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FRAUNHOFER INSTITUTE FOR MOLECULAR BIOLOGY AND APPLIED ECOLOGY IME

How Fraunhofer IME researchers determine why certain substances should not reach the environment ...

ANNUAL REPORT 2016/17

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FRAUNHOFER INSTITUTE FOR MOLECULAR BIOLOGY AND APPLIED ECOLOGY IME

Assessing risks to the environment and consumers
In dialog with Prof. Dr. Christian Schlechtriem

Multiple sclerosis and neuropathic pain
Novel concepts for diagnosis and treatment

Protecting harvests, curbing diseases
New strategies for the sterile insect technique

ANNUAL REPORT
2016/17

With regard to our reporting requirements, we have compiled information on publications, patents, dissertations, master's/diploma and bachelor's theses as well as on our networks and cooperations in science and industry in a separate annex to this annual report. You can also download the 'FACTS 2016/17' of the Fraunhofer IME from our website:

http://www.ime.fraunhofer.de/en/publikationen/jahresberichte.html

Legend

MB Department ..... Molecular Biotechnology Division

TM Department ..... Translational Medicine Division

AE BR Department ..... Applied Ecology and Bioresources Division

Please note that we do not use academic titles in the body text of our articles.

Table of Contents

Expanding scientific frontiers and creating innovative solutions for a healthy and sustainable tomorrow

Molecular Biotechnology

Biotechnology is the basis of the bioeconomy and contributes sustainably to the knowledge-based production and industrial use of biogenic raw materials. On behalf of our customers, the Fraunhofer IME Molecular Biotechnology Division establishes tailored plants and microbes for applications such as the production of food and renewable raw materials, the manufacture of technical and pharmaceutical proteins, and the handling of anthropogenic pollutants including greenhouse gases, which we can exploit to produce valuable substances. Our synergistic activities in the fields of green, red and white biotechnology have allowed us to become established successfully in the research landscape and on the market. We offer our partners in academia, industry and the regulatory authorities a comprehensive research and service portfolio.

Translational Medicine

Translational medicine contributes steadily and substantially to the development of new approaches for the diagnosis and treatment of diseases that are inadequately understood or controlled. The field of translational medicine spans the value chain, from target identification through active agent screening and translational preclinical validation to clinical trials. One research focus is the repositioning of known active agents within the disease areas of pain, rheumatoid arthritis, sepsis, multiple sclerosis and inflammation. We offer a specialized spectrum of disease models as well as highly sensitive analysis, bioinformatics and biomarker platforms. Our clinical trials follow quality-by-design standards to reduce attrition rates and generate as much scientifically relevant information as possible.

Applied Ecology and Bioresources

We develop experimental and model-based methods for the assessment of risks to ecosystems posed by potentially hazardous substances, as well as for the analysis of consumer exposure to such substances within the environment. We often act as scientific mediators between commercial producers and the regulatory authorities. Another focal point of our work is the identification of active substances from bioresources such as plants, microbes and insects, plus the sustainable agricultural production of active substances from plants. We also develop biotechnological methods for the control of pest and vector insects and utilize insects to generate protein from organic waste.

Welcome




The Fraunhofer IME has grown rapidly in recent years. Its former Senior Executive Director, Prof. Dr. Rainer Fischer, established and expanded the institute with great success. In the many years under his leadership, the IME has grown into a world-leading applied life sciences research institute with approximately 540 employees spread over six locations in Germany. Prof. Dr. Fischer was also Chairman of the Fraunhofer Group for Life Sciences. On April 1, 2017, he stepped down from his role and left the Fraunhofer-Gesellschaft to pursue other activities.

We therefore started 2017 with a new management team. Responsibility for running the institute was handed over on January 1 to a provisional triumvirate: Prof. Dr. Stefan Schillberg, Prof. Dr. Christoph Schäfers and Prof. Dr. Dr. Gerd Geisslinger, the latter also elected acting Executive Director. Prof. Dr. Fischer remained as a member of the institute management team until his leaving date.

In addition to the changes in management, the IME has also been restructured to accommodate the broadening of our research and development portfolio in recent years, with its different technologies, methods, research topics and customers. Previously, the institute comprised two major divisions: the Applied Ecology Division and the Molecular Biology Division. Now our key areas of expertise are spread over three divisions: “Molecular Biotechnology”, “Translational Medicine” and “Applied Ecology and Bioresources”. In all three divisions, our research efforts are focused on the identification, production, specific application and evaluation of substances, ranging from biotechnological products to active agents for clinical applications.

