Fraunhofer IGB

FRAUNHOFER INSTITUTE FOR INTERFACIAL ENGINEERING AND BIOTECHNOLOGY IGB

ANNUAL REPORT 2014 | 15

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CONTENTS

"THE FRAUNHOFER IGB – RESEARCH AND DEVELOPMENT IN FOUR LOCATIONS"

The major challenges of the twenty-first century – such as fighting diseases and hunger, and ensuring the global supply of water, raw materials and energy – cannot be handled by any one individual. A collaboration of competent partners is required. Aside from the Fraunhofer Institute's cooperation with industry, the collaboration with universities is of crucial importance. A central partner of the Fraunhofer IGB is the University of Stuttgart, with which, not only is there a close relationship in research and teaching with its Institute of Interfacial Process Engineering and Plasma Technology which I am the head of, but also with many other institutions. As a result, we could in the past year, in cooperation with other institutes of the University of Stuttgart, open the project house "NanoBioMater", funded by the Carl Zeiss Foundation as well as start several projects funded by the Ministry of Science, Research and the Arts as part of the research program "Bioeconomy Baden-Württemberg."

To strengthen the fields of medicine, chemistry and energy, we have been in close collaboration with the universities of Würzburg, Munich and Halle-Wittenberg since 2009, and have initiated project groups in Würzburg, Straubing, and Leuna through financial support of the Free State of Bavaria and the *Land* of Saxony-Anhalt.

While the Project Group BioCat in Straubing successfully went through the evaluation process in 2013, the Project Group "Regenerative Technologies in Oncology" in Würzburg and at the Fraunhofer CBP located in Leuna were evaluated in 2014. The review board, comprised of a high-level committee of representatives from science and industry, confirmed the success of their work. Thus, provisions were given so that all three sites could be transferred to federal and state-level funding at the beginning of 2015; they now function as branches of the Fraunhofer IGB.

The Project Group "Regenerative Technologies in Oncology" in Würzburg was expanded into the Translational Center "Regenerative Therapies for Oncology and Musculoskeletal Diseases" through financial support from the Free State of Bavaria. The Translational Center covers the entire value chain of regenerative therapies – from product development of new cell-based transplants and biologized medical products, preclinical tests, up to their approval. Therefore, the business area medicine of the Fraunhofer IGB as well as the Fraunhofer Group for Life Sciences is permanently strengthened.

Since 2009, the Project Group BioCat has been contributing to the development of new catalysts and catalytic processes to empower the business areas chemistry and energy. With financial support from the Free State of Bavaria, a second pillar alongside the core competence "biological and chemical catalysis", is currently being established to work on the development of chemical energy storage. Together with the Fraunhofer UMSICHT's Sulzbach-Rosenberg branch the Straubing branch forms the Center for Energy Storage, which develops technologies and provides expertise from system analysis via the development of processes and components to the implementation of chemical and thermal energy storage.

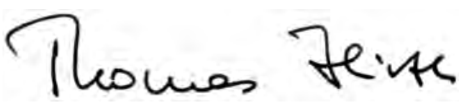
In addition to the successful evaluation last year, the Fraunhofer Center for Chemical-Biotechnological Processes CBP could achieve another major success. As a result of the successful interim evaluation of the leading-edge BioEconomy cluster, more funding now flows to its key partner, the Fraunhofer CBP, which is one of the core partners of the pinnacle group BioEconomy. Together with associates from industry and science, the Fraunhofer CBP is working intensely on the scaling of fractionation and conversion processes for the production of chemical products from renewable resources and their transfer to the demonstration scale. With the construction of a pilot plant for the cultivation of microalgae and further facilities for the chemical conversion of renewable raw materials into chemical products as well as the reprocessing of reaction mixtures, the instrument-based equipment at the Leuna branch could be extended significantly.

The Fraunhofer IGB has been dedicated to the topic of sustainability since 2011. With the publication of the second sustainability report of the five Stuttgart Fraunhofer Institutes, under the auspices of the Fraunhofer IGB, and the first sustainability report of the Fraunhofer-Gesellschaft, the year 2014 was also very special in the area of sustainability. As the first of four major, non-university research institutions in Germany, the Fraunhofer-Gesellschaft launched a sustainability report in October 2014 and it continues to pursue an agenda of long-term sustainability management.

Due to the strong focus of our business areas and core competences on social areas of need and the principle of sustainability, the Fraunhofer IGB was able to develop optimally in the past year and we were able to prepare well for the challenges the Institute will have to face in the coming years. In addition to the further advancement of our research and development activities, we have especially devoted ourselves in the last year to long-term staff development and jointly developed, in a participatory process, the leadership guidelines for the Institute. Next to our mission and the Institute's strategy, these guidelines are an important element for cooperation in the Institute as well as a reliable practical guide for managers and they also give guidance to staff.

My staff and I would be very pleased if we have piqued your interest in our research and development work with this annual report and we would welcome if you would cooperate closely with us in the future. With you, we want to lastingly shape the future of the regions, of Germany and of Europe through innovative developments.

In this sense, I hope you enjoy reading the new annual report of the Fraunhofer IGB and look forward to your suggestions and cooperation.



Best Regards
Thomas Hirth

FRAUNHOFER IGB IN PROFILE 2014

9 Fraunhofer Alliances

2 Fraunhofer Groups

5 Departments

3 Branches

20 Members of Advisory Board

27 Nations

45% Female representation

5 Prizes and awards

125 Students

46 Doctorate students

365 Fraunhofer employees

84 University employees

449 Employees

12 Associate lecturers

7 BoGy high school students

15 Apprentices

12.4 Mio € Personnel costs

7.9 Mio € Non-personnel costs

77% Own revenues

1.4 Mio € Investments

22.7 Mio € Total budget

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 the 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. Some 390 experts in the fields of chemistry, physics, biology and engineering work effectively together at the Fraunhofer IGB, its branches at Leuna, Straubing and Würzburg, and our Stuttgart University IGVP partner institute. 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 environmental technology.

Competences

Departments in Stuttgart

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

Branches of the institute

- Fraunhofer Center for Chemical-Biotechnological Processes CBP, Leuna branch
- Bio-, Electro- and Chemocatalysis BioCat, Straubing branch
- Translational Center "Regenerative Therapies for Oncology and Musculoskeletal Diseases", Würzburg branch

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, society and the environment."

EVER BETTER TOGETHER.

ADVISORY BOARD OF THE FRAUNHOFER IGB

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

Members

Dr. med. Susanne Arbogast
Roche Diagnostics GmbH

Dr. Gerd Eßwein
Freudenberg New Technologies SE & Co. KG

Ltd. Ministerialrätin Dr. Renate Fischer (until April 2014)
Ministry of Science, Research and the Arts of the State of Baden-Württemberg

Swantje Nilsson
Federal Ministry of Food and Agriculture (BMEL)

Prof. Dr. Matthias Frosch
Faculty of Medicine, University of Würzburg

MinDirig Dipl.-Ing. Peter Fuhrmann
Ministry of the Environment, Climate Protection and the Energy Sector of the State of Baden-Württemberg

MinDirig Dr. Fritz Holzwarth
(until April 2014)
Federal Ministry for the Environment, Nature Conservation, Building and Nuclear Safety (BMUB)

Dr.-Ing. Bernd Krause
Gambro Dialysatoren GmbH

Dr. Henk van Liempt
Federal Ministry of Education and Research (BMBF)

Dr. Christian Naydowski
VOITH Paper Holding GmbH & Co. KG

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

Prof. Dr. Dr. h. c. Ralf Riedel
Dispersive Solid Group, TU Darmstadt

Prof. Dr. techn. Günter Scheffknecht
Institute of Combustion and Power Plant Technology, University of Stuttgart

Dipl.-Ing. Otmar Schön
HYDAC Technology GmbH

MinR Dr. Joachim Wekerle
Ministry of Finance and Economics of the State of Baden-Württemberg

Dr. Günter Wich
Wacker Chemie AG

Prof. Dr. Karl-Heinz Wiesmüller
EMC microcollections GmbH

Dr. Wieland Wolf
ProBioGen AG

Dr. Markus Wolperdinger
(Chair)
Linde Engineering Dresden GmbH

Permanent guests

Prof. Dr. Herwig Brunner
(Former Director of the Fraunhofer IGB)

Prof. Dr. Dieter Jahn
(Chair of Advisory Board 1999 – 2013)

SERVICES AND INFRASTRUCTURE

Our contract R&D services range from natural sciences and engineering basic research to the development of new applications in laboratory, technical, and pilot plant scale; including the design, construction, and testing of pilot plants. We also offer patent and market surveys, feasibility studies and comprehensive consultancy in our areas of expertise as well as analysis and testing. We provide seminars and workshops for executives and introduce young students to the fascinating world of science and technology.

Infrastructure and laboratory equipment

The Fraunhofer IGB has modern laboratories equipped with the latest technology. A new pilot plant building is scheduled for completion mid-2015. Our central storage facilities for chemicals and hazardous substances are shared with the other institutes on the Stuttgart Fraunhofer campus.

Quality systems

At the Fraunhofer IGB, we ensure by established and standardized processes and procedures that the quality of our services and products meet the respective requirements. A quality management system ensures that our tests are accredited in accordance with DIN EN ISO/IEC 17025. A quality assurance system ensures that legal guidelines of Good Manufacturing Practice and Good Laboratory Practice (GMP/GLP) are met.

Accredited testing

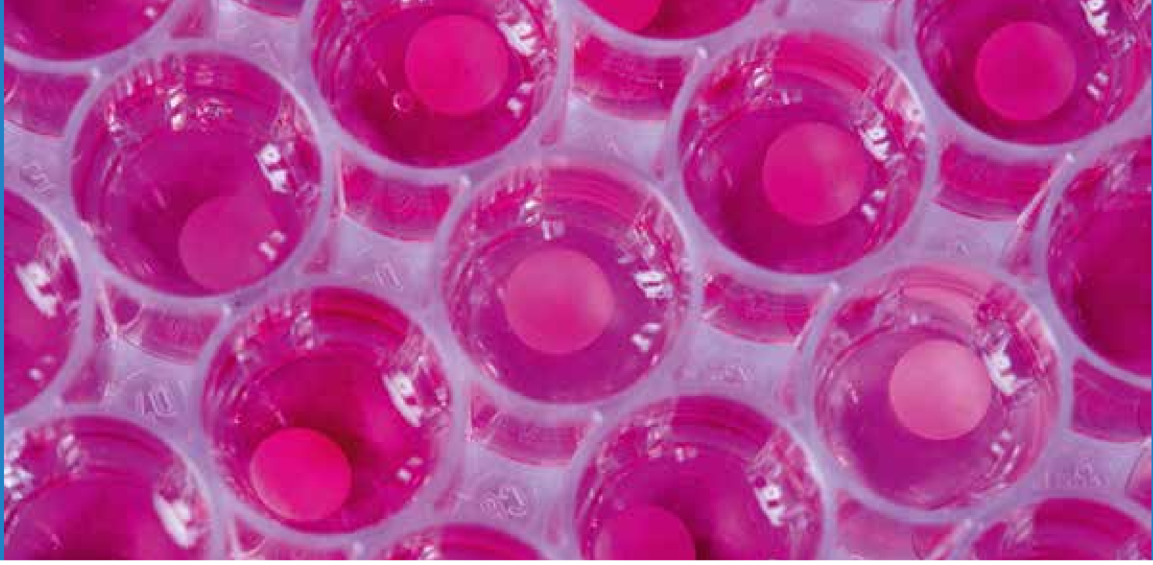
The accreditation of selected reference laboratories and test procedures of our analytics guarantees that our proprietary, in-house test methods and procedures are sufficiently validated and that the quality of our tests is assured even where no standardized methods are available.

The following analytical methods and test procedures are accredited according to DIN EN ISO/IEC 17025:

- High-performance liquid chromatography (HPLC)
- Ion chromatography (IC)
- Gas chromatography (GC, GC/MS)
- Atomic emission spectrometry (ICP-OES)
- Electron spectroscopy for chemical analysis (ESCA/XPS)
- In-vitro cytotoxicity testing of medical devices
- In-vitro phototoxicity testing of solutions and substances

Accredited biocompatibility and phototoxicity testing

We perform tests for in-vitro cytotoxicity of medical devices according to DIN EN ISO 10993-5 using cell lines or our in-house designed 3D skin equivalent. Additionally, in vitro phototoxicity testing was included in the accreditation report in 2014. With our in-house methods we can investigate solutions and substances with respect to their phototoxic potential. The test method is in accordance with the OECD Guideline 432 and the INVITTOX Protocol no 121. The investigation of the potential photoactive substances is performed on our three-dimensional skin model.



Good laboratory practice (GLP) test facility

Our area of expertise 9 GLP test facility ("Cell-based test systems for the determination of biological parameters") is used in research and development projects for investigating different biological parameters of samples/substances using cell-based assays. Examples are the testing of bioactivity and immunogenicity, the screening of TLR agonists/antagonists and antimicrobial substances as well as the detection of pyrogens and microbial residues (pathogen-associated microbial patterns).

GMP unit for manufacturing of clinical materials

The manufacturing of medical devices, investigational medicinal products (IMPs) and cell-based and tissue engineering products (e.g. ATMPs) for clinical trials requires processes according to Good Manufacturing Practice (GMP). We develop GMP-compliant manufacturing processes in our 215 m^2 certified GMP unit in Stuttgart – also for collaborative development with partners from industry. Different manufacturing authorizations (collagen, cartilage) have already been granted.

Special services

Physico-chemical analytics

quality control, food analysis, trace analysis, analysis of residues, environmental analytics, water analysis

High resolution 400 MHz NMR analytics

molecular structure elucidation, reaction monitoring, development of novel experimental NMR methods, low temperature analytics

Surface and particle analytics

characterization of chemical, physical and morphological properties of surfaces, thin layers, powders and particles

Microbial evaluation

testing of antimicrobial effects and photocatalytic properties of surfaces

Biochemical and molecular biological analytics

diagnostic microarrays, RNA and protein expression profiles, protein analysis using MALDI-TOF/TOF mass spectrometry (also quantitative)

Cell biology analysis

cell characterization, single cell preparation/microdissection, flow cytometric analyses, quality and sterility control of tissue engineering products

Cell-material interactions

testing of cytotoxicity/biocompatibility of medical devices, assessment of phototoxicity of substances and solutions, evaluation and testing of chemicals (REACH) and nanomaterials

For detailed information on our analytical services offer, please visit:
www.igb.fraunhofer.de/analytics

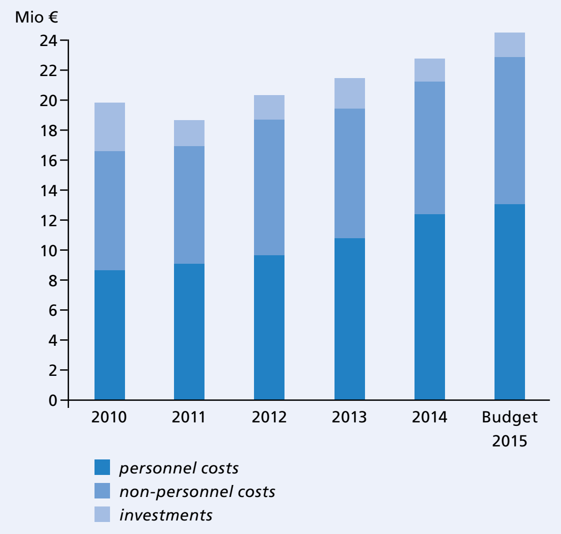
KEY FIGURES

Budget of Fraunhofer IGB

The total budget for 2014 amounted to 22.7 million euros, of which 21.3 million euros were allocated to the operational budget (personnel costs: 12.4 million euros; non-personnel costs: 7.9 million euros). A total of 1.4 million euros was spent on investments.

77 percent of the operational budget was financed from the Fraunhofer IGB's own revenues generated from contract research projects. 34 percent of the Institute's revenues came directly from industry.

Development of budget



Revenue from contract research 2014

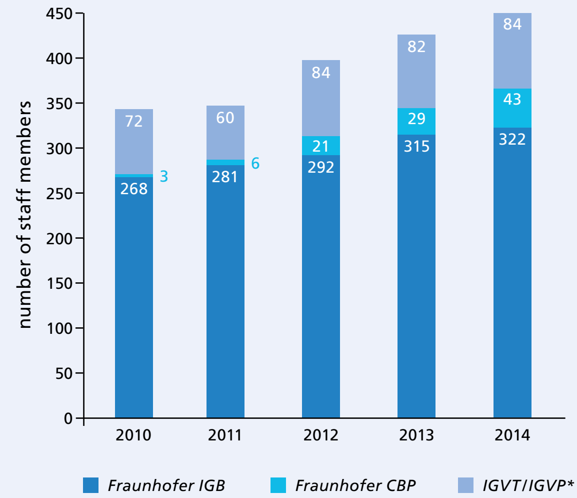
Personnel

At the end of 2014, the Fraunhofer IGB in Stuttgart and its project groups in Straubing and Würzburg had a staff of 322 of which some 90 percent were scientific or technical employees. Women made up 50 percent of the total. The Fraunhofer CBP in Leuna was able to expand its staff once more, giving a year-end headcount of 43 (proportion of women: 40 percent).

The Institute of Interfacial Process Engineering and Plasma Technology IGVP at the University of Stuttgart counted a staff of 84 as at December 31, 2014, predominantly scientists and doctorate students as well as technical staff and student research assistants. Women constituted 31 percent of the total.

The Fraunhofer IGB, CBP and IGVP employees work closely together and have remarkably culturally diverse backgrounds, with 40 members of staff coming from 27 different nations outside Germany.

Development of staff members



* Stuttgart University's Institute for Plasma Research IPF was integrated into the Institute for Interfacial Engineering IGVT in January 2013. Numbers since 2013 refer to the merged Institute of Interfacial Process Engineering and Plasma Technology IGVP.

Staff composition as at December 31, 2014	Fraunhofer IGB	Fraunhofer CBP	IGVP
Scientists	90	9	17
Technical staff	73	16	13
Doctorate students	4	–	42
Administrative and secretarial staff	32	2	3
Apprentices	9	2	4
Scholarship holders	7	–	1
Work students/master students/student apprentices	19	8	(7)
Student research assistants	88	6	4
	322	**43**	**84**

ORGANIZATION CHART

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Dr. Achim Weber
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- Inorganic Interfaces and Membranes
- Particle-based Systems and Formulations
- Plasma Technology and Thin Films
- Polymeric Interfaces, Biomaterials and Biopolymers

MOLECULAR BIOTECHNOLOGY

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- Infection Biology and Array Technologies
- Functional Genomics
- Molecular Cell Technologies
- Enzyme, Strain and Process Development for Biotechnology
- Analytics

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- Heat and Sorption Systems
- Physico-chemical Water Technologies
- Nutrients Management
- Aseptic Technologies
- Prototype Development

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- Algal Technology
- Bioprocess Engineering
- Bioenergy
- Integrated Water Management

CELL AND TISSUE ENGINEERING

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Prof. Dr. Katja Schenke-Layland
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- Biomaterials and In-vitro Test Systems
- Cardiovascular Tissue Engineering, Bioimaging and Bioreactors
- GMP Production of Cell-based Products

BRANCHES OF THE INSTITUTE

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Translational center "Regenerative Therapies", Würzburg
Prof. Dr. Heike Walles
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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 with various universities and non-university research institutes, as well as interdisciplinary collaboration with 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 sustainability standpoints.

Networking with universities

Basic research is a must for the applications of tomorrow. Thus the Fraunhofer IGB maintains close contacts with neighboring universities, both through scientific cooperation and through the professorial and other teaching commitments of Fraunhofer employees. Our project groups have enabled us to extend our scientific network to locations outside of Stuttgart, including the USA. The Fraunhofer IGB is particularly closely allied to the Institute of Interfacial Process Engineering and Plasma Technology IGVP at the University of Stuttgart, which is chaired by Fraunhofer IGB director Prof. Hirth.

- **Priv.-Doz. Dr. Susanne Bailer**
  Private lecturer in the Faculty of Energy Technology, Process Engineering and Biological Engineering at the University of Stuttgart
- **Dr. Kirsten Borchers**
  Associate lecturer in the Faculty of Energy Technology, Process Engineering and Biological Engineering at the University of Stuttgart
- **Prof. Dr. Dieter Bryniok**
  Professor of Environmental Biotechnology at Hamm-Lippstadt University of Applied Sciences
- **Prof. Dr. Thomas Hirth**
  Professor, chair and director of the Institute of Interfacial Process Engineering and Plasma Technology IGVP at the University of Stuttgart
- **Prof. Dr. Petra Kluger**
  Professor of Tissue Engineering at Reutlingen University, Faculty of Applied Chemistry
- **Dr. Christian Oehr**
  Associate lecturer in the Faculty of Energy Technology, Process Engineering and Biological Engineering at the University of Stuttgart
- **Priv.-Doz. Dr. Steffen Rupp**
  Private lecturer in the Faculty of Energy Technology, Process Engineering and Biological Engineering at the University of Stuttgart
- **Prof. Dr. Katja Schenke-Layland**
  Professor of Biomaterials in Regenerative Medicine at the Department of Women's Health, Research Institute for Women's Health at the Eberhard Karls University Tübingen;
  Adjunct Associate Professor at the Department of Medicine/Cardiology at the University of California Los Angeles (UCLA), Los Angeles, CA, USA

- **Dr.-Ing. Ursula Schließmann**
  Teaching activity in the Faculty of Energy Technology, Process Engineering and Biological Engineering at the University of Stuttgart
- **Prof. Dr. Volker Sieber**
  Professor and chair of Chemistry of Biogenic Resources at the Technische Universität München
- **Prof. Dr. Günter Tovar**
  Adjunct professor and private lecturer in the Faculty of Energy Technology, Process Engineering and Biological Engineering at the University of Stuttgart;
  Deputy director of the Institute of Interfacial Process Engineering and Plasma Technology IGVP at the University of Stuttgart
- **Prof. Dr. Heike Walles**
  Professor and chair of Tissue Engineering and Regenerative Medicine at the University of Würzburg

Fraunhofer Sustainability Network

Sustainable development is arguably the key political objective of our time. What sustainability means in concrete terms for the Fraunhofer-Gesellschaft was defined early on by the society's Sustainability Network, to which over 20 institutes belong. The Fraunhofer IGB was significantly involved in this process, with Prof. Thomas Hirth acting as spokesman of the network. Project results fed into the compilation of a guide for sustainability reporting within the Fraunhofer-Gesellschaft according to the internationally recognized Global Reporting Initiative (GRI) standard. In 2014, the first sustainability report of the Fraunhofer-Gesellschaft was published. Thanks to its vanguard role in the German research landscape, Fraunhofer is coordinating a joint project designed to provide a framework for implementing internal sustainability management. Please, read more about these latest developments in the highlights chapter on page 32.
www.nachhaltigkeit.fraunhofer.de

Fraunhofer International Business Development (IBD) Network

International cooperations and joint development activities with globally active partners are also of strategic importance for the Fraunhofer-Gesellschaft. The Fraunhofer IGB is an active member of the Fraunhofer-Gesellschaft's International Business Development Network, where various Fraunhofer Institutes exchange views on specific issues regarding cooperation with international partners. Best-practice examples serve as the basis for an even more efficient use of resources when initiating and pursuing cooperation projects. The network is in close contact with the International Business Development of the Fraunhofer-Gesellschaft.

Fraunhofer EU Network

The EU Network is a platform accessible to all Fraunhofer employees where they can exchange information and experience both with regard to strategic aspects of funding and how to handle application and tendering procedures effectively, as well as on how to ensure the smooth implementation of EU-financed projects.

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

The Fraunhofer IGB is a member of the EU Working Group for Research and Technological Development Organizations (RTOs) in Baden-Württemberg, which aims to promote the regional exchange of information concerning EU funding for non-university research establishments.

THE FRAUNHOFER CBP'S NETWORKING ACTIVITIES

Leading-edge BioEconomy Cluster

The leading-edge BioEconomy Cluster integrates research and industrial activities relevant to the bioeconomy in Central Germany. The cluster's core objective is the sustainable value creation from non-food biomass such as wood as input for the production of materials, chemical products and energy. The Fraunhofer CBP assumes a pivotal role in scaling up and industrial implementation of the production processes developed.
www.bioeconomy.de

Science Campus Halle – Plant-Based Bioeconomy (WCH)

The Science Campus Halle (WCH) pursues the systematic and sustained development of a multi-disciplinary center for plant-based bioeconomy. The WCH thus provides an important base for future applications such as those implemented industrially in the neighboring regional leading-edge BioEconomy cluster, as well as interdisciplinary-trained professionals for industry. The Fraunhofer CBP is an associate member of the WCH.
www.sciencecampus-halle.de

Competence Center for Wood Composites and Wood Chemistry (Wood k plus)

The Competence Center Wood k plus is one of the leading research institutes in the fields of wood composites and wood chemistry. The Fraunhofer CBP is a partner in the COMET program (Competence Centers for Excellent Technologies), where it contributes its expertise in lignocellulose fractionation and the development of biotechnological and chemical processes.
www.wood-kplus.at

FRAUNHOFER GROUPS AND ALLIANCES

Fraunhofer Institutes working in related subject areas cooperate as groups, foster a joint presence on the R&D market and help define the Fraunhofer-Gesellschaft's business policy. Institutes or departments of institutes with complementary competences collaborate in the form of Fraunhofer "alliances" to develop business areas together and offer market solutions along the entire value chain. The Fraunhofer IGB is an active member of the Fraunhofer Group for Life Sciences and an associated institute of the Fraunhofer Group for Materials and Components – MATERIALS due to its strong focus on materials science. Furthermore, it is a member of various Fraunhofer Alliances and optimally integrated within the Fraunhofer network.

Fraunhofer Groups

Fraunhofer Group for Life Sciences
www.lifesciences.fraunhofer.de

Fraunhofer Group for Materials and Components – MATERIALS (associated institute)
www.vwb.fraunhofer.de

Fraunhofer Alliances

Fraunhofer Building Innovation Alliance
www.bau.fraunhofer.de

Fraunhofer Big Data Alliance
www.bigdata.fraunhofer.de

Fraunhofer Energy Alliance
www.energie.fraunhofer.de

Fraunhofer Food Chain Management Alliance
www.fcm.fraunhofer.de

Fraunhofer Nanotechnology Alliance
www.nano.fraunhofer.de

Fraunhofer Photocatalysis Alliance
www.photokatalyse.fraunhofer.de

Fraunhofer Polymer Surfaces Alliance POLO®
www.polo.fraunhofer.de

Fraunhofer Cleaning Technology Alliance
www.allianz-reinigungstechnik.de

Fraunhofer Water Systems Alliance (SysWasser)
www.syswasser.de

In addition, Fraunhofer Institutes carry out joint activities within Fraunhofer internal research programs. Examples of IGB involvement are the lighthouse projects "Cell-free Bioproduction", "Theranostic Implants", "Critical Rare Earths" and "E^3-Production".

For further information on our networking activities please visit:
www.igb.fraunhofer.de/network

HIGHLIGHTS 2014

PROJECTS, RESEARCH GROUPS, COLLABORATIONS

Project groups become institute branches

In the last five years three project groups were set up at the Fraunhofer IGB – in Leuna, Straubing and Würzburg. With the start-up financing by the relevant federal states having come to an end, and with the groups having been successfully evaluated in 2013 and 2014, in 2014 all three project groups were transferred over to the combined federal and state-level financing arrangements (*Bund-Länder-Finanzierung*) of the Fraunhofer-Gesellschaft, thereby becoming permanent branches of the Fraunhofer IGB.

The setting-up of the Fraunhofer Center for Chemical-Biotechnological Processes CBP at the Leuna chemical park, made possible by the *Land* of Saxony-Anhalt and by various project funding arrangements, became official on April 1, 2009, and the groundbreaking followed in December 2010. On October 2, 2012, the new building was inaugurated in the presence of Federal Chancellor Angela Merkel. In May 2014 the project group at the CBP, under the leadership of Gerd Unkelbach, was given a positive evaluation.

The Fraunhofer project group BioCat, financed by the Free State of Bavaria, began its work in August 2009 and in 2012 celebrated the inauguration of the new laboratory building in the Schulgasse in Straubing. The project group, led by Prof. Dr. Volker Sieber, received a positive evaluation as early as the start of 2013. At the end of 2013, BioCat also received a notification of funding for the "Center for Energy Storage" at the Straubing site; since then, the Free State has been continuing to provide funding for the Center and will do so until the five-year period ends.

There is also news from the IGB site in Würzburg. Following a positive evaluation of the project group "Regenerative Therapies in Oncology" led by Prof. Dr. Heike Walles this project group, which has been financed by the Free State of Bavaria since 2009, has also been included in the combined federal and state-level financing arrangements of the Fraunhofer-Gesellschaft. Thanks to additional funding from Bavaria, in mid-July 2014 the project group became part of the new Fraunhofer Translational Center "Regenerative Therapies for Oncology and Musculoskeletal Diseases". The Free State is funding the Center's work over a period of five years with a sum of ten million euros; the funding notification was issued in November.

Pilot plant for isobutene production on an industrial scale 1

Last year the Fraunhofer IGB further developed its cooperation activities with partners in industry and research. In collaboration with Global Bioenergies GmbH, an industrial pilot plant will be set up at the Fraunhofer CBP in Leuna for the manufacture of isobutene from biogenic raw materials. The Leipzig-based biotechnology company is linked to the IGB in the BioEconomy leading edge cluster. Within the cluster, research facilities and companies work together to play an active part in shaping the transition from fossil-based raw materials to renewable ones. It is planned that, in the future, up to 100 metric tons of isobutene will be produced in the pilot plant each year. This industrial base material is used, for example, for the manufacture of plastics and fuels. The German Federal Ministry of Education and Research (BMBF) is funding the project, set to last three years, with 5.7 million euros.

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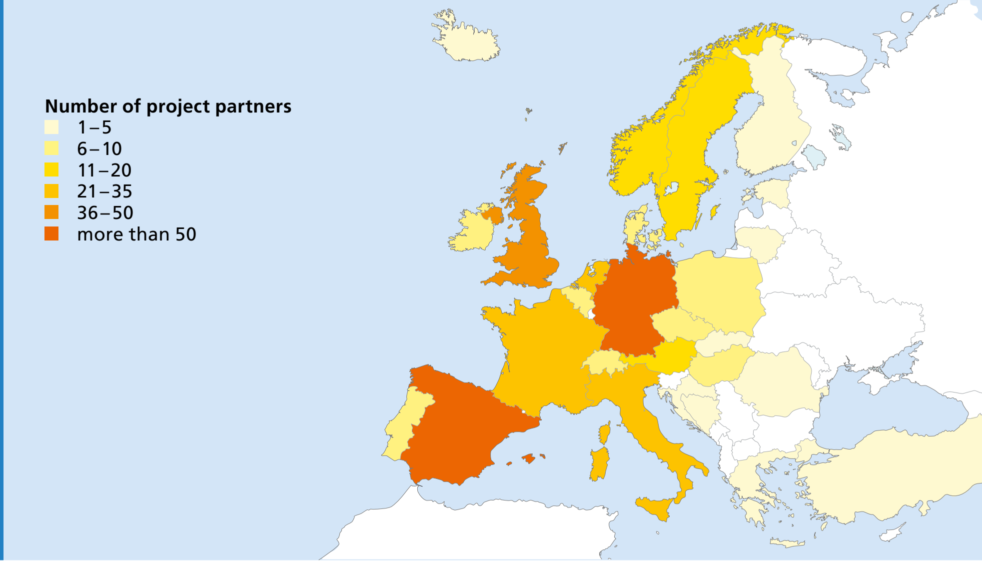
Production of collagen implants for treating cartilage damage 2

In the medical research field, the Department of Cell and Tissue Engineering at the IGB has, since 2014, been cooperating with the Esslingen-based biotechnology company Amedrix. Together, the development of collagen implants for the treatment of damaged cartilage is being driven forward. The aim is biological therapy methods which will make expensive operations unnecessary in the future. In the IGB laboratories, the manufacture of the implants needed for this is now being optimized and implemented in accordance with the valid guidelines of the Medical Devices Act. The Institute, with a 215 m^2 GMP (Good Manufacturing Practice) unit, fulfils the required conditions. In this building, processes can be developed for the manufacture of cell-free medical devices or cell-based tissue engineering products in accordance with the standards of Good Manufacturing Practice (GMP).



FRAUNHOFER IGB INTERNATIONAL

News regarding European research funding

From FP7 to Horizon 2020

The 7th Research Framework Programme of the European Union, abbreviated FP7, with its specific subprograms "Co-operation", "Capacities", "People" and "Ideas" has been the most important instrument of European research funding from 2007 to 2013. Since 2014 it has been replaced by the 8th Framework for Research and Innovation, "Horizon 2020".

Looking back at a successful era with FP7

During the last seven years, the Fraunhofer IGB successfully secured 61 EU calls for proposals, implementing and enhancing knowledge out of its five business areas. The Fraunhofer IGB acts as project coordinator for 24 of these projects.

With 37 projects on "Research for the Benefit of SMEs" the Fraunhofer IGB was mainly involved in the subprogramm "Capacities". In "Cooperation", 19 projects were successfully negotiated covering the areas of health, knowledge-based bio-economy, nanosciences, nanotechnologies, materials and new production technologies. Furthermore, the Fraunhofer IGB was involved in the Marie Curie Actions which supported, among other things, individual fellowships for international researchers as well as innovative training networks.

The accepted project volume in which the Fraunhofer IGB was involved under FP7, amounted to approximately 37 million euros.

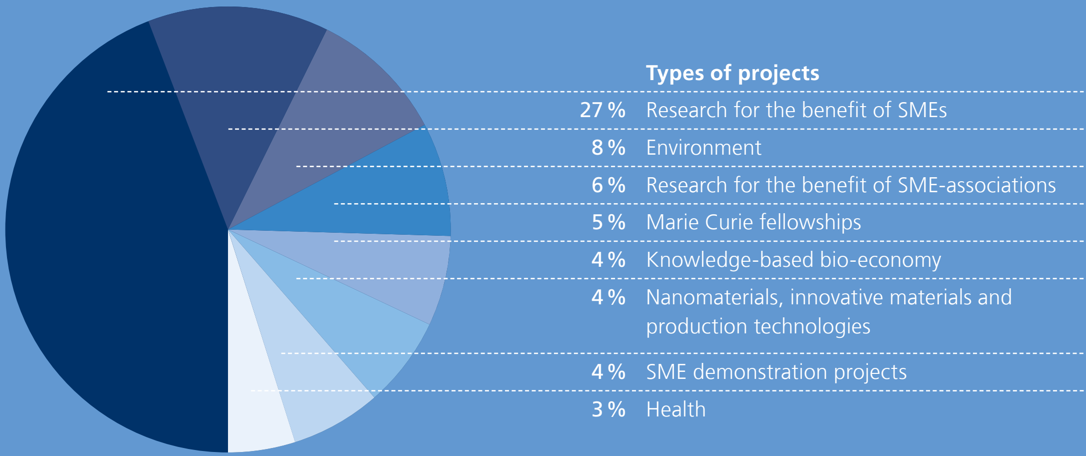
Latest FP7 projects run until 2018

Ovoshine, which started in September 2014, is the latest FP7-supported project of the Fraunhofer IGB. The project consortium consists of ten project partners from seven European countries. Ovoshine intends to develop a low-cost, low-maintenance and effective system to sterilize eggshells using hot air and Excimer UV lamps.

Within FP7, the Fraunhofer IGB collaborated with 230 SMEs and SME-associations, 104 research facilities and 54 large scale enterprises from 28 European countries. Partners from Asia, North and South America, as well as from Africa, were represented in the consortia.

Outside of Germany and Spain, most of the project partners are from the United Kingdom, France, Italy and the Netherlands.

Currently, 33 FP7 projects are still running, 13 of which are coordinated by the Fraunhofer IGB. In 2014, 11 projects were successfully completed. The last FP7-funded projects will be completed in 2018.



The 61 FP7 projects involving the IGB are assigned to subprograms as follows:

Cooperation: 19 projects
Health, knowledge-based bio-economy, nanomaterials, innovative production technologies, environment

Capacities: 37 projects
Research for the benefit of SMEs, SME-associations as well as SME demonstration projects

People: 5 projects
Marie Curie fellowships

Horizon 2020 – Present and Future

In January 2014, the 8th EU Research and Innovation Programme called Horizon 2020 entered into force. It combines all funding programs of the European Commission related to research and innovation. Beside the main sections "Excellence Science", "Industrial Leadership" and "Societal Challenges", Horizon 2020 covers also measures in pursuing the cohesion policy objectives (broadening participation), activities to increase social acceptance of science (science with and for society) as well as direct measures of the Joint Research Centre and the European Innovation and Technology Institute for integration of higher education, research and innovation.

The Fraunhofer IGB submitted its first project proposals under Horizon 2020 in spring 2014. It had its first success in the section "Industrial Leadership" with a subject of the industrial process for utilization of renewable raw materials for chemical and energy applications. The project "SteamBio", which is coordinated by the Fraunhofer IGB, aims to provide stable concentrated feedstock for the process industries by upgrading lignocellulosic biomass (e.g. agro-forestry residues from remote rural sources) through a flexible superheated steam torrefaction and grinding process. Eleven project partners from four European countries will do research from February 2015 for three years together in this challenging project.

Further proposals from different business areas of the Fraunhofer IGB are in preparation or already in the evaluation phase.

For further information on the Fraunhofer IGB EU-funded projects please visit:
www.igb.fraunhofer.de/eu-projects

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AERTOs Biobased Economy Initiative

European research institutions working together for innovative value chains

The Fraunhofer IGB is an active network partner in a consortium of seven European research institutions. Since June 2014, Fraunhofer IGB, VTT (Finland), TNO (The Netherlands), SP (Sweden), Technalia (Spain), SINTEF (Norway) and VITO (Belgium) have bundled their scientific forces to collectively develop new methods and value chains for the use of lignin and algae. The joint project on the theme, Biobased Economy, is being funded for two years from the resources of the participating research institutions. Contentwise, in four work packages, the scientists focus on the improvement of known, and the exploration of new value chains of lignin and algae. In addition to technical research, one group works on the corresponding market vision in relation to aspects of innovation in bioeconomy. The project is to be considered in the context of "AERTOs Community" (Associated European research and technology organizations), an initiative which was originally launched in 2008 as an ERA-Net project. The objective of this ERA-Net project coordinated by Fraunhofer, was the development of common European research infrastructures. Since the successful completion of the project, activities are continued within the AERTOs Community in a highly ambitious manner.

Thailand 1 + 2

IGB becomes a member of the 1st International Advisory Committee for TISTR

The IGB was invited by the Thailand Institute of Scientific and Technological Research to the first meeting of an international advisory committee. Together with other eminent scientists from Stanford University, USA, the National Institute of Advanced Industrial Science and Technology AIST, Japan, Massey University, New Zealand, and the Swedish innovation agency Vinnova, Sabine Krieg, working at the IGB in Research Strategy and Business Development, evaluated the future strategy of the research organization and discussed, at management level, aspects for future internationalization and the development of innovative competence.

Sustainable cooperation through clever minds

Within the framework of the project "Integrated Resource Management in Asian cities: the urban nexus" (see p. 110), Fraunhofer IGB's Roman Schindler, a Master's student at the University of Hohenheim, worked for three months in Korat, Thailand. As an intern of the GIZ, he was able to analyze, from June to August, problems in operating a fermentation plant from the municipal's solid, organic waste. On this basis, he wrote his Master's thesis entitled "Improving the Treatment of Biowaste in Korat, Taking into Account Energy Production, Utilization of Treated Waste in Agriculture, and Purification of Wastewater." Mrs. Ruth Erlbeck (GIZ), the project coordinator, took over the care of the on-site supervision while scientific support occured via Dr. sc. agr. Andreas Lemmer (University of Hohenheim) and Dr.-Ing. Marius Mohr (Fraunhofer IGB).

China 3

Environmental technologies in focus

At the end of November, scientists from the Fraunhofer IGB visited the Tianjin Economic-Technological Development Area (TEDA), a zone designated to economic development by the Chinese government. As early as 1984, the region was identified as an outstanding location for the establishment of innovative companies in the field of technology development and has since been characterized primarily by its good infrastructure. It is a particularly suitable location for selected flagship projects that involve international participation. The region, which is south of Beijing, is currently ahead of Shanghai as the location with the strongest presence of international companies in China. The focus of the discussion conducted at this highest of levels was on topics such as wastewater treatment, sanitary systems and urban infrastructure. Upon the completion of successful conversations, the IGB team, together with companies, will develop initial concepts.

Excellent bridgeheads

Since October 2014 and for the period of one year, Dr. Liangfei Dong of Changzhou University (Jiangsu Province, People's Republic of China) has been researching at the Fraunhofer IGB in the subject area of water technologies (Department of Environmental Biotechnology and Bioprocess Engineering). In his own research, Dr. Dong has shown a particular interest and has already participated in professional seminars and scientific discussions. His stay is financed as part of a visiting scholars' program between the Fraunhofer-Gesellschaft and the Department of Science and Technology of the provincial government of Jiangsu, China. The agreement for the visiting scholars' program was signed in September 2013, and aims to further networking with this province which is rapidly growing economically, and as well, gain bridgeheads via excellent scientists and multipliers for further cooperation in China. In order to give rise to a lasting partnership of activities, preparation is underway for a German-Chinese Symposium on environmental technologies in Changzhou, which may take place in 2015.

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PRIZES, AWARDS, HONORS

Medal of honor of the town of Leuna – Recognition of site's commitment

In 2012, the Fraunhofer Center for Chemical- Biotechnological Processes in Leuna was inaugurated by the German Federal Chancellor Angela Merkel. The fact that the research institution, which is part of the Fraunhofer IGB, has located there is essentially due to the commitment of Prof. Dr. Thomas Hirth. The Leuna municipal administration has now acknowledged his dedication by awarding Prof. Hirth the medal of honor of the town of Leuna. As Prof. Hirth saw it, the attractiveness of the site in Saxony-Anhalt lay in the hundred years tradition that the chemical industry had in Leuna together with the infrastructure in the regional economy and research landscape grown out of this.

