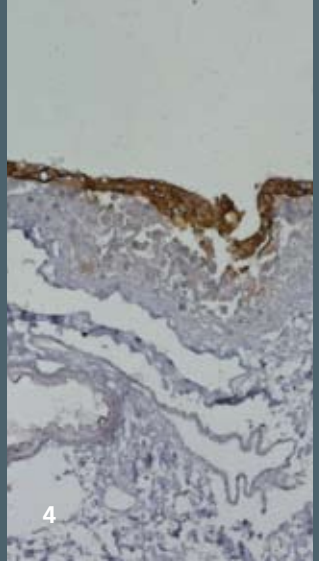
2D Caco-2 assay

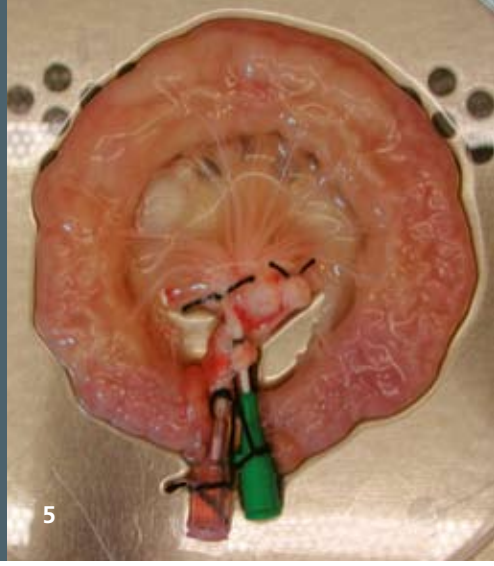
The use of the 2D Caco-2 assay as a tool for bioequivalence studies to test the permeability of immediate-release solid oral doses forms has been approved by the American Food and Drug Administration (FDA). The assay is based on the reseeding of the immortalized cell line (heterogeneous human epithelial colorectal adenocarcinoma cells) Caco-2 on porous synthetic membranes (Fig. 1). After a predefined cultivation time the cells form a closed cell layer and different permeation studies can be carried out by applying the test substances. The simple assembly of the assay enables the conducting of many tests in parallel and the classification of the new substances with regard to their solubility and permeability. Because its assembly lends itself to standardization, the assay qualified for accreditation in December 2009 by the relevant body, the Deutsche Gesellschaft für Akkreditierung (DGA). The test system is registered as a house method for the classification of substances by their preferred transport mechanisms, and thus enables us to certify the analysis results.

3D dynamic cultivated intestinal tissue model

Oversimplified monolayer cultures can often only reflect the complex anatomy of the small intestine in an inadequate manner. For this reason, complex tissue models are necessary to enable the complete extrapolation of *in vitro* data to the human organism in the future and meaningfully reduce animal experiments. Such systems have to simulate the physiological microenvironment of the small intestine *in vitro*. The co-cultivation of intestinal epithelial cells (Caco-2 cells or primary porcine epithelial cells) and vessel-lining endothelial cells on a biological collagen scaffold simulate the gut-blood-barrier of one villus in a simplified manner (Figs. 2, 3 and 4). Using perfusion, we were able to carry out absorption studies in a miniaturized bioreactor module, which promise good comparability with *in vivo* data. Under these specific dynamic conditions, characteristic high prismatic cell growth could be attested for the epithelial cells through the histological data. Furthermore, the 3D tissue model shows an increased robustness against particular substances due to its natural villus structure. This enables the application of drugs in their existing galenic form. Consequently particle formulations do not have to be dissolved before testing, because the cells under dynamic conditions in the advanced 3D tissue model can sustain the barrier even under high shear stress. This also improves the comparability of the *in vitro* with the *in vivo* test conditions.







Ex-vivo perfusion

The perfusion of complete intestinal segments enables the analysis of how substances are absorbed via the adjacent circulation system in this part of the organ. Due to the establishment of a specialized tissue culture medium and the construction of a sophisticated bioreactor system, jejunal gut segments of rats and pigs can be cultivated over a period of several days at the Fraunhofer IGB, Stuttgart (Fig. 5). This experimental set-up enables the analysis of the absorption of potential active ingredients and the evaluation of their toxicity with regard to primary epithelial cells, which exhibit a longer vitality within the environmental tissue. Cultivation of complete tissue segments allows the analysis of up to four intestinal sections of one animal in parallel. This can lead not only to a meaningful reduction in the number of donor animals, but to the increased validity of each series of animal experiments.

Application of the intestinal models

While the 2D Caco-2 assay is predominantly used for wide-screening analysis to classify different substances in terms of their permeation behavior, the complex tissue models will additionally be used for the evaluation of studies concerning the intestinal bioavailability and absorption of potential active ingredients.

Moreover, the reproduction of diseased intestinal tissue offers the future possibility of developing new forms of therapy for different intestinal inflammations (e.g. Crohn's disease), enzyme defects of the intestine (e.g. fructose intolerance), and cancer. The establishment of such models using human cells additionally offers a potential for scientific proof of the positive effect of enriched or "functional food" on the human organism. The dietary supplements could help to improve health and to reduce existing disease.

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Project Partners
We thank EVONIK Industries for financing a project to develop intestinal test systems.

1 *2D Caco-2 assay on porous synthetic membranes (HE staining, 400x).*
2 *Cross-section of human small intestine (jejunum, HE staining, 200x).*
3 *3D intestinal tissue model with structured collagen scaffold and Caco-2 cells (HE staining, 200x).*
4 *3D intestinal tissue model with primary porcine epithelial cells (staining of cell-cell contacts with anti-E-Cadherine, 200x).*
5 *Isolated porcine segment of the small intestine for the ex vivo perfusion.*

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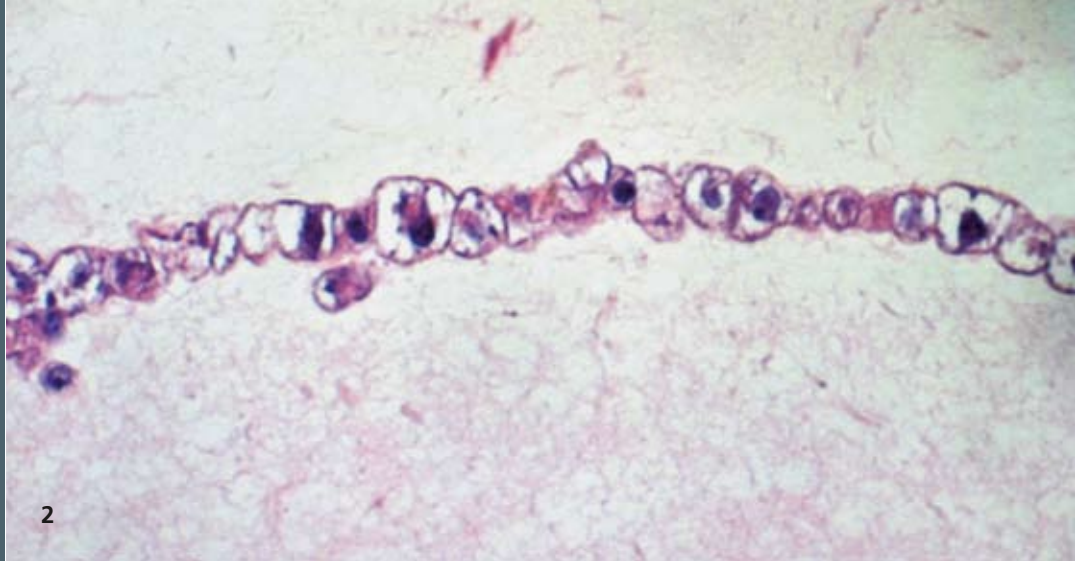


2

HUMAN *IN VITRO* LIVER SYSTEMS FOR PHARMACEUTICAL AND TOXICOLOGICAL TESTING

Dr. rer. nat. Johanna Schanz

Drug-induced liver injury (DILI) is the most common reason cited for withdrawal of an approved drug or failure of new drug candidates. Therefore, the liver represents an interesting test system for pharmacological research and risk assessment of new agents. Human systems are of particular interest because findings with animal models may not be directly applicable due to interspecies metabolic differences.

The challenge in developing human liver models is to maintain the functionality of hepatocytes (liver cells) *in vitro* for days or weeks. Therefore, Fraunhofer IGB is focusing on the development of human-like microenvironment culture methods to counteract the loss of cell functionality. The microenvironment of hepatocytes in the body includes a suitable carrier structure (matrix) for the cells, an adequate nutrient supply and contact with other non-parenchymal cell types of the liver.

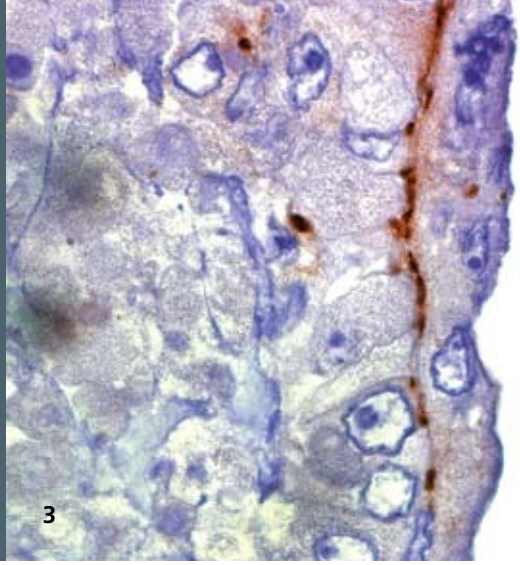
Collagen-hydrogel sandwich culture

For the cultivation of primary liver cells (hepatocytes) in the three-dimensional culture, we use a GMP-compliant collagen-I matrix developed at the IGB. This natural connective tissue allows the hepatocytes to organize in three dimensions and to build vital cell to cell connections.

Thus the differentiated "liver cell" phenotype and the functionality of mature hepatocytes can be preserved *in vitro* for up to two weeks. In addition, small intestinal submucosa (SIS) can also be used as start-up scaffold material for the sandwich cultures. This substrate has the advantage that it contains not only collagen type I but also other essential components such as growth factors.

Vascularized liver model – co-culture of endothelial cells and liver cells

This model is based on a matrix with a vascular system (BioVaSc – biological vascularized scaffold) which permits the cultivation of hepatocytes and endothelial cells under similar physiological conditions as in the liver. The dynamic culture of the matrix in a bioreactor system ensures an optimal supply of the cells and for the removal of toxins and breakdown products. Flow velocity, flow, pressure and pulse of the supply cycle are modulated and controlled by computer software. The three-dimensional culture growth and liver-specific function of hepatocytes (albumin synthesis, urea synthesis, bile acid formation and phase I and phase II metabolism) could be detected for several weeks. AST, ALT and LDH release as well as lactate formation were used to test vitality and metabolic activity. The vascularized liver model is currently undergoing intense testing with different chemical agents.



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Pre-clinical functionality tests

The liver models developed at the Fraunhofer IGB can be utilized for the investigation of new drugs and their possible cytotoxic and hepatotoxic metabolites.

The simple sandwich model allows for the parallel implementation of a large number of experiments. The vascularized liver model allows the testing of drugs in a complex, organ-like system and also the analysis of multiple application and long-term effects. Furthermore, the vascularized liver model is an interesting model for studying stem cell differentiation or other scientific issues.

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[1] Linke K., Schanz J., Hansmann J., Walles T., Brunner H., Mertsching H.: Engineered liver-like tissue on a capillarized matrix for applied research, Tissue Engineering 2007; 13, 1-9

Project partner

Prof. Dr. Andreas Nüssler, Technische Universität München

Funding

We would like to thank the Fraunhofer-Gesellschaft for financing the project "Vascularized liver module for accelerated drug development" within the MEF program.

Awards

Tierschutz-Forschungspreis (Animal Welfare Research Prize) 2009 of the German Federal Ministry of Food, Agriculture and Consumer Protection
Fraunhofer prize for human-centered technology 2009

1 *Hepatocytes in vitro, monolayer.*
2 *Hepatocytes in vitro, sandwich culture.*
3 *Vascularized liver model with formation of bile canal structures.*

1

IMPROVED MANUFACTURING PROCESS FOR COAGULATION FACTOR VII

Dr. rer. nat. Hans Weber

Patent protection for the first biopharmaceuticals is expiring in the next few years. The manufacture of so-called biosimilars or biogenerica is thus increasingly gaining in importance. A considerable proportion of the production costs of a pharmaceutical protein is the result of high purification costs. Advances in the field of analytical characterization of products have challenged the dogma that "the process determines the product". These advances open new paths to the manufacture of safe and, due to alternative cleaning processes, inexpensive biopharmaceuticals which then become globally available to more patients.

Blood coagulation factor VIIa

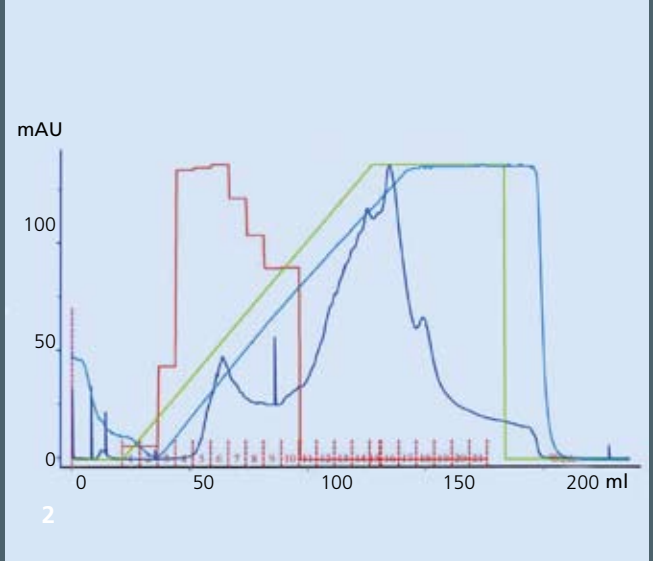
As an example the Fraunhofer IGB has developed an improved manufacturing and conditioning method for coagulation factor VIIa (FVIIa), an essential factor for the blood coagulation cascade. Factor VIIa is a glyco-protein with N and O glycosylations and contains several gamma-carboxy-glutamic acid residues in the N-terminal area as a further modification. Thus, it is characterized by a charge heterogeneity which is shown by isoelectric focusing. The original glutamic acid residues are modified post-translationally in a complex, vitamin K-dependant process. These modifications bind bivalent cations. From a physiological point of view these are the calcium ions.

Cost-intensive conditioning due to complex media

The Novo approved product is expressed and exported with genetically engineered animal cells, in media which contain fetal calf serum (FCS). The complex composition of the media in which the target protein is only contained as a minor component makes the downstream processing (DSP) difficult. Thus, all FCS components in the medium and all proteins from lysed cells are to be separated by means of multi-stage separating processes. Affinity chromatography processes reveal the highest selectivity. The process used here is an immuno-affinity chromatography whereby immobilized antibodies (AB), which are directed against the target protein, bind the target protein with a high selectivity. The following cleavage of the AB-protein bond and thus the elution of the target protein must occur under conditions which damage neither the target protein nor the immobilized antibody. This means costly development of a suitable proprietary monoclonal antibody for the DSP which needs to be expressed in a cell line, immobilized and separated from the target protein as the decomposition of the substrate cannot safely be avoided.

Advantageous purification for defined media

Advances in the understanding of metabolism and physiology of animal cells facilitate novel media for cell cultures which do not need complex and barely defined components such as FCS. This ensures an improved product purity and safety. In addition, defined media provide chances for a simpler and less costly DSP for which only commercially available and comparatively cheap standard separation media such as ion exchange chromatography (IEX), hydrophobic interaction



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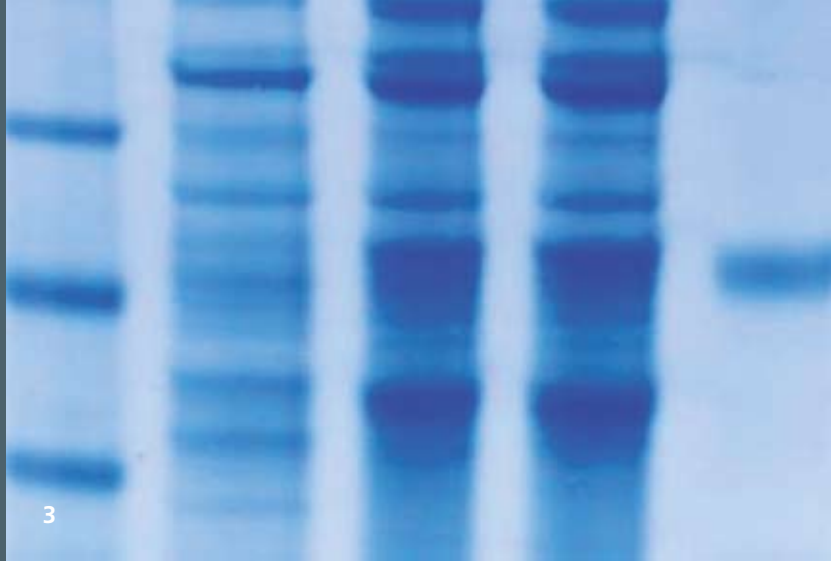
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chromatography (HIC) and gel filtration are used. The relevant documentation for these separation media already exists for approval by the authorities, i.e. there is no need for them to be created and submitted by the manufacturer. The Fraunhofer IGB used a special serum-free and low-protein medium for the recombinant manufacture of factor VII into which factor VII is secreted as a proenzyme.