Let us arouse your curiosity by presenting some of the impressive research achievements in the three IME divisions. In this report, progress in the Molecular Biotechnology Division is highlighted in a joint article by the teams at our Aachen and Münster locations. Turn to page 48 to find out how plants can be used for the development of vaccines and how they provide valuable raw materials for industry.

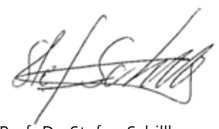
The article starting on page 32 describes our research activities in the Translational Medicine Division: Researchers from our Frankfurt/Main and Hamburg locations have joined forces to develop new approaches for the treatment of multiple sclerosis and neuropathic pain.

We also present some fascinating insights into the work carried out by our Applied Ecology and Bioresources Division. For example, read our interview starting on page 40 to see how trout, carp and a crab only a few millimeters in length can be used for environmental and consumer protection.

Finally, we wish to extend our wholehearted thanks to our business and collaboration partners for their excellent and constructive cooperation, and to our staff for their outstanding contribution to the success of the IME. Last but not least, on behalf of all IME personnel, Prof. Dr. Stefan Schillberg, Prof. Dr. Christoph Schäfers and Prof. Dr. Dr. Gerd Geisslinger wish to thank Prof. Dr. Rainer Fischer for his outstanding achievements and service to the IME over a period of almost 20 years.

Prof. Dr. Dr. Gerd Geisslinger

Prof. Dr. Christoph Schäfers



Prof. Dr. Stefan Schillberg

Prof. Dr. Rainer Fischer

Frankfurt/Main, Aachen and Schmallenberg, March 2017

The Institute

Fraunhofer IME Profile

The Fraunhofer IME is an applied life sciences research institute which, until the end of 2016, comprised two major divisions: the Applied Ecology Division located in Schmallenberg and the Molecular Biology Division located at the main site in Aachen, with groups also in Münster, Giessen, Frankfurt/Main and Hamburg. At the beginning of 2017, the institute was reorganized to better reflect the research specialties of the different project groups and departments. Coinciding with the departure of the institute's long-term Senior Executive Director Prof. Dr. Rainer Fischer on April 1, the Fraunhofer IME was restructured into three new divisions representing its core competencies:

- Molecular Biotechnology Division: Aachen and Münster
- Applied Ecology and Bioresources Division: Schmallenberg and Giessen
- Translational Medicine Division: Frankfurt/Main and Hamburg

On January 1, 2017, institute management responsibilities were therefore transferred to a provisional triumvirate comprising Prof. Dr. Stefan Schillberg representing the Molecular Biotechnology Division, Prof. Dr. Christoph Schäfers representing the Applied Ecology and Bioresources Division, and Prof. Dr. Dr. Gerd Geisslinger representing the Translational Medicine Division. Prof. Dr. Dr. Geisslinger was also elected the provisional overall Managing Director of the institute. Prof. Dr. Fischer remained a member of the institute's management team until his leaving date.

Following this reorganization, we continue to offer client services spanning the entire value chain of product development and assessment. Our interdisciplinary organization allows us to integrate expertise in relevant scientific disciplines covering all three areas, in cooperation with external institutions and partners if required, providing a basis for the successful completion of complex projects. Our laboratories, with state-of-the-art equipment including GMP facilities and complex facilities for environmental simulations, allow a wide spectrum of research and development services. Our work is closely linked with basic research within our university departments and we benefit from large international networks.

Fraunhofer IME therefore remains a strong partner for contract research in the areas of pharmaceuticals, chemicals and agriculture, as well as environmental and consumer protection. Our research and development portfolio focuses on industry, small and medium enterprises and on the public sector. In 2016, Fraunhofer IME collaborated with more than 100 national and international industrial clients and several international industrial associations, for whom confidential projects were conducted.