European "Young Scientist Award" for Prof. Dr. Schenke-Layland 1

Prof. Dr. Katja Schenke-Layland received the "Young Scientist Award" for her outstanding research in the field of tissue engineering and regenerative medicine. The European branch of the Tissue Engineering and Regenerative Medicine International Society (TERMIS-EU) gives the award every year. Presentation of the award took place on June 10 during the Society's annual international conference in the Italian town of Genoa. The award is given to scientists for demonstrating evidence of high quality publications, leadership activities, grant income and recognition amongst the wider international TERMIS community.

LEWA prize for innovation in process engineering 2

Young scientist Daniel Frank was awarded the LEWA prize for his achievements in the field of process engineering. The annual honor from the Leonberg-based company LEWA is awarded for excellent theses in the area of process engineering at the University of Stuttgart. Daniel Frank, who did his PhD at the Institute of Interfacial Process Engineering and Plasma Technology IGVP, carried out research into the manufacture of potassium fertilizer from liquid manure for his dissertation. In doing so he supplied the foundations for establishing for a new pilot plant at the IGB.

First place in the ideas competition "Town 2.0 – How do we bring the energy revolution into the town?" 3

A further award-winning thesis was written by Matthias Stier, also a PhD student at the IGVP. The "Stiftung Energie und Klimaschutz Baden-Württemberg" (Baden-Württemberg Foundation for Energy and Climate Protection) paid tribute to his work on biocatalytic methanol production from biogas with first prize in the ideas competition "Town 2.0 – How do we bring the energy revolution into the town?". With the method researched by Stier, important platform chemicals for the storage of regenerative energy can be efficiently obtained; these can be used among other things as a fuel in fuel cells. At the Fraunhofer IGB, a follow-up project has already developed out of his dissertation.

Excellent Master's thesis in the field of "Pharmaceutical biotechnology" 4

Andrea Hornberger received the annual prize for Outstanding Master's Thesis by Students of Pharmaceutical Biotechnology from the company Boehringer Ingelheim Pharma GmbH & Co. KG for her work on the non-invasive diagnosis of endometriosis using Raman spectroscopy, which the Biberach University of Applied Sciences student performed at the Fraunhofer IGB. Endometriosis is a painful and common women's disorder in which the womb lining grows outside of the uterine cavity. With the help of Raman spectroscopy it will be considerably easier to detect the disease in the future.

Brilliant idea – Biological coating for implants

Improving the long-term stability and integration of medically engineered implants into their surrounding tissue by equipping them with a biological coating was the concept presented by IGVP PhD student Mara Ruff in the "ideaTrophy 2014" competition sponsored by the company Freudenberg, which was chosen in December 2014 as one of two winning ideas. The biological coating in question consists of an extracellular matrix formed by human cells grown in the laboratory. The scientists introduced a small reactive molecule to gain a long-term stable connection between this extracellular matrix and the implant, leading to a tissue-specific biological surface which enhances implant ingrowth.

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PROMOTING YOUNG TALENTS

The Fraunhofer-Gesellschaft is keen to make early contact with the researchers of tomorrow and give them exciting insights into research opportunities. For this reason, the Fraunhofer IGB is active both in promoting young talents and getting young people interested in research and technology.

Girls' Day at Fraunhofer Stuttgart campus 1

We currently have the best educated cohort of young women in Germany there has ever been, with girls making up more than 50 percent of high-school graduates. Despite this, girls still tend to opt disproportionately for typical female jobs or courses when choosing an apprenticeship or higher studies. Girls' Day – a nationwide event initiated by the German Federal Ministry of Education and Research (BMBF) – at the Fraunhofer campus in Stuttgart gives young women an insight into the Fraunhofer Institutes and the careers available in engineering, IT and the natural sciences. The researchers open the doors to laboratories and test areas, offices and workshops, where they use practical examples to demonstrate how interesting their work is. This is a good opportunity for young women to find out more about what scientists do through talking to the scientists in real life, on a one-to-one basis. In 2014, there were 93 interested participants in Stuttgart, some of whom visited the "Nature's own chemical plant" and "Customized tissues from the lab" information stations at the Fraunhofer IGB.

www.stuttgart.fraunhofer.de/girls-day

BoGy – vocational and academic career orientation at academic high schools

Seven high-school students completed their "BoGy" internships at the Fraunhofer IGB in 2014. 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 vocational occupations in a research institute (technical assistants, laboratory technicians). The students assisted on real projects, became acquainted with methods for identifying particular substances and helped out with the planning and performing of experiments as well as the documentation of the test results. The internship gives the youngsters a detailed picture of the work that goes on in a research institute and helps them to make better-informed career choices.

www.stuttgart.fraunhofer.de/bogy

Fraunhofer Talent School 2

Dr. Kai Sohn, deputy head of the Molecular Biotechnology Department, led a workshop on the topic of genetic analysis for the fifth time. The aim of the workshop, entitled "CSI Stuttgart – from genetic fingerprint to identification of the perpetrator" was to create a better understanding of the fundamentals of the genetic code. To do this, DNA was isolated from the participants' saliva samples and characterized molecularly. Every participant got to take home his or her personal "DNA portrait".

www.stuttgart.fraunhofer.de/talents

3

Open day for university students 3

In November, 2014, 78 science and engineering students from various universities and universities of applied sciences visited the Fraunhofer campus in Stuttgart. Through presentations, interviews and tours they had the chance to find out about the institutes' highly varied fields of work as well as opportunities for starting their careers at the Fraunhofer-Gesellschaft – in particular at the Stuttgart institutes. Extremely positive feedback and constantly high numbers of participants reflect the success of the event, which has taken place once a year since 2007.
www.stuttgart.fraunhofer.de/checkpoint

Apprenticeship training at the Fraunhofer IGB

In addition to the education and training of young people pursuing academic studies, the Fraunhofer IGB is also expressly committed to enabling young people of all backgrounds to train at Fraunhofer. For over ten years we have been providing youngsters with apprenticeships in the recognized (requiring formal training) vocational occupations of office administrator, chemical lab technician and biology lab technician and, since 2013, also of IT specialist for system integration. When not attending vocational training college, the apprentices have the opportunity to work alongside more experienced colleagues in the many diverse fields of activity of a research institute, and so learn the skills for a career in research or industry. Many of our apprentices choose to go on to study or to participate in an advanced occupational training course designed for full-time employees and sponsored by the institute.
www.igb.fraunhofer.de/career

IGB supports German youth science competition "Jugend forscht"

For over a year now, IGB employee Dr.-Ing. Thomas Hahn has been giving students of the high school in Spaichingen advice and practical help in isolating latex from a plant of the spurge family, which also grows in arid regions. This is an example of how the Fraunhofer IGB supports the girls in latex extraction and analysis. Several awards, including the "Jugend forscht" special prize "Renewable Raw Materials", the gold medal in the category Environmental Science at the International Conference of Young Scientists (ICYS) and a gold medal at the Nuremberg Trade Fair "Ideas – Inventions – New Products" (iENA) show that the commitment is bearing fruit.

In November 2014, approximately 50 selected "Jugend forscht" participants from all over Germany followed the invitation of the German Federal Environmental Foundation (DBU) to discuss "green" career opportunities. Experts from the fields of ecology and sustainability offered a lot of helpful advice for the young talents' future careers. One of these experts was IGVP PhD student and DBU scholar Matthias Stier with his workshop "Everything from biomass – Renewable raw materials and their utilization".

For further information on promotion of young scientists and training please visit
www.igb.fraunhofer.de/career

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SUSTAINABILITY INCREASINGLY IMPORTANT

"Seeing sustainable development as a defining issue of the 21st century". This was the message being conveyed by author Ulrich Grober at the meeting of the Fraunhofer Sustainability Network in November 2014. He referred to the words of Kofi Annan, former UN Secretary-General, paraphrasing them as follows: "If the guiding principle of sustainability serves as a compass for the major transformation of society, priorities will be adjusted."

Sustainability communications as a tool 1

For Fraunhofer, this means that we develop solutions to problems which extend beyond the requirements of the present into the lives of future generations. With the issue of sustainability having acquired greater significance in corporate policy in the past few years, the Fraunhofer-Gesellschaft was the first of the four major non-university research institutions in Germany to publish its understanding of sustainability, its goals and its measures in a sustainability report – by way of a first step towards transparent sustainability communications and as a tool for a long-term sustainability management strategy. Prof. Thomas Hirth presented the report to the public at a press conference in October 2014 together with Prof. Reimund Neugebauer, the President of the Fraunhofer-Gesellschaft. In the process, he illustrated how the concept of sustainability permeates the major research fields at Fraunhofer, for example in the manufacture of plastics from wood chips in the research area of energy and raw materials.

At the same time as the Fraunhofer sustainability report was presented, the five institutions at the Fraunhofer Institute Center Stuttgart presented what was already their second sustainability report. The Fraunhofer IGB had taken the lead role in drawing up the report. In the report, the Center's institutes show how important responsible research is to them. The cross-institute sustainability working group founded in 2011 has set itself the goal of, on the one hand, boosting conduct in the workplace that demonstrates awareness and conserves resources while on the other, supporting cross-links between research activities on the campus. In the reporting period between 2012 and 2013 it put into practice numerous initiatives and measures. The sustainability report illustrates the highlights.

Researching together responsibly 2 + 3

One of these highlights in 2013 was the 'research exchange'. In order to utilize the richness of ideas at the Fraunhofer site in Stuttgart, three cross-institute project teams received start-up funding for their projects that had a connection to sustainability; this financing was provided jointly by the five Stuttgart institutes. In autumn 2014, the three project teams presented their results as part of a poster exhibition in the main building of the Institute Center. Researchers from the Fraunhofer IGB were involved in two projects: in "Recycling of carbon dioxide (CO_2) in algae production", a project by the Fraunhofer IBP and IGB, a process for flameless, low-emission combustion was for the first time combined with the cultivation of microalgae. This linking of technologies enables, alongside material recovery, the efficient energetic recovery of biogas. In the project "Concept for a Future Center with a Sustainable Technology Academy in the metropolitan region of Stuttgart",

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participants from all five institutes are developing ideas for an interactive learning and experience platform which aims to give visitors an understanding of phenomena, circumstances and technologies in the context of the concept of sustainability.

The integration of sustainability into the business processes of a research organization is the focus of the project being initiated jointly by the Fraunhofer-Gesellschaft, the Helmholtz Association and the Leibniz Association, the "Sustainability Management Manual". Here, Fraunhofer is building on the experience from the last few years and, together with scientists and management experts from 25 individual institutions, is developing a common understanding of "sustainability management" in non-university research organizations. With the aim of developing practical recommendations for the fields "Research with social responsibility", "Staff" and "Building and Operation", participatory methods are used and hence a wide range of interests integrated. The Fraunhofer IGB is coordinating the project together with the Fraunhofer Institute for Environmental, Safety and Energy Technology UMSICHT and the headquarters of the Fraunhofer-Gesellschaft.

In the lighthouse project "E³-Production" (see p. 114) the Fraunhofer IGB is looking, among other things, at the evaluation of production processes giving consideration to sustainability criteria. The projects mentioned show that the research aimed at socially relevant and future-proof solutions relies increasingly on the integration of different disciplines and interests.

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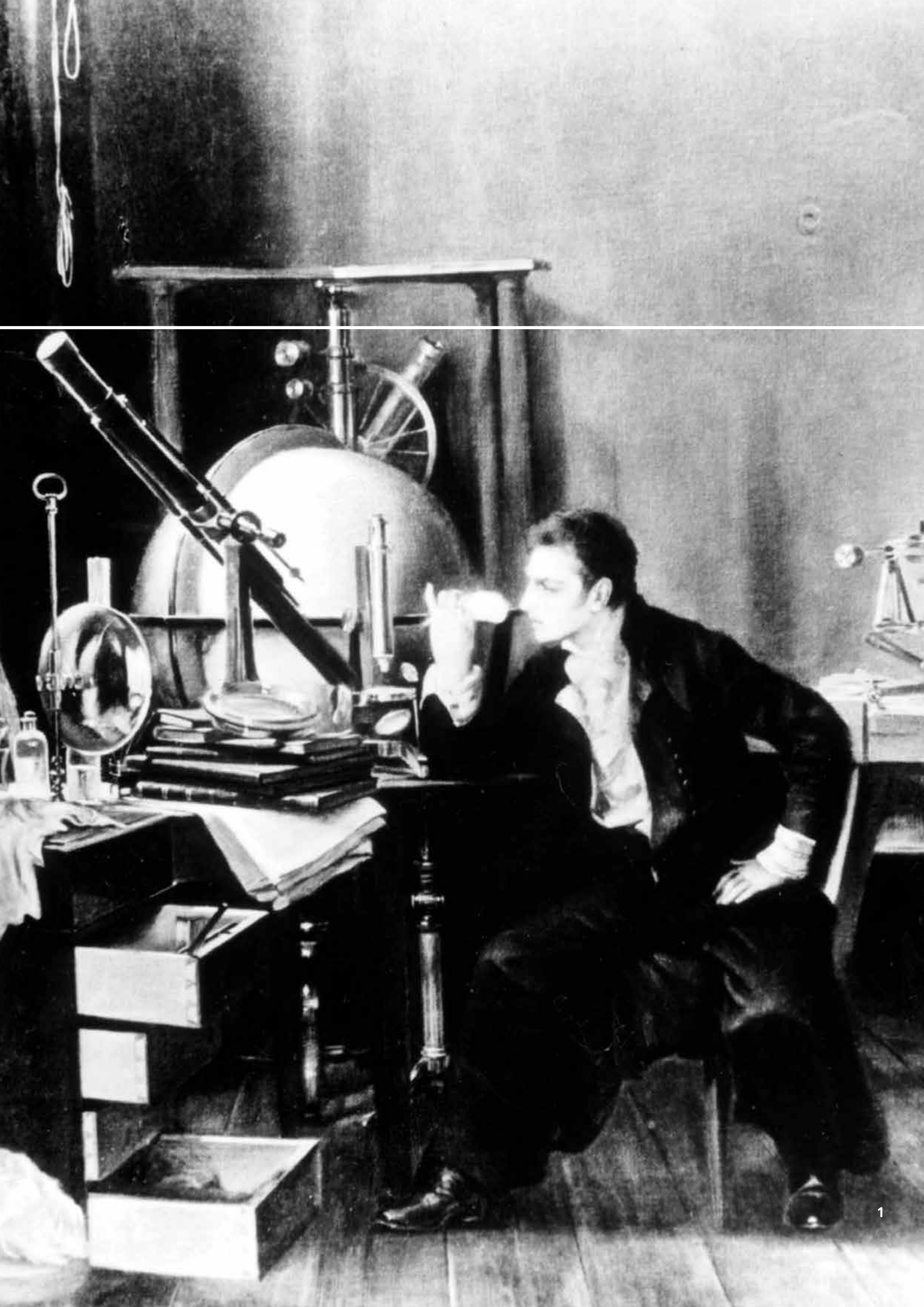
Further information on sustainability and research in the Fraunhofer-Gesellschaft:
www.sustainability.fraunhofer.de



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COMPETENCES

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 66 institutes and research units. The majority of the nearly 24,000 staff are qualified scientists and engineers, who work with an annual research budget of more than 2 billion euros. Of this sum, around 1.7 billion euros is generated through contract research. More than 70 percent of the Fraunhofer-Gesellschaft's contract research revenue is derived from contracts with industry and from publicly financed research projects. Almost 30 percent 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.

International collaborations with excellent research partners and innovative companies around the world ensure direct access to regions of the greatest importance to present and future scientific progress and economic development.

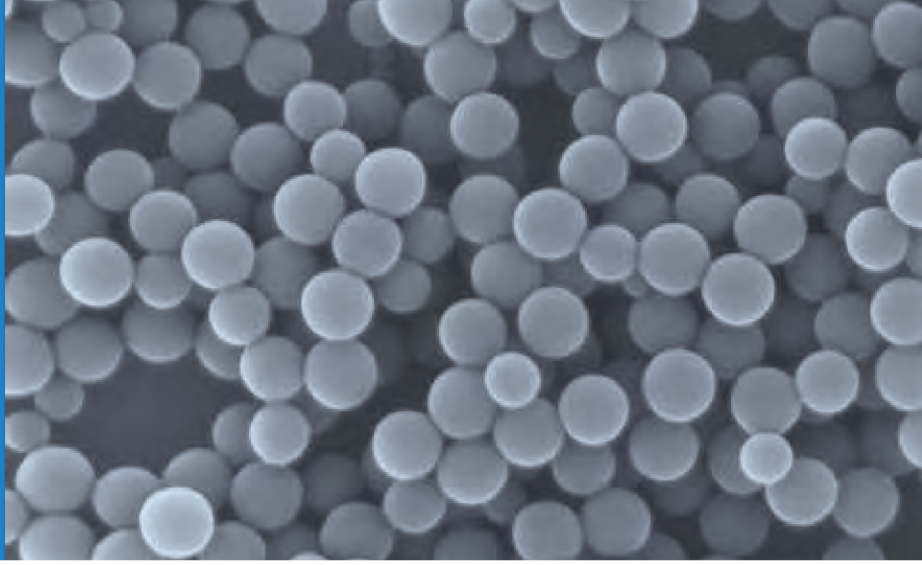
With its clearly defined mission of application-oriented research and its focus on key technologies of relevance to the future, the Fraunhofer-Gesellschaft plays a prominent role in the German and European innovation process. Applied research has a knock-on effect that extends beyond the direct benefits 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.

www.fraunhofer.de

1 *Joseph von Fraunhofer (1787 – 1826).*



INTERFACIAL ENGINEERING AND MATERIALS SCIENCE

Interfaces play a key role in many technical areas such as the automotive sector, technical textiles and in medical technology. For many surfaces, properties are required that are very different from those intrinsic to the bulk of the material concerned. Besides these material surfaces, inner interfaces in composite materials are becoming increasingly important. Examples are membranes used in separation technology as well as materials for energy conversion, such as separators in fuel cells or thin films in photovoltaics. Another instance of the growing significance of interfaces is as barriers in packaging materials.

Finally, in response to the growing complexity of demand, we combine various technical processes under the aspects of material and energy efficiency. With regard to technical realization, we have established a large variety of methods which involve either films being deposited from the gas phase or the precipitation of thin films or particles from the liquid phase.

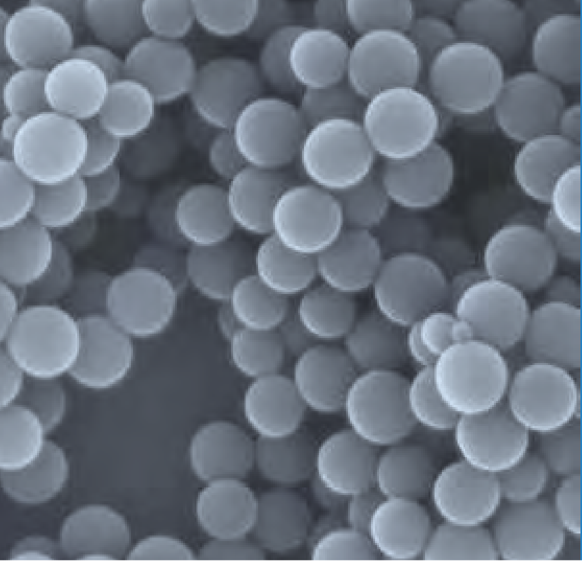
Established preparation methods

- Deposition of thin films by chemical and physical means, i.e. chemical or physical vapor deposition
- Deposition of nanoparticles using various 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 nanofibers by electrospinning

To achieve reliable processes, all steps of the process development have 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 also be used 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 nanoparticles), we use several methods to deliver information which is space-resolved on the nanometer scale. Application-relevant properties such as the separation and permeation properties of films (membranes, barriers and corrosion protection) as well as the specific separation capabilities of polymeric adsorber particles or the dispersibility of modified carbon nanotubes and graphene are examined in customized experimental set-ups.

Established characterization and diagnostic processes

- Determination of interfacial energy with different types of tensiometers
- Logging of the topography and geometric patterning of surfaces on the nanometer scale using a variety of AFM probe modes as well as scanning electron microscopy
- Determination of adsorption properties either by means of microcaloric measurements at the liquid phase (measurement of adsorption enthalpy) or by means of gas adsorption with simultaneous measurements of specific surface area (BET)
- Determination of film thicknesses using ellipsometry or microscopic techniques
- Qualitative and quantitative estimation of the chemical functions at surfaces and in thin films using IR spectroscopy in ATR mode, IR microscopy, confocal Raman and fluorescence spectroscopy as well as MALDI-TOF-MS



- (matrix-assisted laser desorption-ionization time-of-flight mass spectroscopy)
- Determination of elemental composition, using electron spectroscopy for chemical analysis (ESCA) and energy dispersive X-Ray analysis (EDX)
- Quantitative estimation of chemical radicals via electron spin resonance spectroscopy
- Plasma process diagnostics: probe measurements, optical and mass spectrometric methods

Apart from the quality of the products, the material and energy efficiency of processes is of foremost concern. One way of tackling this is to miniaturize entire functional units which are manufactured as a combination of several thin films. The internal structure and the chemical composition of these layers are significant for the role of the films in modulating the transport of materials (membranes), of electrons (conductors and semi-conductors) or photons (fiber optics). This also opens up applications for thin-film components in photovoltaics, in batteries and in organic electronics. The challenge and objective of our process engineering development work is to find the best ways of combining thin films using a variety of specialized techniques.

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

Range of services

- Development of processes for the plasma modification of surfaces
- Thin films as protective layers (scratch and corrosion protection), barriers against permeation, and for use as reservoirs for the targeted release of substances (formulations)
- Functionalization of surfaces (chemical and biochemical)
- Development and evaluation of plasma-cleaning and plasma-sterilization processes

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- Development of inks by using biomaterials to create biocompatible or bioactive printed structures
- Synthesis and preparation of nanostructured materials with tailored surfaces
- Novel formulations using core-shell particles
- Characterization of nanoparticles, measurement of the particle sizes and particle size distribution by optical methods or in an electrical field
- Development of membranes and membrane modules
- Manufacturing and testing of membranes in pilot scale
- Surface and layer characterization
- Development of methods and plants
- Scaling up of laboratory processes to produce thin films on large format surfaces and scaling of nanoparticle production for greater volumes

Infrastructure and technical equipment

- Plasma reactors for cleaning, sterilization, coating and functionalization
- Equipment for sputtering and parylene coating
- Electron (SEM) and probe (AFM) microscopes
- Equipment for the analysis of surfaces and thin films
- Chemical-nanotechnical laboratories for the synthesis and preparation of nanostructured (bio)materials and surfaces
- Pilot plants for the manufacturing and testing of membranes

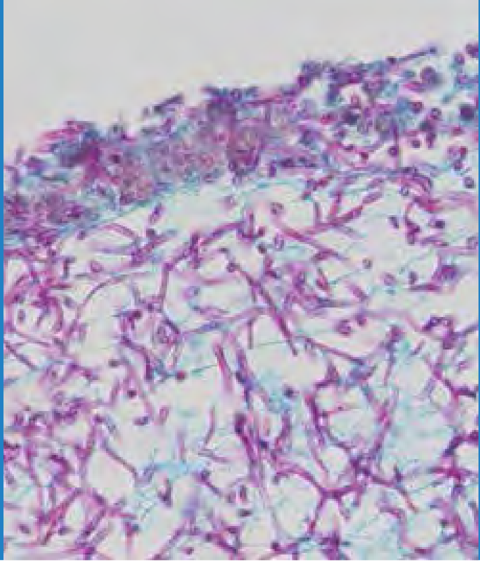
MOLECULAR BIOTECHNOLOGY

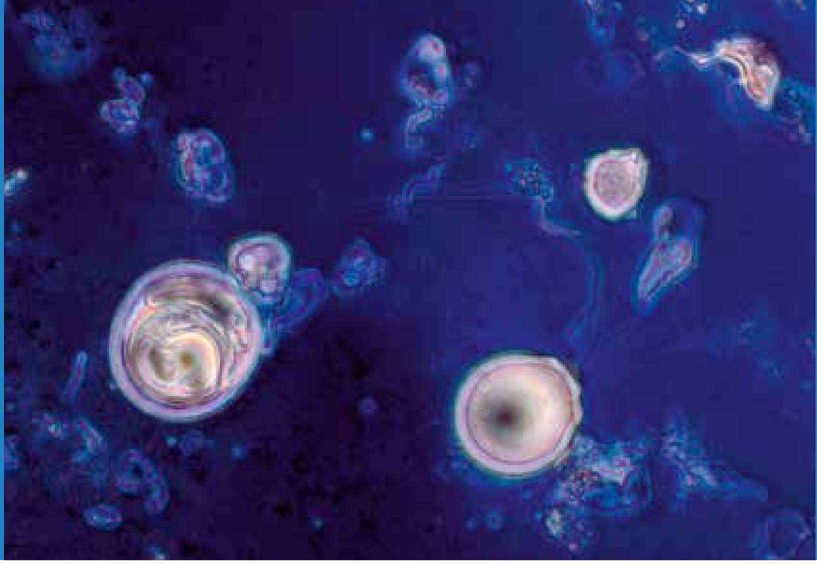
The Molecular Biotechnology Department focuses on work in the fields of pharmaceutical biotechnology, diagnostics and chemistry. Thus, for instance, we use our know-how for the functional genome analysis of pathogens (infection biology) in order to develop new approaches for the screening of anti-infectives. We develop new diagnostic methods based on nucleic acid technologies (diagnostic microarrays and using next-generation sequencing based diagnostics) or by means of cell-based assays, e.g. with a cell-based pyrogen assay. A further focus is the development of production strains or cell lines for industrial and pharmaceutical biotechnology. In the past, we have developed production processes for pharmaceutical proteins such as interferons and factor VII as well as for chemical products such as biosurfactants and dicarboxylic acids. Our work extends from the metabolic engineering of production strains to the development of integrated bioprocesses for effective downstream processing. In addition to microorganisms, we also focus on enzymes as a key to render sustainable raw materials available for biotechnological processes as well as for the enzymatic synthesis of chemicals (e.g. epoxides from fatty acids).

The core competences of the department lie in the application of molecular-biological and biotechnological methods for genomics, transcriptomics, and proteomics. A further asset is our accredited analytics, which can also be used for metabolome analyses. Metabolic engineering for strain development, integrated in a bioprocess and focused on simplified product purification, is a central competence for both microbial production processes and for the production of pharmaceutical proteins from mammalian cell lines. In infection biology, the combination of methods of functional genome analysis with our expertise in cell culture technology and biology of pathogens gives us a unique selling point in the development of infection models, test systems (e.g. as for the screening of anti-infectives), as well as virus-like particles for targeted drug delivery and diagnostics.

Our goal is to use nature's toolbox to create biotechnological value chains and develop, for example, biobased chemicals such as biosurfactants or polymer building blocks, along with new diagnostics and therapeutics. The new technologies in genome and proteome analysis, for example, allow comprehensive analysis of entire microbial communities from the environment or the bioreactor, as well as of the interaction between microorganisms and the human individual in the shortest of times. This enables the identification of the impact of microbiota on human health – both via host-pathogen interactions and in synergistic form (probiotics). The malignant transformation of the body's normal cells can also be investigated. Using this information, measures for specific treatments for individual groups of the population can be applied. Thus personalized medicine may become reality. In industrial biotechnology, too, the quick availability of genomes and the analysis of cellular circuits make it possible to identify new metabolic pathways, to also optimize processes in the reactor that can then be ideally exploited for the production of chemicals or enzymes.

With our competences, we provide services, in cooperation with other departments of the Fraunhofer IGB, to different areas in the business fields of medicine, pharmacy and chemistry. For instance, in the field of biocatalysis we work closely with the BioCat branch based in Straubing, while we collaborate with the Fraunhofer CBP branch in Leuna to develop our laboratory-scale bioprocesses up to 10 m^3 scale. In addition,





within the Fraunhofer Group of Life Sciences there is scope for process development of pharmaceutical proteins up to the GMP production of clinical test samples.

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Range of services

- Screening of targets and active compounds for anti-infectives (infection models, screening assays)
- Gene expression and proteome analyses (2D-/LC proteomics, Real-time PCR)
- Next-generation sequencing of genomes and transcriptomes
- Development of DNA microarrays: design of probes, manufacturing of arrays, sample preparation procedures
- Cell-based assays: antiviral assays (GLP), pyrogen detection (GLP), mutagenicity, toxicity
- Development of production cell lines and processes for recombinant production of proteins (biosimilars), protein purification and characterization
- Cell-free protein synthesis
- Development of high-throughput enzyme assays and screening processes
- Strain and parameter screening in multi-fermenter systems
- Development of integrated fermentation processes for industrial biotechnology with a focus on downstream processing of raw materials and upstream processing of products
- Chemical-physical and biochemical analysis

Infrastructure and technical equipment

- Molecular-biological laboratories conforming to safety levels L2, S1 and S2 of the German GenTSV (genetic engineering safety regulations)
- Microarray facility, universal microarray platform
- Quantitative real time PCR (qRT-PCR LightCycler 480)
- Next-generation sequencing facility (Illumina HiSeq2000, Roche GS Junior)
- Proteomics facility using high-resolution MS techniques (2D gel electrophoresis, nano-LC-MALDI-TOF/TOF, HPLC-ESI-MS/MS)
- Fermentation plant for suspension and adherent mammalian cell culture up to 10 liters (non-GMP)
- Protein purification equipment
- Pulping machines (ball mills, etc.), multi-fermentation bioreactors for bioprocess development, and bioreactors (up to 30 liters); S2
- Accredited analytical lab (by the Deutsche Akkreditierungsstelle GmbH): GC-MS/MS, LC-MS/MS, GPC, IC, ICP-AES and ICP-MS

PHYSICAL PROCESS TECHNOLOGY

The Physical Process Technology Department is involved in developing processes and process components based on physical and physical-chemical principles. Our customers are manufacturers of process components, contractors and process system suppliers, and come from sectors such as pulp and paper, metal processing, the food industry and the supply of drinking water.

Current main themes

- Heat storage using thermo-chemical processes
- Use of sorption systems to remove moisture from gases, in particular from air to provide water
- Drying in a superheated steam atmosphere with integrated recovery of volatile materials
- Recovery of inorganic nutrients
- Production of soil-improving substrates from organic residuals
- Electrolytic and photolytic water treatment
- Stabilization of foods and biogenic products using pressure change technology
- Use of electric fields for selective substance separation
- Microwave technology for defined and fast energy charge

Apart from our technical competence and specialized expertise, a hallmark of the quality of our R&D activities is our focus on sustainability. Thus, for example, we replace flows of raw materials by recycling, upgrading or overhauling processes for the efficient use of regenerative energy and find ways to improve the efficiency of energy use. This also leads to improved economic efficiency of processes, meaning that our approach satisfies both ecological and economic demands at the same time. One example of this is the development of a process to store heat from waste heat or solar heat without losses during the time of storage. The intention is to be able to provide heat energy for industrial use at any time and, thanks to the high energy density, at any location; thus the supply is not directly linked to when and where the energy has been generated. Potential applications are drying processes in production, supplying heat to buildings, or the concentration or thickening of highly contaminated process wastewater with vacuum vaporization.

Our development work on processes and process components extends from initial laboratory-scale characterization and analytics via simulation and software modeling to design and system integration in industrial applications. For developing and designing our technical solutions, we have access to the latest 3D CAD design software, which is directly linked by data interface to various numerical simulation programs. For standard modeling we use COMSOL Multiphysics® like the theoretical modeling 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 to generate them in a defined way. From the data thus gained we can proceed to realize demonstration prototypes using the many resources at our disposal – workshops, laboratories and pilot plant facilities, as well as a network of industrial partners.

The Physical Process Technology Department is staffed by scientists from various disciplines – such as process engineering, chemical engineering, food chemistry, mechanical and electrical engineering – who work together in multi-disciplinary project teams. Projects may also involve collaboration with specialists from other Fraunhofer IGB departments, such as microbiologists and bioengineers, or from other Fraunhofer Institutes, leveraging synergies in expertise to address specific issues.

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Range of services

- Process development carried out by an interdisciplinary team drawn from the areas of process, mechanical and chemical engineering
- Design and operational specifications including characterization of automation algorithms, to enable industrial prototypes
- Feasibility studies and preliminary investigations in laboratory and pilot-plant scale

Infrastructure and technical equipment

- Laboratory systems for investigating the treatment options for industrial process water e.g. like floculation and oxidation properties
- Pilot plants for advanced oxidation processes (AOP) such as electro-physical precipitation, ozone, hydrogen peroxide, photolysis by UV radiation, ultrasound, anodal oxidation (direct or indirect), and cathode reactions
- Mobile pilot plants for on-site feasibility investigations and demonstrations, for example for drying with superheated steam or for water treatment
- Design and simulation software (SolidWorks, CST Micro-wave Studio®, COMSOL MultiPhysics®, Design-Expert Workstation)

ENVIRONMENTAL BIOTECHNOLOGY AND BIOPROCESS ENGINEERING

The core areas of the Department of Environmental Biotechnology and Bioprocess Engineering are the development of (bio-)process engineering processes in the fields of water management, bioenergy, environmental technology, algal technology, product recovery from organic raw materials and waste materials, and interfacial biology.

A focal point are new approaches to the development of system concepts for energy, waste and water management in industry and for communities. Alongside aerobic and anaerobic methods for wastewater purification and water treatment, hybrid methods are being used. We prefer to treat organic waste materials such as biodegradable waste or sewage sludge anaerobically, as this process allows the economical generation of biogas as a renewable energy source. Maximum efficiency is achieved through the integration of several steps to establish short process chains.

The processes are always designed on the basis of microbiological or process engineering principles such as, for example, the growth and degradation kinetics of the particular organisms, and ranges from the planning, commissioning and optimization of laboratory and pilot plant facilities through to the planning, construction, commissioning and optimization of innovative demonstration plants in cooperation with our industrial partners. In the field of environmental technology, processes and special reactors are available for the purification of industrial wastewater, exhaust air and contaminated soils. Bioleaching, biosorption and bioprecipitation are used specifically for the recovery of metals from process waters and wastes.

In algal technology we use microalgae as a natural and sustainable aquatic source of raw materials; these provide a number of valuable substances such as omega-3 fatty acids, pigments, proteins for the food, feedstuff and cosmetics industries among others. In addition, for energetic utilization, oil and starch can be specifically produced from microalgae. We are developing new biorefinery concepts for maximum utilization of algal ingredients.

To enable resource-conserving production in companies (the ultraefficient factory) we are developing robust process engineering concepts and methods, among other things for the production of basic chemicals such as, for example, methane, ethanol and methanol, which can be utilized either energetically or materially. In bioprocess development, the retention or immobilization of biocatalysts has an important role. The unique selling point of the department is the intelligent link between unit operations of mechanical, thermal and chemical process engineering (incl. reprocessing technology) with bioprocesses using modeling and simulation methods.

In interfacial biology, methods for the analysis of microbial contamination on surfaces and in processing media (biofilm formation) and antimicrobial treatments are used and tests are established for this purpose. Biosensors are developed for real-time monitoring of water systems for the detection of contaminants.

The Environmental Biotechnology and Bioprocess Engineering Department 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 sustain-

able technology options, the department can help industry, communities and policymakers design a balanced future. Combining our competences with those of other Fraunhofer IGB departments, we serve the needs of the chemical, energy and environmental business areas.

Range of services

- Development of regional-level system concepts for energy, waste and water management
- Concepts for resource-conserving production in companies – the ultraefficient factory
- Wastewater and water purification methods for industry and communities
- (Bio-)process engineering processes for water purification
- Development of utilization concepts for both inorganic and organic waste materials
- Digestion processes for producing biogas from a range of organic substrates in different temperature ranges
- Aerobic and anaerobic tests on the degradability of organic residues
- Fermentation tests in line with VDI 4630
- Development of photoautotrophic processes for microalgae and cyanobacteria cultivation in photobioreactors including process control and automation
- Development of heterotrophic processes for microalgae
- Biotransformation of renewable raw materials and industrial waste materials into basic chemicals and energy carriers (methanol, ethanol etc.)
- Downstream processing technologies such as membrane-based filtration processes, liquid-liquid extraction, and extraction with supercritical media
- Analysis of microbial contamination on surfaces, including development of test procedures
- Development of real-time processes for monitoring water systems for contamination
- Bioleaching, biosorption, bioprecipitation processes for recovery of metals from different types of process water and waste streams using different reactor configurations
- Modeling of processes and simulation of process lines

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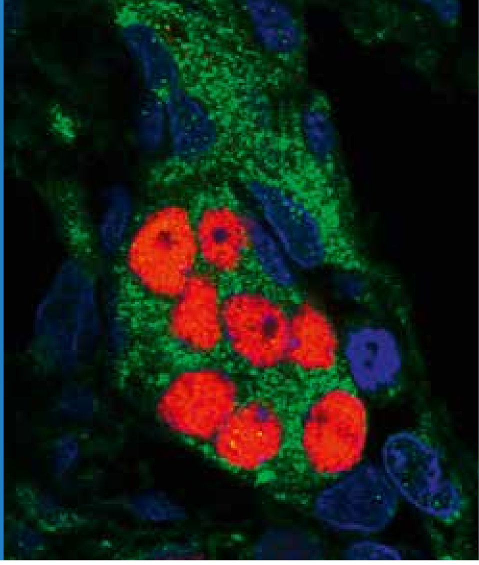
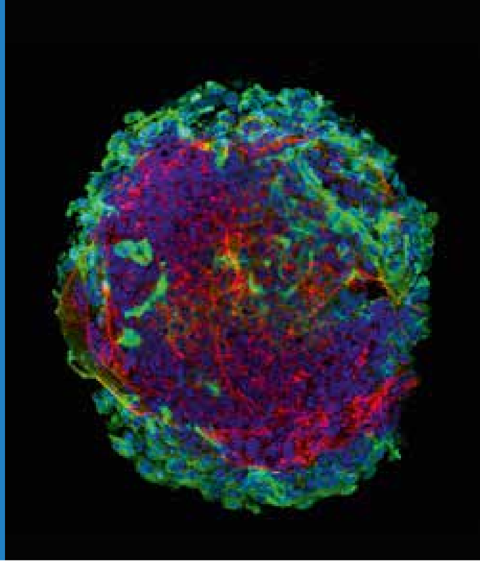
Infrastructure and technical equipment

- Pilot plant for environmental and bioprocess engineering applications
- Bioreactors of various sizes (laboratory, pilot and industrial scale) for aqueous substrates, substrates containing a high level of solids, gaseous substrates, including cell retention
- Analytics for substrates and fermentation products, protein analytics, online mass spectrometry
- Mobile pilot plants on a m³-scale to generate basic engineering data for the planning of demonstration plants
- Demonstration and reference plants for anaerobic and aerobic wastewater treatment, high-load digestion, bioenergy, algal technology
- Demonstration sites for wastewater treatment, bioenergy, and cultivation of algae
- Photobioreactors of various sizes with special control and automation concepts for laboratory, outdoor and greenhouse applications
- Test facilities for different membrane processes (e.g. rotating disk filtration)
- Equipment and official approvals for handling pathogenic organisms
- Special apparatuses for testing antimicrobially finished materials
- Test facilities for cell disruption and extraction with solvents or supercritical fluids
- GIS applications using the ESRI ARC-INFO software; process simulation and automation (MATLAB, Siemens programming)





CELL AND TISSUE ENGINEERING

The focus of the Department of Cell and Tissue Engineering is the development of functional in vitro 3D tissue models from isolated primary human cells under GLP (Good Laboratory Practice) or GMP (Good Manufacturing Practice) guidelines for applications in regenerative medicine, tissue engineering, medical device development and cell-based assays for biocompatibility and stem cell differentiation tests.

We develop synthetic, natural and hybrid biomaterials for the maintenance and differentiation of pluripotent (human embryonic stem (ES) and induced-pluripotent stem (iPS) cells) and adult stem cells. We further design biofunctionalized nano- or micro-structured material surfaces for the isolation of pure cell cultures from human tissues, particularly adult stem cells. The physiological culture of 3D tissue models is achieved with specially developed computer-controlled bioreactor systems which mimic the biomechanical environment of a specific organ or tissue.

The sterility and quality control for cell-based transplants is a complex process, which typically requires multiple transplants for testing. Therefore, we have established non-invasive test methods, Raman microspectroscopy and multiphoton microscopy, for the pre-implantation analysis of tissue-engineered constructs, which drastically reduces production and quality assurance cost, while increasing the safety of the transplanted constructs.

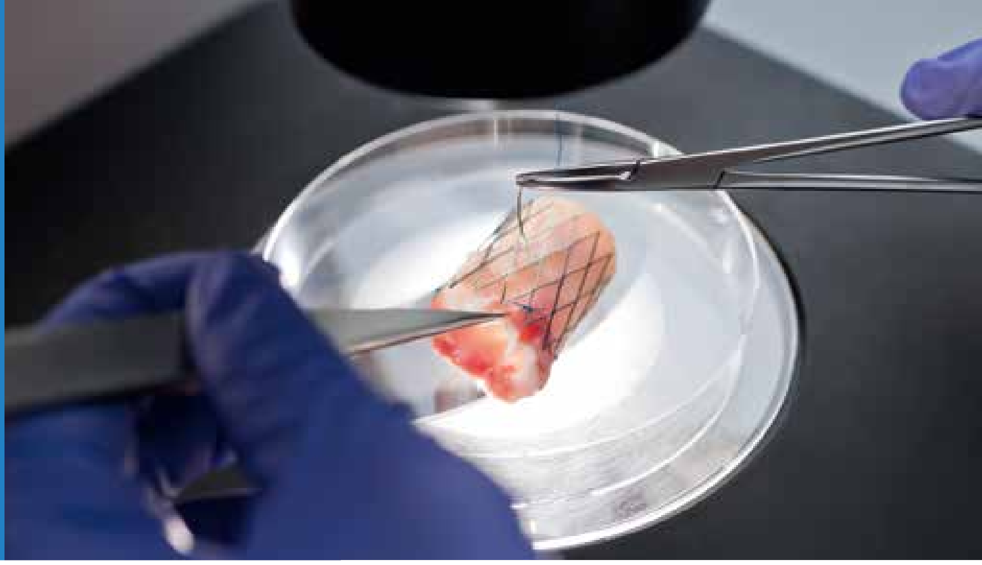
We have developed a two-layer 3D human skin equivalent that has been patented (EP 1 290 145B1). The skin model can be extended to include cell types, such as melanocytes or tumor cells. Furthermore, the skin model is a cost-effective human-based pre-animal test system for penetration and distribution tests of chemicals. Further questions in regard to cell differentiation and death, as well as tumor development and metastasis, can be studied with our model.