Results: purification with high selectivity

Anion exchange materials have been used for the purification of FVII and its activation as FVIIa. A high degree of selectivity has been achieved through the special properties of the target protein whose net charge is influenced via calcium concentration. When the concentrations of free calcium ions are low, the gamma-carboxy-glutamic acid residues are present with a double negative charge. These charges are neutralized with bound calcium. The net charge of the protein molecules impacts both the binding and the elution behavior on the ion exchanger. With a combination of two separation steps on the anion exchange materials on which the concentration of free calcium ions was modified, it was thus possible to achieve a highly selective purification. Such highly selective separation processes with standard separating media are also called "pseudo-affinity chromatography".

As factor VII can, under suitable conditions, be transferred into the target factor VIIa on positively charged boundary layers and thus also on anion exchange materials, a purification scheme which only utilizes anion exchangers and membrane processes will be used making the production of this biogeneric product cost-efficient.

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CinnaGen, Teheran, Iran

1 *Production of factor VII.*
2 *Pseudo-affinity chromatography of FVII with FVII-bioactivity distribution.*
3 *SDS gel electrophoresis of marker proteins (left lane), different FVII purification steps (lanes 2, 3, 4) and purified FVII (right lane).*

CHEMISTRY

Dr. Christian Oehr

The chemical industry is one of the most important and research-intensive lines of business in Germany. Many innovations in other businesses such as the automotive, electrical, construction and packaging industries would not be possible without the contributions of the chemical industry.

The chemical industry is characterized by its resource and energy intensive processes. Dependence on the import of base materials, the limited availability of fossil resources worldwide – including competition for their energetic utilization – and the necessity to consider the effects on both climate and environment, result in approaches which focus on the promotion of a more efficient utilization of existing resources, including:

Utilization of renewable resources

It creates a greater choice of resource sites and promotes the development of new concepts of a combined material and energetic utilization of resources which is even climate neutral.

Process-intensification for a more efficient utilization of energy and resources

The focus here is on developments in the field of upstream and downstream processing with effective separation of material flows by means of membranes or through the recirculation of material flows (recycling, sustainable waste management).

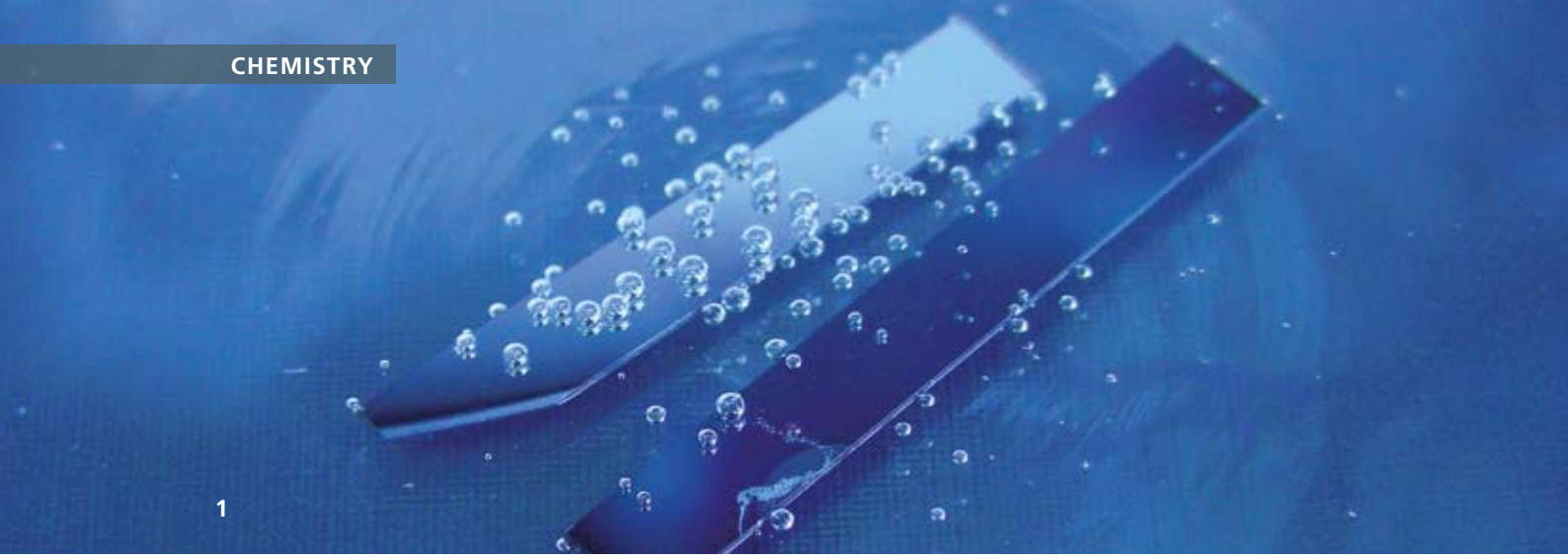
Decoupling of volume and surface properties by means of interfacial process engineering

Tailor-made coatings which are themselves geared towards resource efficient process engineering create new possibilities as to the choice of base materials for workpieces and thus for new products based on a sustainable selection of resources.

Evaluation and replacement of critical substances

Chemical substances, insofar as they are represented in the market on a large scale, are systematically investigated with regard to their risk potential in accordance with EU regulations.

On the following pages you will find examples of our diverse research work with which we face the challenges of these new approaches.



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SWITCHABLE BIOMATERIAL SURFACES: NANOSTRUCTURED ANATASE-IMPLANT SURFACES WITH DYNAMIC ANTI-FOULING PROPERTIES

Dr. M. Haupt, Dr. C. Oehr, Dr. E. Decker, Prof. Dr. J. Geis-Gerstorfer, Dr. F. Rupp, Dr. L. Scheideler, Dipl.-Biol. S. Sinn, Dr. C. von Ohle, Dr. H. P. Wendel

Photo-catalytic surfaces made from TiO_2 in the crystalline anatase configuration (a tetragonal modification of titanium dioxide) which can be switched by means of UV light radiation are already widely used in surface coatings for example as self-cleaning or anti-fogging coatings. In Japan streets, tunnel walls and lamp glass are coated with TiO_2 to reduce air pollution. In Germany the first wall paints and roof panels with a photo-catalytic coating have been launched. In addition, the use of photo-catalytic TiO_2 coatings is tested within the scope of energy technologies for solar cells such as the Grätzel cells. Recently, attempts to decompose CO_2 in order to achieve a reduction of the greenhouse effect are being discussed.

Project objective

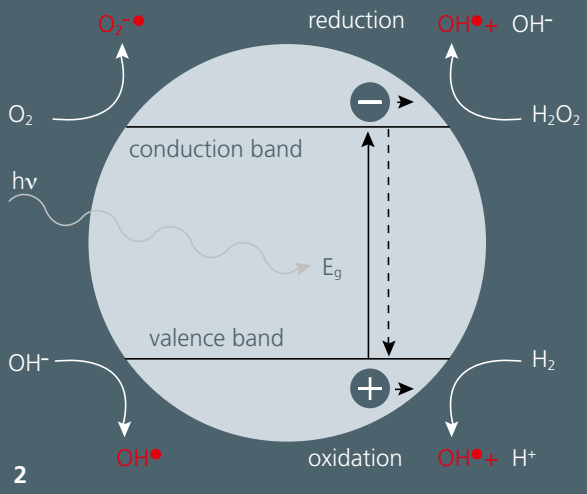
In a research project funded by the Landesstiftung Baden-Württemberg the Fraunhofer IGB in cooperation with partners from Tübingen University is developing photo-catalytic coatings on implants for dentistry and researching their properties. Ideally, organic substances will be removed from the surfaces and decomposed in the presence of the photo-catalyst and UV radiation due to the formation of radicals (Fig. 1 from [1]). The photo-catalytic layers can thus be used as antibacterial coatings or for disinfection in medical engineering [2, 3].

Electron spin resonance for the detection of radicals

The challenge mainly lies in the provision of quantitative evidence of the photo-catalytic effect of TiO_2 coated surfaces. Such proof is essential for measuring the success of the surface coating, its photo-catalytic effect and any necessary optimization. The electron spin resonance (ESR) method is an investigation method which determines the quantitative activity of the radicals of such surfaces and which enables the detection of radicals. In the case of UV radiated photo-catalytic surfaces the radicals generated (e.g. hydroxyl radicals, Fig. 2) can be caught with "spin-trap" substances and subsequently stabilized. Both the quality and the quantity of the spin-trap adducts are then verified with the aid of ESR.

Results

The chart shows the dose-effect relationship of the hydroxyl radical amount and the UV-A-radiation dose measured with ESR [1]. In this case the linear accumulation of the hydroxyl radicals can be noted when the UV-A rises. On the basis of these experiments the amounts of radiation dose different species of radicals related to the UV doses are determined and compared with different catalytic samples. This way it is possible to optimize coatings with regard to the amount of radicals generated at a specific dose of radiation.



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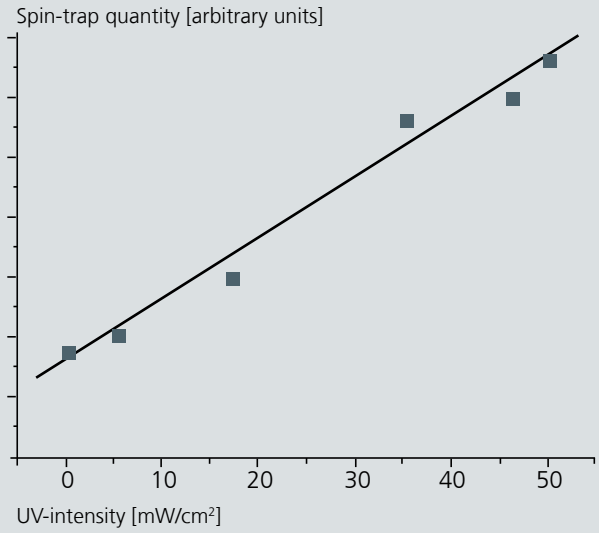
Outlook

Together with its project partners the Fraunhofer IGB characterizes and develops photo-catalytic coatings. In addition, the Fraunhofer IGB also analyzes the chemical composition of contaminations and the wetting properties of surfaces as requested by customers.

Relationship of hydroxyl radical quantity and UV-A radiation dose [1] measured by means of ESR.



1 *TiO_2-coated Si wafer under UV-A radiation in an aqueous solution [1]: Organic surface contaminations are decomposed while creating gas.*

2 *Creation of radicals through photo-catalysis in the presence of water and oxygen on a TiO_2 surface [1].*

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[2] Rupp F. et al. (2009): Periodontol 36 (Suppl. 9): 77

[3] Scheideler L. et al. (2009): Biomaterialien 10, S1: 113

Project partners

Tübingen University, University Hospital Tübingen, University Centre of Dentistry, Oral Medicine, Maxillofacial Surgery; Tübingen University, University Hospital Tübingen, Department of Thoracic, and Cardiovascular Surgery

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Funding

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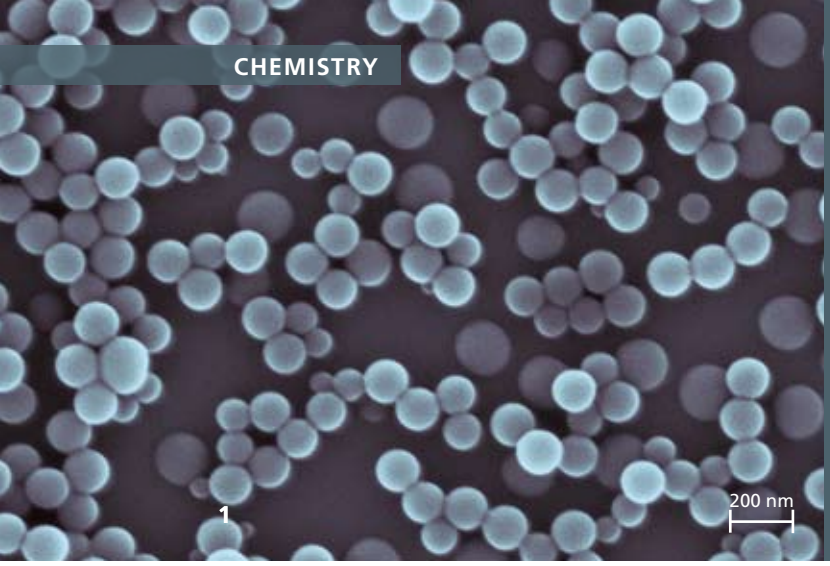


1

NANOCYTES®-APPLICATIONS – ENZYME IMMOBILIZATION FOR INTELLIGENT PACKAGING MATERIALS

Dr. rer. nat. Achim Weber, Dr. rer. nat. Daniela Pufky-Heinrich

Enzymes are versatile biocatalysts which are increasingly being used for industrial purposes. However, the technical application of an enzyme is often limited by insufficient long-term stability under real life processing conditions and due to recycling problems. These weak spots can be avoided by immobilizing the enzymes. Moreover, the immobilization also provides the opportunity for improving the catalytic features and for avoiding protein contamination in the product.

Objective of the development

The focus of the project presented here is the development of active and intelligent packaging materials for monitoring the quality and shelf life of foodstuffs. This comprises the development of an active barrier layer to determine putrefaction gases in foodstuffs on paper and plastic materials in packaging for foodstuffs. We intend to achieve these targets by means of enzymatically modified nanocarrier systems.

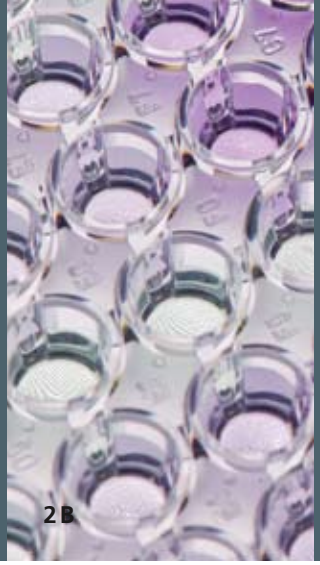
With our NANOCYTES® technology we can couple biomolecules such as peptides, antibodies or enzymes to particulate systems in the nanometer range (Fig. 1). Here the basic properties and advantages of the conjugates are founded on their small size and the resulting volume/surface effect. For customer-specific applications we adapted bioconjugation strategies: through customized particle surfaces and the selection of suitable coupling strategies enzymes can be immobilized on the particle surface whilst retaining their full activity.

Linker-mediated coupling of silica nanoparticle surfaces

Amino and carboxylized silica nanoparticles were coupled to various different oxidoreductases such as laccase, glucose oxidase and catalase. Covalent links between the particle surface and the enzyme are generated by means of linker-mediated synthesis techniques. Through selection of suitable linker molecules it is possible to create molecular spacers to ensure the activity of the enzyme and reduce unspecific coupling. Determination of the concentration and activity of the coupled enzymes is carried out through suitable fluorescence assays (Fig. 2).

One-step enzyme coupling with "surfmers"

A new method for the manufacture of polymer particles with surface-active functional anchor sites is emulsion polymerization through utilization of polymerizable tensides, also called surfmer (derived from the words **surf**actant and momo**mer**). The customized anchor sites of these polymer active ester surfmer particles are particularly suited for the coupling of biomolecules, due to the fact that the nitrogen-nucleophilic structural units of the enzymes can be linked in a single process step. The advantage of this process is that during the co-polymerization process with a co-monomer the utilized polymerizable tensides are built into the polymer structure. As a result, the tenside does not separate from the particle surface and causes agglomeration during further utilization of the polymer particles (Fig. 3). In addition, the active ester unit which functions as the anchor point provides ideal reactivity



with sensitive biomolecules whilst ensuring maximum stability during the manufacture, storage and transport of such polymer particles.

Immobilized enzymes

On both particle types the enzymes laccase, glucose oxidase and catalase were immobilized and their enzyme activities were compared with each other. The immobilized enzymes on both the silica nanoparticles and the surfmer particles showed enzymatic activities upon being coupled. As an example the chart shows the activity of glucose oxidase immobilized on surfmer particles and on hydrolized surfmer particles. On the surfmer particles the enzyme couples specifically onto the designated bonding site. On hydrolized surfmer particles the enzyme bonds unspecifically as specific bonding is no longer possible due to the hydrolysis of the reactive groups.