At the end of 2016, the institute employed 541 personnel working at the Schmallenberg, Aachen, Münster, Giessen, Frankfurt/Main and Hamburg locations. We have close ties with the Institute of Molecular Biotechnology at the RWTH Aachen University, the Department of Biology and Biotechnology of Plants at the University of Münster, the Department of Applied Entomology at the Justus-Liebig University Giessen, the world's first Institute for Insect Biotechnology, founded in Giessen in 2016, and with the Institute for Clinical Pharmacology at Goethe University, Frankfurt/Main. A further 64 employees at the Fraunhofer Center for Systems Biotechnology (CSB) in Santiago de Chile provides Fraunhofer IME with a direct presence on the South American market.
We cooperate with many international research partners and remain in close contact with universities and other research organizations. Our aim is to recognize trends and developments as they emerge, and to develop and implement novel research strategies and technologies.

IME within the Fraunhofer-Gesellschaft

Cooperating within the Fraunhofer Group for Life Sciences – advancing key areas together

The Fraunhofer-Gesellschaft is the leading organization for applied research in Europe, conducting research at 69 institutes and research units at locations throughout Germany. The Fraunhofer-Gesellschaft employs about 24,500 personnel working with an annual research budget of 2.1 billion euros, more than 1.9 billion euros of which is generated through contract research. More than 70% of the Fraunhofer-Gesellschaft's contract research revenue is derived from contracts with industry and from publicly financed research projects. International collaborations with excellent research partners and innovative companies around the world ensure direct access to regions with the greatest importance to current and future scientific progress and economic development.

Fraunhofer institutes working in related subject areas cooperate as larger Groups to promote collaboration in related disciplines and offer customers a unique source of coordinated joint services. Currently, there are seven such Groups, representing different areas of the research and development market.
IME is part of the Fraunhofer Group for Life Sciences, a scientific and technological organization of highly qualified experts from the key areas of modern life sciences: personalized diagnostics and biopharmaceuticals, regenerative medicine for healthy aging, chemical safety and environmental quality, food safety and consumer protection, and new sources and processes for biobased chemicals.
The Fraunhofer Group for Life Sciences includes six Fraunhofer Institutes as well as one Fraunhofer research institution. Prof. Dr. Rainer Fischer became

the Chairman of the Fraunhofer Group for Life Sciences at the beginning of 2016. At the beginning of 2017, he handed responsibility temporarily to the Deputy Chairman, Prof. Dr. Norbert Krug, and on February 20 the Chairman's position was filled by Prof. Dr. Horst-Christian Langowski, with Prof. Dr. Krug again serving as deputy.
http://www.lifesciences.fraunhofer.de/en.html

Engaged in alliances and Fraunhofer's Sustainability Network – uniting complementary competencies and promoting sutainable development

Fraunhofer Alliances facilitate customer access to the services and research capability of the Fraunhofer-Gesellschaft. Institutes or institute departments with complementary expertise cooperate in alliances. They provide expert advice on complex issues and coordinate the development of appropriate solutions. Fraunhofer IME is involved in two alliances:

Big Data:
http://www.bigdata.fraunhofer.de/en.html

Food Chain Management:
http://www.fcm.fraunhofer.de/en.html

The Fraunhofer-Gesellschaft strives to promote and implement sustainable development, and the Fraunhofer Sustainability Network actively supports this goal. At the forefront of this approach is a stronger linking of both the research topics and the personnel who have a close connection to sustainability. In this manner, Fraunhofer aims to make its research more efficient while taking account of the growing complexity of research in the context of sustainable development.

https://www.fraunhofer.de/en/about-fraunhofer/profile/sustainability/fraunhofer-sustainabilitynetwork.html

Advisory Board

Advisory board members advise the Fraunhofer-Gesellschaft as well as the individual institutes and promote their connection to partners from industry, science and the public sector. In 2016, the following representatives from government, industry and academia were members of the Fraunhofer IME Advisory Board:

Dr. Harald Seulberger (Chairman)
BASF SE, Limburgerhof

Dr. Carl Bulich
German Plant Breeders' Association, Bonn

Dr. Friedrich Dechet
Industrial Association Agrar, Frankfurt/Main

Prof. Dr. Adolf Eisenträger
German Federal Environment Agency, Dessau

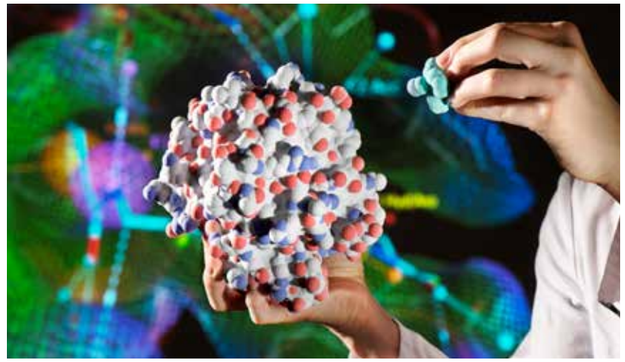
Dr. Gerhard Görlitz
Bayer CropScience AG, Monheim