Additionally, we are developing methods for the creation of cardiovascular implants, regenerative therapies and in vitro 3D test systems. Due to the lack of regenerative potential in the adult cardiovascular system, we primarily work with human ES and iPS cells, as well as complex bioreactor systems. We study our engineered systems in vivo in established small and large pre-clinical animal models in close collaboration with the Department of Medicine/Cardiology at the University of California Los Angeles, where we also have access to human GMP-iPS cell lines.

In collaboration with the Department of Women's Health at the University Hospital of the Eberhard Karls University Tübingen we establish novel biofunctional implants, regenerative therapies, medical devices and in vitro 3D test systems in the fields of women's health and rare diseases.

Competences

- Isolation and culture of primary cells from different tissues and species in accordance with current GLP or GMP regulations
  - Skin and skin tumors, as well as cardiovascular and urogenital tissues
- Biomaterials design using synthetic materials, tissue-specific human recombinant extracellular matrix proteins, or a hybrid approach combining both for matrix and scaffold design, as well as nano- or micro-structured material surfaces
- Derivation of tissue-specific cells from pluripotent and adult stem cells
- Design of tissue-specific, computer-controlled bioreactors



- Establishing methods for the non-destructive characterization of cells and tissues by Raman microspectroscopy and multiphoton microscopy

ADMET (absorption, distribution, metabolism, excretion and toxicity) are pharmacokinetic and toxicological properties that must be tested during drug development. Using our test systems, we are able to test these properties in a more human situation than animal experiments, with the hope to eventually replace animal tests, as required by the 3R's initiative (replacement, refinement, and reduction).

Another goal is the use of our complex tissues as transplants in regenerative medicine. In our GMP manufacturing unit, we offer process development and manufacturing of autologous transplants (Advanced Therapy Medicinal Products, ATMPs) as Investigational Medicinal Products (IMPs). 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 the manufacturing authorization for investigational medicinal products.

Range of services

- Cell culture technology of primary human cells and mammalian cell lines
  - In vitro testing of cytotoxicity according to DIN ISO 10993-5
  - In vitro testing of phototoxicity according to OECD guideline 432 and INVITTOX protocol no 121
- Cell biology analysis
  - Molecular-biological, histological and immunohistological methods
  - Flow cytometry (FACS)
  - Modern digital image processing techniques such as microdissection
  - Raman microspectroscopy and multiphoton microscopy

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- Establishing of various 3D tissue models
  - Alternatives to animal testing in cosmetics R&D
  - ADMET testing in substance and drug screening
  - Target screening for new therapeutics and infection biology
- Development of specific computer-controlled bioreactor systems for the culture of 3D tissue models
- Process development, manufacturing and testing of cell and gene therapeutics as investigational medicinal products or ATMPs (phase I/II clinical studies)

Infrastructure and technical equipment

- Cell culture laboratories conforming to safety levels S1 and S2 of the German GenTSV (genetic engineering safety regulations)
- State-of-the-art equipment such as an inverse fluorescence microscope, a multiphoton microscope system, a Raman microspectroscopic system, FACS and laser-capture microdissection instrumentation
- GMP production unit (cleanrooms, separate quality control area, storage facilities)

FRAUNHOFER CENTER FOR CHEMICAL-BIOTECHNOLOGICAL PROCESSES CBP

The Fraunhofer Center for Chemical-Biotechnological Processes CBP in Leuna, central Germany, closes the gap between the lab and industrial implementation. By making infrastructure and plants (pilot scale and miniplants) available, the center makes it possible for cooperation partners from research and industry to develop and scale up biotechnological and chemical processes for the utilization of renewable raw materials right up to industrial scale.

Within the past five years, laboratories and plants, offices and storage facilities have been built on more than 2000 m², thanks to core funding from the *Land* of Saxony-Anhalt, project funding through the German Federal Ministries of Education and Research and Food and Agriculture as well as the Fraunhofer-Gesellschaft. This has resulted in a unique platform for the development of new processes up to commercially relevant dimensions that have a direct link to the chemical industry on the one hand, and Fraunhofer research on the other. After the successful evaluation in 2014, the project group at Fraunhofer CBP has been transferred into the combined federal and state-level financing arrangements of the Fraunhofer-Gesellschaft at the beginning of 2015.

Joint projects involve partners from industry, academia and non-university research establishments, and currently focus on the following specializations:

- Obtaining high quality extractives from biogenic raw and residual materials
- Pulping of lignocellulose, separation and use of its components to make further products
- Development of processes to obtain new technical enzymes
- Manufacturing of biobased alcohols, acids and olefins using fermentation and chemical processes
- Functionalization of vegetable oils, e.g. biotechnological epoxidation and ω-functionalization

The core focus of the Fraunhofer CBP's activities is the sustainability of processes along the entire value chain involved in generating products based on renewable raw materials. The goal is to achieve integrated, cascading material and energetic utilization of ideally the entire components of any given plant biomass, using the biorefinery concept.

Process development thus concentrates on the following aspects:

- Exploiting the carbon synthesis potential provided by nature
- The energy and resource efficiency of the processes developed
- Minimizing waste streams
- Reducing CO_2 emissions
- Utilizing plants that are not suited as either human food or animal feed
- Integration of the processes developed into existing systems, for example to obtain biogas from residual biomass

Small and medium-sized enterprises frequently do not have the resources of their own to realize the transfer of these new technologies from the laboratory to industrial implementation. The center's pilot scale and miniplant facilities offer these customers an excellent platform for process development.

Range of services

To solve process-technical issues, the Fraunhofer CBP provides modular process capacities of up to 10 m³ fermentation volume and continuous plants capable of high-pressure processing up to 20 kg per hour, plus a wide range of processing, treatment and reconditioning techniques and methods. This versatile "flexible biorefinery" facilitates the conversion of raw materials such as vegetable oils, cellulose, lignocellulose, starch and sugar into chemical products.

Infrastructure and technical equipment

- Pulping and component separation of lignocellulose using organic solvents, with a capacity of 1 metric ton of biomass per week
- Fermentation capacities of 10/100/300/1000 and 10,000 liters, equipment for downstream processing of fermentation products
- Reactors for enzymatic processes up to 1000 liters
- Various process units for chemical reactions under ATEX conditions (continuous up to 20 kg/h or batch up to 100 liters at temperatures up to 500°C and pressures up to 300 bar)
- Mechanical and thermal separation processes (including high-temperature rectification up to 350°C at reduced pressures and extraction with l-propane and sc-CO_2), also under ATEX conditions

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BIO-, ELECTRO- AND CHEMOCATALYSIS BIOCAT, STRAUBING BRANCH

After a positive evaluation in 2013, and at the end of five-year, start-up funding from the Free State of Bavaria at the close of 2014, the Project Group "Catalytic Processes for a Sustainable Supply of Raw Materials and Energy on the Basis of Renewable Resources BioCat" was transferred into the federal and state-level financing arrangements of the Fraunhofer-Gesellschaft. As "Bio-, Electro- and Chemocatalysis BioCat" the group at the Straubing branch of the Fraunhofer IGB has continued in its work.

Focus is on the development of new chemical catalysts and biocatalysts and their application in technical-synthetic and electrochemical processes. Based on substrates such as biomass, CO_2, and waste streams, the entire spectrum of catalysis is used to develop new sustainable and resource-efficient chemical products. Here, homogeneous and heterogeneous chemical catalysis, enzymatic and whole cell catalysis, electrocatalysis, and especially their combinations are utilized. In the case of using plant biomass, the goal is to achieve the substantial use of the material variety of biobased molecules and to exploit the potential of chemicals and biocatalysis so as to achieve a considerate transformation while obtaining important functionalities. Successful examples of our work include the transformation of terpenes (residual material of wood processing) to biosurfactants, biobased epoxides or monomers, especially impact-resistant, cold-stable polyamides. Other recycled material flows are vegetable oils and fatty acids, lignin and nitrogenous sugar, which are, for example, converted to functionalized carboxylic acids, conductive polymers, and monomers for polyesters and hydrocolloids.

Furthermore, BioCat transfers the expertise of chemical catalysis onto mineral residues to also develop these as a source of secondary raw materials. Even with inorganic residues, the variety of the mostly complex mixtures of different elements constitute an access to new products, where BioCat in this instance, has in view the production of new catalysts and the provision of raw materials for the German industry. The combination of chemistry and biotechnology also offers BioCat the opportunity to develop new energy- and resource-efficient processes in this field.

The group has also developed new methods of managing electrical energy by binding and converting CO_2 in the storage of chemical energy. These products and the corresponding methods are first provided to companies for the production of bulk and fine chemicals. Second, they can be used to store energy in fuels, such as in the form of longer-chain hydrocarbons, and can therefore make a contribution to the success of the energy turnaround. Here, the goal is the best possible utilization converting raw material to the biobased final product.

The BioCat branch unites biotechnologists, molecular biologists, and chemists who, in addition to their respective expertise in biotechnology and chemistry, have in-depth knowledge in the fields of biogenic raw materials, natural materials, and residual streams. By combining these different disciplines, it is possible to offer – apart from professional advice – development work in the areas of (i) new catalysts or catalyst optimization and existing processes, (ii) new materials, and (iii) new reactions which is carried out hand-in-hand with clients. The development work is supported primarily by existing analytical methods such as GC-MS, LC-MS, NMR and electroanalysis.

Thanks to the closely linked expertise in chemical catalysis and biocatalysis, BioCat has already successfully evaluated established processes in the chemical industry and outlined cost-effective and resource-efficient alternatives for the client.

The scarcity of fossil resources and the aspired reduction of CO_2 emissions due to climate change represent a huge scientific challenge for society and science. Since the biomass resource for a change of chemical raw materials is limited, we rely, apart from wastes and residues, mainly on CO_2 as an essential carbon source – and thus combine the need for CO_2 reduction with material value. Against the backdrop of "sustainable chemistry" the BioCat Group aims to accelerate and decisively shape the development of the new generation of catalysts and processes.

For this, BioCat works closely with the TU München, the departments of the Fraunhofer IGB, and the branch Sulzbach-Rosenberg of the Fraunhofer UMSICHT. In collaborative projects, topics for the conversion of renewable resources and the use of hydrocarbons to store electrical energy are pursued.

Range of services

- Screening of biocatalysts and chemical catalysts
- Molecular biological and technical optimization of enzymes and enzyme reactions
- Synthesis of fine chemicals
- Development of methods for waste recycling
- Development of methods for integrating the use of renewable resources in existing processes
- Conducting studies in the field of renewable raw materials
- High-resolution NMR analysis (400 MHz) in solution for the purposes of molecular structure elucidation, reaction kinetics, deep temperature analytics, and developing techniques
- Electroanalytical methods (e.g. cyclic voltammetry, chronoamperometry, electrochemical impedance spectroscopy)

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Infrastructure and technical equipment

- Autoclave unit with several parallel laboratory-scale reactors (material: Hastelloy C22, volume: 100 ml/reactor; pressure: up to 300 bar, temperature: up to 400°C)
- Various bioreactors up to 40 liters
- Automation platform for high-throughput methods
- Analysis: GC-MS, LC-MS, HPLC and FT-IR with online probe
- 400 MHz NMR spectrometer

TRANSLATIONAL CENTER "REGENERATIVE THERAPIES FOR ONCOLOGY AND MUSCULO-SKELETAL DISEASES", WÜRZBURG BRANCH

The project group "Regenerative Technologies in Oncology" was positively evaluated in February 2014, and, as a result has been transferred to the federal and state-level financing arrangements of the Fraunhofer-Gesellschaft in July 2014. In addition, a further sponsorship program was initiated by the Bavarian Ministry of Economic Affairs and Media, Energy and Technology. Its aim is the establishment of the Würzburg Translational Center "Regenerative Therapies for Oncology and Musculoskeletal Diseases" as Würzburg branch of the Fraunhofer IGB. The favorably evaluated project group was transferred to the Translational Center as the departments of "Test Systems" and "Bioreactors".

Regenerative medicine plays a central scientific role in Würzburg. Established since 2009, technologies are being used to develop new products, implants, and cell-based therapies for biotechnology as well as for medical engineering and the pharmaceutical industry. The department's focus is on diseases of the musculoskeletal system such as osteoarthritis, which is widespread. In the EU projects BioInspire and VascuBone, we develop stem cell-based musculoskeletal therapies. Preclinical studies are conducted with international partners in Norway and Austria. Clinical trials of these new, innovative ATMPs (Advanced Therapy Medicinal Products) are being prepared in Germany, Austria and Norway. The cultivation of our vascularized matrix (BioVaSc-TERM®) in specific bioreactors, with which we produce complex vascular implants, has now also been established under GMP conditions in cooperation with the University Hospital of Würzburg.

To expedite the transfer of these new therapies into clinical development and medical care, the Bavarian Ministry of Economic Affairs has provided the Translational Center Würzburg with development project funds totalling ten million euros over a period of five years. The interdisciplinary team focuses on the expansion of cooperation with the University Hospital of Würzburg and the Fraunhofer ISC for the establishment of the theranostics field. Other key partners are the Musculoskeletal Center Würzburg (MCW) for the area of implants, the Chair of Functional Materials in Medicine and Dentistry (FZM) for the field of biomaterials, the Comprehensive Heart Failure Center (DZHI) for preclinical testing of medical devices, and the Comprehensive Cancer Center (CCC) for the area of Test Systems.

The focus of the department Test Systems is on oncology. Hence, methods for the standardization of human 3D tumor models in different levels of complexity have been established. These include models for lung and breast cancer, colorectal cancer, and a form of leukemia. In addition to the rate of division and apoptosis of tumor cells, different molecular activations and inhibitions of signaling cascades can be measured with an active agent after treatment. Based on these data and clinical data, "in silico" models are created in cooperation with the Department for Bioinformatics, to predict biomarker profiles for targeted therapies. In co-culture models with the tumor stroma, the interaction of agents, including biologicals such as antibodies and tumor cells, can be analyzed.

The complex tissue models were registered as a trademark in 2015. They include models of human barriers such as skin (Skin-VaSc-TERM®), cornea, intestine (GutVaSc-TERM®), trachea (TraVaSc-TERM®), lung (LunVaSc-TERM®), and the blood-cerebral barrier. We adapt these models to diseases (disease models) or simulate infections of pathogens, and establish long-term cultures. Using the tissue models, we also simulate interactions of medical products with the human body, such as stents, to optimize the surfaces of the implants.

In the section Bioreactors, a bioreactor platform has been developed for applications in tissue engineering, regenerative medicine, and for the extracorporeal preservation of organs and tissues. A basic specification of our system is that the bioreactor platform is applicable to a large user community in the field of research and development and within industry.

Contact

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Range of services

- Isolation of primary human stem and tumor cells
- Co-cultures for generating human vascularized tissue models, particularly for the human barrier organs
- Optimization of culture conditions and tissue-specific differentiation of iPS cells
- Tissue models using iPS or primary human cells
- Co-cultures to generate human solid tumors in vitro as tumor test systems
- Disease and infection models based on the tissue models
- Biological cell analysis of tumor tissue: molecular biological, histological, and immunohistochemical methods, flow cytometry (FACS)
- Target screening for new tumor therapeutics
- Specific bioreactors, sensors and incubators for tissue engineering
- Human vascularized (tumor) tissue for the optimization of medical products

Value chain

- Simulation of clinical therapy regimens involving the examination of the active principle and/or the side effects of a new drug candidate using vascularized human tumor and tissue models (disease models)
- Use of the tissue models in the process development to optimize drugs or diagnostic agents
- Implementation and validation of in-vitro tests as alternatives to animal testing (preclinical development phase)
- Studies on the efficacy of new pharmaceutical agents that are currently undergoing evaluation for clinical use
- Cooperation with the Faculty of Medicine of the University Hospital of Würzburg (organization of clinical phases I–III)

Infrastructure and technical equipment

- Cell culture laboratory for work on safety levels S1 and S2 GenTSV (genetic engineering safety regulations)
- Preclinical study unit – in cooperation with FMZ, DZHi and the University Hospital of Würzburg
- Cell analysis: inverse fluorescence microscope, FACS, microdissection system, Raman spectroscopy

INSTITUTE OF INTERFACIAL PROCESS ENGINEERING AND PLASMA TECHNOLOGY IGVP

The Institute of Interfacial Process Engineering and Plasma Technology IGVP headed by Professor Thomas Hirth is part of the Faculty of Energy Technology, Process Engineering and Biological Engineering of the of the University of Stuttgart. At the end of 2014, the institute had a research budget of around 3.4 million euros. A staff of 42 scientific, technical and administrative employees along with 42 doctorate students and 7 other students worked at the three IGVP facilities (Pfaffenwaldring 31, Allmandring 5b and Nobelstrasse 12).

The institute is organized in the two departments "Interfacial Process Engineering" and "Plasma Technology", with research carried out by six working groups. Close cooperation with the Fraunhofer IGB makes it possible to pursue projects from basic research to application. This approach is reflected in the variety of funding sources received by the IGVP, including the German Federal Ministry of Education and Research (BMBF), the German Federal Foundation for the Environment (DBU), the German Research Foundation (DFG), the EU, the *Land* of Baden-Württemberg, various foundations and industry. Key partners include the Max-Planck-Institut für Plasmaphysik in Garching, the KIT and DIFFER in the Netherlands.

Research and teaching

The IGVP focuses on the design, functionalization and characterization of surfaces and materials of inorganic or organic origin as well as of bio-, nano- and hybrid materials and their interaction. Likewise, interactions with biological interfaces as occurring in infection of human cells with viruses, bacteria and fungi, are being studied. Further activities include the simulation and engineering of interfacially driven processes, e.g. in membrane technology and biotechnology.

On the second part, scientific contributions cover the wide range from fusion oriented high-temperature plasma physics to industrial applications of low-temperature plasmas. A focal point is research on these plasmas for surface activation and deposition of new coatings as well as the development of new plasma sources and processes, as fostered by the synergy between microwave and plasma physics know-how. Research in fusion related plasma physics reaches from fundamental investigations of plasma dynamical processes and simulation of electromagnetic waves to plasma heating with high-power microwaves and development of corresponding transmission systems.

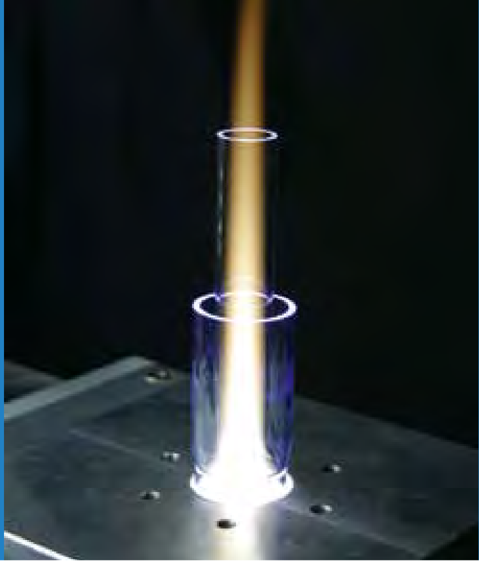
Teaching activities are centered on the subject areas of interfacial process engineering, infection biology, nanotechnology, industrial biotechnology, biomaterials, resource-efficient processes as well as plasma physics and plasma technology.

INTERFACIAL PROCESS ENGINEERING

Biological-Medical Interfaces

Priv.-Doz. Dr. sc. nat. Susanne M. Bailer

- Identification of biomarkers
- Screening for enzymes and microorganisms
- Microarray technologies
- Interactions between microorganisms and surfaces
- Host-pathogen interactions (viruses, bacteria, fungi)
- Virus-based therapies
- Synthetic biology
- Development of cell-based assays and 3D tissue models
- Cell-free protein synthesis



Chemical-Physical Interfaces

Dr. rer. nat. Monika Bach

- Composite materials, bio- and nanobiomaterials
- Nano- and microstructured (bio-)functional surfaces
- Biomimetic coatings for medicine and biotechnology
- Core-shell nano- and microparticles
- Characterization of interfaces and surfaces
- Bioprinting of artificial tissues

Interfacial Processes

Dipl.-Ing. Matthias Stier

- Process development for industrial biotechnology
- Microalgae production processes in photobioreactors
- Sorption heat storage, superheated steam drying
- Crystallization and recovery of inorganic nutrients
- Particle suspensions and emulsions in electric fields
- Membrane development and membrane processes
- Water treatment

PLASMA AND MICROWAVE TECHNOLOGY

Plasma Technology

Dr.-Ing. Matthias Walker, Akad. Oberrat

- Plasma source development (low/atmospheric pressure)
- Microplasmas
- Plasma coatings and processes for industrial applications
- Plasma diagnostics and characterization of plasma
- Modeling and simulation of plasma
- Plasma physical and plasma chemical processes

Microwave Technology

Dr.-Ing. Walter Kasparek

- Microwave heating and diagnostics for fusion experiments
- Microwave transmission systems and dedicated antennas
- Mode converters for oversized waveguides
- Millimeter-wave photonic components
- Testing of components in the microwave spectrum
- Reflectometry of millimeter waves in fusion plasmas

Contact

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Plasma Dynamics and Diagnostics

Dr. rer. nat. Mirko Ramisch

- Magnetic plasma confinement
- Fundamentals of turbulent plasma dynamics
- Probe and imaging diagnostics
- Physics of turbulent transport
- Flow/turbulence interaction
- Wave phenomena and wave type conversion
- Heating mechanisms using microwaves

SELECTED R&D RESULTS 2014

183 Projects

4 Fraunhofer lighthouse projects

22 Fraunhofer internal projects

27 Projects funded by federal ministries

59 Industrial projects

21 Projects with universities, municipalities or funded by foundations

38 EU projects

5 Projects funded by the *Land* of Baden-Württemberg

MEDICINE

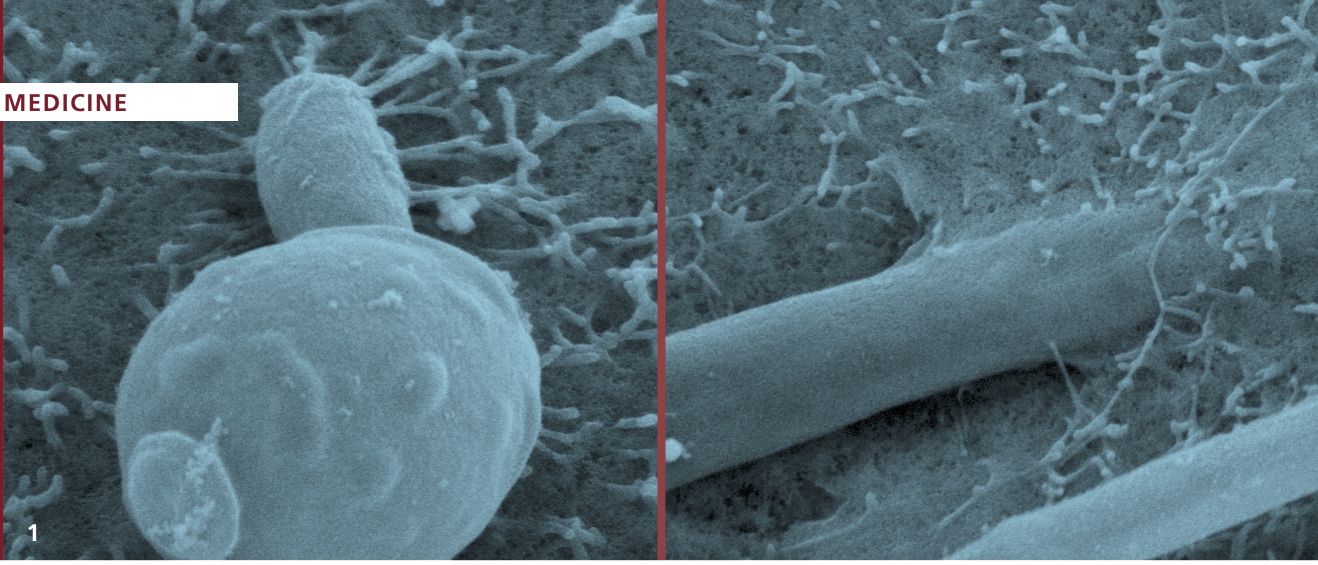
Increased survival rates offered by regenerative medicine, quicker and more accurate diagnostics using molecular-biological approaches, and a coordinated interaction between biologized implants and their physiological environment are scientific trends which improve healthcare provision and, at the same time, can reduce costs. In the medicine business area at the Fraunhofer IGB, we develop solutions in mostly interdisciplinary projects, based on our competencies in tissue engineering, biomaterials, immunology and infection biology.

Regenerative medicine – The focus of regenerative therapies is on the development of human cell-based therapeutics, autologous transplants and biologized implants. The Fraunhofer IGB and its Würzburg branch, with the Translational Center "Regenerative Therapies", cover the entire value-added chain right up to GMP-compliant manufacturing of cell-based implants (Advanced Therapy Medicinal Products, ATMPs) and – together with a network of physicians – phase I clinical studies. Our quality control systems identify potential contaminants (microorganisms, viruses) by non-destructive means, using spectroscopic, cell-based or molecular methods based on GLP and GMP guidelines. A new approach towards producing dimensionally stable tissue-like structures (e.g. cartilage, fat tissue) is pursued by the 3D printing of human cells on UV-crosslinkable hydrogels.

Diagnostics – New scientific strategies to combat infectious diseases are a high priority. Here, the combination of methods of functional genome analysis with our expertise in cell culture technology and infection biology results in a unique position for the development of infection models and diagnostics. We develop new diagnostic methods based on nucleic acids (diagnostic microarrays, biomarker development using high-throughput DNA sequencing) or by means of cellular reporter systems (cell-based pyrogen assay). This information helps to initiate measures for specific treatments or to develop personalized medicines for different population groups.

Medical engineering – For the optimization of surface properties of established medical devices such as stents we use plasma processes to generate bioactive or antibacterial surfaces; we then test the effectiveness and biocompatibility of these surfaces on in vitro tissue models. We also develop biodegradable coatings for bone implants that promote self-healing through cell adhesion. For disinfection and removal of pyrogenic residues we establish plasma sterilization processes for reusable sterile containers in terms of optimum effectiveness and material protection.

As a partner of the Fraunhofer Food Chain Management Alliance, we make a contribution to healthcare through the development of physical hygienization processes that protect the foodstuff's properties. Our medicinal research contributes to the Fraunhofer Group for Life Sciences' competences; in addition we are networked in the Fraunhofer Big Data Alliance.



1

OPTIMIZED DIAGNOSTICS FOR TREATING INVASIVE FUNGAL DISEASES

Ekkehard Hiller, Kai Sohn, Steffen Rupp

Significance of fungal infections

Fungal infections pose a growing medical problem and cause significant costs for healthcare systems around the world. In fact, invasive fungal diseases are among the leading causes of morbidity and mortality in severely immunocompromised patients, particularly affecting those with leukemia, patients who have recently undergone bone marrow or organ transplants, individuals who have spent long periods in intensive care, premature babies, and people with congenital or acquired immunodeficiency.

The vast majority of infections are caused by *Candida* and *Aspergillus* species. Changes in epidemiology observed in recent decades involve the emergence of a series of new pathogens that can also affect immune-competent people. *Cryptococcus neoformans*, for example, infects up to 700,000 individuals each year.

Especially the emerging pathogens like *C. glabrata*, *C. krusei* or *A. terreus* often show intrinsic resistance to many antifungals posing a serious treatment challenge. The mortality rate of 35–40 percent owing solely to candidiasis exceeds that of deaths caused by Gram-negative bacterial sepsis. Collectively, invasive fungal diseases place a heavy economic burden on healthcare systems, which amounts to several billion euros in Europe alone.

Furthermore, the widespread practice of administering preventive or empirical treatment without diagnostic proof of invasive fungal disease is leading to high, yet avoidable, costs, particularly since such treatment is often associated with severe side effects, and promotes the development of resistance.

Development goal: reliable diagnosis of pathogens

In order to achieve successful, cost-efficient treatment, the fast, reliable and species-specific diagnosis of fungal pathogens is indispensable. Despite this, safe, rapid diagnostics still present a challenge even today. Available diagnostic approaches are not sufficient to fulfill the demands of quick, accurate diagnostics, resulting in great clinical need.

The FUNGITECT project funded by the EU strives to address precisely this need. The project consortium includes both leading academic research institutes and SMEs that hold excellent market positions.

2

Molecular markers for personalized therapy

This work is intended to develop and validate a specific set of new molecular markers for invasive fungal diseases that can ultimately be commercialized. Such markers may consist of DNA, RNA or proteins, or may be based on the enzyme activity of pathogenic fungi.

Ultra-efficient diagnostic assays, developed with the aid of next-generation sequencing (NGS), bioinformatics platforms and mass spectrometry should facilitate the development of optimized treatment strategies that are tailored to each individual patient and thus allow us to achieve:

1) a diagnostic basis for the prompt, extremely effective treatment of patients with invasive fungal diseases
2) lower levels of overtreatment and reductions in side effects, including the emergence of resistance to antifungal agents
3) a reduction in the excessive costs of clinical treatment for fungal diseases.

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Funding

The "FUNGITECT" project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 602125.

Project partners

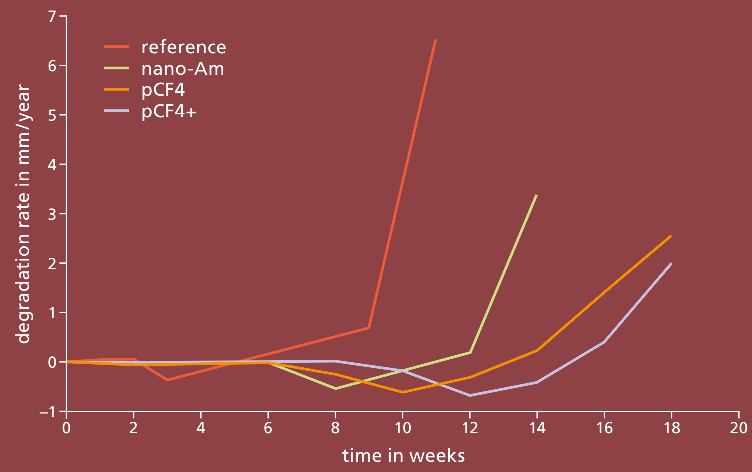
St. Anna Kinderkrebsforschung, Vienna, Austria | Medizinische Universität Wien, Vienna, Austria | Javna Ustanova Univerzitet U Tuzli Universitas Studiorum Tuzlaensis, Tuzla, Bosnia and Herzegovina | Genedata AG, Basel, Switzerland | Molzym GmbH & Co KG, Bremen, Germany

Further information

www.fungitect.eu

1 *Invasive growth of Candida albicans in an in vitro skin model.*

2 *Combined nano-HPLC and MALDI mass spectrometry for the analysis of biomarkers.*



1

FUNCTIONAL COATINGS FOR RESORBABLE BONE IMPLANTS

Michaela Müller, Veronika Schönhaar

Biodegradable materials instead of permanent implants

Treatment of bone fractures and defects in load-carrying regions currently involves the use of materials such as titanium or steel alloys that remain in the body permanently. These implants need to be replaced after a few years or decades. Such revision surgery is becoming increasingly common as a result of the general increase in life expectancy. However, it is associated with a health risk to the patient, due for example to nosocomial infections, as well as with costs to the health system. There is therefore a great need for new implant materials that initially support the defect and promote bone healing, but are then completely degraded.

Current approaches are based on implants made of magnesium and iron alloys, whose degradation in vivo is still unsatisfactory. As part of the internal Fraunhofer joint project "DegraLast", a new generation of biodegradable, load-bearing bone implants is being developed. Degradation depends on several factors that are independent of the material, e.g. the geometric shape and porosity of the implant as well as the site of implantation. The focus of the Fraunhofer IGB is therefore on the development of coatings or surface modifications to control the initial degradation of the implant as well as the adhesion and proliferation of bone cells.

Focus: Interactions of material and coating

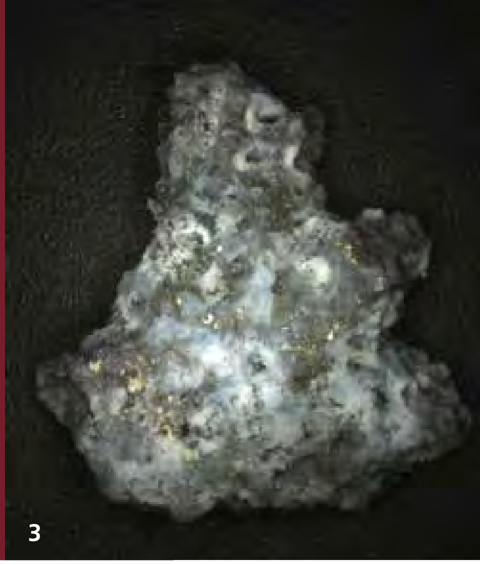
Part of the joint project involves the development of alternative magnesium alloys and iron composite materials. These require different coating strategies: the initial degradation must be delayed for magnesium-based implants, but accelerated for iron-based implants. Biocompatibility should be improved in both cases.

Evaluation of implant degradation in vitro was performed with a defined and standardized procedure involving exposure to various typical media. Media with increasing complexity and similarity to in vivo fluids were used: physiological saline, phosphate buffered saline (PBS), Hank's balanced salt solution (HBSS) and Dulbecco's Modified Eagle's Medium for cell culture (DMEM). Evaluation of the degradation of the materials was carried out with visual assessment as well as gravimetric, pH and potentiometric analyses. Various coatings and surface modifications were applied to the materials for these tests.

The results of the exposure tests showed that the rate of degradation was strongly correlated with the composition of the medium. Regardless of the material, the lowest degradation rates were found in the DMEM cell culture medium and the highest rates were found in physiological saline and PBS.

The reference alloys were coated with various different materials. These included polyelectrolyte multilayers and bioactive calcium phosphate sputter coatings (in collaboration with Dr. Roman Surmenev, Tomsk University), as well as cell adhesion-promoting biopolymers and various aminofunctional polymer layers. With the magnesium alloys, passivation layers were also formed with fluorocarbon plasma treatment.


2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Delayed degradation in magnesium alloys

The exposure studies showed that degradation of the magnesium alloy could be delayed with various surface treatments. The degradation rate in millimeters per year is shown in Fig. 1 with data from an uncoated magnesium alloy (reference), a sample with a ca. 30-nanometer layer of aminofunctional plasma polymer (nano-Am) and two different passivation treatments with plasma (pCF4 and pCF4+). The time point of degradation of the base material could be varied by adjusting the thickness of the applied coating and / or the parameters of the passivation process. Whether the rate of degradation and not just the time point of degradation can be adjusted by the surface, treatment cannot be determined from the results available so far.

We were unable to detect any significant increase in the degradation rate of the iron alloys with the coatings that were tested (including lactide / glycolide copolymers).

However, various coatings significantly improved the biocompatibility. The study of compatibility and cell adhesion was carried out in the Department of Cell and Tissue Engineering.

Outlook

The most promising coatings are currently being tested for their osteoinductive activity in vitro.

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Funding

We would like to thank the Fraunhofer-Gesellschaft for funding the project "Neue Werkstoff- und Technologieplattform für biodegradierbare lasttragende Knochenimplantate – DegraLast" within the scope of its market-driven prospective research program (MAVO).

Project partners

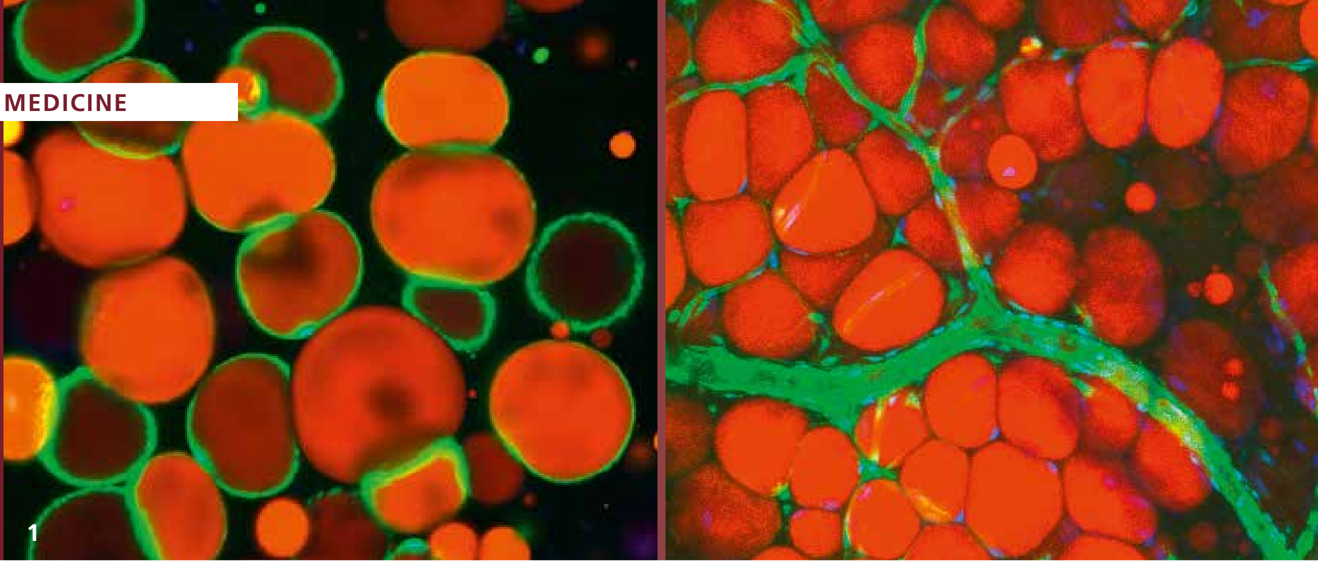
Fraunhofer IFAM, Bremen, Germany | Fraunhofer IFAM, Dresden, Germany | Fraunhofer ILT, Aachen, Germany | Fraunhofer IBMT, St. Ingbert, Germany

1 *Degradation rate of an Mg alloy in Hank's balanced salt solution (HBSS).*

2 *Reference Mg alloy before exposure; sample diameter 18 mm.*

3 *Reference Mg alloy after exposure for 11 weeks; 23% residual mass.*

4 *Mg alloy treated with pCF4+ after exposure for 18 weeks; 62% residual mass.*



DEVELOPMENT OF ADIPOSE TISSUE WITH MATURE ADIPOCYTES IN A THREE-DIMENSIONALLY STABLE BIOMIMETIC MATRIX

Birgit Huber, Kirsten Borchers, Petra J. Kluger

Volume and dimensionally stable adipose tissue

Severe burns with deep wounds, congenital deformities, removal of tumors or trauma can lead to the loss of or damage of adipose tissue. To date, there are no methods to create replacement tissue. Therefore, medical science is still unable to produce a well-defined and three-dimensionally stable substrate transplant consisting of a patients own adipose cells. The use of mature fat cells (adipocytes) in combination with a volume stable, printable matrix may open new perspectives in reconstructive and plastic surgery.

Isolation of mature adipocytes

The current gold standard for the production of fat cells is their differentiation from stem cells. This process is time consuming and expensive, and a large amount of tissue is required for the isolation of stem cells. However, little research has been performed on the use of already differentiated fat cells. At the Fraunhofer IGB, a method for the isolation of mature adipocytes has now been established.

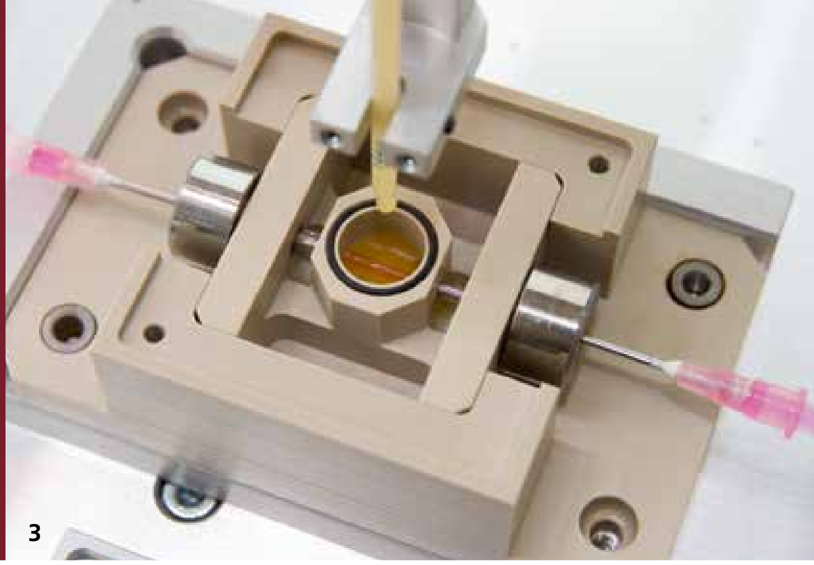
Approximately 50 percent of adipose tissue is made up of mature adipocytes. Due to the abundance of adipocytes in fat tissue, very little tissue is required to isolate enough cells for a fatty tissue construct. Because the body's own cells are not immunogenic and have a low mortality rate of less than 10 percent per year, adipose cells are a promising cell type for creating long-term and stable adipose tissue implants. The cells obtained at the Fraunhofer IGB have great lipid vacuoles and thus have the typical phenotype of native adipocytes in adipose tissue (Fig. 1).