Benefits for consumers

The motivation for the utilization of intelligent packaging materials is to increase consumer safety. These packaging materials will enable consumers to examine the shelf life and quality of the foodstuffs.

1 *Scanning electron microscope image of p(styrene-co-AUPDS-1%)-nanoparticles, 100,000 times enlarged.*

2 *Fluorescence assays to prove enzyme activities.*
A) By means of color reaction (blue) it is possible to prove successful coupling of glucose oxidase with surfmer-nanoparticles;
B) bicinchoninic acid-assay: assay for the quantitative, photometric determination of proteins.

3 *Ultrasound treatment for the re-suspension of the surfmer nanoparticles after centrifugation.*

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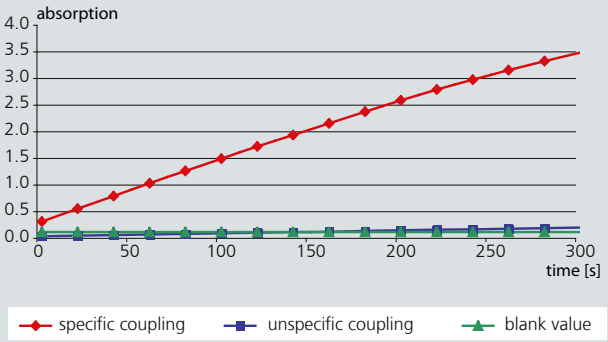
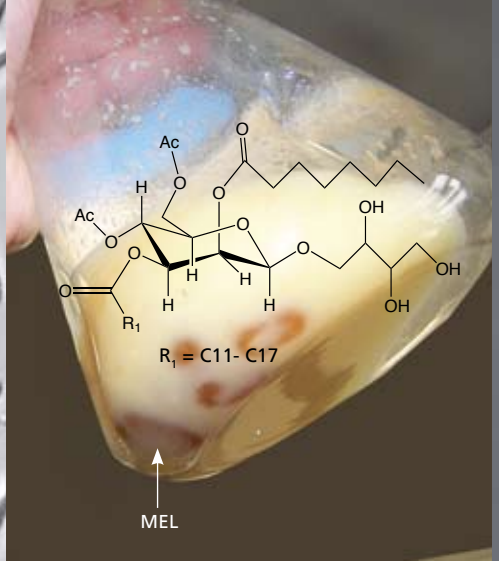
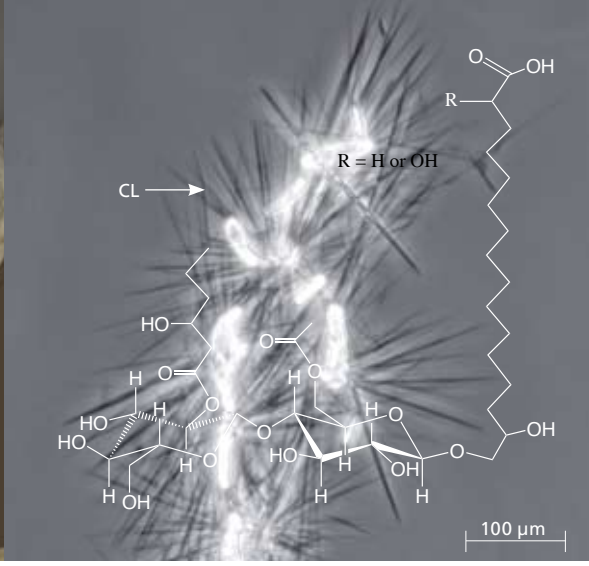
Enzyme activity of glucose oxidase with specific (red) or unspecific (blue) coupling to p(MMA-co-MUPDS-3%)-nanoparticles







BIOSURFACTANTS – PRODUCTION AND OPTIMIZATION

Dipl.-Biol. (t.o.) Dipl.-Ing. (FH) Susanne Zibek, Dipl.-Biol. (t.o.) Michael Günther

Surfactants are used in a wide range of application fields from the textiles industry to mining. Currently, they are produced on a scale of almost 14 million tons worldwide. While a majority of surfactants are still manufactured from fossil resources, surfactant production is increasingly shifting to chemical processes based on renewable resources. However, these types of synthetic "biosurfactants" exhibit only limited structural variability.

Biosurfactants, the sustainable alternative

Many microorganisms naturally produce surface-active compounds, the biosurfactants, which encompass a broad spectrum of molecular diversity. These compounds include glycolipids, lipopeptides, lipoproteins and heteropolysaccharides, among others. The properties of these biosurfactants regarding performance, degradability and sustainability are often comparable to or even often outrange synthetic surfactants and are of interest for many different fields of application. Improved production and purification processes, effective production strains and a higher demand for "green" products have made several biosurfactants ready for the market in recent years. The best example is sophorolipids from *Candida bombicola*, which is currently produced by several companies as an additive for household cleaners and dishwashing agents.

Promising glycolipids

Two other groups of biosurfactants, the cellobiose lipids (CL) and mannosylerythritol lipids (MEL) (Fig.1), showing promising properties are currently being characterized for surfactant applications like cleaning agents and cosmetic formulations.

They are produced in significant quantities by smut fungi of the *Ustilago* and *Pseudozyma* genera. In addition, both types of compounds exhibit antimicrobial properties that also make them interesting for the clinical and pharmaceutical sectors. However, before these glycolipids can be commercially produced improvements are necessary in terms of yields and surfactant performance.

Aims and approach

Fraunhofer IGB is focusing on the biotechnological optimization of the synthesis of the glycolipid surfactants, cellobiose lipids and mannosylerythritol lipids (Fig. 1), using several fungal microorganisms. Using this approach, tailor-made surfactant mixtures will be obtained and, in cooperation with Cognis GmbH, tested for their use in different applications. The aims of the project are the characterization and improvement of the surfactant products with regard to optimal properties for their respective applications in cleaning agents, cosmetics and special industrial uses. A further major objective is developing an efficient fermentative production process.

For these ends – optimization of both the biosurfactants and their fermentation processes – we are pursuing the following approaches:

- Genetic modification of biosurfactant-relevant metabolic pathways in the microorganisms used,
- Enzymatic modification of the biosurfactants, and
- Optimization of bioprocess engineering strategies.

2

Current results and outlook

The optimization of the synthesis process for both biosurfactants resulted in product concentrations of up to 16 g/L for cellobiose lipids (Fig. 2) and 100 g/L for mannosylerythritol lipids. To achieve these values, two different cultivation methods were investigated: a fermentation process with growing cells under nitrogen limitation and a fermentation process using resting cells. Using these strategies, sufficient amounts of surfactants could be generated for extensive application tests.

The results derived from the applications testing will be used for developing strategies for structure-tailoring of the surfactants to improve their surfactant performance, using genetic, enzymatic and process engineering methods. In addition, the fermentation process will be further optimized to achieve glycolipid production with a high time-space yield.

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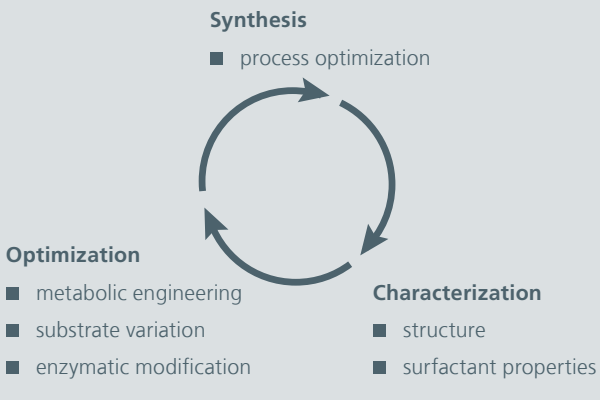
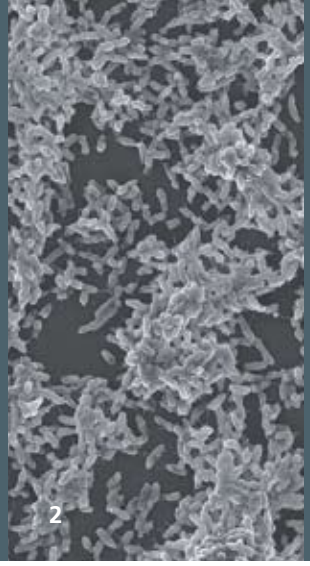
Outline of project methodology



1 *Cells of the smut fungus Ustilago maydis in its haploid, vegetative single-cell stage (left). At high product concentrations, mannosylerythritol lipids are deposited as oily pearls (center, with structural formula), cellobiose lipids as needle-shaped crystals (right, with structural formula).*

2 *Multi-fermenter system for the optimization of cultivation conditions.*

1



2

CONTROL OF BIOFILM DEVELOPMENT THROUGH INFLUENCING MICROBIAL COMMUNICATION

Dr. rer. nat. Iris Trick, Dipl.-Biol. Frauke Purschke

Biofilms are natural, ubiquitous structures of microbial communities which have great impact on a large number of processes. The formation of biofilms creates many advantages for organisms living in communities. They participate in essential decomposition processes, colonize plants, animals and humans and form part of their natural flora. On the other hand, they can cause serious illnesses, create considerable disadvantages and costs for health care, industrial processes, technical equipment and consumer goods.

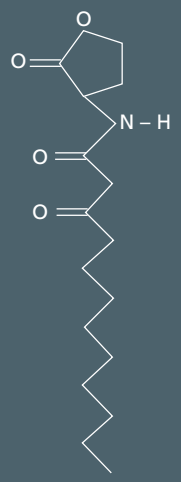
For a long time such microbial populations were regarded as a cluster of single, independently organized individuals. The discoveries of Nealson et al. in the 1970s [1] concerning the control of bioluminescence in *Vibrio fisherii* clearly demonstrated that microbial cells communicate via biochemical molecules. In the meantime it has been established that not only bioluminescence but also the formation of biofilms, the production of toxins and the formation of spores are controlled via so-called signal molecules.

Signal molecules control biofilm formation

Biofilms are microbial communities which are embedded in an extracellular matrix that adheres to a wide variety of surfaces (Figs. 1, 2). Microbial communication is an essential condition for the formation of biofilms. The phenomenon of both, species-specific and interspecies-specific communication of microorganisms is controlled by means of signal molecules, so called quorum-sensing molecules. They are essential for the formation and decomposition of biofilms. The signal molecules are produced by microorganisms and diffuse into the liquid which permeates the biofilm. In this process the biochemical molecules are absorbed by other cells, thus supporting the exchange of signals. From a chemical point of view signal molecules are mostly small molecules, e.g. homoserine lactones (Fig. 3). It is assumed that the formation of biofilms can be controlled through the targeted utilization of these signal molecules. Initial results from our own investigations at the Fraunhofer IGB already exist [2]. The chart shown alongside shows the impact of signal molecules of different organisms (farnesol and 3-oxododecanoyle-homoserine lactone (3OC12HSL)) on biofilm formation of *Pseudomonas aeruginosa*. Depending on the development stage of the biofilm the addition of signal molecules can either trigger an inhibiting effect or promote biofilm formation.

Reporter strains make signal molecules visible

The Fraunhofer IGB has long since been working on the targeted utilization of microbial biofilms and strategies for the avoidance of biofilms. Therefore, it was a natural step to develop a suitable methodical tool within the scope of a research project which makes the effect of microbial signal molecules visible on the basis of various species of reporter strains. Using the example of a biofilm forming *Escherichia coli* strain the fluorescence induced by signal molecules can be verified microscopically (Fig. 4). The utilization of these microbial strains in special flow cells extends existing analyses of biofilms and their adherence to surfaces, the status of the biofilm maturation and the decomposition of existing biofilms.



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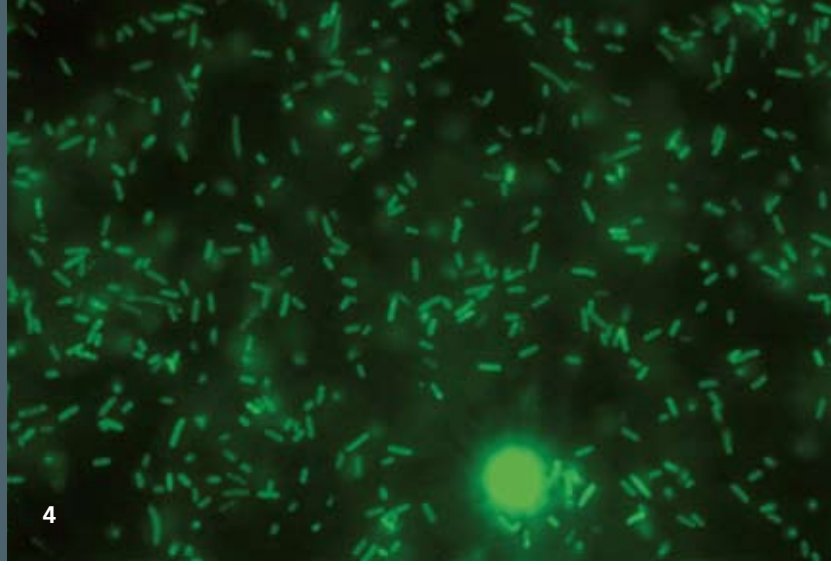

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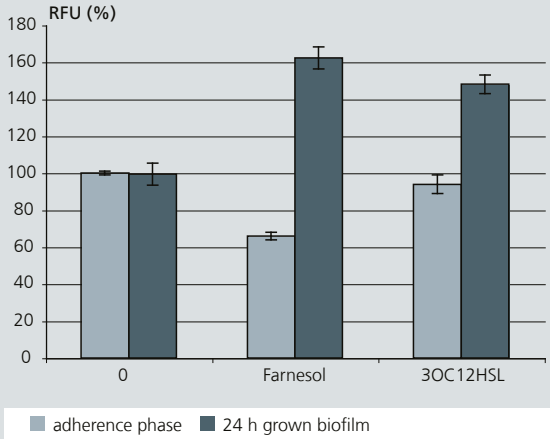
Outlook

The aim is to develop novel methods for a simple and speedy identification of new signal molecules and their effect on biofilm formation. This is to be analyzed in different organisms through combining different methods for studies of biofilms. Beyond that, it is intended that the biological methods developed here shall be applied to the control of biotechnical processes for the targeted utilization or avoidance of biofilms.

Influence of signal molecules on the biofilm formation of *P. aeruginosa*



Farnesol or 3OC12HSL were added during the adherence phase or to a 24 h grown biofilm, respectively. The impact on biofilm formation was determined by means of fluoresceindiacetate and the relative fluorescence unit (RFU) was measured.

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Funding

The research project was funded within the frame of the internal Fraunhofer promotion program „Challenge“ and elaborated from January 1, 2008 to December 31, 2009. The authors wish to thank the Fraunhofer-Gesellschaft for the opportunity of working with this exciting and promising subject.

1 *Natural biofilm on a porous glass surface, visible extracellular matrix.*
2 *Biofilm of Pseudomonas aeruginosa.*
3 *3-oxododecanoyle-homoserinlactone from Pseudomonas aeruginosa.*
4 *Biofilm of an Escherichia coli reporter strain which reacts to signal molecules by producing a fluorescent protein.*

ENVIRONMENT

Dipl.-Ing. Siegfried Egner

Against the background of world-wide discussions concerning the greenhouse effect and the shortage of resources, resource-saving management and environmental protection are gaining in importance. Modern industrial societies are therefore faced with the task of harmonizing economy and ecology. Resource-saving management and protection of the environment are interdisciplinary tasks requiring extensive research and development into an ecologically and economically sustainable contribution towards a sustainable development.

In this sense the Business Area Environment at the Fraunhofer IGB stands for technological developments which contribute towards avoiding environmental impacts and ensuring technological progress by interweaving ecological and economic sustainability.

In a number of joint European and national projects with partners from research and industry Fraunhofer IGB is developing processes and system components which help to save resources such as water and energy, are climate-friendly, improve material recycling and help to improve the use of renewable resources. A case in point is the further development of the innovative infrastructure concept DEUS 21 for a decentralized energy and water management extended to cases of urban redevelopment. Further examples are the substitution of chemical solvents with dry physical processes, for instance in industrial manufacturing of structural components, the extension of the lifetime of metalworking fluids, the recovery of substances from agro-industrial process water as high-quality fertilizers or the generation of algal biomass for material and energetic utilization.

1

2A

2B

BIOLOGICAL SENSORS FOR ONLINE MONITORING OF DRINKING WATER PIPES

Dr. rer. nat. Iris Trick

Clean drinking water is vital for man. Water pipes are in permanent danger of being contaminated. In addition, drinking water supply constitutes a potential target for terrorist attacks. Thus, it is essential that threats to public health are recognized at an early stage.