Prof. Dr. Heyo Kroemer
Georg-August-Universität Göttingen

Prof. Dr. Roland Kubiak
RLP AgroScience GmbH,
Neustadt a. d. Weinstraße

Head of Division Andrea Noske,
Federal Ministry of Education and Research,
Berlin

Dr. Dr. Christian Patermann
Formerly Director Directorate General for Research and Innovation of the European Commission, Bonn



Prof. Dr. Joachim Schiemann
Federal Research Centre for Cultivated Plants
Julius Kühn-Institut, Braunschweig

Prof. Dr.-Ing. Ernst Schmachtenberg
Rector, RWTH Aachen University

Dr. Hans-Ulrich Wiese
Formerly member of the Executive Board of Fraunhofer (permanent guest)

The annual meeting of the Advisory Board was held on April 21, 2016, at the University of Münster (Westfälische Wilhelms-Universität). The Executive Board of the Fraunhofer-Gesellschaft was represented by Prof. Dr. Alexander Kurz.

Molecular Biotechnology – strategic business fields

Molecular Biotechnology
Research, Development and Services

http://www.ime.fraunhofer.de/content/dam/ime/de/documents/Publikationen/Research-Development-Services_Molecular-Biotechnology.pdf

Prof. Dr. Stefan Schillberg
stefan.schillberg@ime.fraunhofer.de

Prof. Dr. Dirk Prüfer
dirk.pruefer@ime.fraunhofer.de

Bioproduction and Industrial Biotechnology

This business field focuses on the identification, sustainable production, processing and optimization of high-value natural compounds, including chemical building blocks, biobased fuels, fine chemicals, biomaterials and proteins for industrial applications and consumer products. These can be produced using a diverse array of organisms, from microbes and animal cells through to plant cells. Here again the value chain is covered: from discovery and screening, the development and optimization of production strains and the transfer of laboratory-scale processes to scale up and pilot-scale manufacturing. IME provides comprehensive expertise in the development of innovative biotechnology platforms and optimized processes. The departments and project groups involved cover a range of different product types, from low-margin bulk chemicals and fuels like isopropanol, isoprene and hexanol, through to plant-based polymers like rubber, inulin, cellulose and industrial starches, and high-value fine chemicals, proteins and industrial enzymes.

Agroscience for Food and Feed

The business field Agroscience for Food and Feed covers the agricultural value chain ‘from farm to fork’ and focuses on the development of new plant traits, crops and enabling technologies to improve the biomass of crops, the quality and yield of agricultural products, the ability of plants to grow in diverse environments and to withstand pests and diseases. These traits are developed using both genetic modification (GM) and non-GM approaches, and key technologies like genome editing or TILLING. The departments and project groups involved in this business field focus on precision breeding techniques, the discovery and efficacy evaluation of plant protection products and the development and testing of GM crops. Based on this wide-ranging expertise, Fraunhofer IME acts as a preferred partner for academic laboratories, SMEs and major agrobusiness companies.

Production of recombinant proteins

The IME offers expertise in all aspects of the design, production, purification and characterization of recombinant proteins, including process development and scale-up from a laboratory process to the manufacture of kilograms of clinical material under GMP conditions. Different systems are available for the production of specific protein products, involving microbes, plant cells, animal cells and whole plants. There has been a recent increase in the demand for recombinant proteins produced at the kilogram scale for the pharmaceutical, agrochemical and cosmetic sectors, and for technological applications. The production capacity of the GMP-compliant IME facilities is used partly for contracts such as these but also for the production of proteins for clinical studies. In addition, the IME has its own new protein candidates in the pipeline, particularly technical enzymes, foodstuff proteins, diagnostic reagents and therapeutic proteins (including human antibodies and products developed using insect biotechnology). These will either be marketed directly or developed further in collaboration with industrial partners.