Construction and culture of three-dimensional tissue models

At the Fraunhofer IGB, we have developed a crosslinked gelatin hydrogel that is similar to the natural, collagen-containing environment of cells in the body [1, 2]. The basic biomaterial, methacrylated gelatin, can be processed by various techniques, such as automated dispensing, inkjet printing or dip coating and further crosslinked to form hydrogels [3]. For the construction of three-dimensional adipose tissue models, we bring a high portion of mature adipocytes into the gelatin gels to reproduce the typical morphology of adipose tissue (Fig. 1). Due to the crosslinking of the gel matrix, tissue models are dimensionally stable and can be created with the strength of native fat by adjusting the degree of crosslinking. Under static culture conditions, the tissue equivalents remain viable for about two to three weeks (Fig. 2). During this time, the cells retain their typical morphology, viability and cell-type specific marker expression.

3D tissue models

For the production of large tissue equivalents, it is essential to incorporate a tubular vascular-like system throughout the construct in order to supply the cells with proper nutrients. Within the framework of the EU research project "Artivasc 3D", the Fraunhofer IGB develops permeable tubes from methacrylated gelatin to perform the role of blood vessels within the constructs. In collaboration with the University of Stuttgart and the industrial partner Unitechnologies SA, we are developing a bioreactor for the culture of perfused adipose tissue-equivalents (Fig. 3).



Therapeutic future: Individualized implants

The aim of the “Artivasc 3D” project is the layer-by-layer assembly of three-dimensional adipose tissue-equivalents using an automatic dispenser with a LED-based crosslinking unit (Fig. 2), with the focus of retaining the viability and function of fat cells. Through the development of printable and crosslinkable biobased biomaterials, we contribute to computer-based, additive manufacturing processes for the future of reconstructive medicine that can replace damaged tissue with biological patient-specific implants.

1 *Mature adipocytes in a biomimetic matrix (left) have a similar morphology to the native adipose tissue (right).*

2 *Macroscopic image of an adipose tissue-equivalent with mature adipocytes in methacrylated gelatin cultured in medium under static conditions.*

3 *Bioreactor for the culture of a vascularized adipose tissue-equivalent. Adipocytes are automatically dispensed in a matrix of photocrosslinkable gelatin in the bioreactor. Crosslinked gelatin hydrogel tubes serve as a blood vessel substitute.*

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References

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[2] Fraunhofer IGB Annual Report 2013

[3] Hoch, E.; Hirth, T.; Tovar, G. E. M.; Borchers K. (2013) Chemically tailoring of gelatin to adjust its chemical and physical properties for functional bioprinting, Journal of Materials Chemistry B. The Royal Society of Chemistry 1: 5675 – 5685

Funding

The “Artivasc 3D” project has received funding from the European Union’s Seventh Framework Programme for research, technological development and demonstration under grant agreement no 263416.

Further information and project partners

www.artivasc.eu

1

AMBULUNG – BIOARTIFICIAL LUNG

Annika Wenz, Kirstin Linke, Markus Schandar, Petra Kluger, Kirsten Borchers

Respiratory support for COPD patients

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death worldwide. Long-term ventilator support is a therapeutic measure that increases life expectancy, improves quality of life and reduces the cost of treatment of COPD patients. However, limited hemocompatibility restricts the use of the currently available "artificial lungs", extracorporeal gas exchange systems for long-term application.

Objective: Portable, cell-functionalized system

The objective of the EU-funded project "AmbuLung" is to develop a portable bioartificial lung assist system that is suitable for long-term ambulatory use. Together with our partners from the Imperial College of Science, Technology and Medicine in London, the Università degli Studi di Firenze and the company Novalung we aim to develop a miniaturized and endothelialized gas exchange system device. The gas exchange membranes of the new mobile AmbuLung are functionalized with bioactive molecules and endothelial cells in order to achieve biomimetic surfaces that prevent the development of thrombus formation and will extend the lifespan of the device.

Biofunctionalization of the gas-exchange membrane

The Fraunhofer IGB is developing heparin-based coatings for the polymethyl pentene (PMP) surface, which are functionalized with cell recognition sites to promote a surface which supports the stable adhesion of endothelial cells. In addition to the layer-by-layer adsorbed coats of albumin and heparin currently used in medicinal products, a carbodiimide-mediated coupling of heparin to PMP-membranes could be demonstated after a previous functionalization in an ammonia plasma treatment. Furthermore, we coupled chemically modified photo-sensitive heparin derivatives directly on PMP. The effectiveness of these coating methods was examined by X-ray photoelectron spectroscopy (XPS). The immobilized heparin layers were then further functionalized with peptide sequences that are found at the formation of cell-matrix connections in natural tissue.

Colonization with endothelial cells

Dynamic bioreactor systems are used to control cell differentiation, expansion, colonization and nutrient supply of endothelial cells on the gas exchange hollow fiber membranes. Initially, human endothelial cells are seeded on both sides of the PMP membrane. After the cells adhere to the membranes, the membranes are placed in a bioreactor under dynamic conditions and cultured up to five days (Fig. 1). Thereafter, the cells are examined for vitality, viability, integrity of the monolayer and for endothelial cell marker expression. This is done by live-dead staining and immunofluorescence staining for Ki-67, PECAM-1 and Von Willebrand factor (vWF).

We were able to colonize large areas of the PMP fiber surfaces with living cells (Fig. 2). The edges of the cell monolayer covered membrane surfaces showed an increase in Ki-67 expression, i.e. dividing cells (Fig. 3), and positive staining of vWF showed that the cells were endothelial cells. The integrity of the monolayer, which is a prerequisite for the anti-thrombogenicity of the surface, was demonstrated by the positive staining for PECAM-1 showing dense cell-cell junctions (Fig. 4).

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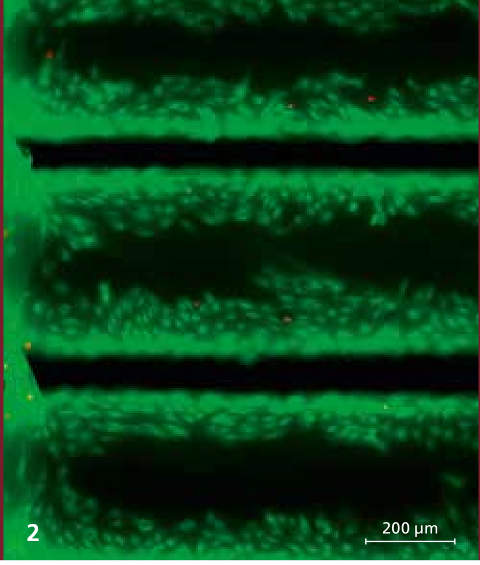

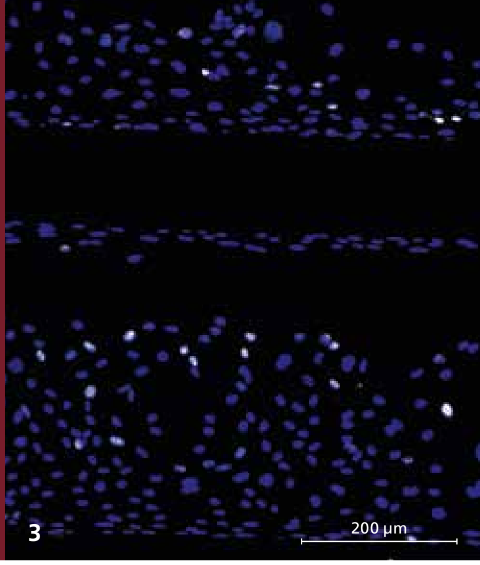

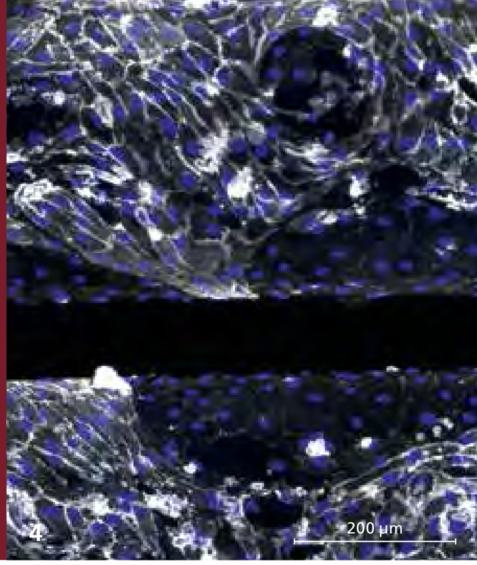

Outlook

The seeding of functionalized membranes will be optimized to reduce the required cell numbers, improve the speed of cell adhesion and achieve stable colonization even under physiological shear stress. Preclinical porcine model testing for functionality and antithrombogenicity will be performed. The first-in-man studies are planned for the miniaturized AmbuLung system containing the biofunctionalized PMP membranes without cells.

1 *Perfusion bioreactor for the nutrient supply of endothelial cells on the fiber mats.*

2 *Live-dead staining of endothelial cells on unmodified PMP fibers (viable cells are green, dead cells stained red).*

3 *The protein Ki-67 (white) is formed in the cell nuclei (blue) of proliferating cells.*

4 *Staining of the protein PECAM-1 (white) showing cell-cell contacts.*

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Funding

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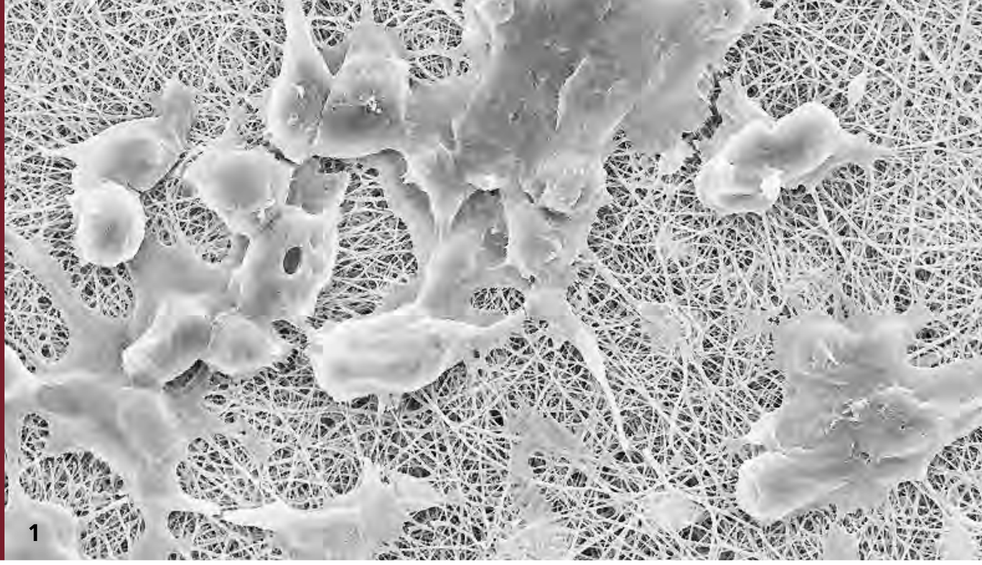
Project partners

Novalung GmbH, Heilbronn, Germany | Imperial College of Science, Technology and Medicine, London, UK | Università degli Studi di Firenze, Italy

Further information

www.ambulung.com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DEVELOPMENT OF BIOMIMETIC MATERIALS FOR CARDIOVASCULAR THERAPIES

Svenja Hinderer, Katja Schenke-Layland

Challenge – the regeneration of heart muscle tissue

According to figures from the World Health Organization, cardiovascular disease is still the number one cause of death worldwide. Here, the heart muscle and heart valves are often affected. Damage to these tissues can occur due to different risk factors such as smoking and an unhealthy diet, which can lead to a heart attack. Furthermore, congenital diseases may be the cause of organ or tissue failure.

The adult human heart cannot regenerate itself after injury, which often significantly reduces the heart function that in turn negatively affects the quality of life of many patients. A large number of scientists across the global are working on the important goal of restoring the normal heart function after injury. Recently, the field has turned towards the development of new biomaterials that can protect cells, influence their behavior and increase engraftment. These materials are often functionalized by mimicking the structure and biochemical properties of the natural extracellular matrix.

(Bio-)functionalized materials

Previous approaches, such as injecting stem cells into the heart muscle, have shown little success due to the lack of cell engraftment and integration into the native heart tissue, as well as the lack of differentiation into functioning cardiomyocytes. One strategy at the Fraunhofer IGB is to immobilize different proteins in a synthetic material to attract and bind circulating endothelial progenitor cells in the blood. We have developed a polyethylene glycol (PEG) hydrogel that allows the controlled and continuous release of the growth factor-stromal cell derived factor 1α (SDF-1α) [1]. Our studies have shown that the SDF-1α protein released from the hydrogel is still functional and thus can recruit progenitor cells. In other projects, we could demonstrate that fibrous, electrospun substrates with SDF-1α can be created. Furthermore, SDF-1α and other proteins and growth factors can either be electrospun into the core of fibers or they can be coated on top of the fibers. Since SDF-1α binds to the CXCR4 receptor of progenitor cells, this technique enables the material processing and modification of the production of off-the-shelf products that have the potential to colonize themselves in vivo.

EU Project AMCARE – Materials for cardiac regeneration

The EU consortium project "Advanced Materials for Cardiac Regeneration" (AMCARE) which includes ten partners from five European countries, under the coordination of Dr. Garry P. Duffy (RCSI, Dublin, Ireland), investigates solutions for the regeneration of inner and outer heart wall infarcts. In the project, natural materials and innovative surgical devices are to be developed that allow for the minimally invasive application of stem cells and nanoparticle-bound growth factors in the area of infarction, to promote the healing of the heart. Outer wall infarction will be treated with an electrospun patch, much like a surgical dressing. Inner wall infarctions will be treated with a hydrogel carrier substrate. Our expertise in the development and approval of biomaterials plays a major role in the consortium, as it is our task to test the in vitro cell-matrix interactions of the final products. We are performing extensive biocompatibility tests in respect to cytotoxicity as well as topological and biomechanical analysis to further identify material properties.

1 *SDF-1α-coated, electrospun carrier substrate with progenitor cells.*

2 *PEG hydrogel.*

3 *Therapies for myocardial regeneration (hydrogel and patch).*

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Funding

We would like to thank the Fraunhofer-Gesellschaft for funding the Attract Group for the development of cardiovascular regeneration technologies and the European Union for funding the project AMCARE in the Seventh Framework Programme for research, technological development and demonstration under grant agreement no 604531.

Further information and project partners

www.schenke-layland-lab.com | www.amcare.eu

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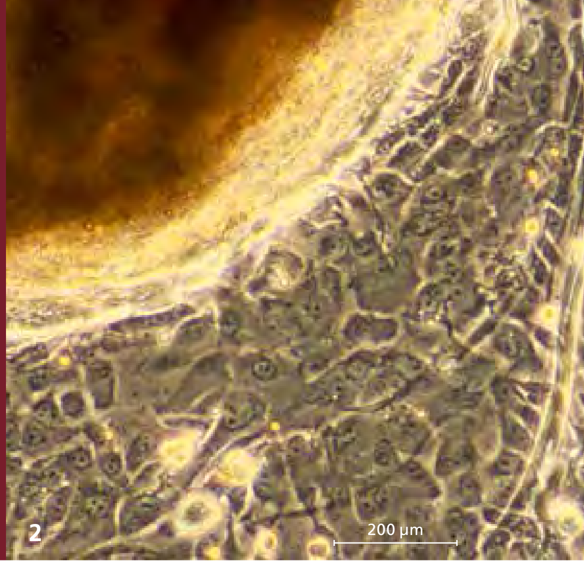

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TRACHEAL TISSUE ENGINEERING FOR INFECTION RESEARCH

Maria Steinke, Katharina Seidensticker, Heike Walles

Background

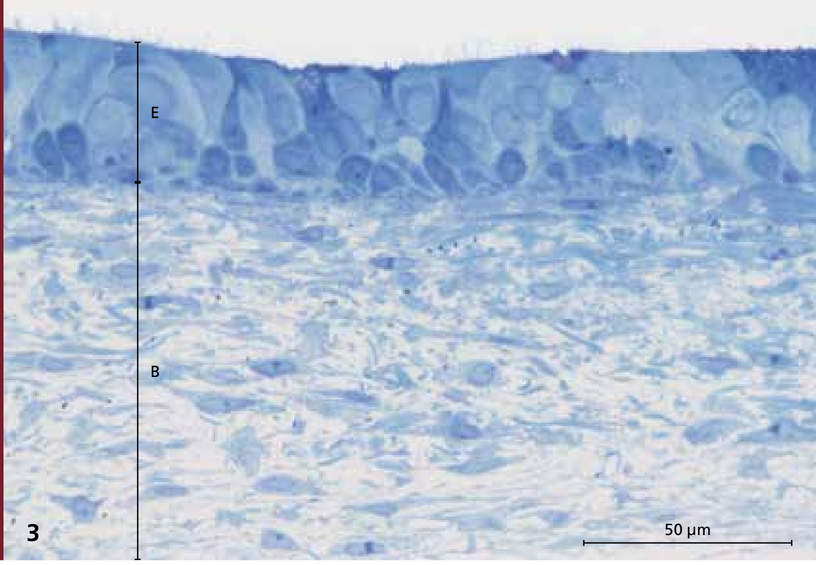
With every breath, we inhale an enormous number of diverse particles and pathogens that are combated by the natural defense mechanisms of our airway mucosa and transported out of our bodies. The majority of these foreign particles are harmless, but distinct pathogens, such as the bacterium responsible for whooping cough (*Bordetella pertussis*), can trigger a serious infection originating in the airway mucosa, especially in children. Because man is the only natural host for this bacterium, data from studies on animals often do not accurately reflect the situation in humans. As a consequence, many aspects of whooping cough infection remain speculative and the development of new drugs and vaccines faces serious challenges.

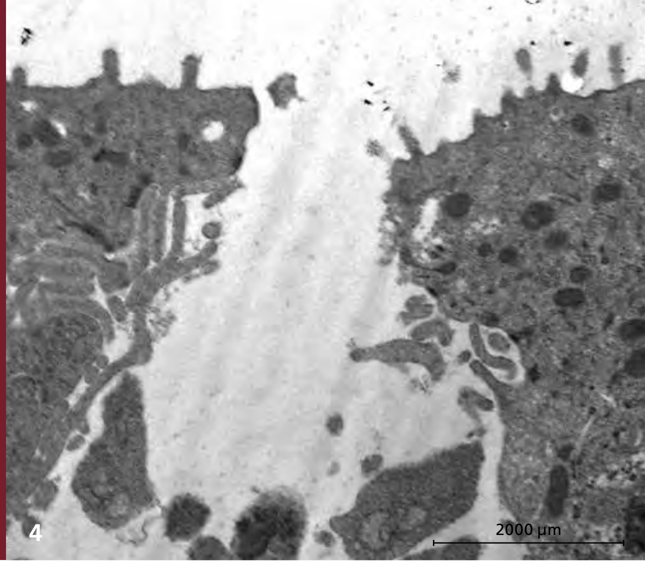
Although protection against *B. pertussis* through immunization is good, whooping cough infections have been increasingly diagnosed in recent years, even in industrialized countries. Recently, this observation led the Centers for Disease Control and Prevention in the US to classify whooping cough as a re-emerging infectious disease. In order to study the interactions between *B. pertussis* and the human airway mucosa and hence to (further) develop appropriate drug treatments, test systems that physiologically model the mucous membranes of the human airway as closely as possible are needed.

Production of a 3D in vitro test system of the human airway mucosa

Using primary cells (isolated from human bronchus biopsies, Figs. 1, 2), the vascularized biological scaffold BioVaSc-TERM® [1] and specialized bioreactor systems, our working group was able to develop a three-dimensional in vitro test system for the human airway mucosa with high in vitro/in vivo correlation. The epithelial surface of this test system consists of basal precursor cells, mucous-producing goblet cells and ciliated airway epithelial cells facilitating the mucocililary clearance of the airways in vivo. Moreover, the tissue model contains fibroblasts that migrate into the biological scaffold, where they restructure and maintain the surrounding connective tissue (Fig. 3). Both airway epithelial cells and fibroblasts contribute to the formation of the basal membrane [2, 3].

In a collaborative project with the University of Würzburg, we recently began infection studies with purified toxins extracted from *Bordetella pertussis* using our 3D in vitro test system. For example, at the ultrastructural level, we observed complete destruction of airway epithelial cells following infection, disrupting the barrier function of the airway epithelium (Fig. 4). The goal of the ongoing studies is to clarify the causes for these significant consequences of toxin application.





Outlook

Our 3D in vitro test system for the human airway mucosa (TraVaSc-TERM®) is ideal for researching the mechanisms of whooping cough infection and can contribute in the long term to the (further) development of suitable drugs and vaccines. We also envision the application of our tissue model in testing inhalable substances and in studying the interactions between the human airway mucosa and medical products such as airway stents.

Standardizing the construction of the test systems and to carry out applicable infection studies requires an interdisciplinary network of biologists, physicians and engineers. Such a network has existed since 2014 in the Translational Center "Regenerative Therapies for Oncology and Musculoskeletal Diseases" of the Fraunhofer IGB under the direction of Prof. Heike Walles in close collaboration with the University Hospital in Würzburg and the University of Würzburg. Our strategic goal is to transfer new therapeutic agents to clinic application quickly and effectively avoiding the use of animal testing.

1 *Human bronchus biopsy material from which cells are isolated to construct the test system.*
2 *Airway epithelial cells that grow from a human bronchus biopsy sample.*
3 *Methylene blue staining of the test system. E: epithelium, B: connective tissue with fibroblasts.*
4 *Electron microscope image after infection with a B. pertussis toxin.*

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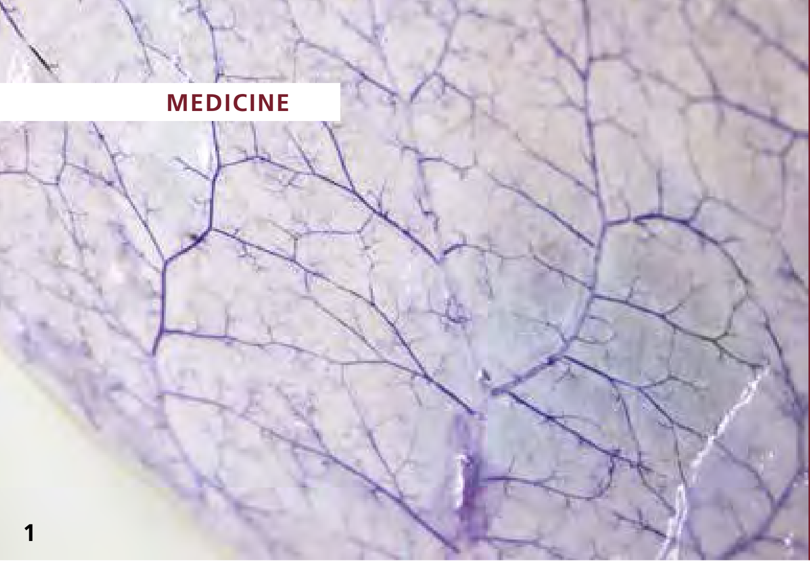
Funding

We would like to thank the German Research Foundation (DFG) for funding the project "Identifikation molekularer Mechanismen von bakteriellen Infektionen humaner Atemwege zur Herstellung antimikrobieller Oberflächen für Atemweg-Stents", reference number WA 1649/3-1.

Project partners

Prof. Dr. Thorsten Walles, Klinik und Poliklinik für Thorax-, Herz- und Thorakale Gefäßchirurgie, University Hospital of Würzburg, Germany | Prof. Dr. Roy Gross, Chair of Microbiology, University of Würzburg, Germany



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VASCUBONE – STRATEGIES FOR BONE TISSUE ENGINEERING

Christoph Rücker, Oliver Pullig, Jan Hansmann, Thomas Schwarz, Heike Walles

Background

The human body possesses the basic ability to heal bones. However, this sometimes leads to defects that necessitate medical intervention to support the healing process. These defects may be caused by severe bone trauma associated with a loss of bone substance or bone atrophy resulting from impaired blood supply. The failure to heal as a result of either pseudoarthrosis or the removal of bone tumors represent additional factors that can transcend the body’s natural ability to heal [1].

A common treatment approach for bone defects is replacement with endogenous material removed from the pelvic bone. The disadvantages of this method include the potential for complications at the donor site and the limited quantity of bone that can be extracted. The potential of tissue engineering offers a future alternative to this method.

Project objectives

The major EU-funded project “VascuBone” consists of a consortium of 19 academic and industry institutions from four European countries, working towards a comprehensive method for bone regeneration. The special challenge of this project is merging of the various fields relevant for bone tissue engineering, ranging from cell biology and signaling to material sciences and the manufacture of synthetic constructs as a foundation for bone replacement, to accompanying measures such as the development of bioreactors and in silico simulations at the Fraunhofer IGB. A non-invasive method for monitoring the efficacy of the bone replacement implant is another challenge to be addressed.

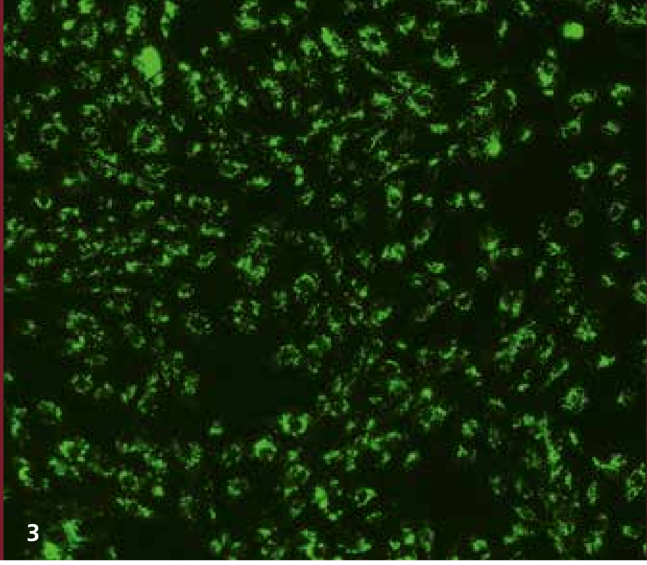
This modular approach is the key to responding appropriately to the nature and extent of each defect: for example, simple measures are required to support the regeneration of smaller defects, whereas complex bone implants must be constructed for larger ones, but both approaches share the same knowledge base and comprise both biocompatible materials as well as cells and growth factors.

Material modification and “scaffold design”

Biocompatible materials such as polylactide (PLA), polycaprolactone (PCL) and tricalcium phosphate (β-TCP) were developed by the partners and used at the Fraunhofer IGB to produce various constructs as supporting structures for bone cells. This required testing them with regard to relevant properties such as biocompatibility, degradation behavior and the potential to effectively populate the material with cells. Our project partners worked on the constructs to increase their hydrophilic properties, maximize the bioactive surface area and validate the coating process in order to provide additional methods for engineering the material characteristics.

Prevascularized bone substitute

The discoveries and developments from the different fields ultimately came together in the construction of a prevascularized implant. The Fraunhofer IGB branch in Würzburg prepared an inherently vascularized supporting scaffold (BioVaSc-TERM®) [3] colonized with endothelial precursor cells and combined with synthetic β-TCP in a dynamic bioreactor system. This structure, known as BoneVaSc-TERM®, provides the foundation for blood supply to relatively large implants, while the β-TCP has an osteoconductive function and therefore serves as scaffold for new bone growth. Moreover, the



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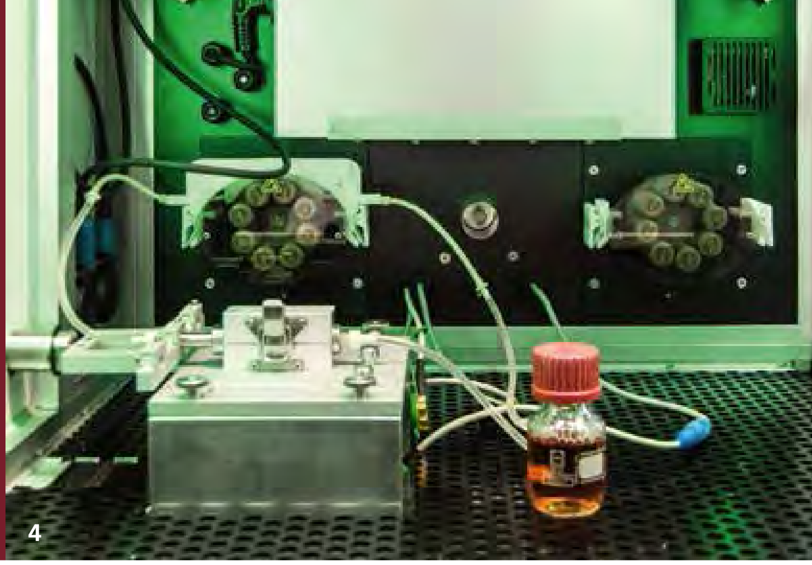

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synthetic material has osteogenic properties due to its prior colonization with cells (osteoblasts or mesenchymal stem cells) and the resulting deposition of new bone matrix. This complex implant, which is able to create an interface with the patient's circulatory system based on the BioVaSc-TERM® to supply the introduced cells, has already proven useful in preclinical in vivo studies of defects of the tibia and jaw bones.

Outlook

In addition to the successful production of prevascularized bone replacement implants and the construction of bioreactor systems needed for this process, this project has yielded discoveries in the various disciplines involved. The production of biocompatible materials and their modification was established. The project partners are now able to coat a variety of different surfaces with diamond nanocrystals to optimize cell adhesion or the potential for precursor cells to differentiate or to link growth factors according to the principle of physisorption.

Moreover, the development of MRI contrast agents that are compatible with bone allows for quality control and the ability to monitor the development of the bone substitute after implantation. By studying the interactions of different cell types in terms of their advantageous effects on bone healing and the impact of patient age on the process, VascuBone offers a basis to broaden the perspectives for personalized bone healing strategies.

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Funding

The "VascuBone" project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 242175.

Further information and project partners

www.vascubone.eu

1 *Vascular structure of the BioVaSc-TERM®, recolonized with endothelial precursor cells (violet).*
2 *β-tricalcium phosphate coated with diamond nanocrystals as a synthetic bone substitute.*
3 *Endothelial precursor cells fluoresce following LDL uptake.*
4 *View of the inside of an incubator system developed specifically for producing implants.*

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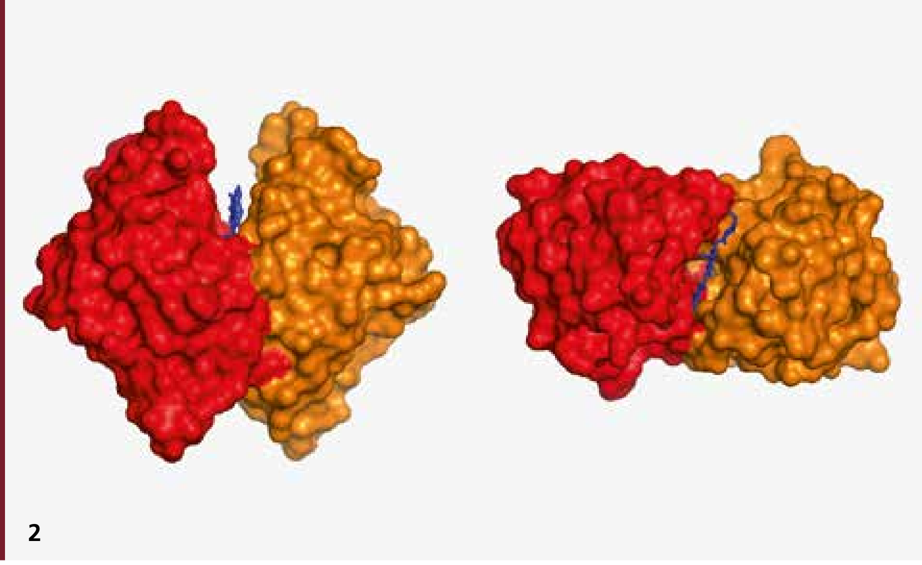

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A SWEET PATH TO DRUG DISCOVERY: CELL-BASED SCREENING TOOLS FOR C-TYPE LECTIN RECEPTORS

Débora Teixeira Duarte, Anke Burger-Kentischer, Steffen Rupp

The Fraunhofer IGB is involved in the Marie Curie Initial Training Network (ITN) ImResFun comprising 13 partners from nine European countries. The key objectives of ImResFun are to study fungal infectious diseases caused by the most common human fungal pathogens, the opportunistic *Candida* species, to understand how epithelia and immune cells respond to fungal infections and to identify means to combat them. Within the project we are focusing on the development of novel host-pathogen interaction systems and on the development of new screening tools based on immune receptors to identify compounds which modulate fungal infections.

Immune receptors – the body's sentinels

Immune receptors of the innate immune system are crucial for the first line of defense against microbial attacks. When fungi like the opportunistic *Candida* species contact the epithelial barriers of the human body, they are recognized by innate immune receptors on the cell surface. This allows the body to monitor the presence of potential aggressors and defend itself accordingly. One class of such receptors is the C-type lectin receptors (CLRs), which recognize sugars and more complex carbohydrates present in the fungal cell wall.

There are several CLRs which are responsible for the recognition of different types of fungal carbohydrates: Dectin-1 recognizes β-glucan (Fig. 2), while Dectin-2, Mincle and DC-SIGN recognize different forms of mannans and mannose-derived glycoconjugates [1]. These receptors are present on the surface of cells of the innate immune system (e.g. macrophages, dendritic cells) as well as in non-immune cells such as keratinocytes.

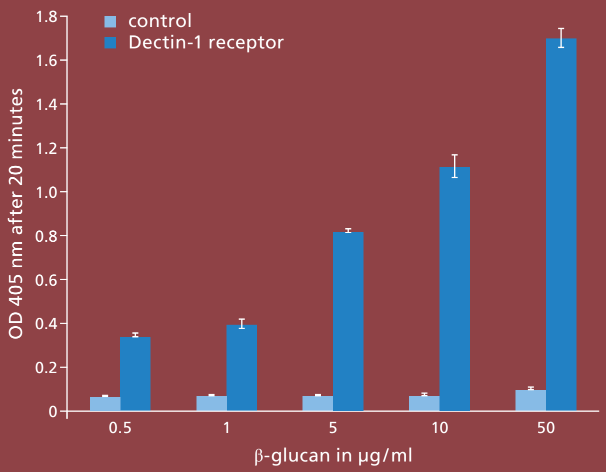
Ringing the bell

The stimulation of CLRs by their respective ligands triggers a signaling cascade which will ultimately lead to the activation of the transcription factor NF-κB. This transcription factor drives the expression of cytokines and chemokines that not only coordinate the innate immune response, but also determine the characteristics of the adaptive immune response. Therefore, CLRs can also be seen as major sensors and regulators of the immune system, which help the body to decide when and how to activate its defense mechanisms.

Besides their roles in fungal infections, CLRs may also be critical for development of inflammatory diseases. For example, one of the best characterized CLRs, Dectin-1, is known to be involved in the pathogenesis of several inflammatory disorders, such as psoriasis, atherosclerosis, asthma, rheumatoid arthritis and inflammatory bowel diseases.

New assays for antifungal screening

In order to exploit the therapeutic potential of CLRs, we are developing reporter cell lines to be used in screenings for new antifungals and immune modulators. The reporter assay employs NIH 3T3 mouse fibroblasts stably transfected with human CLRs and secreted alkaline phosphatase (SEAP) as a reporter gene, inducible by NFκB (DE 10 2006 031 483, EP 2 041 172) [2]. The binding of an agonist to the receptor



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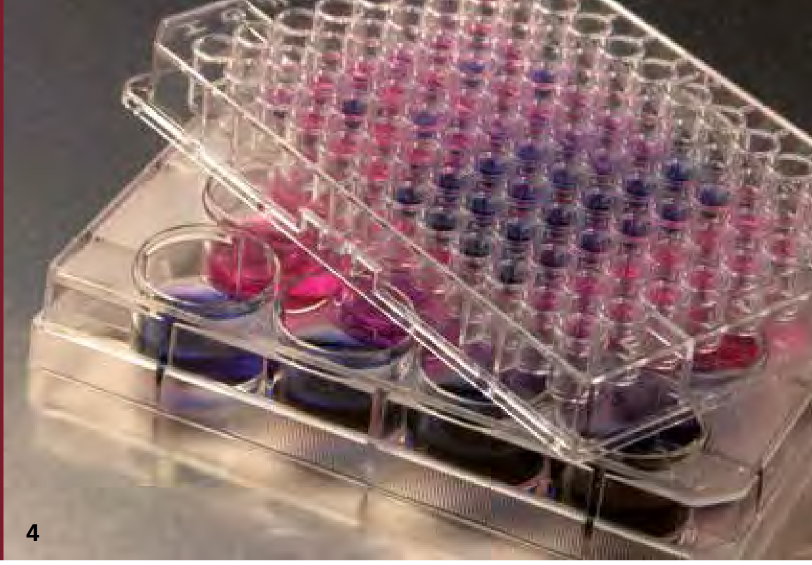

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can be detected through photometric analysis of the cell culture supernatant, after addition of the substrate (Figs. 3, 4).

A Dectin-1 reporter cell line was established by reconstructing the CLR signaling cascade inside NIH 3T3 fibroblasts. For this purpose, a multicistronic cassette with the receptor and all the required adaptor proteins was stably integrated into the genome of the reporter cells. The signaling cascade was properly integrated in the reporter cells and the assay was validated using known Dectin-1 agonists (β-glucans from different sources) and antagonists (Fig. 3).

Outlook

The Dectin-1 reporter cell line is currently used to investigate host-pathogen interaction, as well as to screen chemical libraries in search of immune modulators and antifungal drugs within the Marie Curie ITN "ImResFun".

1 *Cell culture flasks.*

2 *3D structure of Dectin-1 bound to a sugar molecule (blue).*

3 *Expression of SEAP following stimulation with β-glucans.*

4 *Cell-based reporter gene assay.*

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Funding

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Further information and project partners

www.imresfun.org

PHARMACY

Current challenges faced by the pharmaceutical industry include improving personalized therapy, the development of new active agents, and the enhancement of the effectiveness of drugs through improved formulations. In the pharmacy business area, the Fraunhofer IGB develops solutions for target and drug screening, pharmaceutical biotechnology and chemistry, including for the formulation and targeted delivery and release of drugs.

Screening and validation of drugs – Based on its own patents the IGB has developed various array technologies, high-throughput sequencing methods and human tissue models and is therefore able to elucidate host-pathogen interactions and make available targets for new anti-infectives. By targeted use of cell-based assays, we identify new drugs, e.g. for immunomodulatory substances or anti-infectives, on the basis of structure-activity correlations. Using complex organotypic 3D complex tissue models – both "healthy" and "diseased" tissues – we characterize potential active compounds in vitro. In particular, models of the human barriere tissues, i.e. skin, intestine, respiratory tract and the blood-brain barrier, are constructed as tissue models from primary or iPS cells, to investigate the absorption, distribution in organ models, toxicity and effectiveness of new drugs. In these tissue models we simulate clinical regimens to identify new prognostic markers, mechanisms of resistance and effectiveness by molecular methods such as gene expression and proteome analysis as well as by histology and confocal Raman spectroscopy.

Manufacturing and processing – We develop processes for the production of pharmaceutical proteins ranging from the establishment of new expression vectors, the strain development in microorganisms and mammalian cells, and the optimization of fermentation processes to the purification of the pharmaceuticals. We offer the production of clinical IMPs in compliance with GMP (Good Manufacturing Practice) regulations via internal Fraunhofer cooperation. Increasingly, we are also implementing cell-free biotechnological methods, which allow for the fast optimization of pharmaceutical proteins, produced in milligram amounts, that can be characterized while using the cell-based systems. Likewise, other highly efficient "cell-free" applications are the introduction of non-canonical amino acids or the coupling of drug and targeting molecules.

Formulation – With regard to the formulation of active agents, we are developing nanoparticulate structures that deliver drugs directly to the target location and then release them in a controlled manner. Virus-like particles represent a novel approach for the packaging and intravenous targeting of drugs.

With our expertise, we contribute to the offerings of the Fraunhofer Group for Life Sciences, facilitating a scope of activity covering the development of medicines from the screening for active agents to the production of test samples.