The German drinking water ordinance requires regular checks for certain pathogens and chemical substances. This is normally done by taking samples and examining them in a laboratory. Standard analysis methods used are protracted and limited to certain parameters: unknown or unexpected toxic substances are therefore not detected in a timely way making these methods unsuitable for use as warning systems which can indicate the presence of chemical or biological substances at an early stage.

Objective: Online monitoring with bio-sensors

In the present project "AquaBioTox" the Fraunhofer IGB together with its project partners Berliner Wasserbetriebe (a water provider), bbe Moldaenke and the Fraunhofer IOSB are developing solutions for continuous online monitoring of drinking water pipes. The aim is to establish a biological broad-spectrum sensor which reacts immediately and reliably to hazardous substances in the water, and indicates their presence by means of automatic image analysis.

Results

The contribution of the Fraunhofer IGB to the AquaBioTox project is the development of microbiological and mammal cell systems which react quickly to the presence of toxic compounds through a reduction in the fluorescence. They can, therefore, be utilized as biological sensors. Currently fluorescence levels are recorded by means of a probe developed by bbe Moldaenke.

Comprehensive screening led to the choice of two strains of bacteria (*Caulobacter crescentus, Escherichia coli*) and two mammalian cell lines (HEK 293, CHO). The test organisms are kept immobilized in the measuring cell on a substrate in small bioreactors with test fluid circulating around them (Fig. 1). In addition, these biological sensors are used in combination with a daphnia toximeter established by bbe Moldaenke to increase the spectrum of the detection system. Table 1 summarizes the currently established reactions of the biological systems used in AquaBioTox. The chart shows the stability of the bio-sensor in drinking water under conditions which meet the relevant applicable regulations, respectively and demonstrates the impact of a toxic compound on the test organisms. Fig. 2 shows a noticeable color change of the microbial system after addition of a toxic substance.

Test substance	*Caulobacter crescentus*	*Escherichia coli*	HEK 293	CHO	Daphnia
Neurotoxin	+	–	–	–	+
Respiratory poison	+	–	+	–	+
Metal ions	–	–	–	–	n. i.
Alcohol	+	+	+	–	n. i.
Aldehydes	+	+	+	–	+

+ system reacts | – system does not react | n. i. substance not investigated

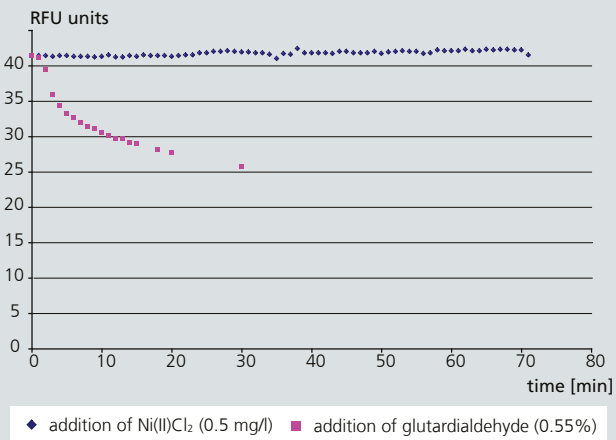
Table 1: Results on spectrum range of sensor system.

Outlook

After completion of the ongoing research project it is intended to transfer and adapt the measuring principle to other areas of application. Amongst other environmental issues the Fraunhofer IGB is concerned with research into semi-decentralized water and wastewater infrastructure systems. The expected increase in these ideas such as the utilization of processed rainwater requires different solutions for online monitoring. Similar functional principles have been validated in the AquaBioTox project and after necessary specific adaptations have been made, online monitoring could replace the currently used complex and very expensive analysis methods which mainly only provide summary parameters.

1 *Measuring cell with microbial test organisms and bbe probe for measuring fluorescence intensity.*

2 *Fixed-bed reactor covered with E. coli RFP before (A) and after addition of glutardialdehyde (B).*



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System Technologies and Image Exploitation IOSB, Karlsruhe

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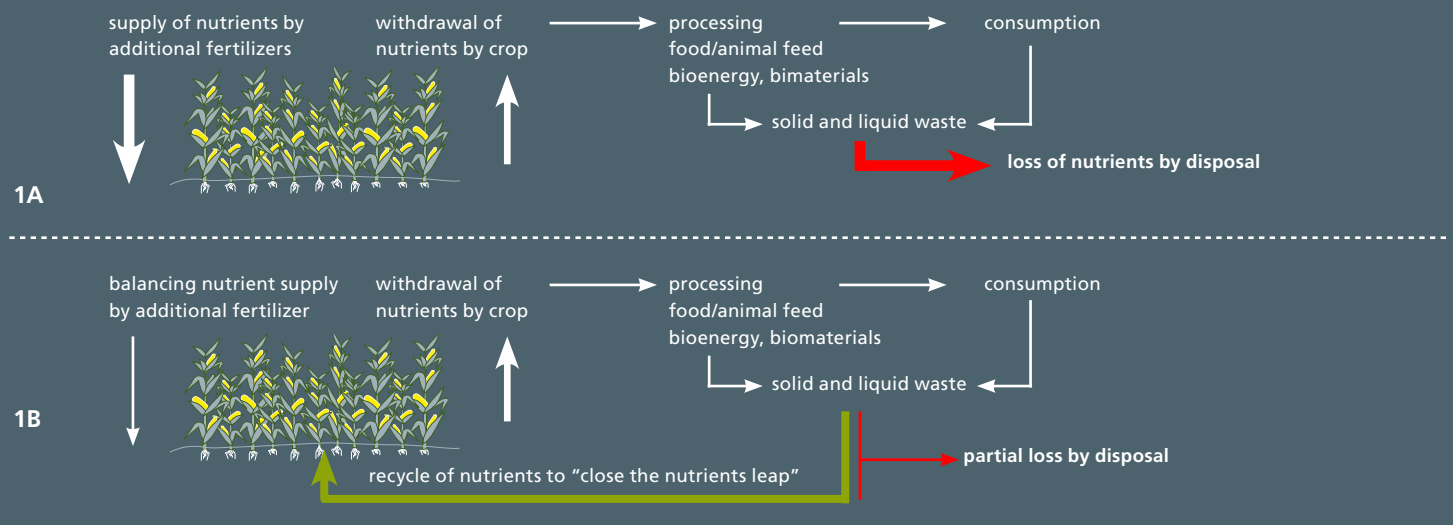
The research project "AquaBioTox: Onlinefähige Trinkwasserüberwachung auf Grundlage eines biologischen Breitbandsensors mit automatischer Bildauswertung" (AquaBioTox: Online-monitoring of drinking water on the basis of a biological broad spectrum sensor with an automatic image evaluation) is funded within the scope of the official submission "Detektionssysteme für chemische, biologische, radiologische, nukleare und explosive Gefahrstoffe (CBRNE-Gefahren)" (Detection systems for hazardous chemical, biological, radiological nuclear and explosive hazardous substances [CBRNE hazards]) within the scope of the federal safety research program and the promotional reference 13N9537 by the German Federal Ministry of Education and Research (BMBF). The working groups of the Fraunhofer IGB would like to thank the BMBF for funding this joint research project.



NUTRIENT RECYCLING AS THE FINAL STAGE IN TOTAL CROP USE

Dr.-Ing. Maria-Soledad Stoll

Nutrients like nitrogen, phosphorus, potassium, calcium are essential for the growth of all living organisms in both flora and fauna. In modern society, the nutrients mostly pass in a flow from soil extraction via harvesting to food production, consumption, and finally waste disposal (Fig. 1A). In order to compensate for the nutrients removed by harvesting, nutrients are added back to the soil in the form of either mineral fertilizer synthesized by chemical processes or organic fertilizer such as manure or compost.

The ever growing demand for food worldwide, together with the competing and rapidly growing demand for crops used to produce bioenergy and biomaterials, means that the market demand for plant nutrients will increase drastically in future.

However, the mineral fertilizer industry is facing a critical situation in the near future due to two main factors: the scarcity of the non-renewable phosphate rock used to produce phosphorus fertilizer, and the high energy requirements (mainly natural gas) of the Haber-Bosch process used to produce nitrogen fertilizer.

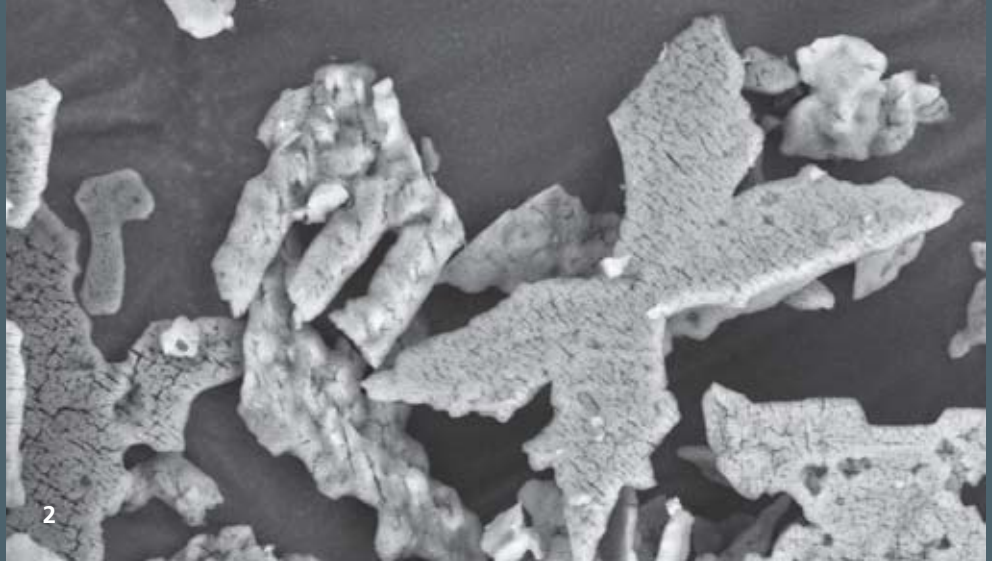
Current nutrient loss in the environment

At the same time, huge volumes of nutrients are being lost due to nutrient removal processes (e.g. nitrification/denitrification, phosphate precipitation with aluminum or iron salts) carried out today as state-of-art in most wastewater treatments plants. Contemporary farming methods can also lead to nutrient loss where the use of fertilizer to increase crop yields is excessive. In this case, surplus nutrients leach to groundwater from oversaturated soils or reach water bodies via surface run-off, leading to undesirable environmental consequences like eutrophication.

Sustainable nutrient management at the Fraunhofer IGB

In general, recycling of nutrients is not standard practice today. Consequently, the current excessive nutrient loss will have a drastic impact not only on the environment, but also on the nutrient supply needed to meet global demand. Therefore, the development and application of innovative and sustainable technologies to "close the nutrients loop" (Fig. 1B) and a much greater political, scientific, and social awareness of the vital role of the nutrients are crucial to ensuring sustainability in the future.

The Fraunhofer IGB recognizes the importance of nutrient recovery and recycling in replacing nutrient removal in order to assure future environmental sustainability that is also commercially viable. Thus, we have established a new research field to develop and implement sustainable and cost-effective technologies and strategies for integrated resource management.



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Our main research activities are focused on:

- Recovery of nutrients such as organic and inorganic phosphorus, nitrogen, potassium and calcium as ready-to-use fertilizers from various sources of residues
- Characterization of the nutrient content of different types of agroindustrial, industrial and municipal residues
- Evaluation of waste with regard to its potential for nutrient recovery
- Development of specific strategies for optimized nutrient recycling as function of the particular waste characteristics

Current projects

Currently, we are developing technologies to recover magnesium ammonium phosphate (MAP, Fig. 2), potassium magnesium phosphate (KMP), ammonium sulfate, and organic phosphorus. The nutrients are recovered as valuable products (Fig. 3) which can be commercialized and recycled in different crops according to specific requirements like crop variety type or soil characteristics.

We are also involved in the characterization and evaluation of various types of solid and liquid waste (e.g. waste from the production of olive oil and from the livestock industry) in order to identify their potential for nutrient recovery and recycling. In addition, we are investigating the recovery of nutrients from animal manure and their recycling as a fertilizer for cabbage as part of an EU-funded project ("EcoBug").

Future activities

The size and structure of the recovered nutrient salts have a direct influence on the efficiency of the plant's nutrient uptake. Thus, future research will be focused on the optimization of nutrient salt crystal growth, to enable modification of size and structure. In addition, research will be carried out on adapting the dosage form of nutrients to suit the plant's needs, e.g. pellets based on digested residuals.

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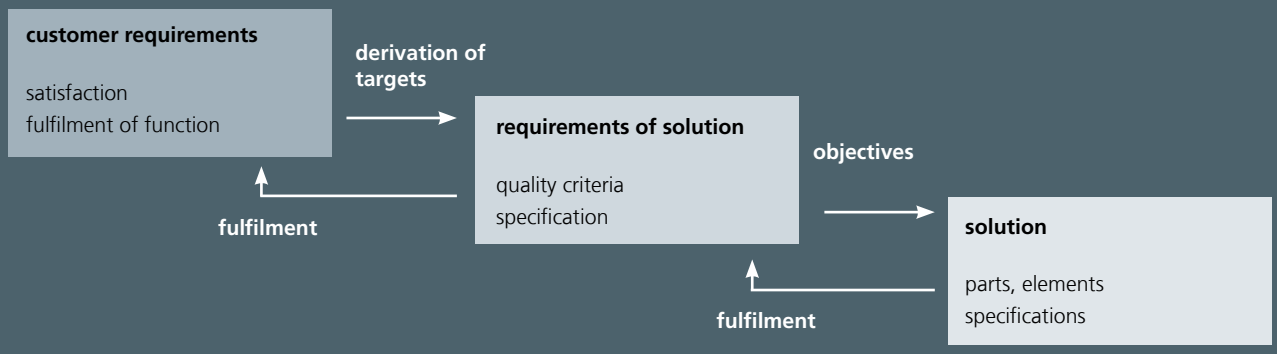
Funding

Part of our current research activities are being funded through the project "EcoBug: Development of an innovative industrial bio-reacting and fermentation process producing an organic insect re-pellent-fertilizer for ecological farming" within the FP7 Framework Program of the European Commission (Grant No. 218467-2).

1 *General nutrient flow diagram in: (A) a non-sustainable system, (B) a sustainable cyclical system.*

2 *Nutrients recovered as MAP from filtered real wastewater after anaerobic treatment.*

3 *Final recovered nutrients as a valuable product (MAP) which can be directly recycled.*



1

APPLICATION OF DESIGN METHODOLOGY FOR THE DEVELOPMENT OF PROCESS ENGINEERING PLANTS AND DEVICES

Dipl.-Ing. (FH) Alexander Lohner

In the product development in mechanical engineering enterprises and in the development of consumer goods the application of design methodology to ensure functionality and quality is commonplace. The continuous design process uses specific methods to clarify customer requirements, solve technical problems systematically, creatively generate ideas, prevent errors and improve technical reliability. In contrast to the design of risk-carrying mass products where these techniques are commonplace, their application to process engineering tasks in the construction of plants and devices has been rudimentary, yet, even though there is a risk of high misinvestments. The purpose of design in process engineering is to translate physical, chemical or biological processes into components, devices and plants. Specifications derived from research often reveal complex problems with conflicting requirements in individual parts of a process which often lead to a conflict between objectives.

Task and target

The development of new process technologies and new areas of process application requires new construction solutions or modifications. The aim of product development in apparatus engineering is to develop technical solutions which are economical and which also meet e.g. the necessary safety standards. By applying the principles of the methodical product development to apparatus and plant construction in process engineering it is possible to preserve functionality, optimize customer benefits, reduce development times and decrease manufacturing costs. A major benefit is that this methodology enables an optimized compromise solution even if individual requirements of certain task are diametrically opposed. Innovative developments are often the result of overcoming contradictions.