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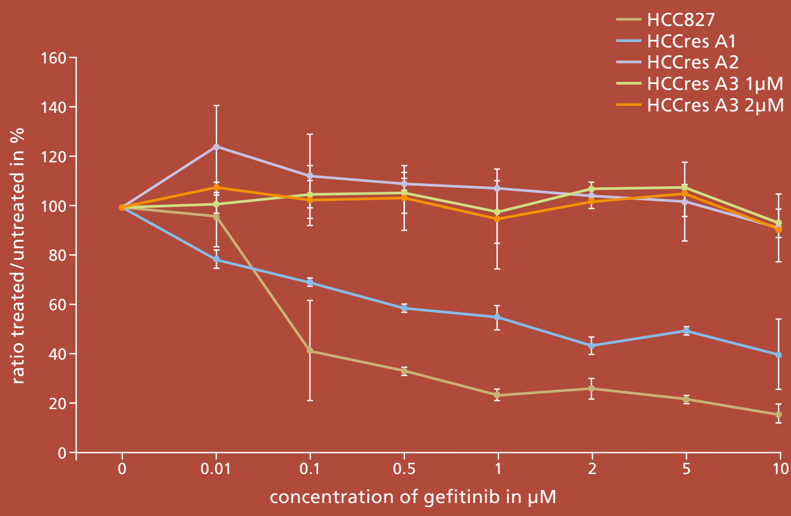


2

3D IN VITRO TUMOR TEST SYSTEMS FOR LUNG, BREAST AND COLON CANCERS

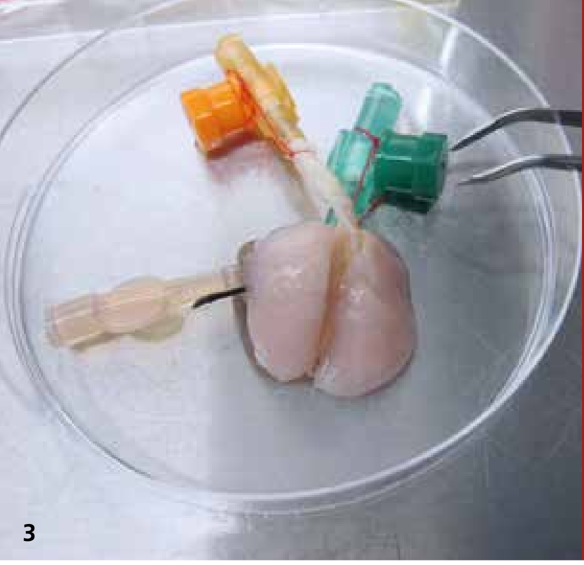
Sarah Nietzer, Claudia Göttlich, David Fecher, Lena Müller, Florentin Baur, Gudrun Dandekar, Heike Walles

3D in vitro test system for lung cancer

Over the past year, we were able to introduce resistant tumor cells into our established 3D lung tumor model. The cells derive from HCC827 adenocarcinoma cells with an activating EGFR (Epidermal Growth Factor Receptor) mutation and respond well to the EGFR inhibitor gefitinib. Long-term therapeutic success with EGFR inhibitors is not yet achievable in the clinical setting due to the very frequent development of secondary resistance. Our generated resistant cells exhibit varying resistance to treatment with gefitinib (Fig. 2). The use of these cells in our established lung tumor model allows us to study the correlations that lead to resistance [1]. By analyzing mutation and signal pathways, predictions based on the combined in silico bioinformatics model (Prof. Dr. Thomas Dandekar, University of Würzburg) can be tested in the 3D model to overcome specific resistance mechanisms. Acellularized rat lungs were reseeded with tumor cells and cultured in a lung bioreactor [2] (Figs. 1 and 3). This test system allows us to develop strategies to provide drugs with a better access to tumors in a tissue that mimics the respective organ. In this as in our other models the rate of cell proliferation is reduced compared to 2D cultures and therefore comes nearer to the real situation in patients.

3D in vitro test system for breast cancer

This year, the model for breast cancer was established for the first time on the SISmuc (Small Intestinal Submucosa with preserved mucosa) matrix. We used two cell lines known to differ in invasiveness. On the SISmuc, one of these cell lines showed a highly invasive growth and the preserved basal membrane structure of the matrix was overcome by these cells. This effect could be increased by culturing in the bioreactor. In the tumor-like tissue generated in this way the former crypt structure of the matrix is no longer evident (Fig. 4). This 3D tumor model also showed that the induction of cell death by chemotherapy differs from that in conventional 2D cell cultures. Like the reduced cell proliferation rate observed in 3D models, this result should represent an improvement in the predictive power of this preclinical model.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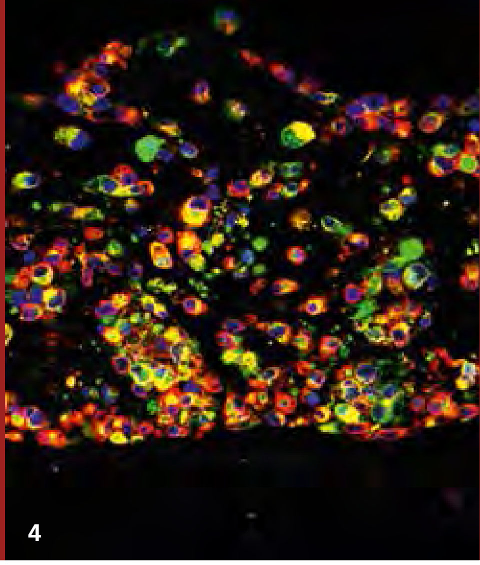
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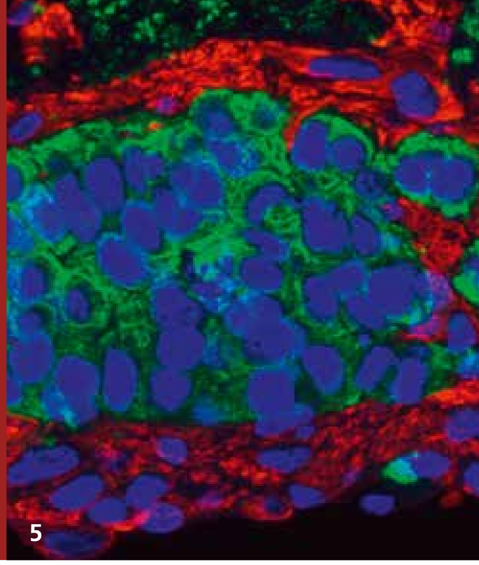
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3D in vitro test system for colon cancer

Colon cancer is the second most common form of cancer in Germany. In order to test new therapies for difficultly treatable colorectal tumors, we are currently developing a colon tumor model based on the SISmuc matrix. This model also simulates the tumor stroma that plays a key role in tumorigenesis. Better cell growth was achieved in the tumor model using a flow bioreactor, which also resulted in a more complex tissue structure (Fig. 5). First substances have been tested (e.g. silibinin) and various cell lines have been used to create the model. In addition to cell lines that are commercially available, early-passage cell lines derived from human xenografts have been used to establish tumor models in collaboration with the University Clinic in Rostock. These cell lines represent distinct subtypes of colorectal cancer, comprising different tumor stages and genetic changes. In future, this will permit clinic-oriented testing of substances.

1 *Recolonization of acellularized rat lung matrix in the lung bioreactor.*
2 *Resistant lung cancer cells.*
3 *Decellularized rat lung.*
4 *Invasive breast cancer cells in 3D.*
5 *Colon cancer cells with stroma in 3D (green: cancer cells, red: stromal cells).*

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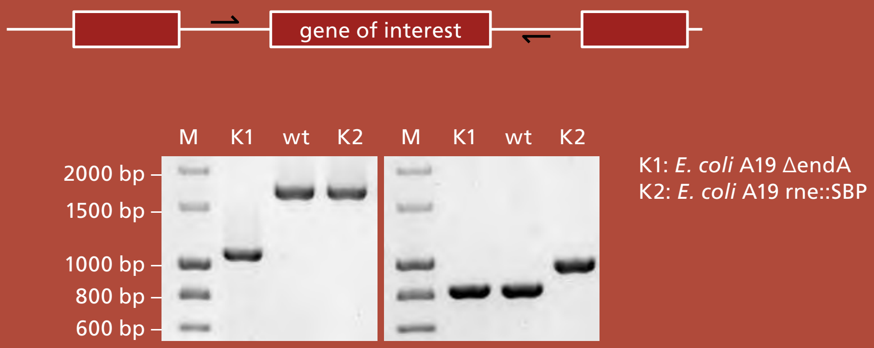
Funding

We would like to thank the Interdisciplinary Center for Clinical Research (IZKF) of the University Hospital of Würzburg for funding the project "Entwicklung eines 3D-Tumormodells und bioinformatische Signalweganalyse zur individualisierten Therapie des Lungenkarzinoms", reference number BD-247, and the Bavarian Ministry of Economic Affairs and Media, Energy and Technology for financial support within the BayernFIT program.

Project partners

Prof. Thomas Dandekar, University of Würzburg, Germany | Priv.-Doz. Dr. Michael Linnebacher, University Hospital of Rostock, Germany



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CELL-FREE BIOPRODUCTION

Daniel Foshag, Christian Kerger, Anke Burger-Kentischer, Steffen Rupp

Initial situation

The cost-effective availability of high-quality, functional biomolecules is crucial for the ability of our developed, modern society to progress. Especially in the healthcare sector, highly complex active substances such as enzymes, complex peptides, pharmaceutical proteins and other synthetic biomolecules are increasingly demanded for example as pharmaceuticals. Currently, peptide-based substances and their production processes are mainly developed using living microorganisms or mammalian cells. This technology has now become very efficient but is clearly restricted on many levels. The considerable material and energy input for instance limits the economic efficiency, and many promising pharmaceutical proteins have a toxic effect on the producing cells.

Cell-free bioproduction

Here, cell-free bioproduction opens up new possibilities. If only components of the organisms which are required for the protein biosynthesis are used, it will be possible to efficiently produce biomolecules with complex and even completely new characteristics in adapted reaction compartments. Although intensive research on cell-free biosynthesis is ongoing, a lot of basics are currently still lacking in order for this technology to be used in an economically efficient manner. Particularly in the international environment, however, first approaches can already be seen in the area of pharmaceutical proteins with a production volume of up to 100 liters, such as toxin-coupled antibodies [1].

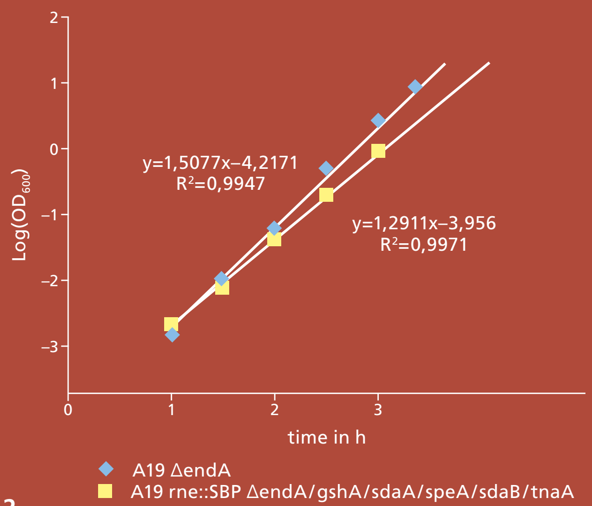
In the Fraunhofer lighthouse project "Cell-Free Bioproduction" significant steps for the industrial implementation of cell-free bioproduction were therefore identified and optimized in collaboration with eight Fraunhofer institutes. A key question for the reduction of production costs is the provision of energy for protein biosynthesis and the elimination of metabolic pathways which degrade the protein produced or its synthesis components, the amino acids. New, improved strains for cell-free bioproduction and new energy generation processes for this were developed at the IGB and implemented on a laboratory scale.

Adapted production strains without enzyme-degrading amino acids

In order to optimize cell-free bioproduction, the development of improved *E. coli* strains without patent protection is essential. For this purpose, metabolic pathways which destroy the starting materials or products of the process must be prevented in particular. Based on patent-free basic strains and using molecular biological methods, we have therefore removed the genes for enzymes which catabolize amino acids from the genome without leaving any residue, so tryptophan, arginine, serine and cysteine in particular are significantly stabilized in the extract (Fig. 1). Genes for known proteases and RNases were also deleted in order to stabilize intermediate products (mRNA) and target proteins. Thus, the proteases lon and OmpT as well as the RNaseE could be deleted or modified in such a way that they no longer disturb the synthesis process and the degradation of mRNA and proteins is reduced considerably. The deletions and insertions introduced had no negative effect on the vitality of the strain (Fig. 2). Using sample proteins such as GFP or CAT, improvements of a factor of three in protein yield were already achieved in the cell-free extract (Fig. 3).

Intrinsic metabolic pathways for energy supply and membrane-based reactor system

Furthermore, we optimized the method for extract production in such a way that it can guarantee a better energy supply for the system. In the process, intrinsic, metabolic pathways are



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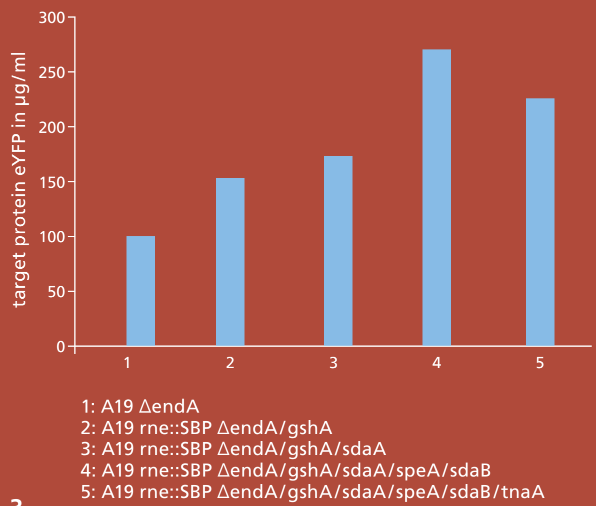

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used which enable the ATP synthase present in the extract to synthesize ATP from ADP. It is important here to control the extract production in such a way that ATP synthase which is as intact as possible is available in what are known as inner membrane vesicles. Using these extracts, we could dispense with the use of PEP as energy-rich substrate. Both by adding glutamate and pyruvate and by adding glucose using the intrinsic metabolic pathways, it was possible to synthesize an amount of protein comparable to that in the conventional extract production by adding PEP. Energy in the new system is now supplied via the respiratory chain by oxygen consumption. By developing a membrane-based reactor system for oxygen supply to the extracts in 50 ml scale, we were able to show that this system is also scalable. This will allow costs for protein production to be reduced by at least 50 percent.

Outlook

With the newly developed system, proteins can be produced in vitro in mg/ml scale at significantly lower costs than previously. By using intrinsic metabolic pathways, the energy necessary for protein synthesis can finally be regenerated via ATP synthase. Previous work has shown that the energy required can also be provided by generating a proton motive force by means of pathways other than the respiratory chain, such as bacteriorhodopsin. In the long term, this also opens up the possibility of developing a cell-free protein biosynthesis system via proton motive forces which are purely chemically produced, independent of metabolic processes [2]. A multitude of toxic proteins or protein fusions with toxins which can only be produced to a limited extent or not at all in vivo can be provided for research and pharmaceutical industry by means of cell-free bioproduction.

1 *Gel electrophoresis (0.8 % agarose, ethidium bromide-stained): genomic DNA of the A19 wild type and of the genetically modified strains was isolated, and the corresponding locus was amplified in order to verify correct insertion or deletion.*

2 *Comparison of the growth rates of genetically modified E. coli strains.*

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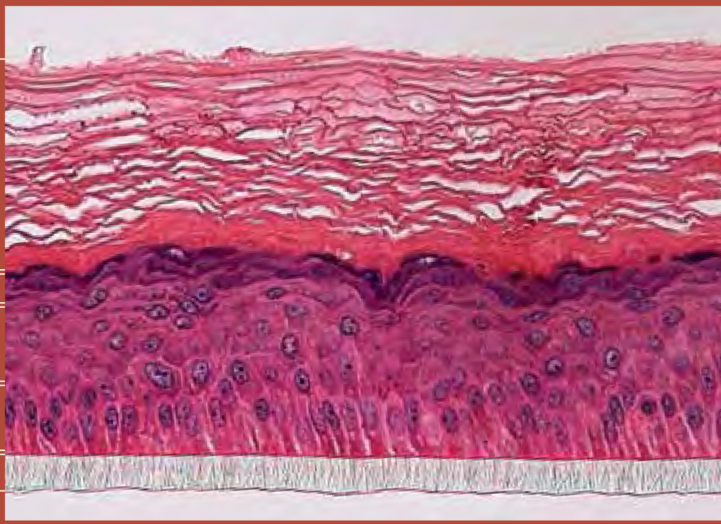
We would like to thank the German Federal Ministry of Education and Research (BMBF) for funding the project " Biomoleküle vom Band" in the "Biotechnologie 2020+" program and the Fraunhofer-Gesellschaft for funding the lighthouse project "Cell-Free Bioproduction".

Further information and project partners

www.zellfreie-bioproduktion.fraunhofer.de

3 *Comparison of the in vitro protein biosynthesis output of extracts of genetically modified E. coli strains. Synthesized eYFP was quantified by incorporation of ^{35}S-labeled methionine.*



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OPEN SOURCE RECONSTRUCTED EPIDERMIS AS A REPLACEMENT FOR ANIMAL TESTING

Florian Groeber, Heike Walles

The need for skin barrier models

Human skin acts as the barrier between the body and its environment; as such, it comes into contact with a huge variety of different substances and formulations. Until now, studies to assess the potential risks posed by new cosmetic, pharmaceutical or chemical substances have been largely carried out using tests on animals.

As an alternative to animal testing, researchers at the Fraunhofer IGB have developed skin models from human cells that mimic the anatomical structure of human skin [1]. Legislations such as the REACH Regulation or the 7th amendment of the Cosmetics Directive call for new tests and also limit studies on animals, resulting in a marked increase in the demand for skin models. In particular, single layer models that reproduce the human epidermis (reconstructed human epidermis) are finding increasing use in industrial research and development.

Predictivity as a prerequisite

For tests carried out using these models to be accepted by legislators, they must first be validated by the European Union Reference Laboratory for Alternative to Animal Testing (EURL-ECVAM). A skin model is compliant with regulatory requirements if it can demonstrate predictivity; that is, the model is able to predict the risk potential of defined test substances. This predictivity must be proven for all toxicological endpoints separately, of which skin irritation is one of the most important parameters that must be tested.

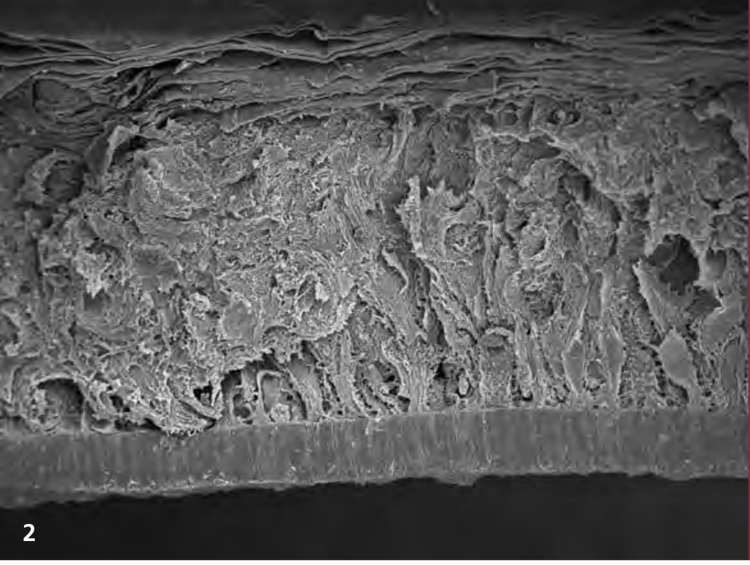
A new approach: the open source model

Until now, only four models developed by three commercial producers have been validated for testing skin irritation and hence availability of a model is strongly dependent on the market strategy of the supplier. To improve the availability of human models, Henkel AG & Co. KGaA therefore introduced a so-called "open source reconstructed epidermis (OS-REp)". Using the same approach as the open source concept in the information technology field, all protocols for producing this model will be made public with no legal restrictions. This means that a broad scientific community can contribute to improving the model.

To demonstrate that the open source model is acceptable for testing under regulatory terms, the Fraunhofer IGB participated in a "me too" or "catch-up" validation study for the OS-REp for skin irritation under the coordination of Henkel AG & Co. KGaA.

Validation studies on 20 substances

Validation studies were carried out in three independent laboratories in accordance with the OECD Test Guideline No. 439 using 20 defined test substances that represent a wide range of irritant effects and chemical properties. The substances were classified according to the viability exhibited by the OS-REp model after the test substance was applied. If the model demonstrated viability greater than 50 percent, it was deemed non-irritant. If the viability of the epidermal cells dropped below 50 percent, the test substance was classed as an irritant.



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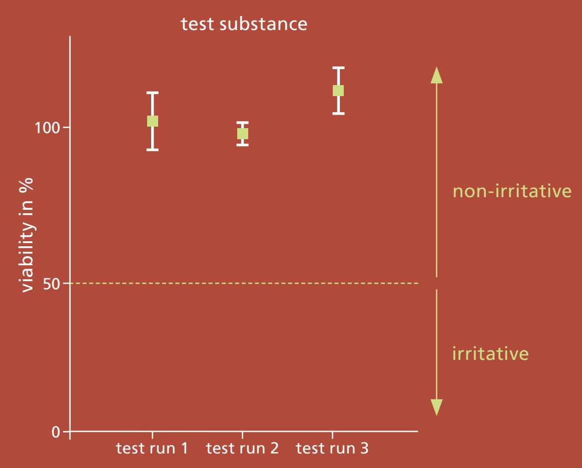

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Results

The OS-REp models produced at the IGB have a histological structure that is virtually identical to that of human epidermis. The basal layer consists of keratinocytes arranged in a highly prismatic structure, and at the same time the keratinocytes become progressively more differentiated in the layers above, ultimately forming a thick corneal layer that represents an important barrier for the epidermis. The excellent match to human epidermis can also be demonstrated by scanning electron microscope images.

The validation studies were also able to demonstrate the high predictivity of the OS-REp testing, measured as a precision of 75 percent. It is also noteworthy that several test runs yielded reproducibly similar results and hence a 95 percent reliability was achieved. Consequently, the OS-REp produced by the Fraunhofer IGB conforms to all quality criteria stipulated by the EURL-ECVAM.

Outlook

These results indicate that the OS-REp is able to predict whether substances or formulations will be skin irritants. Thus, following assessment by the EURL-ECVAM, the model can also be used in studies that conform to regulations as a complete replacement for animal testing. This is an essential requirement for reducing the number of animal models needed to assess risks without affecting public safety.

1 *Cross-section of reconstructed human epidermis that can be used as an alternative to animal models.*

2 *Scanning electron microscope image of reconstructed human epidermis.*

3 *Results of a skin irritation test in three independent test runs.*

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Funding

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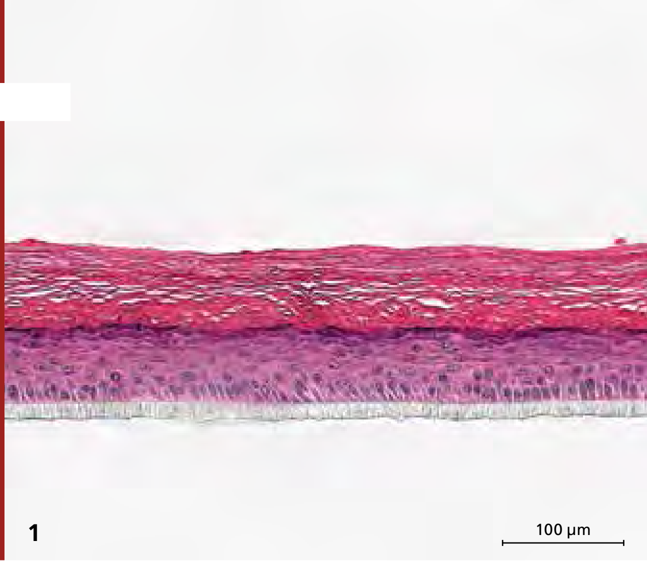
Project partners

Henkel AG & Co. KGaA, Düsseldorf, Germany | Freie Universität Berlin, Berlin, Germany | Fraunhofer Institute for Manufacturing Engineering and Automation IPA, Stuttgart, Germany | Universität Würzburg (Prof. Krohne), Würzburg, Germany

Further information

www.tissue-factory.com



AUTOMATED TESTING WITH IN VITRO TISSUE MODELS

Jan Hansmann, Thomas Schwarz

Drug development costs

There has been a long-held belief that the total cost of researching and developing a new drug lies somewhere around the one billion dollar mark [1]. But if we take the entire research and development expenditure of a pharmaceutical company and divide it by the number of products successfully brought to market, much higher R&D costs are revealed. Figures from the twelve largest pharma companies for the period from 1997 to 2011 calculated in this way result in totals between 3.7 and 12 billion US dollars per drug [2].

The primary reason for exploding costs are high failure rates during mandatory clinical trials. On average, just one drug is successful for every ten candidates in the preclinical development phase [3]. The discrepancy between the results of preclinical and clinical investigations reflects a lack of methods for assessing the safety and efficacy of active ingredients in realistic, complex biological environments.

Improved reliability thanks to in vitro human tissue models

Before the start of clinical trials, drugs are subjected to initial testing, for instance on cell cultures or in animals. Cell cultures represent an extremely artificial test system, whereas the differences between humans and animals limit the predictive power and transferability of results from animal testing. This is where human tissue manufactured using tissue engineering methods comes in. It offers new possibilities for closing the gap between animal testing and the administration of drugs to human subjects in clinical trials. As the tissues are engineered from human cells, they allow more accurate assessments of the effects that a test substance will exhibit on humans.

Despite the advantages of such human tissues manufactured in the lab, their wider industrial application is thwarted by aspects such as production costs and the availability of in vitro tissue models. Automated production techniques could help to lower manufacturing costs and increase availability in the future. However, validation studies are required for regulatory approval test methods, and these entail extremely high staff costs.

Automated testing with skin models

Test protocols that have already been validated and received regulatory approval, e.g. for evaluating the corrosive and irritative properties of a substance, support the applicability of artificial tissues in the cosmetic, chemical and pharmaceutical industries. One of the most frequently used in vitro models is, in fact, artificial skin (Fig. 1). A project funded by the Fraunhofer-Gesellschaft has already demonstrated that large quantities of skin tissue can be manufactured in an automated process. The next logical step is to develop technologies that allow automated tests to be performed on these tissue models.

Automation reduces processing time and increases reproducibility

The manual characterization of substances using in vitro tissue models involves different subprocesses of varying complexity and is subject to strict test protocols. The project described here involves the development of a library of automated

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process steps for conducting various test protocols fully automatically. For example, we were able to test the quality of a skin model's barrier properties using the ET-50 method (Fig. 2) with a dual-arm robot (Fig. 3). The use of dual-arm robots allows us to perform the process employed with conventional cell culture devices, making excellent comparability with manual tests possible (Fig. 4). The high degree of precision and reproducibility achieved with this automated process has resulted in unprecedented levels of standardization.

Technology platform for automated implant manufacture

This technology represents the first step towards setting up an automated laboratory where test systems can be produced, substance testing performed and, in the medium term, implants can also be manufactured under the required technical conditions. The emerging Fraunhofer Translational Center in Würzburg and its partners will develop technologies for client-specific manufacturing and downstream test processes to be performed in a flexible, cost-efficient manner.

1 *Skin tissue model for pharmaceutical agent testing.*
2 *Manually characterizing the toxic effect of a substance.*
3 *Platform for automated substance testing.*
4 *Standardized application of test substances to a tissue model.*

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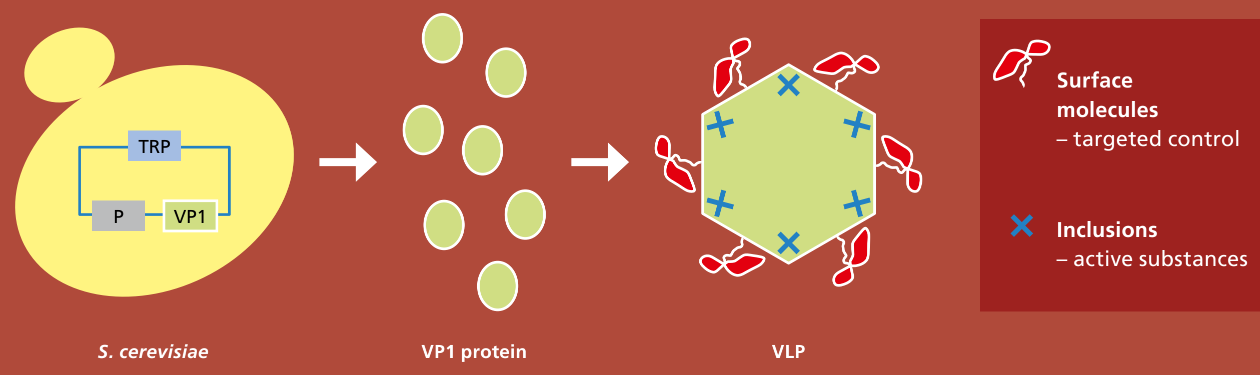
Project partners

YASKAWA Europe GmbH, Robotics Division, Allershausen, Germany

Further information

www.tissue-factory.com



VIRUS-LIKE PARTICLES – A BIOCONTAINER FOR THE TRANSPORT OF ACTIVE SUBSTANCES AND VACCINATION

Susanne M. Bailer

Background

In addition to their desired therapeutic effect, many drugs elicit serious adverse effects. Direct administration of a medicinal product at the target site can dramatically reduce the side effects. Several new active substances can be used only in this way.

The development of vaccines requires the design of vehicles that have high valence target structures on their surfaces (i.e. there are many of them) that are present in combined form.

Virus-like particles (VLPs) are biobased capsules that resemble viruses and have a wide range of applications. VLPs can arise in the process of virus replication as natural non-infectious by-products that contain no viral genetic material. Alternatively, VLPs can be produced by genetic engineering processes in which protein building blocks spontaneously assemble into hollow geometric structures.

Potential applications of VLPs

VLPs are ideal for packaging and targeted control of active substances (drug delivery) as a result of their ability to transport therapeutic agents in high concentration, with minimal side effects and in a targeted manner through intravenous routes.

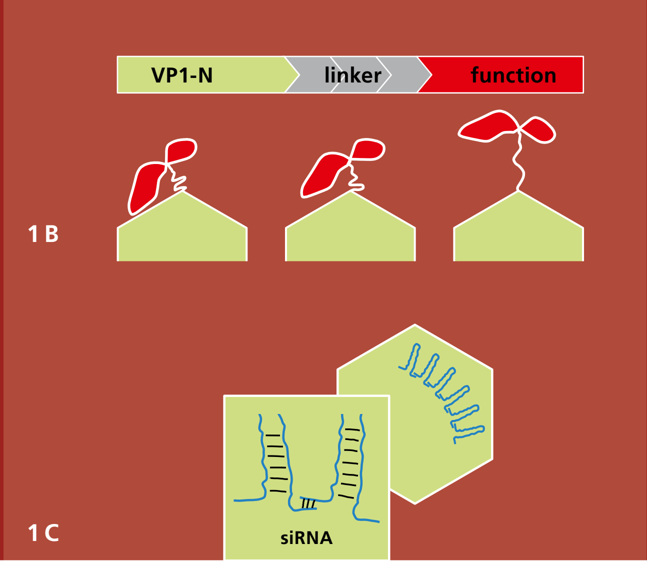
Because of their stability, size and multivalency, VLPs also make an excellent basis for vaccines, for examples against viruses, which cannot be cultured or can only be cultured with difficulty in vitro, or against foreign proteins that are presented on the surface. Because of their biocompatibility and wide range of potential applications, the pharmaceutical industry has shown great interest in VLPs.

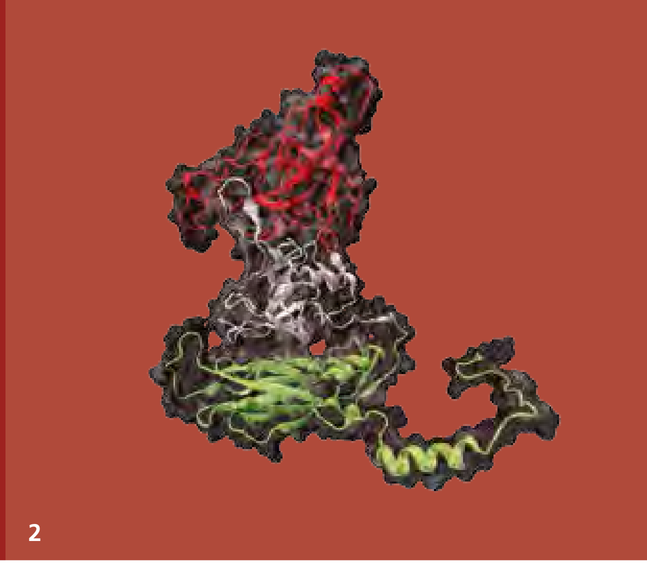
Goal: A modular VLP building system

At present, the widespread use of VLPs is limited by the lack of standardized and efficient processes, which, much like a modular construction system, are suitable for producing a variety of different VLPs that can transport specific loads to various target sites. Moreover, the purification steps of such a production process must be developed specifically for each protein and VLP. Such a process that must be designed empirically and individually is time- and cost-intensive and therefore poses a challenge for production at an industry-scale.

In a new undertaking at the Fraunhofer IGB, we hope to develop a modular system as a platform technology for producing VLPs. A basic module structured with an internal capsule will be incorporated with a functional, variable and complex protein surface that can be used either for targeted control of VLPs (drug delivery) or for the development of vaccines.

For example, antibody fragments or antigens could be used to create a surface that is functional and multivalent. Because the basic module always remains unchanged and only the protein surface is configured as needed, the production of VLPs, unlike current systems, can be standardized and hence would be reproducible and cost-effective.





Non-enveloped viruses from the *Caliciviridae* family will be used as the base. We will develop a plasmid that allows the synthesis of the virus proteins – the capsules of these viruses consists of a single type of protein – in the yeast *Saccharomyces cerevisiae*. This organism has proven to be ideal for protein synthesis for pharmaceutical purposes because it generates few side effects and is cost-effective.

As "proof of principle", VLPs that conduct active agents specifically to surface markers of cancer cells via antibodies will be produced.

Outlook

There is market demand for a modular system that uses a standardized process and has a wide range of potential applications. In addition to global corporations, SMEs in particular are sharing the pharmaceutical market for drug delivery methods and vaccine development.

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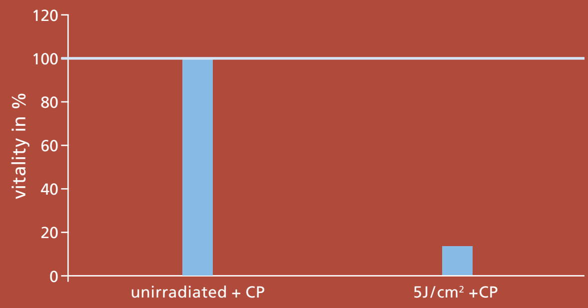
We would like to thank the Fraunhofer-Gesellschaft for funding the project "Vari-VLP" within the scope of its SME-oriented internal research program (MEF).

1 *Platform technology for producing virus-like particles (VLPs).*
A *The virus protein VP1 (green) is produced in a recombinant process using yeast as an expression vector and spontaneously assembles into a biocontainer to produce VLPs. Both the surface and the capsule within can be used for targeted control (red) or to contain therapeutic substances (blue).*
B *A modular vector system codes for the VP1-N capsule that is connected to various surface domains (red) via linker variants.*
C *Therapeutic siRNAs (blue) are arranged through homologous regions and hence can be administered in an efficient manner.*
2 *Structural model of a Calicivirus VP1 protein.*



Cell activity in % (regarding corresponding control without irradiation)	**Interpretation**
100–70	non-phototoxic
69–0	phototoxic

1

HUMAN SKIN IN VITRO SYSTEM FOR SUBSTANCE PHOTOTOXICITY TESTING

Sibylle Thude

Phototoxicity

Substance phototoxicity is characterized by a chemical irritation of the skin that is induced by ultraviolet (UV) light, but does not involve the immune system. Phototoxic substances reach the skin by topical application to the skin or through the circulation system via ingestion or intravenous injection. The scientific mechanism behind phototoxicity is due to molecular changes that occur within a substance when it absorbs light energy photons. The reaction can cause rashes, swelling and inflammation that appears as an exaggerated sunburn. In some people, symptoms can last for over 20 years after a phototoxic medication has been stopped. Common drugs that are known to cause phototoxic reactions in some people are ibuprofen, doxycycline and promethazine.

In vivo based phototoxicity studies

The most scientifically sound method for testing the phototoxicity of a substance is on human subjects. However, because this is often not practical and sometimes ethically questionable due to potential photoallergenic reactions, many national substance approval authorities, such as the US Food and Drug Administration, require animal testing for phototoxic reactions, particularly for water-insoluble substances or complete drug formulations. In these tests, different chemicals are applied to the shaved backs of mice or guinea pigs and exposed to UV radiation. The animals are caged for several days while analysts wait for swelling or sores to appear. These types of studies are painful for the test animals and can be replaced with human-based in vitro test systems.

The development of an in vitro human-based phototoxicity test system

At the Fraunhofer IGB in Stuttgart, we have developed and accredited a phototoxicity test system to replace in vivo test studies. The three-dimensional skin test model consists of multiple layers of viable epithelial cells (*stratum basale*, *stratum spinosum* and *stratum granulosum*) under a functional *stratum corneum*. Quality is checked via histological sectioning and staining. Barrier function verification is required before using the model for testing. UV-radiation with a defined, but non-cytotoxic, dose is performed after topical application of the test substances. An MTT assay is used to quantify the viability of the skin model after incubation at 37°C, 5 percent CO_2 and 95 percent humidity. Parallel testing of a known phototoxic substance serves as positive control. A substance is considered phototoxic when cell viability of the treated and irradiated skin model is decreased by more than 30% compared to the corresponding non-irradiated control and a cytotoxic effect is excluded.

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Beyond the gold standard

The current most recognized in vitro test for phototoxicity is called the 3T3 Neutral Red Uptake Phototoxicity Assay, based on the Balb/c 3T3 mouse fibroblast cell line. The test has been shown to have a positive correlation to the human system. Our test model has significant advantages over the 3T3 system. We use human keratinocytes, which are more species- and mechanistically specific than the 3T3 model. Our model is also a three-dimensional system with a full epidermis that is much closer to the human in vivo environment, as opposed to the 3T3 test, which is a simple monolayer model. Furthermore, we use primary cells that are only passaged three times, which ensures there is no decrease in cell photosensitivity, which can occur with a cell line that is passaged numerous times. We also use a radiation unit that allows the setting of specific wavelengths for application-defined radiation doses.

Accreditation

Our in vitro human-based phototoxicity test method (in accordance with the OECD Guideline 432 and the INVITTOX Protocol no 121) was observed by the "Deutsche Akkreditierungsstelle" DAkkS in June 2014, and was certified in December 2014 as an accredited assay procedure.

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1 *Phototoxicity test results: example shows the phototoxic substance chlorpromazine.*

2 *Irradiation Unit BioSUN++ for the application of accurately defined UV light.*

3 *Accreditation certificate.*

CHEMISTRY

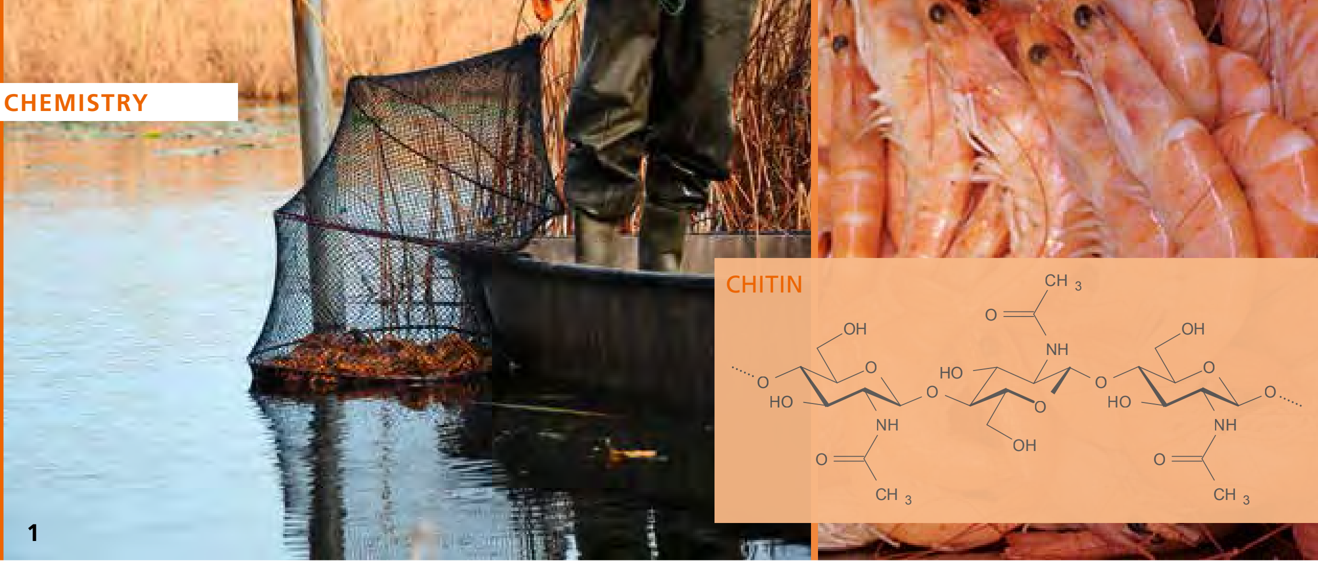
The chemical industry is one of the most important and research-intensive economic sectors in Germany. Many innovations in other sectors, such as in the automotive, electrical and electronic, construction and packaging industries, would not be possible without the contributions of chemistry. Resource- and energy-intensive processes characterize the chemical industry. The dependence on the import of raw materials, the limited availability of fossil resources worldwide – even in competition with energy use – and the need to consider the impact on both the climate and the environment mean that at the foreground of our work are also initiatives to make the use of fossil resources more efficient or create substitutes for them.

Biobased chemicals and materials – Our activities are aimed at the development of biotechnological (fermentative or biocatalytic) processes for the production of chemicals and fuels from renewable resources, biogenic residues or microalgae, and the coupling of these with chemical processes. The Fraunhofer Center for Chemical-Biotechnological Processes CBP in Leuna offers new ways of transferring the use of renewable raw materials to an industrial scale.

Process intensification and integration – Substance separation is a key step in many sectors of the chemical industry, since both raw materials and synthesis or fermentation products are often present as mixtures. Our focus is on the development of methods for upstream and downstream processing for a more efficient use of raw materials and energy, with the effective separation of material flows occurring by means of membranes or other separation techniques. The integrated recirculation of material flows and the recovery of valuable materials (recycling) as part of a sustainable waste management represent here the current fields of action. An increase in efficiency through better conversion rates is achieved, for example, through an intensive energy input using microwaves.

Functional surfaces and materials – By the decoupling of volume and surface properties of materials through interfacial process engineering, e.g. in the form of customized coatings, which are, in turn, procedurally geared towards efficient use of resources, new possibilities result as to the base materials of workpieces and thus for new products based on a selection of sustainable raw materials.

We also examine chemicals for their potential risk (e.g. within the scope of REACH). The diversity of our research and development work shows how we are meeting the challenges of these new approaches. This may involve cooperation with other institutes of the Fraunhofer Group for Materials and Components – MATERIALS, or with the Fraunhofer Nanotechnology, Photocatalysis, Polymer Surfaces POLO® and Cleaning Technology Alliances.



1

CHITINOUS FISHERY WASTE AS A NEW RAW MATERIAL BASE FOR THE PRODUCTION OF BIOBASED POLYMERS

Lars O. Wiemann, Volker Sieber

Utilization instead of disposal

Based on current estimates, every year 6-10 million metric tons of chitin-containing fishery waste accumulate worldwide – within the 28 EU states it is approx. 280 000 metric tons – from the processing of crustaceans, and it is an upward trend [1]. This waste is problematic because it has to be disposed of within the EU. For SMEs along the coasts of Ireland, England and Poland in particular, the expensive disposal presents major, indeed existential challenges – and it is precisely here that the EU-funded ChiBio project comes into play. At the end of 2011 the international ChiBio team, with partners from science, research and industry and under the direction of the BioCat project group in Straubing, began its work: the aim was to establish a multi-stage process following the principle of a biorefinery by means of which valuable biobased monomers can be obtained from the chitin in the crab shells which can then be used in the polymer industry.

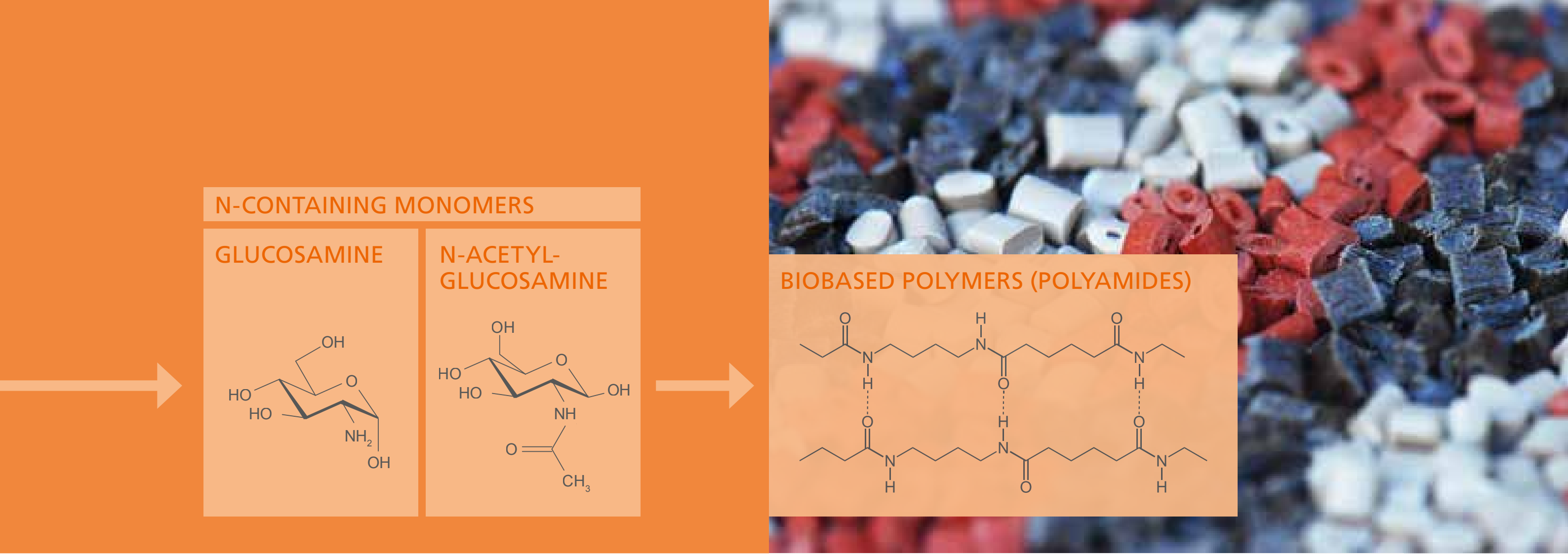
Pre-treatment of the crab waste and extraction of biogas

In order to prevent the natural process of decay and also contamination with microorganisms harmful to health, new methods have been developed for the pre-treatment of the waste. The two key steps are the removal of the meat residues (proteins and lipids) and the mobilization of the chitin. Irish ChiBio partners have discovered two new strains of bacteria which are capable, by means of a fermentation process, of gently releasing the chitin. The optimized process comprises a combination of chemical and biotechnological steps and, in respect of the crab shells, permits chitin yields of 13–14 percent with European shell waste and 16–18 percent with Asian shell waste which has less $CaCO_3$. The exact composition of the shell components is to a large extent species-specific and subject to regional and seasonal fluctuations; the chitin content of the shell raw materials tested in the project lay between 14 and 30 percent.

The protein and lipid fraction separated off was tested by the Department of Environmental Biotechnology and Bioprocess Engineering in Stuttgart for its potential for biogas extraction. During fermentation of this organic waste fraction in a batch method, good biogas yields of 460–900 ml/g organic dry mass were obtained within 5 to 15 days.

Enzymatic depolymerization of chitin

A search has been underway for new microorganisms and enzymes for the purpose of cleaving the macromolecular chitin and releasing saccharide monomers. As with the cleaving of cellulose, this requires numerous different enzymatic activities which had to be appropriately optimized and coordinated. The Norwegian working group led by Prof. Vincent Eijsink and colleagues from the Department of Molecular Biotechnology at the Fraunhofer IGB have succeeded in making available different chitinolytic enzymes (chitinases, chitobioases, hexosaminidases, deacetylases) from, among others, new strains such as *Amantichitinum ursilacus* and *Andreprevotia ripae* [2]. Together with the Czech SME Apronex, methods have been developed for making available the required enzymes



or enzyme cocktails in industrial quantities using recombinant technology. Using appropriately tailored enzyme cocktails it was possible to break down the chitin from European shell waste by purely enzymatic means into N-acetylglucosamine or glucosamine. Through further optimization of the process, a green and economical alternative to chemical chitin cleavage should therefore be available in the future.

Biobased monomers for the polymer industry

In order to be used as building blocks for polymers, the sugar molecules released must be converted in such a way that precisely two functional groups remain per molecule. To this end, two different routes were taken in the ChiBio project.

On the one hand, the BioCat working group worked on an atom-efficient reaction cascade for the enzymatic conversion of glucosamine into bifunctional N-containing heterocycles (including dicarboxylic acid). Here it was possible, through variation of the sequence of oxidation and rearrangement reactions within the cascades, to obtain new molecules which can be used as a precursor for monomer synthesis.

In a second approach used by the Technical University of Munich (Prof. Thomas Brück), the chitin hydrolysates served as a substrate for specialized oil-forming yeasts. Out of numerous strains, it was possible to identify three which grow well on the chitin hydrolysates and attain high lipid yields of 35–50 percent based on the cell dry weight. The lipid composition largely consisted of unsaturated fatty acids of chain length C16–C18, which enabled the downstream chemical functionalization to a dicarboxylic acid as a comonomer for polyamides by industrial partner Evonik.

Industrial partner Clariant AG and the Fraunhofer ICT were involved in the purification of the intermediate and end products. At Evonik, biobased polyamides were ultimately manufactured successfully from the different dicarboxylic acids and characterized.

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Funding

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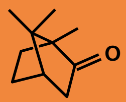
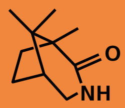
Further information and project partners

www.chibiofp7.eu

1 *Using biotechnological methods, N-containing monomers can be obtained from the shells of crustaceans for use in the polymer industry.*



Camphor



Camphor lactam

1

DEVELOPMENT OF NEW HIGH-PERFORMANCE POLYAMIDES BASED ON RENEWABLE RAW MATERIALS

Harald Strittmatter, Claudia Falcke, Marion Wölbing, Volker Sieber

Background and objectives

Terpenes are secondary plant substances that accumulate in large quantities as by-products of cellulose production. To date, these substituted cyclic or bicyclic, partially functionalized hydrocarbons are mainly utilized for the energy supply of the cellulose factories. The aim of the work presented here is the synthesis of various terpene derivatives that can be used as monomers for the preparation of new biopolymers. One result would be reduced consumption of fossil resources. However, the substitution pattern of the cyclic terpenes can also be used specifically to generate polymers with novel properties.

Conversion of camphor to lactam

ε-caprolactam, the monomer used for the production of polyamide 6 (PA6) is synthesized from cyclohexanone by conversion to the oxime and subsequent Beckmann rearrangement. Camphor is a natural product that can be regarded as a substituted bicyclic derivative of cyclohexanone, from which a biobased lactam can be produced in a similar reaction [1].

Polymerization of the camphor-based lactam

The polymerization of camphor-based lactam can take place using a procedure analogous to that used for preparation of polyamide 6, either via hydrolytic or anionic polymerization (reaction in mold, RIM). In anionic polymerization, the lactam is melted together with a catalyst (usually a lactamate) and the reaction is then started by addition of an activator (usually an acyl lactam). Polymerization takes place within a few minutes at temperatures of about 200 °C. For hydrolytic polymerization, the lactam ring is first opened with water at temperatures around 250°C under pressure in an autoclave. Excess water and water released by the subsequent polymerization is removed by applying a vacuum. If instead of a pure 'camphor lactam', a mixture with, for example, ε-caprolactam is used for the polymerization, copolymers are formed.

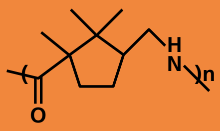
Properties of the resulting biopolymers

Initial tests have shown that a mixture of 'camphor lactam' and ε-caprolactam results in PA6 copolymers with properties that are significantly different from those of the standard polymer. For example, the resulting plastics have greatly improved impact strength at low temperatures.

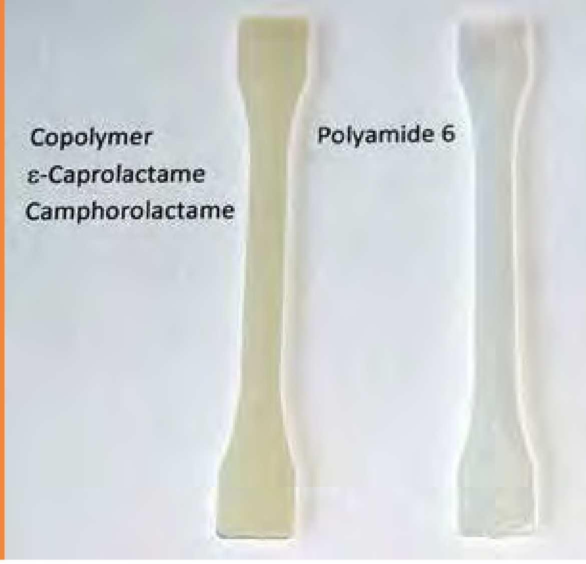
Due to the bridged-ring structure of camphor and its lactam derivative, the units of the polyamide product also contain cyclic units, resulting in a plastic that is significantly more amorphous and transparent than PA6.

Advantages of the new polyamides

In contrast to most other biopolymers, which are manufactured from sugar or starch and therefore reduce the availability of foodstuffs for the population, the polyamides described here are derived from recycled plant residues. Camphor is produced on an industrial scale from pinene, the main component of turpentine oil. Turpentine is available in large quantities from cellulose production and is currently used for energy production.



Polyamide



Polyamides of camphor are not only "green" – they also have promising properties, as described above. With their broad raw material base, camphor polyamides have the potential to become new and important members of the plastics family.

Further studies

The aim of further studies (in addition to continuing work on the polyamide from camphor lactam and the corresponding copolyamide) is to produce further copolymers with PA6 and investigate the material properties of the various plastics.

Furthermore, we plan to synthesize other terpene-based polymers and copolymers. Apart from camphor, other terpene ketones such as menthone or carvone (which can be derived from limonene) are promising starting materials that can be converted first to lactams and then to polyamides according to the method described above. Terpene alcohols, i.e. terpenes bearing a hydroxyl group, can be oxidized to ketones and thus serve as a substrate for the Beckmann rearrangement to lactams. The double bond present in the ring system of many terpenes can also be oxidized with various methods to form ketones, which can be converted to lactams using the pathway described above and then polymerized. Possible substrates for this pathway include the most abundant terpenes, α-pinene and 3-carene.

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Funding

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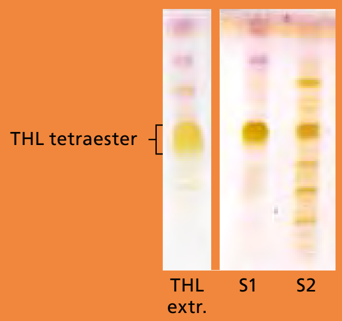
1 *Polyamide derived from "camphor lactam".*



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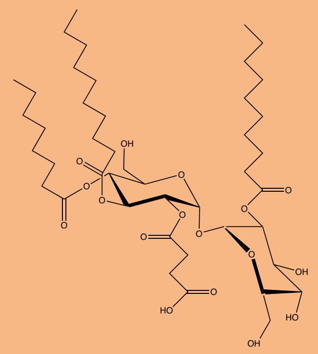
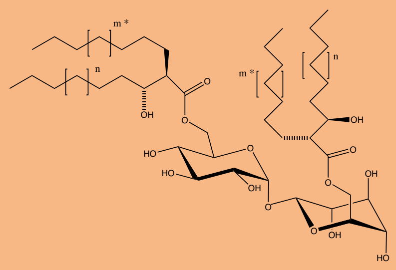
ANIONIC THL TETRAESTER



2 A

NON-IONIC, CELL WALL-BOUND THL DIMOCYLATE



2 B

TREHALOSE LIPIDS – NEW MICROBIAL BIOSURFACTANTS FROM VEGETABLE OILS

Michael Günther, Georg Geiger, Susanne Zibek

Biosurfactants – Microbial, surface-active substances

Surfactants are surface-active molecules which we encounter daily in detergents and cleaning agents, cosmetics, foodstuffs, and pharmaceuticals. The major amount of the annual need of approximately 18 million metric tons worldwide is produced chemically and on the basis of crude oil. Nowadays, about one quarter is produced vegetable oil based.

Besides chemical manufacturing, there is the alternative to produce surfactants with the help of bacteria or fungi in a bioreactor. These natural, non-toxic biosurfactants are particularly suitable for use in cosmetic and body care products, pharmaceuticals or for the decontamination of soils contaminated by oils or heavy metals. Only few of these surfactants are already produced on an industrial scale, because their manufacture is still comparatively cost-intensive.

For a number of years, in several national and international cooperation projects, the Fraunhofer IGB has therefore already been working successfully on the production of different classes of surface-active microbiological glycolipids – mannosylerythritol lipids and cellobiose lipids [1 – 3]. As a result, improved fermentation and purification methods were established and new potential applications were identified. Furthermore, the metabolism of the production strains was examined and the gene clusters relevant for biosurfactant synthesis could be determined. These gene targets now serve as the starting point for strain optimizations.

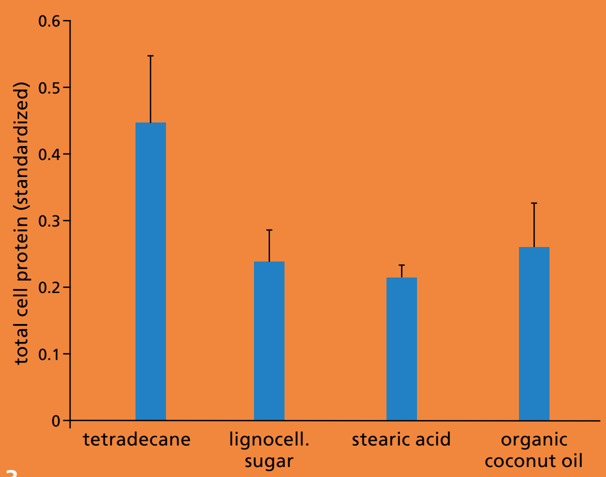
Trehalose lipids from renewable raw materials for new areas of application

The research activities have recently been expanded to include the class of trehalose lipids (THL), which are produced e.g. by bacteria of the *Rhodococcus* genus. The known potential applications for these glycolipids include the biological decontamination of contaminated sites and also the use as antimicrobial, therapeutic agents [4]. In addition, the Fraunhofer IGB would like to test THL as surfactants for cosmetic and household products.

THL have already been known since the 1970s but have been subjected to little research using modern methods as the previous cultivating procedures had two key disadvantages: some of the glycolipids are membrane-bound, thus making their purification difficult. Furthermore, the microorganisms used were isolated from oil spill contaminated soils, and as a result the THL biosynthesis of these strains is induced efficiently by the addition of long-chain, crude oil-based alkanes. The focus of our research is on the utilization of renewable raw materials as a substrate for cell growth and glycolipid synthesis. Moreover, we would like to establish a cultivation procedure which enables a complete secretion of the glycolipids.

Fractionated production of anionic and non-ionic biosurfactants

The results thus far show the secretion of anionic trehalose tetraesters by *Rhodococcus erythropolis*, when plant oils are supplied after the end of the growth phase (Figs. 1 and 2A). These secreted THLs can be extracted from the culture supernatant. By extracting the cell mass, we also gain the membrane-bound, non-ionic glycolipids known as di- and



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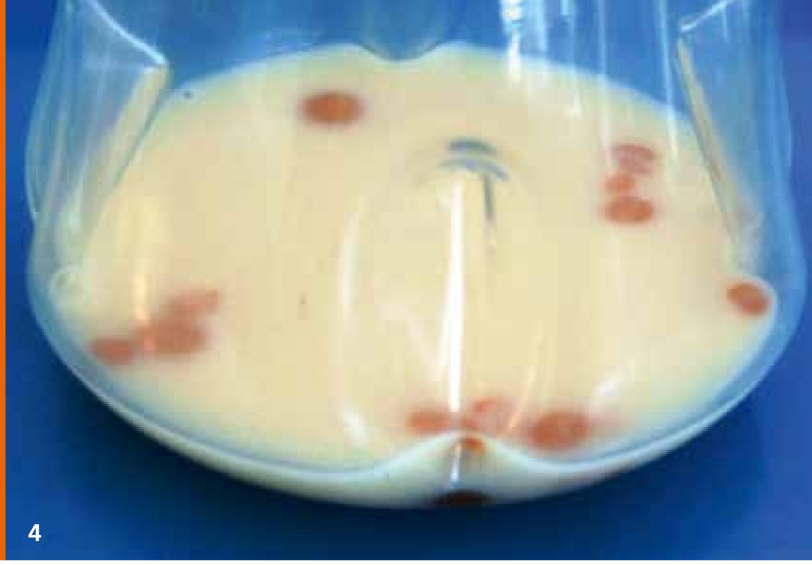

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mono-mocylates with unusually long fatty acid residues (Fig. 2B). By adapting the purification protocol, we thus achieve a fractionation of the glycolipids in more hydrophilic or more hydrophobic molecules. Using a new chromatographic method, it was possible to produce pure trehalose tetraesters, which we are now examining for their surfactant properties. Furthermore, we observed that sugars from lignocellulose-containing residual materials, fatty acids such as stearic acid and also plant oils such as organic coconut oil are suitable as alternative carbon sources for the growth of *Rhodococcus erythropolis* (Fig. 3).

Fermentation optimization and product characterization

Further studies concentrate on the optimization of the fermentation process and a customized feeding strategy (Fig. 4) in order to increase the space-time yield. The glycolipid fractions produced are subsequently examined in terms of their physical, chemical and bioactive properties and selected according to their possible applications. Anionic trehalose tetraesters with shorter side chains may be particularly suitable as emulsifiers and wetting agents for instance; possible applications as therapeutic substances are conceivable for long-chain di- and monomocylates.

1 *Thin-layer chromatography of R. erythropolis THL extract compared with THL tetraester standard (S1) and a mixed standard of different THL esters (S2).*

2 *Molecular structure of an anionic THL tetraester (A) and of a non-ionic, cell wall-bound THL dimocylate (B).*

3 *Growth of R. erythropolis with different carbon sources determined by the content of total cell protein.*

4 *The feeding strategy is decisive for cultivations of R. erythropolis, because nutrient and oxygen deficiency conditions can result in unproductive cell agglomerates.*

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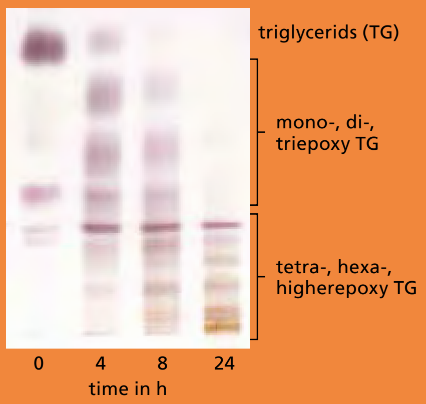
Funding

The project "Organic for surfactants (O4S)" has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 286859.



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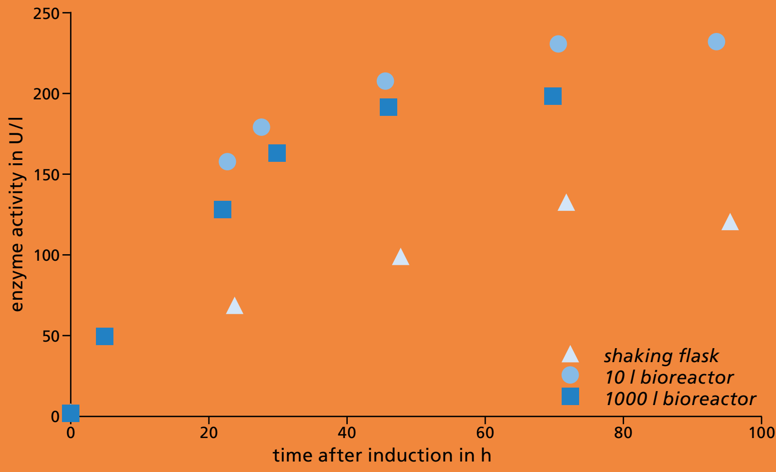


2

REFINING OF OILS AND FATTY ACIDS BY ENZYMATIC CATALYZED REACTIONS

Nicole Werner, Fabian Haitz, Katja Patzsch, Susanne Zibek

Vegetable oils

In addition to polysaccharides, sugar or aromatics from wood and straw, vegetable oils are also important raw materials for industry [1]. According to estimates by the U.S. Department of Agriculture, the global production of vegetable oils will be approximately 175 million metric tons in 2014/15 – this corresponds to an increase of 3.3 percent compared to the previous year. The most significant oils include palm oil (36 percent), soybean oil (27 percent), rapeseed oil (15 percent) and sunflower oil (9 percent) [2]. However, rare vegetable oils such as crambe oil or lallemantia oil are also of increasing interest, as their use does not compete with the food sector [3]. On the basis of these vegetable oils, synthetic building blocks are obtained by chemical modification. These can then be processed into biocompatible plastics, additives, lubricants, plasticizers and stabilizers by further chemical procedures.

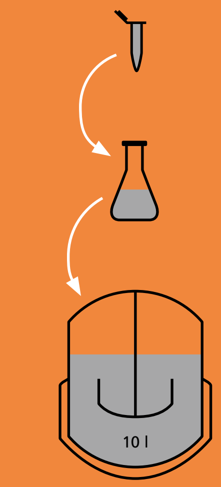
The synthetic building blocks from vegetable oils can alternatively be made available using biotechnology by means of lipid-modifying enzymes such as phospholipases or lipases under milder and therefore more environmentally friendly and high selective reaction conditions. A breakthrough of enzymes as biocatalysts in the chemical industry has not yet been achieved, as enzyme production is often associated with costs which are too high. The development of efficient expression systems and production processes is therefore an important step towards reducing production costs and guaranteeing the economic efficiency of enzyme-based processes.

New technical enzymes

The Fraunhofer IGB develops efficient, recombinant expression methods for the production of industrial enzymes on a pilot plant scale. There is a focus on the development of optimized production strains and process procedures for the manufacture of lipid-modifying enzymes, particularly lipases with perhydrolase activity, to be used for the production of epoxides or esters as synthetic building blocks based on vegetable oils.

In contrast to classic lipases and esterases, lipases with perhydrolase activity show only low hydrolyse activity but high perhydrolase activity to catalyze the formation of peracid from carboxylic acids and hydrogen peroxide. Then the formed peracid oxidizes unsaturated fatty acids in plant oils to epoxides (Fig. 1). Perhydrolase active enzymes are therefore of great interest for the production of triglyceride epoxides or epoxides from free fatty acids and corresponding esters of the vegetable oils, currently produced by purely chemical processes [3].

Several fungal lipases with perhydrolase activity were identified by the Fraunhofer IGB. One of these lipases was recombinantly expressed in the methylotrophic yeast *Pichia pastoris*. The lipase expression was regulated by the very strong, methanol-inducible alcohol oxidase 1 promoter (AOX1). Methanol is a low cost induction agent but it requires certain safety precautions due to its flammability and toxicity. While planning the facilities at the Fraunhofer CBP, these were taken into account in the form of ex-protection zones and safety interlocks. It was therefore possible to scale-up the fermentative enzyme production (Fig. 2).



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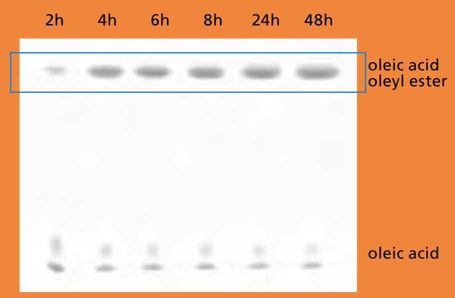

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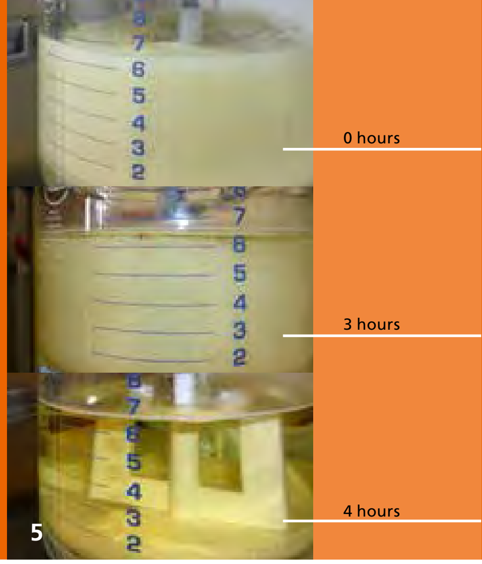

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Outlook: Scale-up of an esterification

The lipases developed at the Fraunhofer IGB were used for different chemo-enzymatic catalysis reactions. The esterification of a fatty acid with a long-chain alcohol, for example, is of particular interest. The emollient ester resulting from this is a valuable starting product for skin care cosmetics such as creams and body lotions.

At the Fraunhofer CBP, a scale-up of the esterification reaction of oleic acid with oleyl alcohol to oleic acid oleyl ester developed in the laboratory was able to be carried out successfully. A lipase identified and cloned at the Fraunhofer IGB (Fig. 3) was used for this. The reaction was analyzed using thin-layer chromatography in which the formation of the ester bond could be detected by the increase in band intensity (Fig. 4). The reaction was also able to be tracked optically. The reaction mixture is initially cloudy as the enzyme is insoluble in oil. The formation of H_2O during esterification causes the enzyme to shift into the aqueous phase and phase separation occurs. The product can be found in the clear phase (Fig. 5).

1 *Reaction of a lipase with perhydrolase activity for the production of epoxides using the epoxidation of lallemantia oil as an example.*

2 *Lipase activities in the culture supernatant of the recombinant P. pastoris strain during scale-up from shaking flasks via fermentation in a 10 liter scale up to a scale of 1,000 liter.*

3 *Scale-up of the esterification.*

4 *Thin-layer chromatography-analysis of the oleic acid oleyl ester formation.*

5 *Course of the esterification of oleic acid with oleyl alcohol in a 10 liter reactor.*

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Funding

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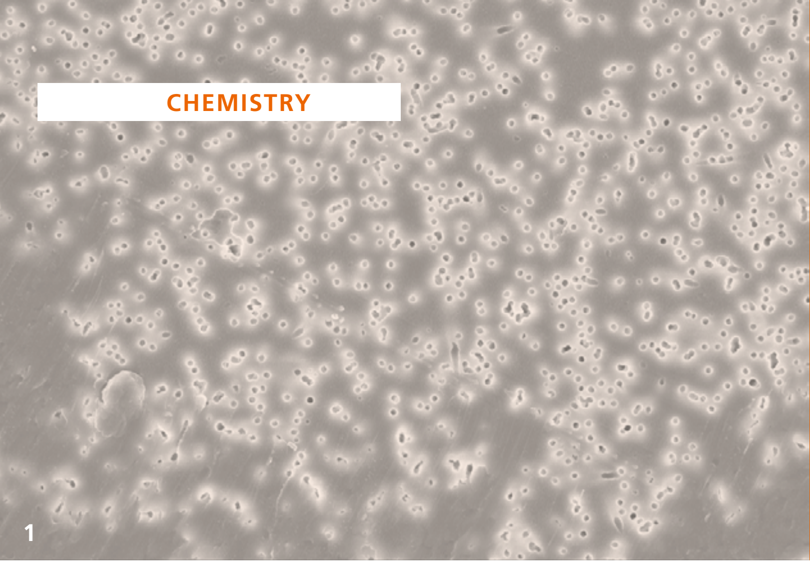
Project partners

Addinol Lube Oil GmbH, Leuna, Germany | DHW Deutsche Hydrierwerke GmbH Rodleben, Dessau-Roßlau, Germany | EUCODIS Bioscience GmbH, Vienna, Austria | Fraunhofer ICT, Pfinztal, Germany | InfraLeuna GmbH, Leuna, Germany | Martin-Luther-Universität, Halle-Wittenberg, Germany | Taminco Germany GmbH, Leuna, Germany | Umicore AG & Co. KG, Hanau-Wolfgang, Germany | Karlsruher Institut für Technologie (KIT), Karlsruhe, Germany | Linde Engineering Dresden GmbH, Dresden, Germany | TLL Thüringer Landesanstalt für Landwirtschaft, Jena, Germany | Hobum Oleochemicals GmbH, Hamburg, Germany



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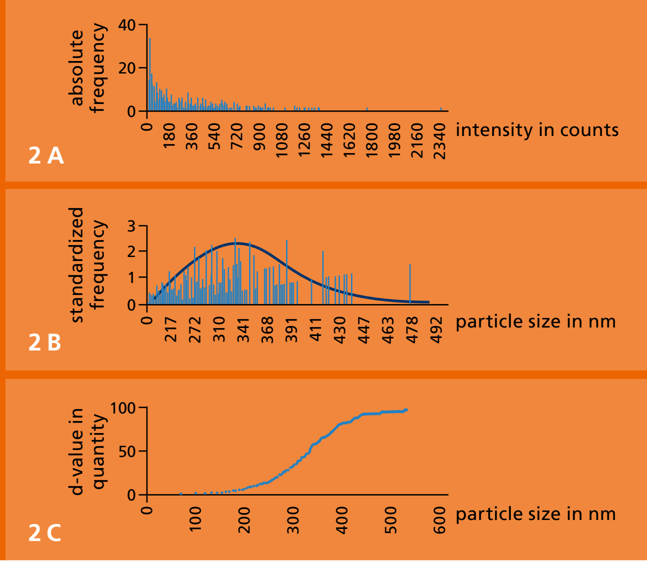


ELEMENT-SPECIFIC ANALYSIS OF NANO-PARTICLES – DETECTION IN COMPLEX MEDIA

Katrin Sommer, Gabriele Beck-Schwadorf

Wide use of nanoparticles

Nanoparticles have found a broad range of applications in recent years due to their small size, and can be specifically equipped with new properties so that they can influence the properties of products. Engineered nanoparticles can be found in products such as electronic and optical devices, in paints and varnishes, adhesives and textiles, as well as in contrast agents for medical purposes, cosmetics, food packaging and even in food products. The extensive use of nanoparticles also leads to increased environmental contamination.

Labeling requirement for nanoparticles

The cosmetics ordinance that came into force in July 2013 requires that all cosmetic and personal care products containing nanomaterials must be labeled. The assessment of what constitutes a nanomaterial is based on the number distribution. According to this distribution, a nanomaterial must be declared if at least 50 percent of the particles have a size of 1 to 100 nm. Current data from the manufacturers are usually based on a volume distribution (mass distribution). This cannot be translated directly into a number distribution. An appropriate labeling requirement for nanomaterials in foodstuffs came into force in December 2014.

Analysis of nanoparticles

Due to the requirements of the legislature, there is an increasing need for a suitable analytical method of characterizing nanoparticles. Current methods use imaging with electron microscopy, such as transmission and scanning electron microscopy (TEM, SEM), or particle measurement based on dynamic or static light scattering (DLS, SLS) or nanoparticle tracking analysis (NTA). With these methods, particles are mainly characterized qualitatively by size distribution, zeta potential, molecular weight and shape. However, these methods are not very selective and are unsuitable for complex polydisperse media, which occur in products such as cosmetics. An element-specific and quantitative method of analyzing nanoparticles directly has not been available until now.

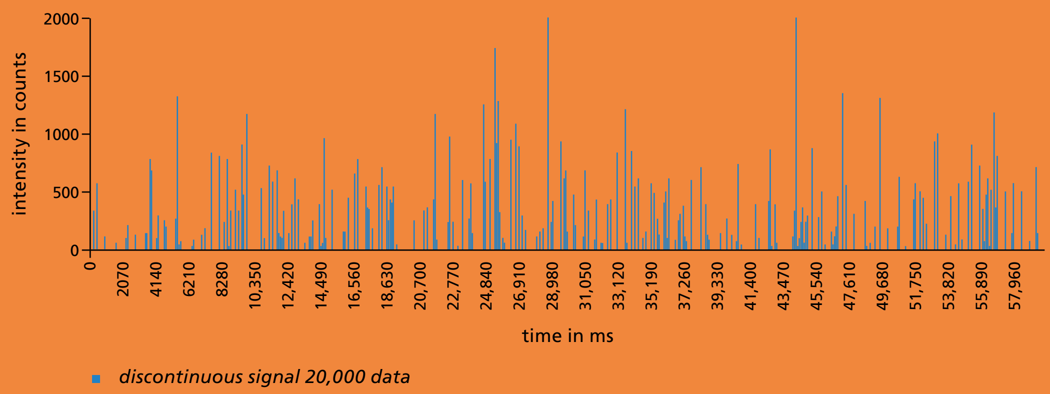
New quantitative element-specific methodology

At the Fraunhofer IGB a method has recently been established for direct, element-specific and highly sensitive analysis of inorganic particles. Particles are analyzed with inductively coupled plasma mass spectrometry (ICP-MS) in single-particle mode (SP-ICP-MS).

The SP-ICP-MS measurement procedure is based on analysis of individual particles. The special feature of this method is that with statistical analysis of the raw data, it is possible to differentiate between the dissolved ionic concentration of the element of interest and the particle concentration.

Our focus at the IGB was on the development of instrumental methods for titanium dioxide nanoparticles in wastewater as well as data analysis and processing without any special software. One critical parameter for the calculation of particle size turned out to be exact determination of the nebulizer efficiency.

Particle concentrations in the sample that are too high may lead to overlapping particles, which may be misinterpreted as larger particles. The sample must therefore be carefully diluted to an appropriate level to ensure that only one particle is detected per measurement window. If this condition is met,



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each signal represents one particle, and the signal intensity is correlated with the number of ions and therefore with the particle size.

A method was developed for suspensions of titanium dioxide particles that allows accurate determination of the nebulizer efficiency using particle calibration in the working range of 1–25 µg/l (mass concentration). This allowed particle sizes with a diameter d_{50} = 333 ± 4 nm to be determined with a relative standard deviation of 1.2 percent. The smallest signal that could be evaluated resulted in a detection limit of 55 nm in ultrapure medium. The method was also used with interference-containing synthetic wastewater matrices.

Advantages and prospects

Compared to existing methods, SP-ICP-MS is a rapid procedure with detection limits down to the ultra-trace region. Due to its selective analysis, it is also suitable for complex polydisperse media and therefore has the potential to be an excellent tool for routine analysis.

SP-ICP-MS can be used for material characterization and quality control by companies, as well as for monitoring by State Offices of Consumer Protection. It is increasingly developing into the analytical method of choice for investigating the persistence and effects of nanomaterials in the environment.

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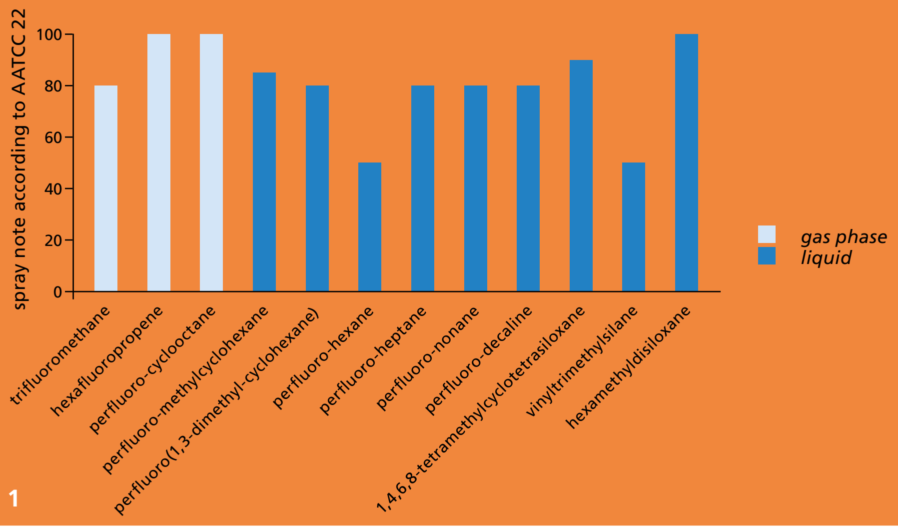
1 *Scanning electron microscopy image of titanium dioxide nanoparticles in wastewater.*

2 *Data analysis of a titanium dioxide nanoparticle suspension.*
A *Histogram of the raw data shows a Poisson distribution of the rare particle events.*
B *Approximation of the Poisson distribution to the normal distribution.*
C *Integration of the density distribution provides a continuous cumulative size distribution.*

3 *Mass spectrum of a titanium dioxide nanoparticle suspension.*



1

PLASMA FINISHING OF TEXTILES WITH OIL AND WATER REPELLENT PROPERTIES

Jakob Barz, Michael Haupt

Background

For conventional textile finishing, water and oil repellent properties are achieved using wet-chemical treatment with perfluorinated organic compounds. Good oil repellency (oleophobicity) requires particularly long fluorocarbon chains. However, molecular fragments of the finishing chemicals may be released during the original treatment as well as the washing and re-impregnation stages. These fragments or their reaction products include perfluorooctanoic acid and perfluorohexanoic acid. These compounds are toxic environmental pollutants that are bioaccumulative and suspected of being carcinogenic.

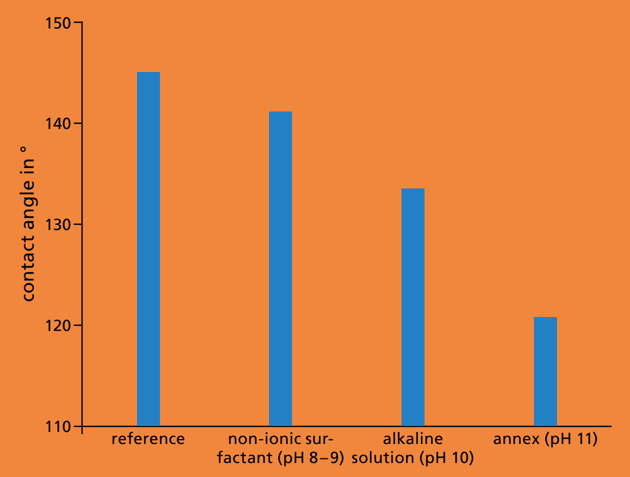
It is therefore necessary to establish more efficient and more environmentally friendly finishing processes that release fewer pollutants and avoid fluorocarbon treatments as far as possible. They are not necessary in an outdoor environment, but oil repellency is still important for personal protective equipment (PPE) such as surgical textiles. Furthermore, coatings should be stably applied to the surface in order to avoid constant post-processing of the fabric.

Plasma technology for textile finishing

Plasma technology is a technique with which coatings can be stably bound to surfaces (with covalent chemical bonds) using minimal amounts of chemicals. One challenge is to achieve a good quality coating together with a high rate of application. In our studies, we have therefore used a new process that uses liquid compounds in addition to coating processes based on gaseous precursors (e.g. perfluorinated alkanes [1]). These make very high deposition rates possible (always based on a defined period) since the quantity of material applied is significantly larger than with conventional processes based entirely on gas-phase technology. The substances are sprayed in the form of a low-pressure plasma and polymerize on the surface [2].

Fig. 1 shows sample measurements for the water repellency of various different finished textiles. In the established test for hydrophobicity according to the AATCC-22 standard (American Association of Textile Chemists and Colorists), a value of 100 corresponds to maximum water repellency, while a value of 0 corresponds to complete wetting. Various coatings prepared from different starting compounds exhibit optimal water repellency (100 points). These include perfluorinated coatings as well as fluorine-free alternatives. Furthermore, both gaseous and liquid compounds can be used for coating, although liquid substances allow higher deposition rates. Oil repellency was also investigated according to AATCC 118. It was found that fluorine-free alternatives had no oil repellency at all, although a certain degree of repellency could be achieved with plasma-based perfluorinated coatings.

After the coatings were subjected to a washing test, there was a tendency for the efficacy to be reduced. This effect is also found with wet-chemical finishing and is due to abrasion, adsorption of surfactants and reorientation of functional groups. An example of the effects of washing on plasma-treated textiles (according to ISO 105 C12) is shown in Fig. 2. This series of measurements shows that the stability of the finishing treatment illustrated depends on pH. Good durability of the coating is obviously possible. However, this clearly depends on the choice of surfactant, as is the case with the wet-chemical method.