Approach

As the design methodology is basically independent of where it is applied, the work methods of systematic design can be adapted to process engineering problems. Design is divided into the following stages: clarification and definition of the task, methodical conception and methodical development. The individual stages require a problem-oriented approach. This means to think in terms of functional structures, cause-effect relationships and systematic impact. Through objective abstraction of the problem presented it is possible to avoid an undesirable limitation of potential solutions. The systematic search for a solution should utilize creativity techniques. It is necessary, therefore, to avoid any predetermination or limitations. In fact, the free play of imagination and consideration of all options is positively to be encouraged. The choice of potential solutions is made by systematic analysis. The necessary criteria are either determined together with the customer or in accordance with market requirements and focusing on both technical and economic aspects. Finally, the criteria are weighed against each other.
The most suitable of all technical options is then chosen and implemented. On occasion it may be necessary to repeat analysis and synthesis several times during the construction

priority ranking of criteria	capacity	costs	reliability	maintenance	wear	feasibility	safety	importance absolute	importance relative	ranking
capacity		2	1	2	2	1	1	8	19 %	**3**
costs	0		0	1	2	0	0	3	7 %	**6**
reliability	1	2		1	1	0	0	5	12 %	**4**
maintenance	1	2	1		1	0	0	4	10 %	**5**
wear	0	0	1	1		0	0	2	5 %	**7**
feasibility	1	2	2	2	2		0	9	21 %	**2**
safety	1	2	2	2	2	2		11	26 %	**1**
								42	100 %	

2

process. The production of blueprints and engineering are done by means of 3-D-CAD systems. Modeling is possible from both directions, bottom-up or top-down. However, it is always important to move from the abstract to the concrete. A combination of 3D-design and simulation of sub-processes reinforces the result. The cooperation of engineers and scientists from different disciplines in interdisciplinary teams perfectly complements this methodological approach.

Benefits for customers

In development projects which aim at producing a close-to-market-launch product, using construction methodology in process engineering provides an opportunity for the development of systematic, optimal solutions. Above all, it helps to minimize potential risks, as process engineering in particular requires substantial financial investment even for process demonstrations at pilot plant scale. Through increasing the degree of innovation it is possible to react more effectively to the market requirement for ever more efficient solutions. It also actively drives the development and design of new markets in the position of technological market leader. As a result it is possible to react to both risks and chances at an early stage.

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Objectives of using QFD

- Short and efficient procedures of decisions
- Advanced safety to achieve good quality process and plant design
- Development of a cost-effective solution according to customers' requirements
- Advanced transparency and traceability of decisions
- Observation and documentation of know-how and experiences
- Efficient use of financial investments

1 *Procedure of QFD (Quality Function Deployment) use.*
2 *Priority ranking of criteria.*

1

GRAYWATER TREATMENT ON RECREATIONAL CRAFTS IN SENSITIVE WATERCOURSES

Dr.-Ing. Tosca Zech

Boating is becoming an increasingly popular leisure activity, attracting ever growing numbers of enthusiasts to watercourses such as lakes, bays, lagoons and costal waters. In order to protect the natural resources in these environmentally sensitive areas, while at the same time allowing intensive touristic usage, wastewater produced on board watercrafts must be treated before discharge into a watercourse. Up till now, technical solutions have only been available for large vessels.

The aim of the project described below is to design a graywater filter system for installation on boats and yachts under 24 m in length. The graywater treated with this system has to be of such quality that it can be safely discharged into the watercourse without fear of pollution. Our partner from industry on this project is Wave International Ltd.

Requirements

Graywater is defined as wastewater produced on board from showers, washbasins, washing machines, kitchen sinks and dishwashers. Technical solutions already exist for the treatment of wastewater from toilets and urinals on board.

The International Maritime Organization (IMO) is a specialized agency of the United Nations that has been regulating the prevention of marine pollution from ships since 1973 through the MARPOL Convention. In order to ensure the implementation of fixed regulations for disposal, MARPOL annexes also prescribe technical equipment on board. These globally recognized regulations do not, so far, include small boats and small yachts. However, increasingly, national legislation is addressing this issue, and regulations at the European and international level are expected in the near future for coastal waters. Therefore, our initial focus is on the development of a graywater filter system for marine applications.

The challenge is to develop a
marine graywater filter system that

- meets future disposal standards,
- ensures high water flow,
- features very compact construction,
- has low energy requirements and
- is robust.

Concept and results

The proposed marine graywater filter system is a multi-stage process. The first stage involves elimination of coarse pollution and large particles, while at the same time subsequent filtration stages are protected from blockage. In the second stage, grease is eliminated by a special filter. This filter was designed for the elimination of oil and separation of grease from bilge water (water collected in the bilge of the boat and often contaminated with engine oil) and has been used effectively for many years. The third, and, where necessary, a fourth, stage involves the elimination of soluble nutrients. The filter media are configured into cartridges or filter bags and can be exchanged easily after use and disposed of on shore.

First, we searched for filtration medium suitable for eliminating soluble nutrients (carbon, nitrogen and phosphorous compounds) from graywater. For this purpose a pilot plant was operated with synthetic graywater and different filter media were screened.

In the screening process, the aim is to make findings quickly while under realistic circumstances. Therefore, filter media were tested configured into cartridges and high filtration velocity was chosen. Comparable and significant results could be derived within 60 minutes. As an example, the chart shows the results of a screening for the removal of carbon compounds, measured as chemical oxygen demand (COD). We were able to demonstrate that with the best filter material configuration loading – and thus COD elimination – could be achieved two to three times higher than with conventional filter cartridges within the same time and at the same capacity (see GWF04 in the chart).

The removal of particulate and colloidal material by the filtration system was tested with real graywater from showers and washing machines. For this purpose, the best-performing filter media from the screening were used in order to identify in turn the best filter media and filtration system configuration. Preference was given to a specially configured activated carbon filter that can be combined with an ion exchange resin.

Outlook

Using the results from particulate material and nutrient removal, work is now under way on constructing a prototype system which will be tested under real conditions on a leisure boat.

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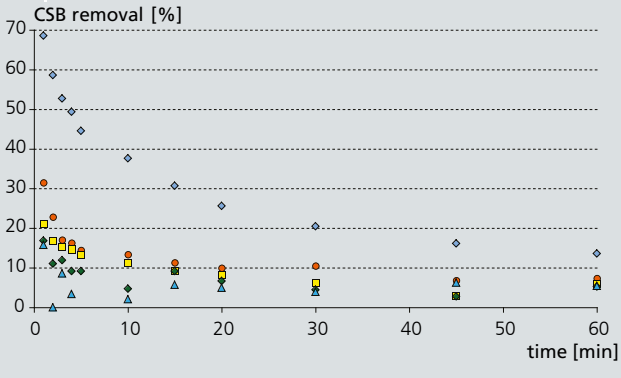
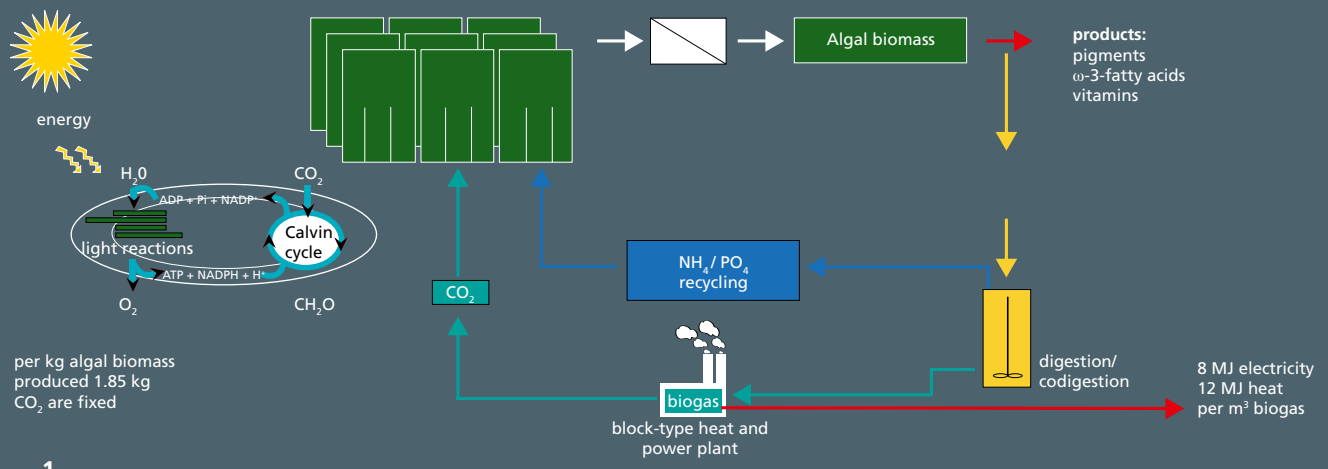
Project partner
Wave International Ltd., UK

Results of a screening for suitable filter media for the removal of carbon compounds (measured as chemical oxygen demand, COD)



1|2 *Tourism has greatly increased in sensitive watercourses.*



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USE OF FILTRATE WATER FROM DIGESTION FOR THE CULTIVATION OF MICROALGAE

Dr. rer. nat. Ulrike Schmid-Staiger

For the economical and sustainable use of algae biomass for material and energy recovery it is necessary to optimize the individual steps of the process chain. The challenges for the sustainable production of microalgae are as follows:

Energy-efficient microalgae production

This requires a photobioreactor which ensures a high photosynthesis rate even at high cell concentrations and whose energy requirements for algae production are lower than the energy content of the algae biomass produced.

Product extraction

Both the solvents themselves and the quality of the solvents have to be adapted to the products; extraction should occur from the wet biomass to avoid energy input through drying processes.

Utilization of residual biomass

After recovery of the valuable products the remaining lignocellulose-free biomass can be used for anaerobic digestion into biogas and thus for an energetic added value.

Recycling of nutrients

On top of the use of exhaust CO_2 gas, the utilization of wastewater containing high amounts of nitrogen and phosphate, adds to cost reduction.

Water recycling

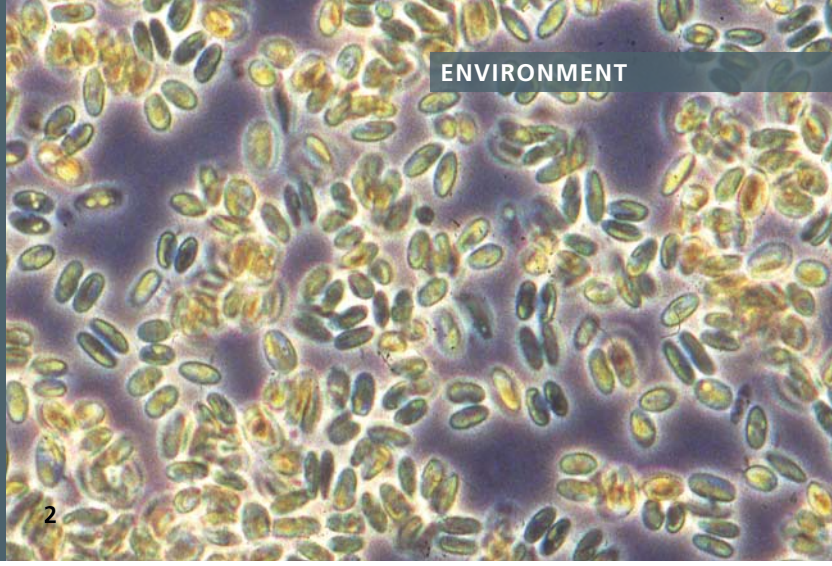
Water can be recycled via a renewed use of the cultivating media and through the utilization of nitrogen and phosphate contained in wastewater.

Using nutrients from wastewater

One aim of the project "Mehr Biogas aus lignocellulosearmen Abfall- und Mikroalgenreststoffen durch kombinierte Bio-/Hydrothermalvergasung" (More biogas from low-lignocellulose waste and microalgae residues through a combined bio/hydrothermal gasification) (EtaMax, page 102) is to close the nutrient cycles between algae biomass generation and energy generation with anaerobic digestion. Wastewater streams from biogas plants for sludge digestion with a high loading rate, so called high-load digestions, stand out due to high ammonium and phosphate concentrations of up to 1,300 mg NH_4 per liter or 200 mg phosphate per liter, respectively. In these high-load digestion plants particle-free wastewater streams are recovered through ultrafiltration with rotating disk filters. Currently the ammonium in these wastewater streams is converted into nitrogen by means of energy-intensive process steps or it is precipitated together with the phosphate. Therefore, it is the intention of the EtaMax project to use these water streams with a high N and P content for algae production (Fig. 1).

Results

During initial tests with *Phaeodactylum tricornutum*, an alga containing the omega-3-fatty acid EPA (eicosapentaenoic acid), it was possible to successfully use filtrate water from two different municipal biogas plants as a culture medium. Depending on the origin of the filtrate water, it was only necessary to add phosphate to achieve an optimal N-to-P ratio for continuous biomass production in the flat panel airlift photobioreactors. The biomass productivities achieved with



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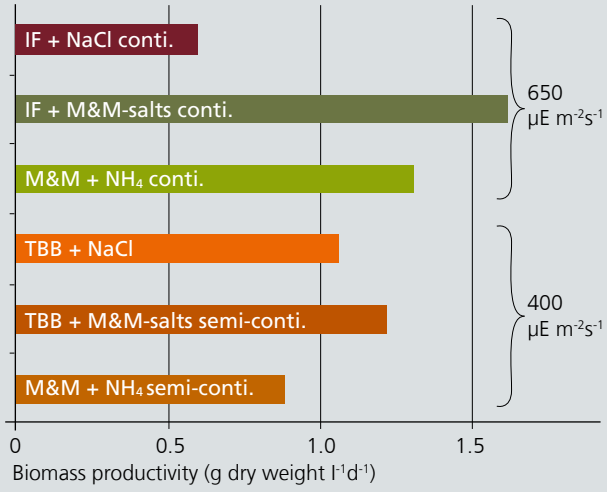
filtrate water were even higher than those generated with the synthetic medium (see chart). This means that synthetic media can favorably be replaced by wastewater streams from anaerobic digestion. This is another step towards the production of algae biomass for energetic utilization (oil, biogas) in combination with the sustainable recycling of water and nutrients which also considerably reduces costs and energy demand.

Biomass productivity of *Phaeodactylum tricornutum* with filtrate water from anaerobic sewage sludge digestion



The filtrate water comes from the high-load digestion in Tauberbischofsheim (TBB) and Ilsfeld (IF) with high ammonium and phosphate concentrations. In the case of semicontinuous cultivation harvest or filtrate water addition, respectively, was carried out after consumption of the ammonium. In the continuous tests a flow rate of D= 0.2 d^{-1} was set. A synthetic medium according to Mann & Myers, 1968 (M&M) was used for control purposes.

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Partners

The partners of the EtaMax-Project for the digestion of substances microalgae are, in particular, FairEnergie, Reutlingen, and Subitec GmbH, Stuttgart. For further project partners see p. 102.

Funding

Parts of the project are funded through the joint research project "EtaMax: Mehr Biogas aus lignocellulosearmen Abfall- und Mikroalgenreststoffen durch kombinierte Bio-/Hydrothermalvergasung" (Grant No. 03SF0350A) within the program "BioEnergie 2021" of the German Federal Ministry of Education and Research (BMBF).

1 *Recycling of nitrogen and phosphate through the coupling of anaerobic digestion and algae production.*

2 *Microscopic photo of Phaeodactylum tricornutum.*

1

ANAEROBIC WASTEWATER TREATMENT WITH MEMBRANE FILTRATION FOR WATER REUSE

Dipl.-Ing. Marius Mohr

Since 2006 the Fraunhofer IGB has been testing a wastewater purification process for the reuse of water in a new development area in Knittlingen within the scope of the project DEUS 21: In 2008 the first pilot plant which was adapted in size to the small number of inhabitants was replaced by a plant which is able to clean the wastewater of approx. 175 inhabitants and which can be easily extended (Fig. 1). In March 2009 this plant for anaerobic wastewater treatment with membrane filtration started operation. At the same time a technology for nitrogen recovery from the plant's effluent utilizing ion exchange was explored.

Separation of solids

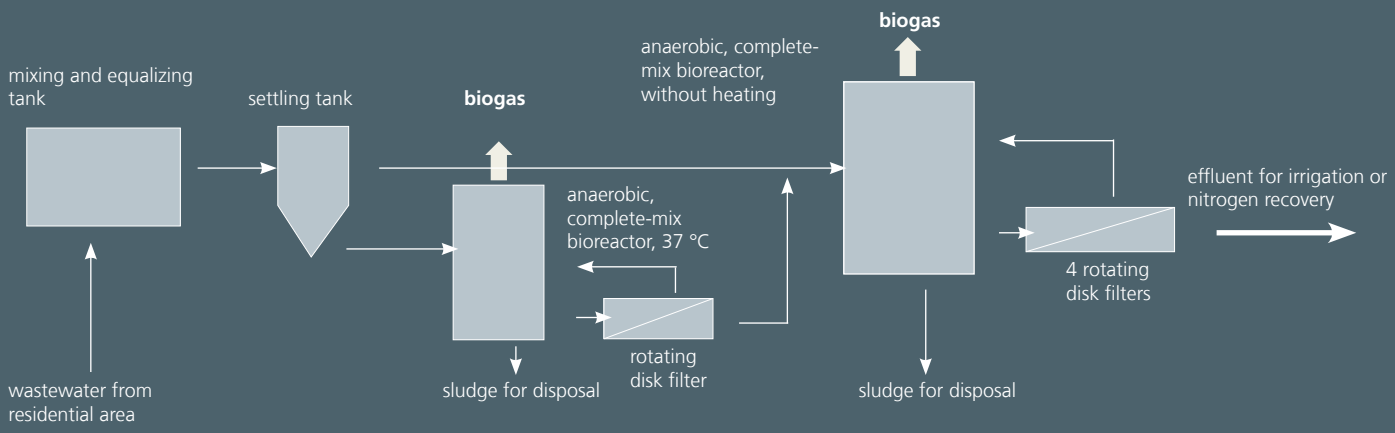
Tests at the pilot plant and also at a test plant had shown that wastewater purification works better if solids are separated beforehand. This is now done in a sedimentation tank. The solids are treated separately at 37 °C by means of high-load digestion with integrated microfiltration producing about 5000 liters of biogas per day (Fig. 2). The overflow of the sedimentation tank (approx. 99 % of the inflow) is treated in a non-heated, complete-mix bioreactor with a volume of 10 m^3. The effluent leaves the reactor via four parallel rotating disk filters the pores of which have a diameter of 0.2 µm. Since there are no treatment plants in Germany in which municipal wastewater is treated anaerobically at low temperatures, the microorganisms responsible for such treatment must first be cultivated. For this reason the load of the bioreactor was slowly increased.

Good cleaning purification performance with biogas yield

In the summer (reactor temperatures of 22 to 27 °C) it was possible to maintain the chemical oxygen demand (COD) of the effluent under 150 mg/l for a period of two months constantly. For one month it was even possible to keep it below 120 mg/l. In autumn/winter (reactor temperatures from 14 to 19 °C) it has so far been possible to stay continuously below the threshold of 150 mg COD/l for one month. The minimum wastewater residence time in the bioreactor was 50 hours in summer and 36 hours in autumn/winter, inflow concentrations are between 400 and 1100 mg COD/l. In the periods specified the average degree of decomposition was around 85 %. Maximum biogas production stood at nearly 2000 liters per day. In the summer the biomass increased by nearly 5.5 kg within a period of two months (weighed as dry matter). Based on the usual dewatering to 25 % of dry matter this equals a sludge volume of 22 liters which needs to be disposed of. Since its start-up in March the membrane filtration has only been cleaned by means of automatic back-flushing with filtrate. It is intended to carry out the first chemical cleaning in early 2010.

Purified wastewater for fertilization

A potential use of the effluent of the plant can be seen in the combined irrigation and fertilization of agricultural areas. In the bioreactor the nutrients ammonium and phosphate, which can be found at relatively high concentrations in the wastewater, are hardly decomposed. Membrane filtration maintains the germ count in the effluent water at a low level,



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which means that it can safely be used for irrigation purposes. Random checks in May showed a complete absence of bacteria of the species *Escherichia coli* in the effluent of the rotating disk filters used although in the reactor sludge their count amounts to one million colony forming units (cfu) per milliliter.

In cases in which the use of the effluent for fertilization purposes is not possible, a method for recovering ammonium from the effluent is being developed. Here zeolite, a silicate mineral is used as an ion exchanger and then regenerated with a concentrated sodium chloride solution [1].

Rainwater treatment

Rainwater, which is collected separately, is stored in underground cisterns and purified by means of an active carbon filter, membrane filtration and a UV lamp. The target is to achieve drinking water quality to distribute the rainwater to the residents of the area and thus to save a large amount of drinking water.

Forecast

In the further course of our investigations the residence time of the wastewater in the bioreactor is continuously being reduced thus increasing the load until ultimately all wastewater produced in the residential area can be purified. The biogas which is produced during the process is used in a combined heat and power unit which will be set up in the spring/summer of 2010. The plant for nitrogen recovery will be optimized in some details to be run in continuous operation from then on. Phosphate recovery can also be achieved successfully: with the MAP technology we are already reaching effluent values below 2 mg/l PO_4-P. This technology should particularly be used in areas without a central wastewater infrastructure where it is not possible to use the water for agricultural purposes.

1 MAP magnesium-ammonium-phosphate

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Project partners

Fraunhofer Institute for System and Innovation Research ISI, Karlsruhe
City of Knittlingen
Eisenmann Maschinenbau KG, Holzgerlingen
EnBW Energie Baden-Württemberg AG, Karlsruhe
Kerafol GmbH, Eschenbach

Funding

We would like to thank the German Federal Ministry of Education and Research (BMBF) for funding the research project "Decentralized Urban Infrastructure Systems DEUS 21", Promotional reference 02WD0850.

Further information

www.deus21.de

1 *Location of the plants in Knittlingen: the water house.*
2 *Diagram of the anaerobic wastewater treatment process.*

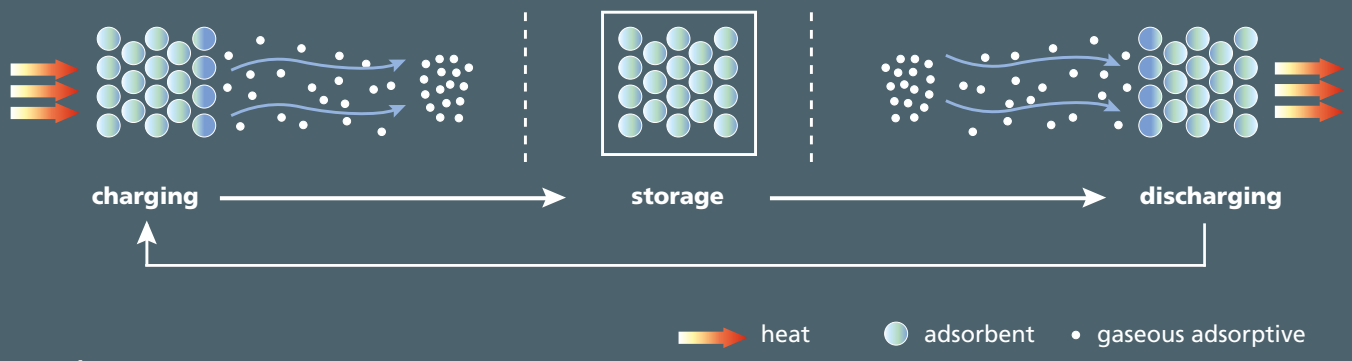
ENERGY

Prof. Dr. Walter Trösch

The fossil energy carriers coal, mineral oil, and natural gas are the residues of biomasses created during the pre-Carboniferous period by means of photosynthesis and laid down during the Carboniferous period. During this period, the earth's net energy content increased steadily. Today, as a result of the anthropogenic utilization of these fossils and the reduction of the overall photosynthesis capacity, this net energy content is steadily on the decrease. The result is rising atmospheric CO_2 – and consequently, climate change.

Making the transition to sustainable energy is thus a key challenge of the 21st century. The Fraunhofer IGB is tackling this challenge in many ways. We have contributed toward: expanding photosynthesis capacity by developing an algae photobioreactor; the exploitation of regenerative energy sources by means of highly innovative membrane technology (fuel cells, osmosis power plants); improved energy efficiency by producing biogas from organic waste (by-products of the food industry and primary agricultural products), and energy savings through process optimization in wastewater treatment technology and anaerobic wastewater treatment as well as in industrial processes such as drying with super-heated steam at ambient pressure. Additionally, the Fraunhofer IGB is working on process technologies and systems for long-term, stable storage of thermal energy and for the purification of biogas for CNG (compressed natural gas) vehicles.

A further field of activity is devising integrated material flow and energy concepts at both local and regional level, replacing the current historically grown solutions with systematic approaches using state-of-the-art technologies. This is why the Fraunhofer IGB is a very active partner in the Fraunhofer Energy, Building Innovation and Water Systems (SysWasser) Alliances.



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ENERGY EFFICIENCY INCREASE THROUGH SORPTIVE THERMAL ENERGY STORAGE

Dipl.-Ing. Mike Blicker

An important contribution to the achievement of climate protection targets is an improved utilization ratio for both fossil and regenerative primary energy sources. This is done by secondary usage of energy which was not used during its first application. A case in point is the utilization of waste heat created by combustion engines during the generation of power from biogas. The waste heat produced typically makes up over 50 % of the energy content of the biogas. This not only shows the great potential which lies in the increase of the degree of efficiency, but also the need for temporal and spatial decoupling of secondary energy utilization. In addition, there are many more processes in commerce, energy supply and manufacturing industry which generate large amounts of waste heat. Against the backdrop that 50-60 % of the EU energy requirements are needed for heat production it becomes apparent that there is great potential for optimizing energy use.

To optimize energy efficiency of processes, there is a need for compact and flexible storage systems to decouple or compensate the supply and demand for heat in terms of location through mobility and with regard to time through minimization of heat loss. Currently available industrially manufactured thermal storage systems regularly only store sensible heat. They usually use water as a storage medium thus restraining the storage density and limiting the storage temperature level to 100 °C at the most. Latent-heat storage units which may achieve slightly better storage density values regularly lack the required flexibility due to their defined operating temperature. The disadvantage of both systems is their permanent heat loss based on the fact that the driving gradient in both systems is the temperature difference between the medium and its environment. Insulation can reduce this effect, but only to a limited extent.

Innovative thermal storage methods

Chemical and sorptive heat storage systems which are counted as thermochemical storage systems, are relatively new, promising technology approaches with considerable benefits compared to both the sensible and the latent-heat storage systems. Here storage densities can theoretically be up to 10 times above those of the medium water; i.e. these systems can store much more energy without requiring a bigger construction volume. This energy is bound by means of physicochemical processes thus almost eliminating thermal loss. The combination of both advantages facilitates the efficient time-based storage of thermal energy and its transport. Due to similarities with heat pumps with regard to thermodynamic processes, sorptive systems can be applied to cooling processes at the same time.

Current special focus: systems with highly porous adsorbent agents

The Fraunhofer IGB is currently working with sorption systems utilizing a physico-sorptive bond between the reaction pair adsorbent (A) – adsorptive (B) with a preferably high energy turnover. This principle is reversible: A + B ↔ AB + heat (Fig. 1). When charging the storage medium, heat is added to substance AB which then dissociates into A and B components. To recover the heat the A and B components have to react with each other again. As long as a reaction between A and B is prevented, the heat which is stored by way of chemical energy cannot be released. The preferred adsorptive is water. It possesses a high phase transition enthalpy, is economic and harmless at the same time. The adsorbent (e.g. zeolite) has to bind the highest amount of water possible by adsorption. For initial investigations a closed system adsorbing water vapor in the pores of zeolites (Fig. 2) and other highly porous adsorbents was chosen and implemented in a small pilot plant (Figs. 3, 4).

Outlook

To translate such technologies to industrial serial production quality further development steps are still necessary. The heat storage densities and thermal output which can be achieved with the currently available technical solutions are still too low to be cost-efficient when used for industrial systems and when compared with the theoretically achievable potential. Here, further need for research exists particularly for solutions concerning heat and mass transport and system configurations. The target is to provide industrially relevant solutions, which enable for instance the operation of biogas-based power plants as fully-fledged combined heat and power plants, by using the waste heat energy via storage systems – at different locations or times.

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1 *Schematic diagram of sorptive thermal energy storage.*
2 *Zeolite balls.*
3 *Zeolite balls in pilot plant reactor.*
4 *Test reactor for investigation of sorption processes, solid matter heat exchanger and storage materials.*

1A

ETAMAX: DRIVING WITH BIOGAS FROM BIOWASTE

Dipl.-Ing. Ursula Schließmann

The utilization of renewable energies creates a sustainable alternative which reduces both dependency on the ever scarcer fossil oil and carbon dioxide emissions at the same time. Here the use of vegetable biomass for the recovery of bioenergy in the shape of power, heat and fuel plays a leading role. Due to its high net energy yield biogas is the most important source of bioenergy. Biogas, a mix of energetically usable methane and carbon dioxide, is created during the digestion of organic matter. In conjunction with the combined heat and power cycle, biogas generation is considered a technology with a very high CO_2 avoidance potential. The potential of biomass for the creation of biogas has so far been insufficiently exploited in general and hardly at all in vehicles.

Project objectives

Coordinated by the Fraunhofer IGB, the project consortium linking partners from research, energy management and industry has therefore focused its activities on easily fermentable, low-in-lignocellulose, wet biomass – particularly on low-cost biowaste and residual algal biomass which constitute no competition for foodstuffs – with a combined, modular process under maximum energy recovery. The aim is the complete conversion into biogas and the simultaneous closing of all materials cycles. The main focus here is on the regional creation and utilization of regenerative methane (biogas). The target is to produce purified biomethane which can be used as fuel for vehicles which are operated on compressed natural gas (CNG).

Modular high-load digestion

Waste materials with a high water content and a low lignin and lignocellulose content from the food industry, kitchen and central market wastes are perfectly suited for digestion. Today such wastes are usually taken to composting plants, which means that the stored energy is lost as heat. In a high-load digestion process which was developed at the Fraunhofer IGB some years ago, and which has since been implemented several times, solid matter from these biowaste groups are almost completely converted into biogas within the space of only a few days.

To ensure that a digestion plant can convert the different substrates, whose water and solid matter content may differ greatly, as efficiently as possible into biogas, the process technology for the individual substances is specifically adapted by means of a flexible multi-substrate high-load digestion plant with different pre-digestion modules. In a central reactor as the second step the digestion water is treated and also converted with a maximum efficiency level into methane.

Additional biomass with algae

The Fraunhofer IGB wants to provide additional wet, low-lignocellulose biomass for the multisubstrate high-load digestion. Energy recovery from algae biomass is already possible in a highly efficient manner today thanks to a photobioreactor platform developed by the Fraunhofer IGB. The algae in the reactors grow to high cell densities using only in sunlight as energy source and carbon dioxide as carbon source plus inorganic nitrogen and phosphate.

EtaMax uses the carbon dioxide which is created as a co-product during the digestion process and during the combustion of biogas as a source for the cultivation of algae. A further algae cultivation substrate is the filtrate water from the digestion process, which contains nitrogen and phosphorous as nutrients (page 94). The aim is to find robust algae which grow rapidly in this flue gas and in the changing seasonal light and temperature conditions in central Europe.

Hydrothermal gasification of digestion residues

Small amounts of residual digestion residues, which cannot be further decomposed in an anaerobic environment, always are formed during the digestion process. For the complete exploitation of these digestion residues it is necessary to examine catalyst-supported hydrothermal gasification under high pressure and high temperatures. Here the same products are created as during the digestion process: carbon dioxide and methane.

Results and outlook

Currently the Fraunhofer IGB is determining the process parameters for transfer onto a technical scale (2 x 3.5 m³) for the digestion of central market waste in a semi-technical pilot plant (2 x 30 l). This pilot plant, which has already been operating for a few weeks, produces about 1000 liters of biogas per kilogram organic dry matter in its start-up phase. The parameters determined in this plant are to be implemented and tested in a demonstration plant on the site of EnBW's combined heat and power station in Stuttgart-Gaisburg. In a future full scale plant it would be possible to generate 300,000 cubic meters of methane gas per year from the municipal biowaste from the city of Stuttgart. After purification it can be used as vehicle fuel for a small fleet of collection vehicles which run on natural gas. This would also be beneficial for air quality.

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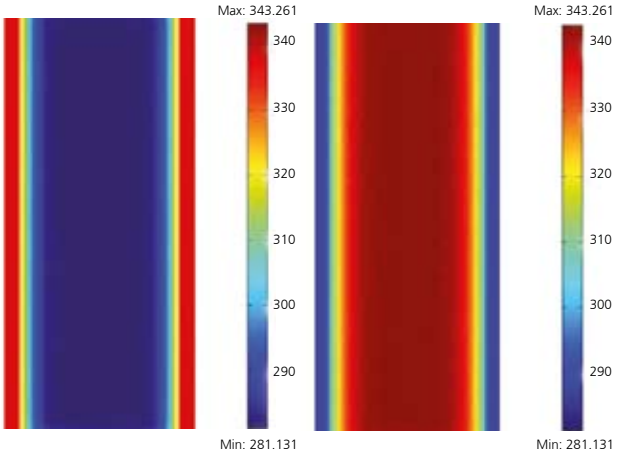
Funding
The joint research project "EtaMax: Mehr Biogas aus lignocellulosearmen Abfall- und Mikroalgenreststoffen durch kombinierte Bio-/Hydrothermalvergasung" is being funded for a period of 5 years by the German Federal Ministry of Education and Research (BMBF) since June 2009 (Grant No. 03SF0350A) within the scope of the program "BioEnergie 2021".