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Outlook

The high deposition rate is an outstanding feature of the new methods based on liquid compounds and plasma. Furthermore, additional coating functions can be provided by admixture of other substances (for example, an antibacterial effect can be achieved with silver compounds or chitosan). These methods are therefore of interest not just in the clothing sector, but also in other areas such as medical technology.

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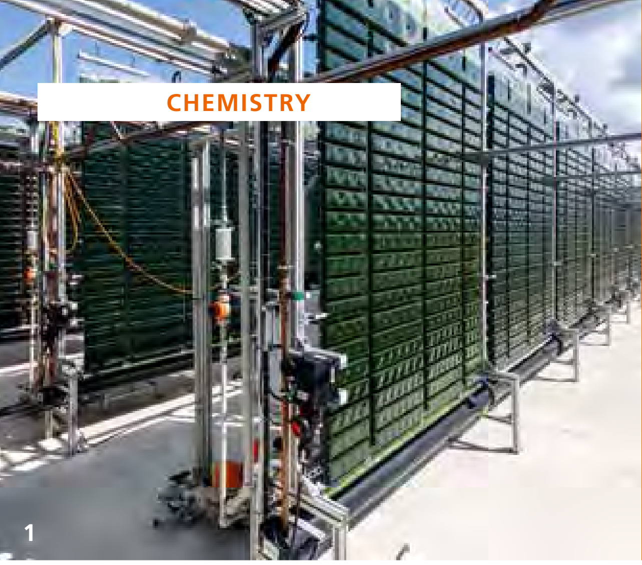
Funding

This work was carried out in cooperation with the Institute of Interfacial Process Engineering and Plasma Technology, University of Stuttgart. We would like to thank the German Federal Environmental Foundation (Deutsche Bundesstiftung Umwelt) for funding this work, reference no AZ 30276.

Project partner

Plasma Electronic GmbH, Neuenburg am Rhein, Germany

1 *Water repellency of plasma-coated textiles finished according to AATCC 22.*
2 *Evaluation of the stability to washing of an octafluorocyclobutane finish according to ISO 105 C12.*
3 *Water-repellent textile surface.*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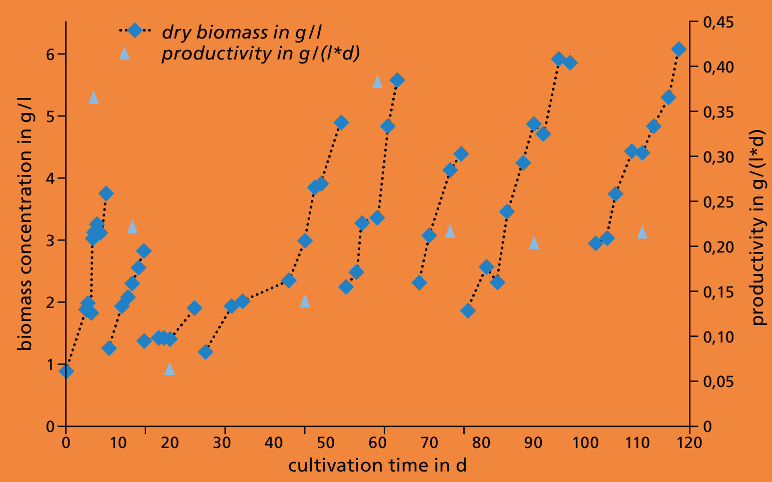

2

PILOT SYSTEM FOR CULTIVATION OF MICRO-ALGAE SUCCESSFULLY PUT INTO OPERATION

Gordon Brinitzer, Ulrike Schmid-Staiger

Microalgae – a new aquatic resource

Microalgae belong to a highly diverse group of microorganisms whose components, when produced through biotechnology processes, can be utilized both as a material resource and for energy purposes. Many algae strains produce high-value substances such as vitamins, carotenoids (pigments) and long-chain omega-3 fatty acids that can be used in the food, feed and cosmetic industries. Once growth is stopped due to limited nutrient availability and adequate light and CO_2 are made available, many algae produce oils (triacylglycerides) or starch as storage products. These major components can be used energetically as a renewable resource for biodiesel, ethanol and biogas production. Further biomass components such as proteins can be useful in feed or food products. Algae do not compete for arable land or potable water, hence microalgae species growing in seawater or brackish water can reduce freshwater consumption. Thus, the chemical industry can produce biomass to be used as both a material and energy source without competing with the production of food.

Biomass production in photobioreactors

Over longer cultivation periods, high biomass concentrations which are a prerequisite of high biomass productivities can only be achieved in closed photobioreactors. The volumetric productivity, i.e. the product of biomass concentration and growth rate, is directly related to the amount of light available to the individual algal cells. High light intensities on the reactor surface have to be distributed to all cells by efficient and targeted mixing because of the mutual shading effect in dense algae cultures. Efficient intermixing in flat panel airlift photobioreactors allows for an optimized specific light availability as demonstrated in several studies by the Fraunhofer IGB.

At outdoor conditions, however, the available sunlight varies over the day and with the seasons and this will affect the volumetric productivity. Therefore, the biomass concentration is a crucial parameter which has to be adjusted to the available light intensities.

The material use of renewable resources is one of the key competences of the Fraunhofer CBP. Sufficient quantities of biomass must be produced to realize a biorefinery concept that makes it possible to utilize the full spectrum of algal biomass components. We plan to produce such quantities in the new algae pilot plant at the Fraunhofer CBP in Leuna. The reactor facility was constructed by Subitec GmbH, a Fraunhofer IGB spin-off. The reactor principle was developed at the Fraunhofer IGB and then commercialized by Subitec GmbH.

The algae plant at the Fraunhofer CBP

Fig. 3 shows the outdoor production plant and the greenhouse. The total capacity of the facility is 11.7 cubic meters within 110 reactors each with volumes totaling 6, 30 or 180 liters. Of this production capacity, 7.2 cubic meters are in four lines each with ten 180 liter reactors outdoors. Scale-up can take place in the greenhouse (from 6 to 30 to 180 liters). This modular construction also facilitates the use of the system to carry out a wide range of experiments.

Operation of the greenhouse system is based on complete process automation and control using the "Totally Integrated Automation" concept from Siemens. A "Supervisory Control And Data Acquisition System" (SCADA) is used to collect data and create a network among independent modules of the system.

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Both visual controls and access points for the user and report outputs take place via "Human Machine Interfaces" (HMI) at the facility. The Fraunhofer IGB was entirely responsible for the design of this system and development of the software.

This software allows the targeted feeding of the culture with nutrients such as ammonium or nitrate, phosphate and iron. This allows, decoupled of harvest cycles, to precisely define the cell concentrations and adjust them to available light intensities. This leads to greater stability and productivity of the process. The pH is controlled by addition of CO_2 by a mass flow controller.

Outlook

The outdoor production plant began operation at the end of June 2014 and 40 reactors were successively inoculated with algae. From the end of July to the end of October of the same year (over 100 operational days), all 40 reactors were operating within approximately 7.2 cubic meters of reactor volume containing the algae *Chlorella sorokiniana* (Fig. 1). Approximately 130 kg of dry biomass were harvested in this time period. Fine-tuning the system in respect to CO_2 utilization and the automation of harvest cycles are planned for the upcoming season.

The Fraunhofer CBP now has an algae production facility available both for CBP research projects and to produce algal biomasses of specific composition on behalf of clients.

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1 *Reactor module of the outdoor facility.*
2 *120-day long-term cultivation of Chlorella sorokiniana.*
3 *Greenhouse and outdoor facility at the Fraunhofer CBP.*
4 *Harvested algal biomass: Chlorella sorokiniana.*

ENVIRONMENT

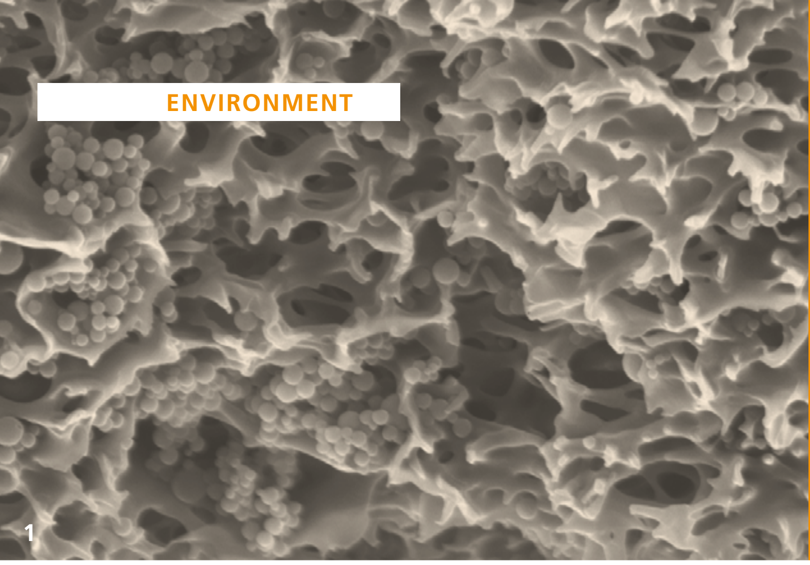
Against the backdrop of the global debate on global warming, resource scarcity and water pollution, resource and environmentally friendly economies are all the more important. In national and international projects with partners from research, industry and communities, the Fraunhofer IGB is developing innovative processes, reactors and apparatuses for a sustainable treatment of urban wastewater and industrial process water, exhaust air, contaminated soils and wastes. The environment business area thus stands for a variety of advanced technological developments that help to prevent a negative impact on the environment, and that combines economy with sustainability. Tasks and resolution approaches are, in many cases, linked with major topics in the business areas energy and chemistry.

Recovery of secondary raw materials – Due to the finiteness of primary raw materials, we develop processes which enable recovery from production and waste streams for reuse as secondary raw materials – in a quality equivalent to that of primary raw materials and with a comparable process complexity. For inorganic raw materials (metals, rare earths), for example, we develop new reprocessing methods by which dissolved mixtures can be selectively separated on a molecular or atomic level. In the area of soil, we conceive of and realize methods for the recovery and processing of dissolved or organically bound phosphorus for use as high-quality fertilizers and soil conditioners.

Improving resource efficiency – In order to increase the efficiency of the raw materials used, our goal is to establish closed loop recycling systems as completely as possible. An example is the entire utilization of biogenic resources, where we combine a cascaded use of the material with energy recovery. In the regenerative production of algal biomass for material and energy use, an additional focus, the climate is saved through the fixation of carbon dioxide and high-value raw materials, such as for organic crop protection.

Wastewater treatment – The Fraunhofer IGB offers innovative, infrastructural concepts as solutions, each of which is adapted to geographic, demographic and regional parameters, for an economical and ecological, semi-decentralized energy and water management. We use a variety of different technologies to prevent the emission of particulate or dissolved, persistent micro-pollutants. The recovery of components from agro-industrial process waters or from municipal wastewater treatment plants in the form of fertilizers combines wastewater purification with material value.

For the inclusion of additional expertise, the IGB is engaged in the Fraunhofer Alliances Building Innovation, Cleaning Technology, Water Systems, Food Chain Management and Energy, the Fraunhofer System Research for "Morgenstadt" as well as in the national technology platform SusChem Deutschland, and is also excellently networked internationally, particularly within Europe.



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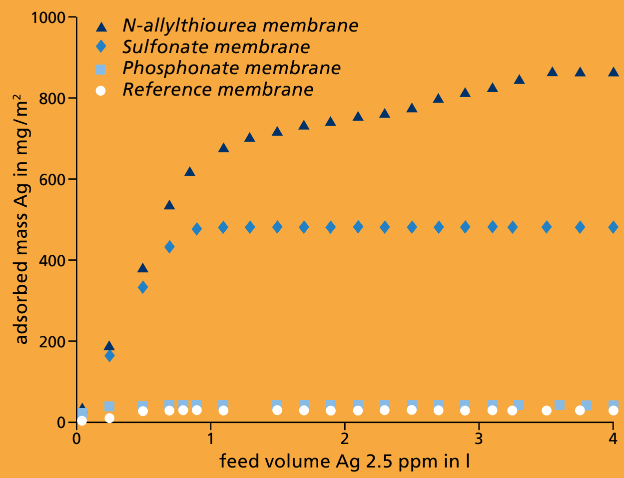


2

MEMBRANE ADSORBERS FOR THE SEPARATION OF RECYCLABLE MATERIALS AND MICROPOLLUTANTS

Klaus Niedergall, Thomas Schiestel

Required: Efficient separation of small molecules

Nowadays various types of membranes for water filtration are already available through commercial channels. A common feature of these membranes is that substantially different separation cut-offs are used for size exclusion. On the other hand, the underlying porous structure, which provides a highly specific surface, remains unused. Membranes for nanofiltration (NF) and reverse osmosis (RO) can in fact partially retain molecular and ionic substances. However, high pressures are necessary for this, which pushes up both the investment and the operating costs.

In principle adsorbers can be used to remove molecular contaminants. Typical adsorber materials are microporous, so as to provide a large specific surface for adsorption. A disadvantage of these materials is the limited mass transport, since the micropollutants have to diffuse into the inner porous structure of the adsorbents.

There is therefore a need for new integrated separation systems. For this purpose we are developing mixed-matrix membranes that, in addition to their filtration function, can adsorptively bind substances dissolved in water.

Manufacturing functional particles as adsorbers

To achieve this, functional submicroparticles are manufactured by means of miniemulsion polymerization. These are between 50 nm and 500 nm in size and can be synthesized from a variety of different, commercially available monomers. The particles provide the best compromise between a high specific surface, safety and functionality and are compatible with the phase inversion process for the manufacture of porous membranes.

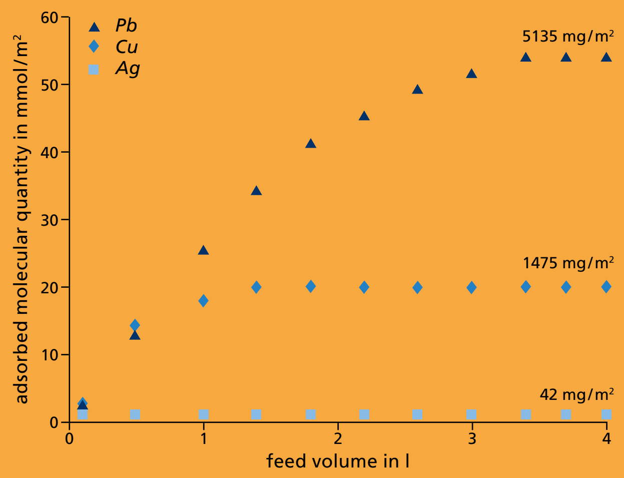
The variation of the particle surface and the combination of different particles enables us to manufacture membrane adsorbers with separation characteristics that can be adapted flexibly for applications in the areas of drinking water, process water and wastewater. A large number of particles with different functional surface groups are now available. The spectrum of functional groups ranges from the fairly hydrophobic pyridine, by way of cationic ammonium compounds to anionic phosphonates and also thiourea.

Embedding the particles in membranes

In a first step the particles were embedded in polyethersulfone flat membranes by means of a phase inversion process (Fig. 1). This showed that, quantitatively, up to 40 percent by weight of the particles can be integrated in the membranes. Most of the particles are easily accessible inside the pores. It was also shown that different particles can be combined in one membrane. In this way various micropollutants, for example, can be removed with just one membrane adsorber [1].

Selective adsorption of the membrane adsorbers [2]

If one compares the adsorption behavior of silver on various membrane adsorbers (Fig. 2), it can be seen that the reference membrane without particles exhibits practically no unspecific adsorption. On the other hand, the membrane with thiourea groups selectively binds over 0.8 g silver per m². However, if



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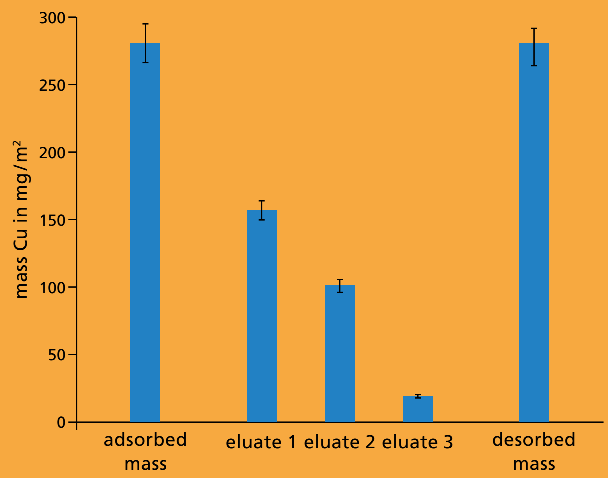

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one compares the adsorption behavior of various metal ions on a phosphonate membrane adsorber, it can be seen that practically no silver is bound, whereas copper and especially lead are adsorbed very well by it (e.g. over 5 g lead per m^2, Fig. 3).

Regeneration of the membrane adsorbers

The regenerability of the systems is important for the cost-effectiveness of the membrane adsorbers. So far we have been able to find suitable solutions for a quantitative desorption in all the adsorptions investigated. Thus copper, for instance, can be completely removed from the membrane adsorber using small amounts of diluted nitric acid (Fig. 4). A pre-enrichment of copper by a factor of 100 is therefore possible. But membrane adsorbers for micropollutants such as bisphenol A can also be completely regenerated by means of a pH shift [1].

Outlook

In further studies we intend to transfer the principle of the membrane adsorbers presented here to hollow fiber membranes. This makes possible both a higher specific separation area and a higher specific adsorption volume. The resulting systems are then to be used to remove toxic substances such as micropollutants or heavy metals from drinking water direct at its point of use. The membrane adsorber systems can also be used to recover valuable metals such as rare earths from process streams.

1 *SEM image of a particle-filled polyethersulfone flat membrane.*

2 *Adsorption of silver ions on membrane adsorbers with different functional groups.*

3 *Adsorption of silver, copper and lead on membrane adsorbers with phosphonate groups.*

4 *Regeneration of a copper-loaded membrane adsorber with diluted nitric acid.*

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Funding

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Further information and project partners

www.molecular-sorting.fraunhofer.de

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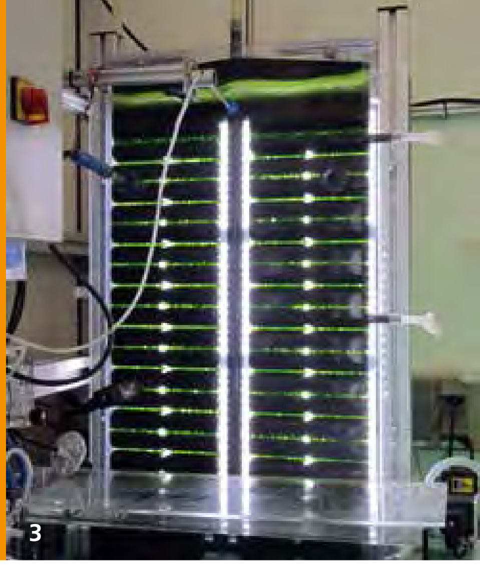

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ORGANIC PLANT PROTECTION PRODUCT FROM MICROALGAE AGAINST FUNGAL INFESTATION

Jennifer Bilbao, Alejandra Campos, Ulrike Schmid-Staiger, Siegfried Egner

Viticulture – in search of an alternative to copper

One of the major problems in modern winegrowing is the fungal infestation of vines. As a result of the harmful effect of fungi, such as downy mildew, not just the harvest but also the quality of the wine produced is severely impaired. Currently, to prevent fungal infestation, most organic winegrowers treat their vines with products that contain the heavy metal copper as an active substance. Copper accumulates in the soil and harms or kills, among others, valuable soil microorganisms.

Currently, the EU-Eco Regulation limits the use of copper to six kilograms per hectare and year and the German organic associations limit its use, on a voluntary basis, to three kilograms per hectare and year. However, the EU is pushing for copper fungicides to be replaced as quickly as possible. Unfortunately, at the moment there are no efficient alternatives to replace copper as a fungicide in organic or conventional viticulture. Therefore, an economical solution is required to support the development and growth of the organic viticulture market. The aim of the EU-funded ProEcoWine project was therefore to develop an environmentally compatible plant protection product made from microalgae which is suitable for organic winegrowing.

Cultivation of the microalgae

At the University of West Hungary, a microalga strain with activity against downy mildew (*Plasmopara viticola*) was successfully selected from their algal culture collection and tested. At the Fraunhofer IGB, growth and biomass production of this microalga in the flat-panel airlift reactors (FPA) developed by the IGB was optimized. In the cultivation process, important parameters such as composition of the culture medium, concentration of CO_2 and mineral nutrients and, in particular, the light intensity on the reactor surface in relation to the cell concentration in the reactor, were determined experimentally. The optimized process was successfully transferred to the outdoor reactors of the Portuguese industrial partner A4F to produce the amount of algal biomass for the field trials in the vineyards.

Processing of the microalgae

To release the fungicidal active substance, the microalgal biomass was disrupted by a mechanical treatment in a ball mill. In the process, it was possible to disrupt more than 95 percent of the cells. The subsequent conservation of the disrupted microalgal suspension was carried out by a thermal method, through air-drying at low temperatures. The dried product underwent several tests and showed a high fungicidal effect. No phytotoxicity effect was determined, meaning that the microalgal product is significantly more suitable for the plant than the existing copper preparations used at the moment.

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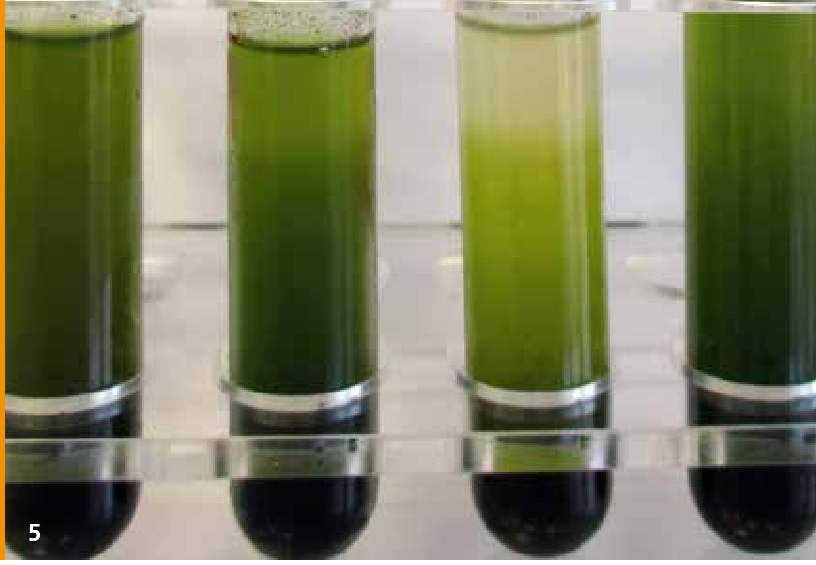

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Field trials

In order to test the effectiveness of the newly developed plant protection product, the project partners carried out appropriate field trials. Here, the product was applied to the vines using the customary spraying equipment in winegrowing. The results were very positive: the algae-based fungicide had success rates comparable to commercial preparations containing copper and the infection rates on the leaves were lower than with untreated vines.

Outlook

Based on these results the intention is, in collaboration with the SME partners, to design a pilot plant for manufacturing the algae-based fungicide for further field trials in different regions and under different climatic conditions. After completion of this test phase, the SME partners aim to commercialize the product in the European market.

Funding

The project "Development of a process to generate a novel plant protection product enriched with micronutrients to replace copper in organic viticulture – ProEcoWine" has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 315546.

Project partners

IAU Service, Freyburg, Germany | A4F Algae for Future, Lisbon, Portugal | Kürzeder & März, Wörth, Germany | Les Vignerons de Buzet, Buzet-sur-Baïse, France | Viñedos de Aldeanueva, Aldeanueva de Ebro, Spain | AlfaLaval, Lund, Sweden | Naturland, Munich, Germany | University of West Hungary, Mosonmagyaróvár, Hungary | Phenobio, Martillac, France

Further information

www.proecowine.eu

1 *Microscopic image of the microalgae tested.*
2 *Inhibition of the sporulation of grapevine downy mildew (Plasmopara viticola) after use of the protection product based on microalgae. Top: untreated leaf sections (control), bottom: treated leaf sections.*
3 *Flat-panel airlift reactor for process optimization.*
4 *Microalgae following disruption in the ball mill.*
5 *Microalgal suspensions with different preserving agents.*

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NEXUS – WATER, ENERGY AND FOOD IN ASIAN CITIES

Marius Mohr

Initial situation

Cities in Asia are undergoing extremely dynamic development – the economy is growing and many people are being drawn from the countryside into towns. But with this huge growth come several challenges: supplying the population with water, food and energy, disposing of wastewater and garbage, and protecting the populace from disasters are all things which need to be safeguarded. At the same time, the people in cities responsible for these matters ought to ensure that natural resources are protected and that the city is offering its citizens a high quality of life. Only in this way can sustainable development be guaranteed long term. Because of the very dynamic situation, this can only succeed if the thinking in sectors is abandoned and innovative solutions are found through synergy (Nexus) between the areas of water, energy and food security.

Concept development for eight cities in six countries

In this context, the Deutsche Gesellschaft für Internationale Zusammenarbeit (GIZ) is advising different key players in selected cities as part of the project: "Integrated resource management in Asian cities: the urban nexus" funded by the German Federal Ministry for Economic Cooperation and Development. Last year, the Fraunhofer IGB contributed to this project in the area of water and wastewater management and developed customized, innovative concepts for some of the cities. To this end, the following cities were visited, discussions held with those responsible and the status quo analyzed in each case: Yogyakarta (Indonesia), Santa Rosa, Naga City (both in the Philippines), Ulaanbaatar (Mongolia), Rizhao, Weifang (both in the PR China), Da Nang (Vietnam) and Korat (Thailand).

The result – tailored and sustainable approaches

For each of the cities, the experts from the Fraunhofer IGB identified approaches for sustainable development in the areas investigated. For example, for a development area outside Weifang they drew up a semi-decentralized, modular water management concept using graywater for the flushing of toilets, and for Naga City a concept for the joint treatment of wastewater from a newly built housing complex, a slaughterhouse, a prison and a school. In Korat, they analyzed an existing but not satisfactorily functioning biogas plant for the treatment of organic household waste and made suggestions for improvement measures.

For a stretch of coastline in Da Nang, currently inhabited by approximately 200,000 people, the Fraunhofer IGB together with the experts from the GIZ developed a concept whose starting point is the collection of wastewater – which previously seeped into pits – through a vacuum system. The wastewater is then treated together with kitchen waste from nearby hotels; the biogas generated can in turn be used for cooking in the kitchens of the hotels. With 45 liters per inhabitant per day, this concept enables twice as much biogas to be produced as in conventional sewage treatment plants in Germany. The plan is for the purified water to be used outside of the rainy season for irrigation purposes for the intensive agricultural activity (Urban Gardening) within the city; this will contribute towards less groundwater being extracted and hence the threat of salinization of the groundwater through subsequent influx of seawater being reduced. Here the nutrients can be left in the wastewater, so that a fertilizing effect is achieved at the same time.

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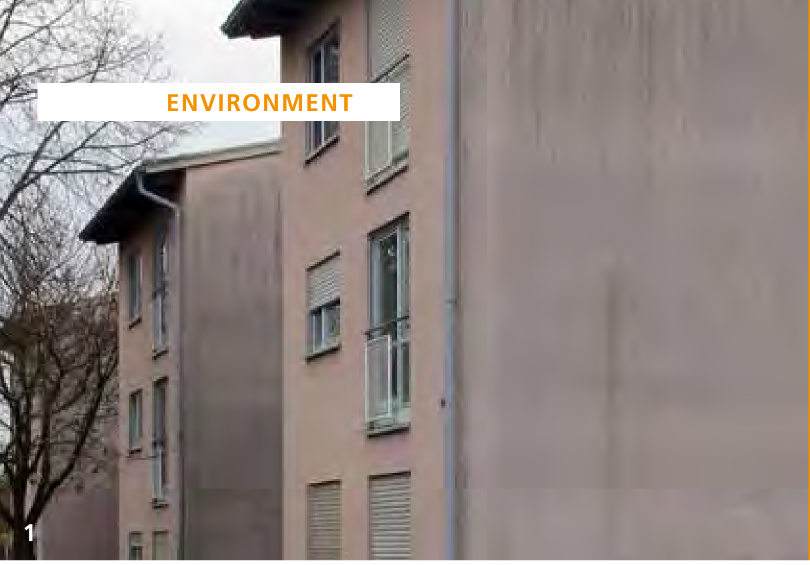
Outlook

Because no investment resources are being made available within the context of the Nexus project, the towns involved have to either finance the implementation of the proposed solutions from their own resources or apply for grants from donor organizations. In Da Nang, a decision has already been made to put into practice the vacuum system – for testing – for 110 sites. Once satisfactory testing of the vacuum system has been completed, the plan is to implement the overall concept from the end of 2015 onwards including use of the energy present in the wastewater and use of the wastewater for irrigation and fertilization.

In September 2014, the mayor of the Georgian capital Tiflis, Davit Narmania, visited the Fraunhofer campus in Stuttgart. He showed great interest in carrying out an analysis of his town as part of the Fraunhofer System Research Initiative "Morgenstadt". The plan is to begin this together with the Fraunhofer IAO in 2015. The experience from the Nexus project will be used in the work.

1 *Combined sewer overflow on the beach at Da Nang, Vietnam.*
2 *"Urban Gardening" in the middle of Da Nang, Vietnam.*
3 *Waste sorting at the Korat garbage dump, Thailand.*
4 *Development area outside Weifang, China.*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AVOIDANCE OF MICROBIAL GROWTH ON FAÇADE ELEMENTS OF BUILDINGS

Iris Trick

Initial situation

In the framework for sustainability of the Federal Republic of Germany, the owners of buildings should be motivated to save energy in apartments and buildings by different incentives like tax breaks or convenient financial funding. According to the Federal Environmental Agency, one of the causes for thermal loss in buildings is based on bad thermal insulation [1]. When accompanied by better insulation in old structures, the heating energy can be decreased by 60 percent. The thermo-technical activities in the building envelopes is a highly important parameter, because they have a life span of many years and therefore are essential to reach the aims of making existing buildings climate neutral.

International consortium aiming for façade optimization

Within the FoAM-BUILD project funded by the European Union, new External Thermal Insulation Composite Systems (ETICS) will be developed for new building and retrofitting applications. The challenge for the Fraunhofer IGB is the testing of the effectiveness of the system regarding the prevention of biofilm development. The growth of organisms on the façades of buildings is an increasing problem, as the algal and fungal development affects the optical impression as well as the health of the inhabitants. Therefore the project addresses the avoidance of microbial growth, too.

It is expected that the technology developed within the FoAM-BUILD project will lead to energy savings of 192,000 kWh to 288,000 kWh over a façade lifetime of 30 years. Additionally, the new biofilm protection system will extend the service life of the façade surface from 5 years to 20 years for a north façade in central Europe.

The FoAM-BUILD consortium comprises ten European organizations and companies including the Fraunhofer-Gesellschaft and DAW from Germany, Smithers Rapra and Smithers Pira from the UK, the National Centre for Scientific Research (DEMOKRITOS) from Greece, ELKEM from Norway, SUNPOR Kunststoff from Austria, TBC Generateur d'Innovation from France, Ateknea Solutions from Spain, Stichting Nederlands Normalisatie-Instituut (NEN) from the Netherlands, and Norner Research AS from Norway.

Moisture monitoring system

Microorganisms grow especially under wet conditions. Active monitoring and control of moisture play a key role in the project. A control system will be developed based on a sensor network to measure moisture and liquid water. Data from the sensors will be combined with an intelligent system for moisture prediction, and the system will respond by activating a ventilator system to dry targeted areas of the façade. The materials and systems will be tested and demonstrated within the project by industrial end-users, with the creation of a demonstration insulation material, sensor network and intelligent system as well as the ventilation system.

Test facility simulates weather conditions

The contribution of the Fraunhofer IGB is the experimental assessment of commercially available and innovative finery materials. There are first results with xerophilic fungi at different temperatures under static conditions. To test the development

of algae and additional fungi on different material surfaces, special equipment was developed in the project. The cultivation of algae and fungi under dynamic conditions is possible using the test facility on a laboratory scale. Various weather conditions and climatic influences can be simulated using the implemented measurement and regulation possibilities. Several samples can be applied and characterized regarding the growth of one species at the same time for a defined time range and under defined conditions in the construction. At the moment, the assessment is based on optical aspects.

Outlook

The test equipment is being tried out. It will be available for testing of other materials as well in the future. The main advantage is that different humidity, temperature and illumination adjustments can be simulated according to real environmental conditions as well as conditions created by calculated guidelines without running outdoor experiments.

1 *Microbial growth on façades.*
2 *Growth of different fungal cultures at different temperatures.*
3 *Sample with algae growth from test facility.*
4 *Photographic description of the newly developed test equipment.*

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Project partners

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Further information

www.foambuild.eu

E^3-PRODUKTION

LIGHTHOUSE PROJECT E^3-PRODUCTION – EFFICIENT, EMISSION-NEUTRAL, ERGONOMIC

Birgit Haller, Jan Iden, Ursula Schließmann

An integrated approach to production

For manufacturing companies it is becoming ever more important to use alternative and regenerative energy sources efficiently and to recycle materials. In an increasingly digitalized and networked production environment the part played by people also needs to be reconsidered.

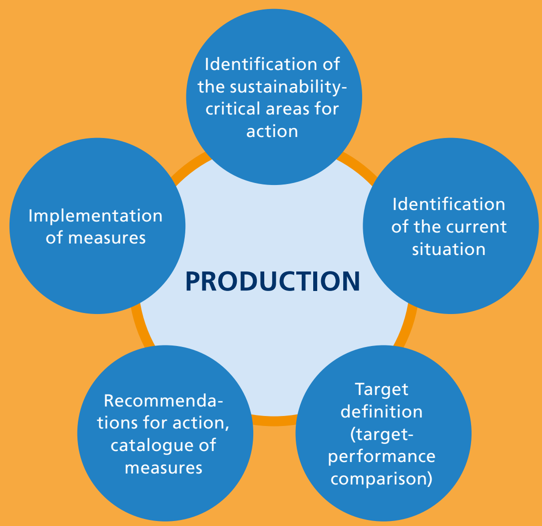
Against this background the aim of the Fraunhofer lighthouse project “E^3-Production” is to research how material, energy and information flows in emission-neutral E^3 factories with energy- and resource-efficient production can in future be better planned, implemented, evaluated and controlled in an integrated approach that takes into account the way people are involved. Integrative approaches and synergies in the production sequence are necessary to achieve this. The project is being carried out by twelve Fraunhofer Institutes under the three topic headings “efficient”, “emission-neutral” and “ergonomic”.

The Fraunhofer IGB is involved in two subprojects. An efficient, high-performance biotechnological process for the separation and concentration of metals from diluted technical process media is being developed in the subproject “Integrated Process Chain Engineering”. The synergetic examination of social and ecological criteria in an efficient production sequence is the focus of the subproject “Sustainability and Cost-Benefit Analysis of Production Processes for German Industry – SUSPROFIT”.

Integrated process technology for separating metals

In the subproject “Integrated Process Chain Engineering”, a fixed-bed circulation reactor was built and a biotechnological process was established for the treatment of used cooling lubricants from the metalworking industry. The fixed-bed circulation reactor developed at the IGB operates on the principle of an ultrashort process chain, since it permits various process steps at the same time: the immobilization of microorganisms on fixed-bed particles, the biologically induced precipitation of the metals, the purification of the particles as well as the separation of the precipitated metals by integrating a hydrocyclone.

The final product of this biotechnological treatment is a highly concentrated metal-bearing solid matter fraction in high quality (> 5 g/kg separated solid material). The particle characteristics, the morphological growth of the microorganisms, the mechanical stability of the particles, the flow properties of the bulk discharge as well as the costs for a scale-up were identified in order to design the fixed-bed circulation reactor. The dimensions were determined for a mass flow in the reactor using modified calculation models from bulk material technology. Suitable microbial populations were enriched from the medium and the ion analysis necessary to characterize the course of the process was established. After validation the process is being operated on a pilot scale over a longer period of time. After that it will be available for other process waters.



Sustainability and cost-benefit analysis

In the subproject SUSPROFIT a practical, industry-specific evaluation system is being developed that identifies the sustainability risks and indicates options for action. For this purpose, existing standards, norms and tools for life cycle assessment, for technology assessment, for energy, environmental and quality management as well as social standards and guidelines for Corporate Social Responsibility management were reexamined regarding their transferability and industry-branch specificity.

The concept of SUSPROFIT is based on these analyses and the principles of sustainable production. Industry-specific sensitive areas of the company are identified using a generic approach comprising a questionnaire. Besides the environmental aspects such as the use of energy and materials, social criteria such as the working conditions are determined and further developed. In each particular case a target-performance comparison shows the company's need for action. Developers or process designers initiate a process of improvement which is reinforced by specific recommendations for action. A label concept assists them in the optimization of the production system. This label concept additionally permits a clear positioning with regard to customers and suppliers.

SUSPROFIT is aimed at manufacturing companies, especially small and medium-sized, and focuses on the production process. The interfaces with supply chains and product life cycles are taken into consideration. During the further course of the project the concept will be elaborated and validated in cooperation with possible users.

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Project partners
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1 *Fixed-bed circulation reactor.*
2 *Implementation of the SUSPROFIT approach.*

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EFFICIENT MATERIAL SEPARATION USING ELECTRIC FIELDS

Carsten Pietzka, Maximilian Kotzur, Thomas Scherer, Siegfried Egner

Material separation in electric fields

Resource and energy efficiency continues to be of growing importance in recovering and processing materials by means of process engineering. The reasons for this are the increasingly restricted access to raw materials, especially in the area of high-tech metals, and rising prices for electricity and fossil energy sources such as oil and gas.

Separating substances as selectively as possible is a fundamental and decisive step both in primary and in secondary processing of raw materials, as well as in biotechnological downstream processing. The state-of-the-art steps required for the separation of substances are complex and therefore cost-intensive; as a result they substantially determine the processing costs, and also the sustainability of the processes. In order to tackle this problem, the Fraunhofer IGB develops processes that significantly enhance energy and cost efficiency compared with established processes or actually enable the selective separation of certain raw materials.

In a number of processes newly developed at the IGB the separation of substances is based on the interaction of charged particles with an electric field. The motion of ions and molecules in the electric field is decisively determined by their charge and mobility, i.e. their separation takes place on the basis of the electrophoretic characteristics. The IGB designs different processes for various applications, to meet the requirements of the particular separation problem in question.

Free-flow electrophoresis

In free-flow electrophoresis (FFE) the separation is effected exclusively on the basis of a different charge and mobility. The materials to be separated are charged into a laminar buffer flow that runs through the process chamber. The elements to be separated are deflected differently by the electric field applied vertically to the direction of flow; in this way they are separated into different fractions. Here, the IGB bases its work on the results gained in the Fraunhofer "Beyond Tomorrow" project "Molecular Sorting", in which the separation of ions with an identical net charge has been demonstrated. Now the FFE method is being further developed within the scope of the lighthouse project "Criticality of Rare Earths". In addition to rare earths, biogenic materials such as proteins or enzymes can also be separated by means of FFE.

Electro-membrane filtration

In electro-membrane filtration (EMF) the material separation in the electric field is combined with mechanical membrane filtration. A reactor is divided into two chambers – the retentate compartment and the permeate compartment – using a standard filtration (e.g. ultrafiltration) membrane. The driving gradient for the material transport across the membrane can be generated both by the transmembrane pressure and by the electric field applied. This permits separation both on the basis of the electric charge and the particle size. As a result, for example, a significantly higher degree of selectivity combined with low energy consumption can be achieved compared with the established ultrafiltration method. The EMF process is currently being used and optimized within the scope of the EU-funded "Whey2Food" project for the fractionation of whey proteins.

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Electrodialysis

Electrodialysis performs the required separation of substances by means of a sequence of ion exchange membranes. Thus, for instance, salts, acids or lyes are separated into a concentrate and a diluate. This method achieves additional selectivity by integrating special membranes that, for example, prevent the transport of polyvalent ions. Besides the actual separation of substances, salts can be split into their corresponding acids and lyes by integrating bipolar membranes in the electrodialysis process.

Electrodialysis is currently being optimized as regards energy efficiency for industrial scale applications within the scope of the EU-funded project "NovEED". These applications are to be found, for example, in electroplating and the mining industry where, thanks to the improved energy efficiency, they permit the recycling of process additives on an industrial scale. Besides this, the integration of electrodialysis in biotechnological downstream processes is a focal point of future work, for example in the purification and concentration of organic acids.

Outlook: Integration of several techniques in an overall process

A further key aspect is that the methods described above can be combined with one another in process chains. For example, electrodialysis or EMF can be used to pre-concentrate the substances that are subsequently to be separated by means of FFE. A further example is the separation of larger molecules before electrodialysis by means of electro-membrane filtration. Combining the various methods developed at the IGB opens up a great potential for new applications. Efficient material separation using a single process is frequently not possible, especially when it is a question of recovering raw materials from solutions with a complex composition.

By integrating the processes described here, the overall process efficiency can be optimized, for example regarding selectivity, number of stages and energy, for the particular application in question. As a result, separation processes become feasible for numerous applications in the treatment of water and the recycling of materials.

1 *Electrodialysis.*
2 *Free-flow electrophoresis.*
3 *Lab construction for electro-membrane filtration.*

ENERGY

An energy supply based on the use of finite primary energy sources such as crude oil, natural gas and coal leads to a rapid rise in the concentration of CO_2 in the atmosphere – and thus to unpredictable climate changes. The transition to a sustainable, environmentally friendly yet reliable and economical source of energy supply – in view as well of the ambitious climate change targets – is therefore one of the major challenges the Fraunhofer IGB meets in the use of electricity, heat, and chemical energy (fuels).