1 *Easy-to-ferment central market waste such as lettuce, fruit and vegetables are now to produce methane as a fuel by means of a new method (A and B).*

2 *In this pilot plant (2 x 30 l) for the digestion of central market waste the process parameters for transfer to pilot scale are being determined (2 x 3.5 m³).*

1



2 (A) (B)

USE OF MICROWAVE TECHNOLOGY FOR EFFICIENT AND RAPID ENERGY TRANSFER IN PROCESS ENGINEERING

Ali-Imran Javaid M. Sc., Dipl.-Ing. Siegfried Egner

Securing our energy needs in times of climate change and dwindling fossil resources is one of the greatest challenges we face today, and thus a key field of activity at the Fraunhofer IGB. One of our principle goals is to find ways of improving and increasing energy efficiency. Our Institute is therefore working on technologies that facilitate a more economical and efficient use of energy. In industry, warming processes and heat input account for substantial consumption of energy. To transfer heat, typically three methods are known: conduction, convection and radiation.

Objective: microwave energy for energy-efficient processes

The new focus on microwave energy in process engineering is regarded as a prerequisite for improving the efficiency and speed of processes. The fields for microwave applications are growing in number as researchers at the Fraunhofer IGB determine ways to optimize the existing processes. Evolution of processes opens up opportunities for inventive technology applications of this emerging energy source in a wide range of process engineering fields.

Direct energy input with microwaves

Microwaves are electromagnetic waves that reside between radio and infrared waves. They have substantially lower frequencies than X-rays and ultraviolet light. Consequently, microwave frequencies do not chemically damage the product; microwaves merely transmit the energy directly into the sample while conventional energy sources transmit energy indirectly by conduction or convection. Microwaves penetrate a product regularly over its entire volume, where they activate the dielectric material. Because the molecules in the interior of the body quickly dissipate the energy produced by the oscillations into heat, a rapid rise in interior temperature results. Molecules located nearer to the surface of the body, on the other hand, can release this energy externally. Thus in such heating processes the inner temperature of a body is higher than the surface temperature. This effect is known as volumetric heating. Fig. 2 shows a modeling of this effect.

Benefits of microwave technology in process engineering

Microwaves as an energy source in processing engineering have many advantages over conventional methods. Besides offering energy and time efficiency, microwave energy is amenable to automation, has potential for selective heating, improves the product quality, can be combined with conventional methods, saves space and above all is eco-friendly due to the fact that it is generated by electricity which in turn can come from renewable sources.

3

Industrial applications and results

Industrial applications of microwave energy include sintering, sterilization and pasteurization of food products, sterilization of healthcare products and irradiation of waste to eliminate pollutants.

The Fraunhofer IGB has carried out several projects including the application of microwave irradiation to induce flash pyrolysis. Extending the conversion process by microwave gasification, it has proven possible to treat many forms of waste down to full mineralization – including tires, sewage sludge, agricultural waste, waste wood, electronic scrap, cables and plastic waste. Flash pyrolysis by microwave irradiation can be performed faster than by conventional methods of energy input, with significant differences in both temperature distribution and heat and mass transfer.

The design and development of an electromagnetically compatible system for process engineering is challenging demanding and requirers a multidisciplinary approach. This is provided at Fraunhofer IGB by a multidisciplinary team of process engineers, electrical engineers and mechanical engineers, who utilize our state-of-the art resources such as coupling software packages for electromagnetic simulation and 3D mechanical design. Our laboratory is equipped with dedicated equipment for demonstrating how microwaves can be used in process technology.

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1 *Typical microwave generator set-up consisting of a magnetron, isolator and an automated tuner in our pilot plant.*

2 *Comparison between conventional e.g. convection (A) and volumetric microwave (B) heating applied to a flat surface material for demonstration.*

3 *Demonstration system with a conveyor belt for the homogenous tempering of materials.*

APPENDIX

Patents granted 2009

In the year 2009 seven patents were granted. These patents are assigned to our business areas as follows:

Medicine

Verbessertes elektrophoretisches Trennverfahren für die Genexpression
EP 1 797 198,
granted November 11, 2009

Zellbasiertes Testsystem zur Identifizierung und Differenzierung von Keimspektren
DE 10 2006 031 483,
granted December 24, 2009

Pharmacy

Three-dimensional skin model
US 7,553,664,
granted June 30, 2009

Human recombinant beta-interferon with enhanced solubility
CA 2,287,521,
granted August 11, 2009
US 7,575,894
(divisional application),
granted August 18, 2009

Chemistry

Verbesserte Mikrogele und Filme
EP 1 299 426,
granted April 8, 2009

Environment

Verfahren zur Herstellung von Bauteilen mit passivierten Endoberflächen
EP 1 544 320,
granted October 14, 2009

Energy

Metal solution-diffusion membrane and method for producing the same
JP 4250525,
granted January 23, 2009

Trade fairs and events

Trade fairs and exhibitions

Ecogerma
Trade Fair and Congress on Sustainable Technologies
March 12-15, 2009, São Paulo, Brazil

Bayern Innovativ-Forum Life Science
Pharma Development – Food & Nutrition – Industrial Biotechnology
March 18-19, 2009, Technische Universität München, Garching, Germany

Hannover Fair Energy
Leading Trade Fair for Renewable and Conventional Power Generation, Transmission and Distribution
Fraunhofer Energy Alliance
April 20-24, 2009, Hannover, Germany

ACHEMA
29th World Exhibition Congress on Chemical Engineering, Environmental Protection and Biotechnology
May 11-15, 2009, Frankfurt am Main, Germany

BIO International Convention
Fraunhofer Group for Life Sciences
May 18-21, 2009, Atlanta, USA

BIOTECHNICA
International Trade Fair, Conferences, Partnering and Award for Biotechnology
Fraunhofer Group for Life Sciences
October 6-8, 2009, Hannover, Germany

WEFTEC
82nd Annual Water Environment Federation Technical Exhibition and Conference
Fraunhofer Water Systems Alliance (SysWasser)
October 10-14, 2009, Orlando, USA

MATERIALICA
12th International Trade Fair for Materials Applications, Surface Technology and Product Engineering
October 13-15, 2009, München, Germany

parts2clean
International Leading Trade Fair for Cleaning in Production and Maintenance Processes
Fraunhofer Cleaning Technology Alliance
October 20-22, 2009, Stuttgart, Germany

Bayern Innovativ Cooperation Forum Drug Development
Strategies – Technologies – Therapies
December 3, 2009, Würzburg, Germany

Workshops, seminars, events

13. Klinischer Studientag
"Klinische Entwicklung und Produktion biologischer Arzneimittel", CenTrial GmbH
January 14, 2009, Stuttgart, Germany

OTTI International Conference
Water Efficiency in Urban Areas
Concepts, Technologies, Socio Economics
January 29-30, 2009, Würzburg, Germany

Materials Valley Workshop
Grenzflächen- und Bioverfahrenstechnologie – Applikation in der Medizin
February 19, 2009, Hanau, Germany

OTTI Forum
Produktgestaltung mit Funktionsschichten
March 23-24, 2009, Regensburg, Germany

14. Kolloquium zur kommunalen Abwasser- und Abfallbehandlung
"Technologie mit Zukunft"
March 26, 2009, Fraunhofer Institutes Center Stuttgart, Germany

Fraunhofer Talent School
Reise ins Genom
March 27-29, 2009, Fraunhofer Institutes Center Stuttgart, Germany

OTTI Forum
Carbon Nanotubes – Auf dem Weg aus der Forschung in die Anwendung
Eigenschaften – Herstellung – Verarbeitung – Produkte – Arbeitsschutz – Toxizität?
April 22-23, 2009, Regensburg, Germany

Girls' Day
Future Day for Girls
April 23, 2009, Fraunhofer Institutes Center Stuttgart, Germany

Information Forum
Chance Klimawandel für die Chemieindustrie
April 29, 2009, Stuttgart, Germany

3rd FEBS Advanced Lecture Course on Human Fungal Pathogens
Molecular Mechanisms of Host-Pathogen Interactions and Virulence
May 2-8, 2009, La Colle sur Loup, France

OTTI Forum
Reinigen und Vorbehandeln vor der Beschichtung
May 13-14, 2009, Neu-Ulm, Germany

Tag der Wissenschaft (Day of Science)
"Zukunft entdecken"
June 27, 2009, Universität Stuttgart, Germany

Fraunhofer Truck
June 30 - July 4, 2009, Stuttgart, Germany

Science Express – "Expedition Zukunft"
July 5-7, 2009, Stuttgart, Germany

Unitag (University Day)
November 19, 2009, Universität Stuttgart, Germany

Checkpoint Zukunft
Day for students
November 23, 2009, Fraunhofer Institutes Center Stuttgart, Germany

Preview 2010

Industrial workshop "Automated Tissue on Demand"
February 26, 2010, Fraunhofer Institutes Center Stuttgart, Germany

Fraunhofer-Technologiezirkel
Technologietrends – Perspektiven für die Märkte von Übermorgen
March 10-11, 2010, Fraunhofer Institutes Center Stuttgart, Germany

Fraunhofer Talent School
Reise ins Genom
March 12-14, 2010, Fraunhofer Institutes Center Stuttgart, Germany

Analytica
22nd International Trade Fair for Laboratory Technology, Analysis and Biotechnology
March 23-26, 2010, München, Germany

GLOBE 2010
March 24-26, 2010, Vancouver, Canada

Hannover Fair Energy
Leading Trade Fair for Renewable and Conventional Power Generation, Transmission and Distribution
Fraunhofer Energy Alliance
April 19-23, 2010, Hannover, Germany

Girls' Day
Future Day for Girls
April 22, 2010, Fraunhofer Institutes Center Stuttgart, Germany

BIO
International Convention
Fraunhofer Group for Life Sciences
May 3-5, 2010, Chicago, IL, USA

OTTI Forum
Produktgestaltung mit Funktionsschichten
June 21-22, 2010, Regensburg, Germany

Tag der Wissenschaft
(Day of Science)
"Entdecken – Forschen – Faszinieren"
June 26, 2010, Universität Stuttgart, Germany

IFAT 2010
World's Leading Trade Fair for Water, Sewage, Waste and Raw Materials Management
Fraunhofer Water Systems Alliance (SysWasser)
September 13-17, 2010, München, Germany

BIOTECHNICA
International Trade Fair, Conferences, Partnering and Award for Biotechnology
Fraunhofer Group for Life Sciences
October 5-7, 2010, Hannover, Germany

parts2clean
International Leading Trade Fair for Cleaning in Production and Maintenance Processes
Fraunhofer Cleaning Technology Alliance
October 12-14, 2010, Stuttgart, Germany

BioStar 2010
Science in Exchange
4th Congress on Regenerative Biology and Medicine
October 13-15, 2010, Stuttgart, Germany

K 2010
International Trade Fair No. 1 for Plastics and Rubber Worldwide
October 27 - November 3, 2010, Düsseldorf, Germany

Unitag (University Day)
November 17-18, 2010, Universität Stuttgart, Germany

Checkpoint Zukunft
Day for students
November 29, 2010, Fraunhofer Institutes Center Stuttgart, Germany

Details may be subject to alterations.
Get further information on our seminars and trade fair participations here:
www.igb.fraunhofer.de

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Rupp, S.
"Biochemisches Praktikum für Diplom-Chemiker und Biochemisches Praktikum für Technische Biologen"
Fakultät Chemie,
Fachrichtung Biochemie

Rupp, S.
"Biochemisches Forschungs-Praktikum für Diplom-Chemiker"
Fakultät Chemie,
Fachrichtung Biochemie

Rupp, S.
Beiträge zur Vorlesung "Moderne Methoden in der Biochemie"
Fakultät Chemie,
Fachrichtung Biochemie

Rupp, S.
Beiträge zur Vorlesung "Biochemie II und III"
Fakultät Chemie,
Fachrichtung Biochemie

Rupp, S.
"Ausgewählte Kapitel der modernen Biochemie"
Fakultät Chemie,
Fachrichtung Biochemie

Rupp, S.
"Medizinische und molekulare Diagnostik"
Fakultät Energie-, Verfahrens- und Biotechnik,
Fachrichtung Biochemie

Tovar, G. E. M., Hirth, T.
"Nanotechnologie I – Chemie und Physik der Nanomaterialien"
Fakultät Energie-, Verfahrens- und Biotechnik,
Master Verfahrenstechnik

Tovar, G. E. M., Hirth, T.
"Nanotechnologie II – Technische Prozesse und Anwendungen für Nanomaterialien"
Fakultät Energie-, Verfahrens- und Biotechnik,
Master Verfahrenstechnik

Tovar, G. E. M.
"Produktgestaltung mit Nanomaterialien"
Fakultät Chemie,
Diplom Chemie

Tovar, G. E. M.
"Biofunktionale Oberflächen – Chemie, Struktur und Funktionen"
Fakultät Chemie,
Diplom Chemie

Tovar, G. E. M., Hirth, T.
"Mitarbeiter-Seminar für DoktorandInnen und DiplomandInnen"
Fachrichtung Verfahrenstechnik, Chemie, Technische Biologie

Technische Universität München, Germany

Sieber, V.
"Grundstoffe und Werkstoffe aus der Natur"
Fachrichtung Nachwachsende Rohstoffe

Sieber, V.
"Bioraffinerie und Naturstofftechnologien"
Fachrichtung Nachwachsende Rohstoffe

Sieber, V.
"Biokunststoffe und ihre Herstellung"
Fachrichtung Nachwachsende Rohstoffe

Sieber, V.
"Grundlagen Chemie"
Fachrichtung Nachwachsende Rohstoffe

Sieber, V.
"Spezielle Biotechnologie"
Fachrichtung Nachwachsende Rohstoffe

Universität Heidelberg BZH, Germany

Sohn, K.
Seminar und Praktikum "Nervensystem: Biochemische Analyse neuronaler Proteine und Lipide"
Medizinische Fakultät, Fachrichtung Biochemie

Sohn, K.
Seminar und Praktikum "Eisenstoffwechsel Blut"
Medizinische Fakultät, Fachrichtung Biochemie

Universität Hohenheim, Germany

Trösch, W.
Beiträge zur Vorlesung "Wasser-, Abwasser- und Abfallbehandlung"
Naturwissenschaftliche Fakultät, Fachrichtung Lebensmittelwissenschaft und Biotechnologie

Trösch, W.
"Angewandte Bioverfahrenstechnik: Energie – Grundlagen und technische Beispiele"
Naturwissenschaftliche Fakultät, Fachrichtung Lebensmittelwissenschaft und Biotechnologie

Trösch, W.
Beiträge zur Vorlesung "Water, wastewater and waste management"
Naturwissenschaftliche Fakultät, Fachrichtung Lebensmittelwissenschaft und Biotechnologie

Walles, H.
"Tissue Engineering"
Fachrichtung Ernährungswissenschaften

Universität Tübingen, Germany

Walles, H.
Ringvorlesung "Aspekte der Regenerationsbiologie und -medizin"
Fachrichtung Medizin

Universität Würzburg, Germany

Walles, H.
"Tissue Engineering"
Masterstudiengang Technologie der Funktionswerkstoffe

Scientific cooperations

With universities

Aristotle University of Thessaloniki, Greece

Charles University, Prague, Czech Republic

Comenius University, Bratislava, Slovakia

Escola de Engenharia de Piracicaba (EEP), Brazil

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

Katholieke Universiteit Leuven, Belgium

Kyoto University, Japan

Julius-Maximilians-Universität Würzburg, Germany

Ludwig Institute for Cancer Research, Stockholm, Sweden

Ludwig-Maximilians-Universität München, Germany

Lund University, Lund, Sweden

Medizinische Hochschule Hannover MHH, Germany

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

Rheinisch-Westfälische Technische Hochschule RWTH, Aachen, Germany

Stanford University, USA

Technische Universität Darmstadt, Germany

Technische Universität München, Germany

Technische Universiteit Eindhoven, The Netherlands

Tierärztliche Hochschule Hannover, Germany

Trinity College Dublin, Ireland

Universidad Complutense de Madrid, Spain

Universidad de Sevilla, Spain

Universidade Metodista de Piracicaba (UNIMEP), Brazil

Universita degli Studi di Bari, Italy

Universita degli Studi di Milano, Italy

Universita degli Studi di Milano-Bicocca, Italy

Universität Bremen, Germany

Universität Gießen, Germany

Universität Greifswald, Germany

Universität Halle-Wittenberg, Germany

Universität Hannover, Germany

Universität Heidelberg, Germany

Universität Hohenheim, Germany

Universität Nürnberg-Erlangen, Germany

Universität Stuttgart, Germany

Universität Tübingen, Germany

Universität Wien, Austria

Université de Toulouse, France

University College Dublin, Ireland

University Hospital Lausanne, Switzerland

University of California at Los Angeles, UCLA Department of Surgery, USA

Scientific cooperations

University of Manchester, UK

University of Novi Sad, Novi Sad, Serbia

University of West Hungary, Sopron, Hungary

Univerza v Mariboru, Maribor, Slovenia

With other research organizations

AIT – Austrian Institute of Technology, Wien, Austria

Bundesanstalt für Materialforschung und -prüfung (BAM), Berlin, Germany

Centre de Recerca i Investigació de Catalunya CRIC, Barcelona, Spain

Centre for Process Innovation CPI, Wilton, Redcar, UK

Centro technológica CARTIF, Valladolid, Spain

Chemical Process Engineering Research Institute (CPERI), Thessaloniki, Greece

European Molecular Biology Laboratory EMBL, Heidelberg, Germany

Dalian Institute of Chemical Physics, Dalian, China

Deutsches Krebsforschungszentrum (DKFZ), Heidelberg, Germany

Deutsches Zentrum für Biomaterialien und Organersatz, Stuttgart-Tübingen, Germany

Flanders Institute for Biotechnology (VIB), Belgium

Institut für Textilchemie und Fasertechnik ITCF, Denkendorf, Germany

Institut für Textil- und Verfahrenstechnik ITV, Denkendorf, Germany

Institut Pasteur, Paris, France

Johann Heinrich von Thünen-Institut, Braunschweig, Germany

Johann Heinrich von Thünen-Institut, Hamburg, Germany

Leibniz-Institut für Katalyse e. V., (LIKAT), Rostock, Germany

Leibniz-Institut für Plasmaforschung und Technologie e. V. (INP), Greifswald, Germany

NMI Naturwissenschaftlich-Medizinisches Institut an der Universität Tübingen, Reutlingen, Germany

Norwegian Institute of Food, Fisheries and Aquaculture Research Nofima, Oslo, Norway

Max-Planck-Institut für Festkörperforschung, Stuttgart, Germany

Max-Planck-Institut für Kolloid- und Grenzflächenforschung, Golm, Germany

Max-Planck-Institut für Metallforschung, Stuttgart, Germany

Max-Planck-Institut für Polymerforschung, Mainz, Germany

Meurice Research & Development, Brüssel, Belgium

Research & Development centre Re/genT, Helmond, The Netherlands

Nor-Tek Teknologisenter, Oslo, Norway

Robert-Koch-Institut, Berlin, Germany

Teknologisk Institutt (TI), Oslo, Norway

With hospitals

Blutspendezentrale, Katharinenhospital, Stuttgart, Germany

Katharinenhospital, Stuttgart, Germany

Klinik Schillerhöhe, Gerlingen, Germany

Klinikum Ludwigsburg, Germany

Marienhospital, Stuttgart, Germany

Olgahospital, Stuttgart, Germany

Robert-Bosch-Krankenhaus, Stuttgart, Germany

Universitätsklinikum Düsseldorf, Germany

Universitätsklinikum Lübeck, Germany

Universitätsklinikum Tübingen, Germany

Universitätsklinikum der RWTH Aachen, Germany

With museums

Bayerisches Hauptstaatsarchiv, München, Germany

Deutsches Bergbaumuseum, Bochum, Germany

Deutsches Museum, München, Germany

Deutsches Schifffahrtsmuseum, Bremerhaven, Germany

Germanisches Nationalmuseum, Nürnberg, Germany

Stiftung Preußischer Kulturbesitz, Rathgen-Forschungslabor, Berlin, Germany

Zentrum für Bucherhaltung, Leipzig, Germany

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

Ph. D. theses

Hampel, M.
Aufbau humaner 3D *in vitro* Testsysteme zur Risikobewertung von Nanomaterialien,
Universität Stuttgart

Kluger, P. J.
Induktion morphologischer und physiologischer Reaktionen primärer humaner Hautzellen durch bioinspirierte nano- und mikrostrukturierte Substrate,
Universität Stuttgart

Pusch, J.
Etablierung einer 3D-Darmgewebekultur zur *in-vitro* Untersuchung der Resorption potentieller Wirkstoffe auf Basis einer natürlichen Kollagenmatrix,
Universität Konstanz

Diploma theses

Appelt, A.
Optimierung der Isolations- und Kultivierungsbedingungen von humanen Keratinozyten und Fibroblasten und Aufbau eines Hautäquivalents für eine automatisierte Herstellung,
Fachhochschule Jena

Aubele, S.
Untersuchungen zum Aufbau eines humanen vaskularisierten Hautmodells,
Hochschule Esslingen

Bohem, M.
Identification, purification and characterisation of wildtype and recombinant chitinases,
Universität Stuttgart

Bühler, H.-R.
Auslegung, Bau und Inbetriebnahme eines Laborversuchsstandes zur Erprobung verschiedener Wärmespeichermaterialien und Wärmetauschergeometrien,
Hochschule Reutlingen

Dehling, M.
Erstellung von Reporterstämmen in *Escherichia coli* zur phänotypischen Untersuchung von Biofilmen,
Georg-Simon-Ohm-Hochschule Nürnberg

Dörflinger, M.
Studies of potential virulence factors in the cell wall integrity pathway of the human pathogenic yeast *Candida glabrata*,
Universität Stuttgart

Görner, S.
Betrieb und Optimierung einer Demonstrationsanlage zur anaeroben psychrophilen Abwasserreinigung mit integrierter Mikrofiltration,
Hochschule für Technik und Wirtschaft Berlin

Hoch, E.
Funktionalisierung von Oberflächen mit Galaktose und Amino- oder Carboxylgruppen zur selektiven Kultivierung von primären humanen Keratinozyten,
Hochschule Mannheim

Hoenig, J.
Versuche zur Benetzung von Zellstoffen zwecks Fasergewinnung für die Papierherstellung durch ein innovatives mechanisches Verfahren,
Hochschule Albstadt-Sigmaringen

Hogk, I.
Etablierung einer TLR2, 5 und 9 stabil defizienten Zelllinie und deren Integration in ein 3D Hautmodell: Zur Untersuchung der Rolle von TLRs bei einer HSV-1 Infektion,
Universität Stuttgart

Huben, T.
Immobilisierung des RGDC-Peptids auf plasmamodifiziertem cycloolefinem Polymer,
Fachhochschule Südwestfalen, Iserlohn

Kizilbay, Z.
Empirische Untersuchungen zur enzymatischen Degradation von Chitin,
Universität Stuttgart

Knauer, L.
Modifizierung von formstabilen Kontaktlinsen zur Verringerung der Proteinanlagerung,
Fachhochschule Südwestfalen, Iserlohn

Maierle, J.
Einfluss von plasmafunktionalisierten Substraten auf die Adhäsion, Proliferation und Genexpression von muskuloskelettalen Zellen,
Hochschule Esslingen

Mathias, J.
Untersuchungen zur enzymatischen Gewinnung von Omega-3-Fettsäuren aus Mikroalgen,
Hochschule Anhalt, Köthen

Neumann, M.
Entwicklung von molekular geprägten Polymernanopartikeln zur Gewinnung von bioaktiven Minorkomponenten am Beispiel von α-Tocopherol,
Fachhochschule Gelsenkirchen

Novosel, E.
In vitro Korrosionstests: Vergleichende histologische und molekularbiologische Untersuchungen an humanen Vollhautäquivalenten und exzidierter Humanhaut,
Universität Stuttgart

Ott, J.
Experimentelle Untersuchungen zur Aufkonzentrierung von industriellen Prozess- und Abwässern,
Hochschule für Angewandte Wissenschaften Hamburg

Peetsch, A.
Elektronenspinresonanz-Untersuchungen zur photokatalytischen Aktivität nanoskaliger Titandioxid-Schichten der Anataskristallstruktur,
Fachhochschule Südwestfalen, Iserlohn

Rank, A.
Herstellung von Fluoresceinisothiocyanat-markierten und TNF-beladenen Silica-Kern-Schale-Nanopartikeln für ein endoskopisches System zur Visualisierung von Tumorzellen,
Fachhochschule Südwestfalen, Iserlohn

Rebel, M.
Systematische Untersuchungen zur Unterdrückung der unspezifischen Adsorption von Biomolekülen an Polymeroberflächen,
Fachhochschule Gelsenkirchen

Rettenmaier, S.
Synthese und Charakterisierung von Nanopartikeln mit Aktivester-Oberfläche,
Hochschule Aalen

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

Schneider, E.
Untersuchung der Endothelzellmigration in biochemischen Gradientenfeldern,
Hochschule Mannheim

Schober, L.
Einfluss von amino- und carboxyfunktionalisierten nano- oder mikrostrukturierten Oberflächen auf primäre humane Fibroblasten,
Hochschule Esslingen

Schulz, D.
Etablierung einer universellen Plattform für globale Genexpressionsstudien in Pro- und Eukaryoten,
Universität Stuttgart

Schumacher, A.
Entwicklung von Quervernetzern zur *in-situ* Polymerisation von Polyethylenglycol zum Aufbau synthetischer dreidimensionaler Gewebestrukturen,
Hochschule Mannheim

Schwegler, S.
Aufbau einer Subkutis mit humanen Adipozyten zur Erweiterung eines Vollhautäquivalents,
Universität Stuttgart

Sesé, J. L. C.
Study of a thermal water desalination technology with a special focus on the vacuum generation by gravitation,
TU Braunschweig

Thurow, I.
Präparation und Charakterisierung ultradünner Protein-einschließender Funktionsschichten für den Proteinübertrag durch den LASER-Induced Forward Transfer-Prozess (LIFT),
Universität Stuttgart

Uebel, D.
Entwicklung einer Screeningmethode für molekulares Prägen von Polymeren mit Peptiden,
Fachhochschule Südwestfalen, Iserlohn

Votteler, M.
Vergleichende Resorptionsstudien zwischen einem erweitertem 3D Darmgewebemodell und einem 2D Zellkultursystem,
Universität Hohenheim

Wegner, U.
Steigerung der nassoxidativen Wirkung von Ozon zur Reduktion von organischer Belastung in wässrigen Medien durch die Kombination mit Ultraschall,
Fachhochschule Gießen-Friedberg

Wilke, J.
Optimierung von Wachstum und Lipidbildung von Mikroalgen im Flat Panel Airlift Reaktor für die Algenölproduktion,
Fachhochschule Weihenstephan

Wursthorn, P.
Entwicklung einer Membran-Elektroden-Einheit für die Direkt-Ethanol-Brennstoffzelle basierend auf sulfoniertem Polyetheretherketon,
Hochschule Furtwangen

Master theses

Aleman, C.
Investigations on the effects of ultrasound processing on biological contamination in metal working fluids,
Universität Stuttgart

Arulnesan, R.
(protected)
Ruhr-Universität Bochum

Campos, A.
Study of the electrolytic precipitation behavior of magnesium-ammonium phosphate for generation of a high quality fertilizer from wastewater,
Universität Stuttgart

Foshag, D.
Expression und Aufreinigung einer rekombinanten Variante des humanen Interferon beta aus einem prokaryotischen Expressionssystem,
Hochschule Furtwangen

Gfell, M.
Entwicklung eines Diagnosechips für den Nachweis humanpathogener Pilze auf Spezies-Ebene,
Universität Konstanz

Heyden, E.
Einfluss von Plasmen auf Polymeroberflächen,
Universität Stuttgart

Khan, S. M.
Design and realization of microwave slotted waveguide array antenna to determine radiation
Patterns & array efficiency for Industrial, Scientific and Medical (ISM) applications,
Polytechnic University of Turin, Italy

Langhof, T.
Elaboration of fundamentals for the conception of a modular thermo chemical heat storage system,
Universität Stuttgart

Ott, J.
Entwicklung einer LC-MALDI basierten Analysemethode für die Biomarkerforschung,
Hochschule Reutlingen

Pusch, K.
Entwicklung eines Bioreaktors zum Aufbau eines *in vitro* Fasziamodells,
Hochschule Albstadt-Sigmaringen

Rahadi, K. D.
Inhibitory effect of ammonia on the anaerobic treatment of high protein wastewater,
Universität Stuttgart

Reutlinger, K.
Methodischer Ansatz zur Untersuchung der Nanotoxikologie auf transkriptioneller Ebene anhand primärer Keratinozyten,
Technische Fachhochschule Berlin

Tubaon, M.
Splitting of stable emulsions by electrolytic precipitation,
Universität Stuttgart

Turgut, C.
Preparation of functional polymer films by combined plasma glow discharge and UV polymerization,
Universität Stuttgart

Bachelor theses

Bieligmeyer, M.
Herstellung und Charakterisierung von *in situ*-gelierbaren Hydrogelen basierend auf Poly(Ethylenglykol) als synthetische extrazelluläre Matrix,
Hochschule Reutlingen

Bucher, M.
Erzeugung nanostrukturierter Oberflächen auf Cyclo-Olefin-Polymerfolien durch Sprühapplikation von Nanopartikeln,
Fachhochschule Reutlingen

Fieting, C.
(protected)
Fachhochschule Hannover

Fink, K.
Charakterisierung und Eignung von Mikroorganismen für den Gewässer- und Trinkwasserschutz,
Fachhochschule Villingen-Schwenningen

Henning, A.
Vorfraktionierung komplexer Proteome mit Hilfe von oberflächenfunktionalisierten Mikro- und Nanopartikeln für die klinische Protein-Biomarkerforschung,
Fachhochschule Südwestfalen, Iserlohn

Kovacevic, A.
Plasmachemische Behandlung von polymeren Vliesstoffen für Anwendungen in der Zellanalytik,
Hochschule Albstadt-Sigmaringen

Lang, R.
Plasmachemische Strukturierung von Fluor-Polymerfolien als Trägermaterial für Algenphotobioreaktoren,
Hochschule Offenburg

Morawietz, T.
Enzym-Silika-Nanohybridpartikel Darstellung und Funktionscharakterisierung für nanostrukturierte Funktionsmaterialien,
Fachhochschule Südwestfalen, Iserlohn

Röhm, R.
Entwicklung eines Prozesses zur selektiven Abtrennung eines organischen Lösungsmittels aus einem erdölhaltigen Gemisch durch einen mikrowellenbasierten Verdampfungsprozess,
Hochschule Offenburg

Taichrib, K.
Untersuchungen zum Aufbau eines bovinen 3D-Hautmodells und Einfluss von Gefrierschutzadditiven bei der Kryokonservierung,
Hochschule Furtwangen

Vojacek, S.
Untersuchungen zur Behandlung von Kantinenabwässern mit hohen Anteilen an organischen Belastungen insbesondere Fetten und Reinigungsmitteln,
Universität Stuttgart

Student research studies

Fessl, S.
Optimisation of a collagen type I matrix for the cultivation of human microvascular endothelial cells and dermal fibroblasts,
Universität Stuttgart

Möller, Y.
Klonierung unterschiedlicher Selektionsmarker in ein mammalisches Expressionsvektor-System,
Universität Stuttgart

Internship reports

Aßmann, C.
Einfluss von strukturierten Oberflächen auf primäre humane Endothelzellen,
Hochschule Esslingen

Hummel, V.
Klonierung von Activator Protein 1 und Interferon stimulated response element in ein Reportergenplasmid,
Hochschule Esslingen

Jaaks, P.
Untersuchung verschiedener Biomaterialien in Bezug auf die Cytotoxizität sowie die Adhäsion, Proliferation und Selektion verschiedener primärer Zellen,
Universität Hamburg

Legner, S.
Entwicklung einer Screeningmethode zur Identifikation neuer Stämme für die Dicarbonsäurebildung,
Hochschule Esslingen

Lipinski, N.
Fermentation von *Candida tropicalis* zur Herstellung langkettiger Dicarbonsäuren,
Hochschule Esslingen

Maierle, J.
Untersuchung primärer humaner Fibroblasten,
Hochschule Esslingen

Rapp, S.
Enzymatische Degradation von Lignocellulose zur Gewinnung von Monosacchariden,
Hochschule Esslingen

Schwinghammer, M.
Validierung eines automatisierbaren Bioreaktorsystems,
Universität Hohenheim

Publications

Books and reports

Baier, M.
Ultrabarriereschichten.
In: Eugen G. Leuze Verlag, 2009: Jahrbuch der Oberflächentechnik, Band 65: 109-117
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Borchers, K.; Genov, S.; Gruber-Traub, C.; Niedergall, K.; Plankalayil, J.; Pufky-Heinrich, D.; Riegler, J.; Schreiber, T.; Tovar, G. E. M.; Weber, A.; Wojciukiewicz, D.
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Kluger, P. J.
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In: Springer Verlag, 2009: Bioreactor systems for tissue engineering, Series: Advances in Biochemical Engineering Biotechnology, Vol. 112: 29-37
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Host-Pathogen Interactions: Methods and Protocols.
Humana Press, 2009: Series: Methods in Molecular Biology, Vol. 470
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Rupp, S.
Introduction: fungal pathogens.
In: Humana Press, 2009: Host-Pathogen Interactions: Methods and Protocols, Series: Methods in Molecular Biology, Vol. 470: 69-70
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Sohn, K.; Rupp, S.
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Journal papers

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Chemie Ingenieur Technik 81 (10): 1591-1597

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Luo, S.; Poltermann, S.; Kunert, A.; Rupp, S.; Zipfel, P. F. (2009)
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