Sustainable energy conversion – The efficient production of biogas from organic waste, by-products of the food industry and agriculture, sewage sludge or wastewater by means of anaerobic technologies has been a key research area at the IGB for decades. Increasingly, low mass flows from decentralized sources are gaining in importance. We make contributions to increase photosynthesis capacity by developing processes for cultivating microalgae. Their storage substances can be used either directly (lipids), after fermentative conversion to ethanol (starch), or after digestion to biogas (residual biomass) for energy. We also advance the exploitation of further regenerative energy sources by means of highly innovative membrane technology (gas separation, ethanol fuel cells, osmosis power plants).

Energy efficiency in engineering processes – Energy consumption in the process industry is substantial; savings are offered via optimizations such as through efficient separation processes as well as through the minimization of process steps. For the separation of high-purity methane from biogas as a basic chemical or fuel, we investigate absorption and membrane processes or ionic liquids that have a high capacity to bind CO_2. Noteworthy in this context are also energy-efficient drying processes with superheated steam at atmospheric pressure as well as methods for rapid energy input by means of microwave fields, e.g. as in pyrolysis processes. We have developed an anti-icing coating on film that makes it possible to operate wind turbines in freezing weather.

Energy storage – To achieve the climate objectives, waste heat that is generated in power plants and many other industrial processes, must be increasingly used. To make excess waste heat available for temporally and spatially decoupled heat requirements, the Fraunhofer IGB is developing thermo-chemical sorption systems for the long-term storage of heat. In addition, new techniques are being developed to utilize electrical energy by binding and converting CO_2 into chemical energy carriers, e.g. in the form of longer-chain hydrocarbons.

Integrated material flow and energy concepts for municipalities and regions are also to be tackled through approaches using state-of-the-art technologies – in order to replace historically evolved solutions. Therefore, the IGB is also involved with the Fraunhofer Alliances Energy, Construction, and Water Systems as well as with the Fraunhofer System Research for "Morgenstadt".

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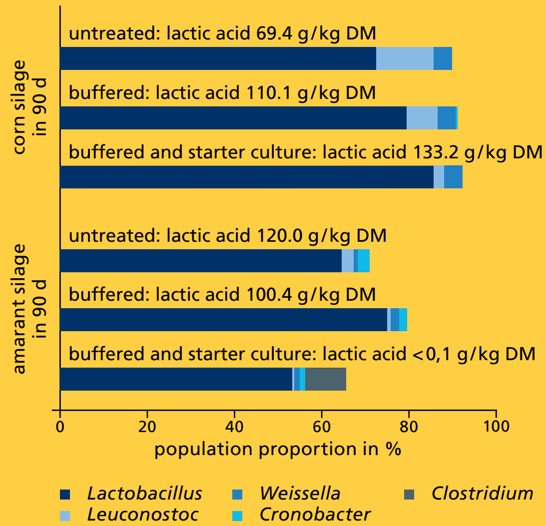

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METAGENOME ANALYSES FOR THE OPTIMIZATION OF THE ENSILING AND BIOGAS PROCESS

Christian Grumaz, Franziska Wiese, Kai Sohn

Optimization potential in the biogas process

Biogas is produced in biogas plants by anaerobic digestion of biomass using bacteria. Nowadays, optimization of the process management to increase biogas yields is implemented at several levels, such as the composition of the inoculum (e.g. liquid manure, sewage sludge) or the utilizable substrates (e.g. corn, grass silage) (Fig. 1). Knowledge of the microorganisms involved in the ensiling and biogas processes and their reaction pathways is, however, still largely incomplete, although identification and process classification of single microorganisms was made possible by previous studies. However, these were mainly based on classical microbiological methods and were thus limited to cultivable organisms. For this reason, a more complete and detailed characterization of the dominant microbiological composition and the metabolic pathways will contribute to the understanding and the more precise control of the biogas production process.

Next-generation biotechnology

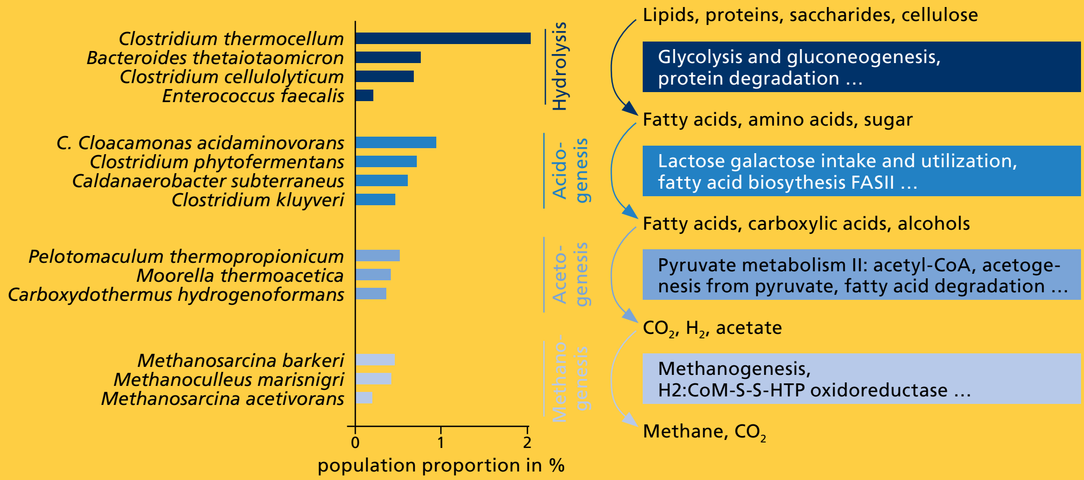
The rapid developments of high-throughput sequencing technologies (Next-Generation Sequencing, NGS), providing dramatic reduction in costs with simultaneous increase in capacity, has opened up completely new dimensions in nucleic acid analytics [1]. The special feature of these technologies is that it is no longer isolated fragments but rather several hundred million fragments that can be sequenced simultaneously. In this way, the microbiological characterization of entire biocenoses can provide an almost complete picture of the microorganisms and metabolic pathways present that have thus far remained undetected using classical microbiological methods [2]. Using direct DNA sequencing, there is no longer need for elaborate cultivation and phenotyping of microorganisms, since almost all species can be identified and their population proportion can be simultaneously determined by stringent, bioinformatic methods. Furthermore, thanks to NGS these so-called metagenome analyses can be carried out on a high-throughput scale, which allows systematic investigation of the ensiling and biogas process under defined conditions and time points.

Microorganisms in the ensiling process

In this context, we worked with the Environmental Biotechnology and Bioprocess Engineering Department and the University of Hohenheim to examine the microbiological composition of different ensiling processes in the substrates corn (Fig. 1A) and amaranth regarding lactic acid production [3]. The ensiling conditions examined included different carbonate buffer concentrations and differently composed starter cultures. Analyses of the corn silages showed a homogeneous distribution of the microbiological population, which mainly consisted of members of the genus *Lactobacillus*, *Leuconostoc* and *Weissella*. In some silage approaches, this correlated with high lactic acid concentrations (Fig. 2). In contrast to this, a shift in the composition of the amaranth silage approaches towards clostridia utilizing lactic acid could be observed, which meant that an increase in the butyric acid concentration was detrimental to the silage. Overall, we were able to determine ten species of bacteria with a high significance for the silage process.

High complexity in the biogas plant

Biogas is produced in biogas plants using anaerobic microorganisms and can be divided into four metabolic steps: hydrolysis, acidogenesis, acetogenesis and methanogenesis. In



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order to identify the species crucial to these processes, a comprehensive metagenome analysis was carried out by way of an example during the production of biogas in a 1 liter reactor (fed-batch). This resulted in a clearly more complex picture of the population consisting of up to 222 detected species. Both the microorganisms identified and the metabolic pathways detected by enrichment analyses were able to be assigned to the corresponding metabolic processes and contributed decisively to increasing the insight into biogas production (Fig. 3, amended according to [4]).

Outlook

Defined large-scale studies on biogas production are to be carried out in the next steps in order to record population dynamics in the fermentation process depending on, for example, the substrate used. This is intended to be the basis for future targeted management and optimization of biogas processes.

1 *Corn silage (A) and fermenting sample from the biogas reactor (B).*

2 *Microorganism composition of corn and amaranth silages which are dependent on lactic acid production (DM = dry mass).*

3 *Most common species in the respective step of the biogas process.*

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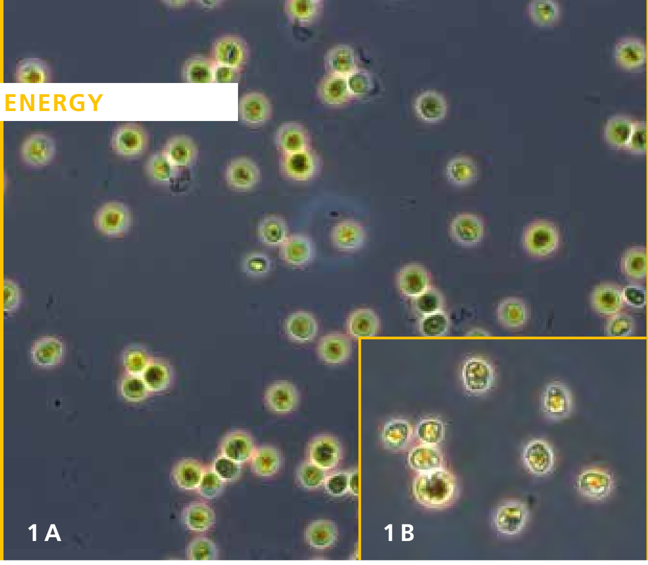

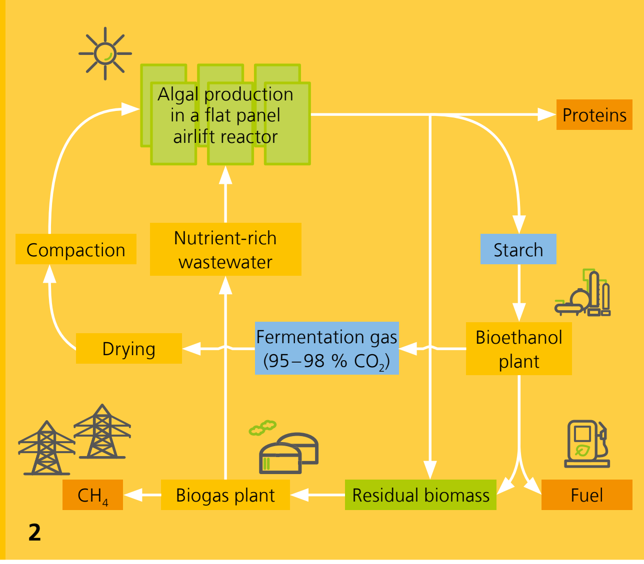

BIOREFINERY BASED ON STARCH-RICH ALGAL BIOMASS

Claudia Holdmann, Christopher Hering, Konstantin Frick, Ulrike Schmid-Staiger

Background

At present, biofuels such as ethanol and biodiesel are produced primarily from organic raw materials such as cereal starches or rapeseed oil. This means that arable land is no longer available for the production of food. Such competition for use can be circumvented by the cultivation of microalgae. These organisms also offer a wide range of other advantages compared to higher plants, including greater yields per unit area and lower water demand. A number of microalgae are able to accumulate starch as a storage product when nutrients are limited. The German Federal Ministry of Food and Agriculture (BMEL) has funded a project in which algal biomass is produced in closed photobioreactors and starch, the main component of these algae, is used for the production of ethanol.

The second major component of these starch-rich algae are proteins. To increase the value of the production chain, we are also investigating whether the algal proteins can be used as a constituent of culture media for the production of ethanol from cereal starches or as a feed ingredient. For closing loops between ethanol fermentation and algae production, two waste streams are utilizable: Fermentation off-gas can be used as a cheap, high-quality source of CO_2 for photosynthetic algae production. The second loop is to use the liquid digestate of digested fermentation mash and algae residues as ammonium- and phosphate-rich nutrient source for algae production. This biorefinery concept enables utilization of the entire biomass and increases the value of the algal biomass (Fig. 2).

Successful screening for the most suitable alga

The first step involved screening the starch production capacity of various algae strains. The microalga *Chlorella sorokiniana* (SAG 211-8k) proved to be the most promising due to its high growth rate and its ability to accumulate large quantities of starch. This alga was then used to establish a two-step process in which first biomass is produced and then, under nitrogen limitation, starch is accumulated in the algal cells. Starch production was optimized in terms of light availability (light on the reactor surface per gram of biomass in the reactor over a defined period).

Outdoor production of starch-rich algal biomass

In order to produce algal biomass suitable for biofuel production, the process has to be transferred to outdoor cultivation conditions using natural sunlight. The challenge is to establish a process that will operate in a stable manner and produce starch-rich biomass even under the variable light and temperature conditions of the natural day-night cycle.

We utilized a test facility with five south-facing 28-liter flat panel airlift reactors to characterize the starch production process using the microalga *Chlorella sorokiniana*.

Increasing the starch content in laboratory and outdoor cultivation

Laboratory and outdoor cultivation experiments have shown that depriving the culture of nitrogen results in an increase in starch content in microalgal cells. In lab experiments, a starch content of 50 percent was reached within two days of nutrient depleted cultivation of the algae. Light availability per gram biomass was hereby a key variable influencing the rate of starch production. This variable can be easily adjusted in the laboratory, but to investigate different levels of light availability in an outdoor setting three reactors with differing cell concentrations are required. Hence, each reactor operates under a different quantity of light per gram of biomass. In this way, the starch content of *Chlorella sorokiniana* increased to 50 percent of dry weight in the outdoor setting as well, but the process required 7 to 8 days due to recurrent day-night rhythm and changing weather conditions resulting in variable process temperatures and light intensities compared to laboratory tests.

Outlook

A pilot algae facility with a volume of 4.3 m^3 was constructed on the site of a bioethanol plant at CropEnergies in Zeitz in cooperation with project partner Subitec. The system involves 24 reactors each with 180 liters and will be used for a pilot scale starch production process. Industry partner Südzucker is responsible for the preparation of the biomass and fermentation of the algal starch to ethanol, as well as extraction of the protein fraction. In the upcoming year, we plan to use the liquid effluent of digested fermentation mash and algae residues as ammonium- and phosphate-rich nutrient source for cultivating the algae.

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Project partners

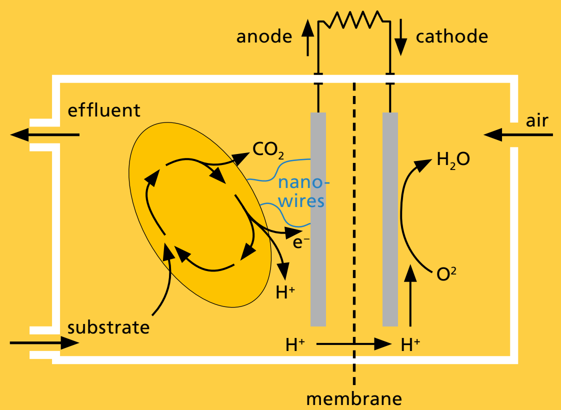
Südzucker AG, Mannheim, Germany | Subitec GmbH, Stuttgart, Germany

1 *Chlorella sorokiniana in the growth stage (A) and with starch granules after nitrogen is depleted (B).*

2 *Biorefinery concept for using starch-rich algal biomass and the recycling of nutrients and carbon dioxide.*

3 *Flat panel airlift reactors in the laboratory that allow light availability to be adjusted as desired.*

4 *Outdoor production of starch-rich algal biomass in flat panel airlift reactors.*



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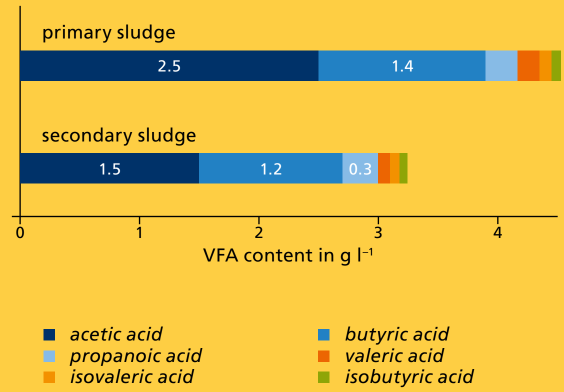


2

ACIDIFICATION OF SEWAGE SLUDGE FOR USE IN MICROBIAL FUEL CELLS

Klaus Brüderle, Dieter Bryniok

Municipal wastewater and sewage sludge treatment

Municipal wastewater undergoes biological treatment in sewage plants. Here, the classic activated sludge process and nitrification are both energy-hungry and cost-intensive process steps because they require complex procedures to stabilize and dispose of the sewage sludge generated during wastewater treatment. Sewage sludge is usually treated anaerobically in digesters to produce flammable digester gas (biogas) that can be utilized in combined heat and power (CHP) plants. The thermal energy released in this process is then used to heat the digesters and to dry the stabilized residual sludge. In small sewage plants or those without digesters, sewage sludge is often simply dried before being taken to a sewage sludge incineration plant. Alternative methods for exploiting sewage sludge would therefore be particularly attractive for these types of wastewater treatment plant.

Generating power from sludge – combining anaerobic acidification and microbial fuel cells

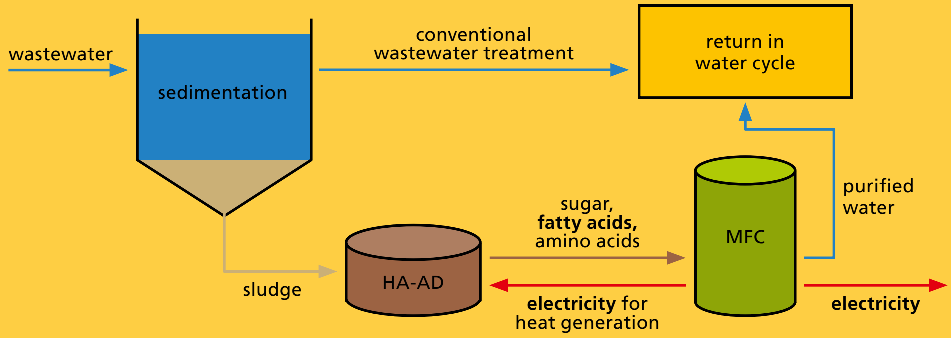
The partial digestion of sewage sludge and subsequent use of the resulting organic acids as substrates for microbial fuel cells (MFCs) constitutes a potential solution. As part of the "MFC4Sludge" project funded by the EU, the Fraunhofer IGB is collaborating with international research institutes and SMEs to develop just such an innovative solution for sewage sludge treatment. This will allow electricity to be produced directly from sewage sludge, thus bypassing the biogas step. The treatment of sewage sludge should ideally render it fully stabilized, and where possible should result in net energy gain. The partial digestion of sludge followed by the oxidization of fermentation products in fuel cells is therefore an extremely promising approach, since digestion reduces the dry matter content of sewage sludge while increasing the chemical oxygen demand (COD). This process is currently the subject of lab-scale investigations at the Fraunhofer IGB. Once this research stage is complete, a pilot plant will be developed, and then constructed and operated within a municipal wastewater treatment plant in northern Spain.

Microbial fuel cells

Microbial fuel cells are galvanic systems in which exoelectrogenic bacteria oxidize carbon sources and transfer the electrons released in this process to anodes via nanowires – mini cell-specific cables. The hydrogen ions created here diffuse through a proton-selective membrane to the cathode where, together with the transported electrons, they serve to reduce the hydrogen to water. This flow of electrons from anode to cathode can be used as a source of energy. As organic substrates, monocarboxylic acids and their dissociated salts, sugars and alcohols can be converted into energy by the organisms in microbial fuel cells. Sufficient research now exists on the use of MFCs in the lab [1 – 3]. However, very few test systems exist on an in-house pilot or pilot scale. Wastewater with a low solid content is the most commonly used substrate.

Anaerobic acidification

The classic biogas process is divided into four main phases, which all occur simultaneously. First, long polymer chains are converted into short-chain molecules in a process of enzymatic hydrolysis, following acidogenesis takes place to convert them into fatty acids and alcohols, such as ethanol. Subsequent acetogenesis turns them into acetate, H_2 and CO_2, and finally methanogenic microorganisms convert them into biogas through a process called methanogenesis.



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In MFCs, organic acids are used as a substrate. Converting these further into biogas serves to lower the electricity yield. For this reason, the anaerobic degradation process had to be adjusted such that no further catabolization took place and the resulting concentration of organic acids was as high as possible. To begin, we examined primary and secondary sludge from a local municipal sewage plant to assess its content and composition, and then compared this with sludge from the wastewater treatment plant in northern Spain. Following this analysis, the sludge was partially acidified in 1 liter jacketed reactors at a temperature of 30°C by reducing the residence time of the sewage sludge from 15 to 4.5 days. At the end of this period, the slow-generating methanogenic microorganisms had virtually disappeared, while the hydrolytic, acidogenic and acetogenic bacteria, which have faster generation times, were heavily concentrated. By decreasing the residence time, gas production – which indicates the presence of methanogenic microorganisms – was brought almost entirely to a halt and the pH-value stabilized at 5.7. The dry matter content was reduced by 40 percent compared with full digestion, and the chemical oxygen demand (COD) increased by 35 percent. The digested product of the primary sludge had an acid content of 3.4 g/l, of which acetic acid and propanoic acid made up the largest share. The secondary sludge yielded as much as 4.5 g/l of organic acids (Fig. 2).

Outlook

Anaerobic acidification of the sewage sludge was successful, and the fatty acids dissociated in the liquid phase are excellently suited to conversion into electricity in MFCs. The next phase in the research project will be to combine this acidification process with a downstream MFC on a pilot scale at a sewage plant in northern Spain, where the continuous production of acidic wastewater flow will be linked with a particulate removal system in order to protect the MFC against undegraded solids in the residual sludge. The project could make a substantial contribution to the sustainable and efficient treatment of municipal wastewater and sewage sludge for use as a source of energy.

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[3] Rosenbaum, M. A.; Franks, A. E. (2014) Appl Microbiol Biotechnol 98(2): 509–518

Funding

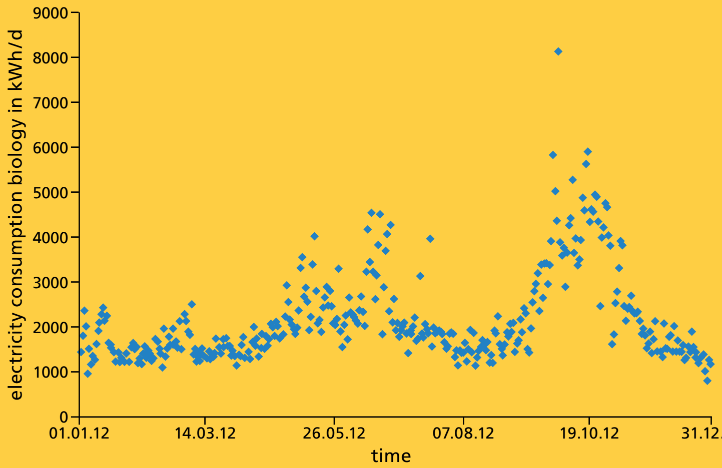
The project "MFC4Sludge" has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 605893.

Further information and project partners

www.mfc4sludge.eu

1 *Schematic diagram of a two-chamber microbial fuel cell.*
2 *Acid spectrum of the partially digested sludge liquor.*
3 *Process schematic of wastewater treatment with partial acidification (HA-AD: hydrolysis and acidogenesis – anaerobic digestion) and a microbial fuel cell (MFC).*

1



2

HIGH-LOAD DIGESTION FOR WWTPS WITH SEASONALLY VARIABLE OPERATION

Werner Sternad, Barbara Waelkens

Initial situation

Wastewater treatment plants (WWTPs) with seasonally variable operation are subject to significant load fluctuations. With the assistance of several engineering companies and the scientific backup of the Fraunhofer IGB, the Verbandsgemeindewerke (public utility company) Edenkoben will be setting up and operating a high-load digestion system at the Edenkoben WWTP for the anaerobic stabilization of sewage sludge. The seasonal burden on the Edenkoben WWTP is due to the vintage campaign (harvest and processing of the grapes). The WWTP's load fluctuates between its lowest load on Sundays and public holidays and peak loads during vintage campaign, from 7,000 up to 120,000 population equivalents.

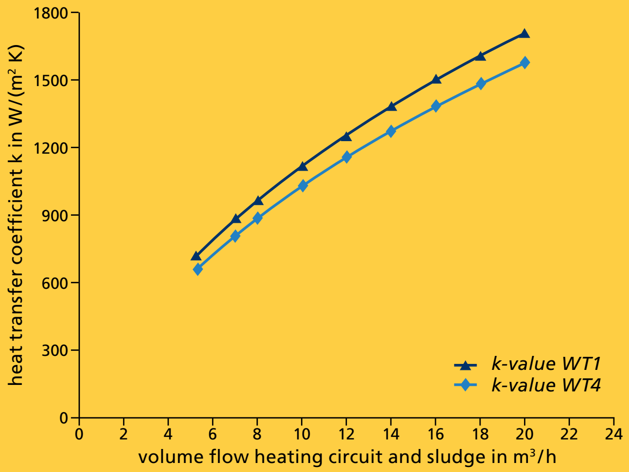
Until now, the sewage sludge has been treated by means of aerobic stabilization resulting in a high energy demand. Fig. 2 shows the electricity consumption of the biological part of the WWTP for 2012. One can clearly recognize that during the vintage campaign (September to December) electricity consumption increases approximately threefold. The operation of a high-load digestion for anaerobic sludge stabilization results in the production of sludge gas (methane and carbon dioxide), which can be converted to electricity and heat through a combined heat and power plant (CHP). In this way, anaerobic sludge stabilization results in an energy gain, whereas the aerobic sludge stabilization used hitherto requires aeration energy.

Serial or parallel operation of two-stage high-load digestion

Sewage treatment plants with seasonally variable operation and anaerobic sludge stabilization already exist. However, owing to the seasonal burden, the sludge quantities fluctuate so much that conventional modes of operation cannot cope, and the digested sludge is stabilized only to an unsatisfactory degree during the relevant (peak) period. The Fraunhofer IGB therefore suggested to the Verbandsgemeindewerke Edenkoben using a two-stage high-load digestion system designed as loop reactors with injection of sludge gas. With this solution, it is possible both to operate the reactors in series for maximum turnover outside of the peak period and to operate them in parallel during the vintage campaign, in order to successfully treat the large quantity of sludge that accumulates at this point.

Heat recovery from the digested sludge

The intention in Edenkoben is to use the sludge gas not only for the generation of electricity but also for heating purposes. In order to supply enough thermal energy in colder months, a heat recovery from the warm digested sludge to the cold incoming sludge is planned at the high-load digestion in Edenkoben. By this means, thermal energy will be recovered from the outflowing digested sludge with a temperature of approximately 37°C and hence most of the CHP heat can be used for other heating purposes.



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Scientific backup – pilot studies, authorization procedures, call for tenders

Pilot studies on the fermentability of the sewage sludge were carried out at the Fraunhofer IGB pilot plant and it was shown that the sludge from Edenkoben is suitable for fermentation in a high-load digestion system.

The Fraunhofer IGB assisted the Verbandsgemeindewerke Edenkoben and the participating engineering companies through scientific support in the course of the authorization procedure, the public invitation to tender and construction and commissioning of the plant. The company carrying out the work – who won the tender – also received scientific support and assistance with the calculation and specification of reactor geometries and volume flows for sludge or sludge gas. In this way, it is ensured that the process of high-load digestion developed by the Fraunhofer IGB can be developed further, tailored to the specific requirements of the particular use, and be used successfully in the future.

Outlook

Construction of the two-stage high-load digestion facility in Edenkoben began successfully with the groundbreaking on July 17, 2014 (Fig. 1). The three-dimensional representation (Fig. 4) produced by one of the participating engineering companies shows what the complete facility, with two-stage high-load digestion, gas tank and machine hall will soon look like. In autumn 2014 the work on the foundations was completed and erection of the buildings commenced. In spring 2015 the machinery installation will take place. This will be followed by the phase of commissioning and inoculation, which means that operations are likely to start in early summer of 2015.

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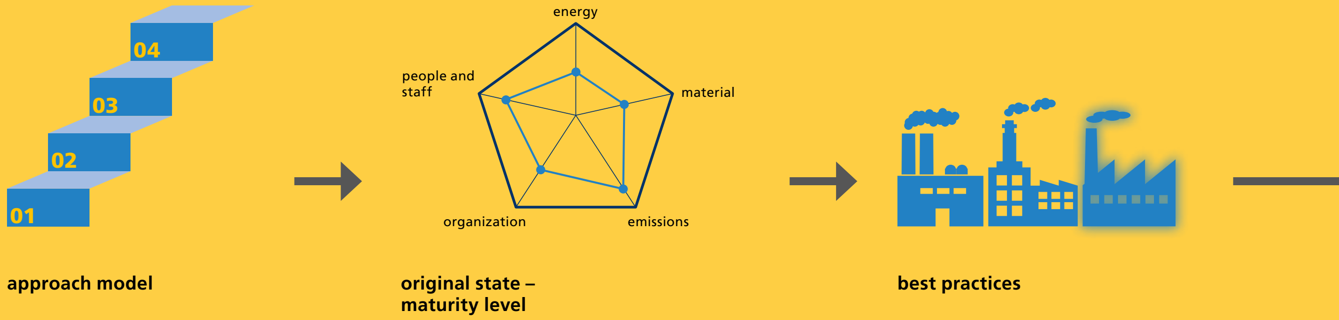
1 *Groundbreaking on July 17, 2014.*
2 *Electricity consumption of the biological part of the Edenkoben WWTP in 2012.*
3 *Heat transfer coefficient of the heat exchangers for heat recovery.*
4 *Three-dimensional representation of the full plant.*



1

THE ULTRA-EFFICIENT FACTORY – PRODUCTION WITHOUT LOSSES IN A LIVABLE ENVIRONMENT

Ursula Schließmann, Jan Iden

Background

The "Ultra-efficient Factory – Resource-conserving production with no emissions in an urban environment" project focuses on the issue of a sustainable economy. As such, the concept strives to reduce environmental stressors and to achieve the most efficient use of resources in order to meet the premise required by a "Green Economy" while introducing innovative technologies. Partial solutions have already been found in this area but a unifying approach is still lacking.

More efficient production processes through technology assessment and innovation

The ultra-efficient factory is a modern approach for companies to be able to produce their goods efficiently and effectively in terms of materials, energy, personnel and capital. Material and energy flows are cyclical and always serve as the starting point for production. The adaptable and emissions-free factory thus ensures that its environment is ecologically and socially sound and integrated within the urban community.

The project re-assesses previously applied technologies and introduces new technological innovations. The goals of the ultra-efficient factory include:

- optimized use of resources,
- the use of better suited materials at minimum required amounts,
- general avoidance of emissions and waste,
- connecting "the right with the right"; i.e. effectiveness and not just blind efficiency.

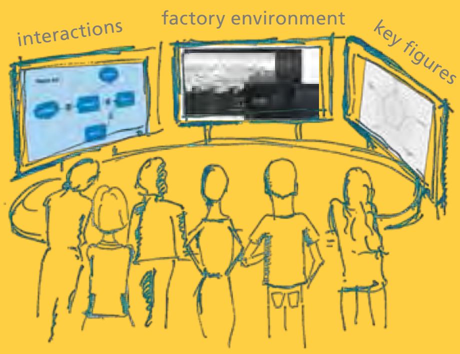
Sustainability by decoupling growth and consumption

A maturity model with a scaled key figure model to evaluate ultra-efficient factory has been developed and a comprehensive sample of best-practice examples of the individual sub-perspectives and efficiency technologies has been prepared. The criteria for an exemplary ultra-efficient production and the target state have been defined. They are being applied and tested at a model company to provide an example. The next step will be to apply this concept to other enterprises.

Thanks to the use of efficiency technologies, not only can the company investments be amortized, but also the necessary return on investments for acquiring effectiveness technologies is generated.

A project approach that is practically-oriented by the integration of companies through workshops and expert talks, coupled with the scientifically-based approach of the participating research institutes, ensures broad transferability and dissemination as well as the adaptability of the results with regard to the specifics of each target group. The methods, models and tools that are developed make a valuable contribution towards creating and implementing successfully operating growth strategies – decoupled from resource use and without negative impact, and potentially even with added value for the community.

The design of the concept, which serves as regulatory framework for the vision of the ultra-efficient factory, represents a first crucial step towards a sustainable economy based on decoupling growth and resource use.



visualization

Outlook

The discussions that have taken place so far are based on a comprehensive view and reveal priority areas and development paths for companies to follow en route to an ultra-efficient factory. In order to achieve an actual, measurable decoupling of the overall economic growth of a company from the resource use and demand required for such growth means putting into practice the knowledge and results that have been gained and taking them into consideration every day in the business processes.

A central element of these activities involves building a web-based information and exchange platform for interested companies, users of the ultra-efficient factory concept and other experts in the field. The platform will contain a comprehensive database with examples of best practices of the individual sub-perspectives and efficiency technologies. The platform also accommodates the ultra-efficient cockpit that offers a company a means to self-evaluate their level of development towards an ultra-efficient factory and indicates priority areas and routes. A training concept should be worked on in parallel to these activities; here, suitably qualified individuals are entrusted with the contents of the concept of an ultra-efficient factory and are trained as ultra-efficiency advisors.

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Project partners
Fraunhofer IPA, Stuttgart, Germany (project coordination) | Fraunhofer IAO, Stuttgart, Germany

Further information
www.ultraeffizienzfabrik.de

1 *Approach model: detailed analysis – maturity model – best practices – visualization.*


1


2

PRODUCING DAIRY PRODUCTS WITH LESS ENERGY AND WATER – A SYSTEMATIC APPROACH FOR GREATER EFFICIENCY

Ana Lucía Vásquez-Caicedo, Katherina Pruß

Huge energy and water-saving potential in the dairy industry

With a turnover of 124.3 billion euros, the dairy sector is an important branch of the food industry. However, the sector has very large energy and water consumption. For every metric ton of processed milk produced, up to 6.47 megawatt hours of electricity and 60 cubic meters of water, almost exclusively drinking water, are consumed.

As part of the EU project EnReMilk there are plans to achieve significant water and energy savings (30 and 20 percent, respectively) in a representative study for mozzarella and milk powder production. To this end, process models have been developed by means of which the savings potential can be assessed on the basis of the consumption figures of existing production facilities. The intention is to achieve savings with the help of innovative technologies developed by the institutions involved in the project.

Case studies with different production approaches

Prior to the study, the most promising technologies when it comes to saving water and energy in the dairy industry, were identified. This included microwave technology for thermal pasteurization and pressure change technology for cold pasteurization. Further promising technologies are spray-drying with superheated steam or, in a closed system, with inert gas, as well as extrusion technology for the texturization of mozzarella. These technologies can potentially be implemented at different points in mozzarella and milk powder production processes. Accordingly, a number of distinct alternative scenarios to current production processes could be identified.

The process models were developed under the leadership of a Dutch University and Research Center in Wageningen, together with experts from the participating institutions. For the process model, the project team compiled a database in which data about water and energy flow and consumption was collected. The database enables the visualization of interconnections between process steps and bottlenecks in the process, along with the resulting effects on the whole process. The Fraunhofer IGB and experts from the dairy industry supported the development of the process models by defining data requirements, collecting these from participating partners in industry assessing its quality, and revising the process models. By means of these models, the alternative process scenarios were assessed and compared to the existing processes on the basis of their energy and water consumption.

EnReMilk identifies significant saving potentials

The simulation in the process model revealed that in normal milk powder production, the greatest consumption of energy occurs during spray-drying. Further significant high energy consumption levels occurred during the concentration of milk and the cleaning of production facilities. The latter also revealed the highest water consumption. In mozzarella production, the ice water cooling and the generation of saturated steam caused the greatest energy consumption, whilst the packaging process required the most water. The different cleaning steps also used considerable amounts of water.

3

Within the milk powder production, the simulation showed that high energy savings can be achieved by means of the drying process with superheated steam or by implementing a closed cycle. Microwave pre-heating of milk concentrate prior to spray drying promises significant water savings, likewise the use of pressure change technology for cold pasteurization. Pasteurization with microwaves, however, has only a minor impact on both aspects. In the case of mozzarella production, the influence of microwave pasteurization on both water and energy consumption was more significant than in the milk powder production. In assessing the water-saving potential it must be taken into consideration that until now, almost exclusively drinking water has been used. However, by implementing an appropriate process effluent treatment system, drinking water can be replaced with recycled water if the quality of the recycled water is sufficient for the intended use.

Outlook

In future project activities, the process models will be further refined by means of improved data collection methods. Furthermore, additional consumption and performance data for the innovative technologies will be collected by means of optimization trials in pilot scale. This way, the potential savings in mozzarella and milk powder production through the use of selected technologies can be quantified even more precisely. In the future this should provide companies in the dairy industry with a decision-making tool for the implementation of novel technologies. In parallel to this, it shall be verified and guaranteed that product quality is maintained – in microbiological and organoleptic terms – and is comparable to that of conventionally manufactured products.

In a further step, a strategy for efficient wastewater purification is being developed as part of the EnReMilk project in order to close the water cycle as far as possible. For this, the water treatment and water recovery technologies must be integrated into the operational infrastructure of food production companies and the quality of the treated water must be assessed.

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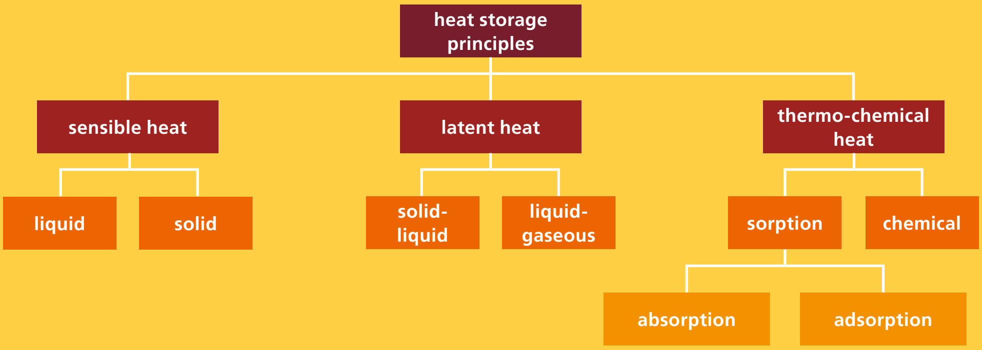
Further information and project partners

www.enremilk.eu

1 *Kick-off meeting on January 21, 2014 in Stuttgart.*
2 *For Mozzarella production a high amount of water is required. EnReMilk will help to reduce the consumption of drinking water.*
3 *EnReMilk will implement novel techniques for the valorization of whey.*



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SORPTION HEAT STORAGE – DEVELOPMENT STRATEGY AND IMPLEMENTATION PROGRESS

Simone Mack

Current situation

In order to meet climate protection targets, we need to increase the utilization factor of both fossil fuels and primary sources of renewable energy. Exploiting renewable sources, however, requires technologies to remove the time lag between energy generation and consumption. The secondary use of energy which is generated in large quantities as waste heat, a by-product of industrial processes in particular, plays a key role in improving economic efficiency. Heat storage systems can store exhaust and surplus heat, thereby bridging the gap between the time heat is produced and when it is needed, e.g. in cogeneration plants.

Today's industrially manufactured thermal stores use water as a storage medium, which means that the storage density is limited and the temperature is restricted to a maximum of 100°C. A further disadvantage is that only sensible heat is stored. The temperature gradient between the storage medium and the environment leads to losses over time. One promising alternative is offered by sorption heat storage, whereby the stored energy is bound by physical processes, preventing thermal losses through the store's insulation and during prolonged storage periods. What is more, this technology offers significant advantages in terms of storage density (theoretically six to eight times higher than with water storage tanks) and potential temperature levels.

Technology strategy

Sorption heat storage represents a new technological approach, the potential of which has already been demonstrated in lab tests. At the Fraunhofer IGB, adsorption and absorption systems alike are studied, implemented in test systems and continuously improved. We have constructed a closed demonstration system for adsorption heat storage, where water vapor is adsorbed in the pores of zeolites and other highly porous adsorbents.

Our aim is to develop a high-performance, cost-effective, modular thermal storage system suitable for industrial applications. In order to achieve this goal, we are pursuing an integrated approach involving the development of materials, components, and processes as well as design concepts that are optimized for industrial production. A series of innovative methods implemented on lab and pilot scales provides the basis for these developments. Future project phases will combine these aspects in demonstration systems, where they can be tested under practical conditions.

Optimizing process dynamics

To improve the process dynamics of the systems, we evaluate and optimize a range of different equipment configurations. In this particular case, as well as examining subcomponents we were particularly careful to ensure that the heat exchanger in the reactor featured a very simple and flexible design. Test series with varying relevant process parameters were conducted on a specially configured test stand, and process dynamics were analyzed.

3

Our investigations show that the measures employed result in markedly lower thermal losses during the charging and discharging process. The new system configuration fundamentally optimized the flow, so that greater quantities of thermal energy could be stored thermochemically per unit volume.

Outlook

The results will help us to achieve our goal of developing new, high-performance thermal stores more quickly and efficiently. In comparison to the theoretical potential of the technology, the efficiency achieved in industrial systems is still improvable. Additional research is required to make the technology more cost-effective, and to gather more extensive practical experience.

Potential end users will benefit from the new heat storage technology on both an economic and a process engineering level thanks to increased energy efficiency and lower energy costs. In industrial plants, in particular, it will pave the way for storing thermal energy in a more flexible and efficient way, allowing it to be used at different times and in different locations.

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1 *Possibilities for thermal energy storage.*
2 *Zeolite packed bed in an experimental reactor.*
3 *Pilot storage unit with a volume of 750 liters in a transportable container.*

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