Translational Medicine – strategic business fields

Translational Medicine
Research, Development and Services

http://www.ime.fraunhofer.de/content/dam/ime/de/documents/Publikationen/Research-Development-Services_Translational-Medicine.pdf

Screening and Bioinformatics

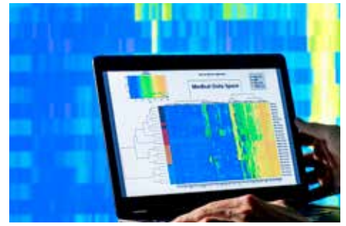
The business field Screening and Bioinformatics uses automated procedures to identify new leads for defined therapeutic targets. The three-dimensional structure of lead molecules holds the key to understanding their function and the development of new active compounds. Our customer service includes the development, validation and implementation of biological screening assays for known and new targets. We have access to libraries comprising more than 500,000 compounds. Furthermore, using bioinformatics techniques, we can identify new active chemicals in virtual libraries. Our range of services is completed by the medicinal-chemical approaches needed for substance optimization and preclinical testing using *in vitro* and *in vivo* models.

Prof. Dr. Carsten Claussen
carsten.claussen@ime.fraunhofer.de

Translational Compound Validation

The business field Translational Compound Validation aims to develop differentiated translational disease models, measurement techniques, technologies and imaging procedures for early assessment of the efficacy and safety of active compounds. In addition to cell-based and cell-free systems, we also conduct experiments on rodents and zebrafish. Our range of models is far wider than the standard spectrum offered by commercial suppliers and thus allows detailed, mechanism-based research. The following platforms are available to our customers: preclinical disease models, epigenetics and optogenetics, biomedical analysis, protein engineering, predictive clinico-pharmacological models, data bionics, pharmaceutical technology and human pain models.

Prof. Dr. Michael Parnham
michael.parnham@ime.fraunhofer.de



Medical Data Space

In terms of translational medicine, the Fraunhofer IME Hamburg facility played the leading role in the establishment of the Fraunhofer Medical Data Space. Modeled on the basic functionalities offered by the Industrial Data Space, the Medical Data Space offers decentralized data management for medical bioinformatics – a service concept allowing autonomous and secure data storage as well as data exchange between networked databases. The Hamburg group has applied this expertise in bioinformatics and has set up the Data Scientist for a number of projects, including the joint development of IME products and services and, on a European scale, in collaboration with the Innovative Medicines Initiative. In this manner, the Hamburg laboratories contribute significantly to the digitization of pharmaceutical research.

Prof. Dr. Carsten Claussen
carsten.claussen@ime.fraunhofer.de

Clinical Research

Clinical research is the decisive step in the development of new discoveries in the life sciences for use in humans. We offer our customers the essential elements needed for successful clinical trials, including the definition of appropriate scientific hypotheses and the patient groups to be treated (stratification into subgroups), combined with an individual, adaptive study design, employing the latest statistical and biomedical analyses. The new approach "quality by design" implemented at our Frankfurt/Main site addresses the complex challenges posed by clinical trials in an attempt to reduce exclusion rates. The combination of excellent study design and expertise in specific indications is a unique selling point of this group.

Dr. Frank Behrens
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Applied Ecology and Bioresources – business areas

Environmental Risk Assessment of Substances

We use our expertise in environmental analysis, experimental environmental chemistry and ecotoxicology, and modeling the bioaccumulation and effects of substances, to assess the risks such substances pose to the environment. We liaise with the regulatory authorities to formulate critical questions and draw up test guidelines to address these risks. On behalf of our partners in industry, we perform and evaluate complex experimental and model-based studies to the highest scientific standards. We use the analysis and classification of molecular mechanisms as screening tools to assess the environmental impact of candidate products. We manage the national Environmental Specimen Bank and perform environmental monitoring projects to identify potential environmental pollutants and check prospective assessments.

Dr. Dieter Hennecke
dieter.hennecke@ime.fraunhofer.de

Food Safety and Quality

The safety and quality of food depend on the production method and on the primary and further processing of agricultural raw materials. We focus on the qualitative properties of raw materials and foods, and the damage caused by harmful substances. For example, we adapt existing methods used to analyze the metabolism of plant protection products in crops and farm animals and use them to study the metabolism of veterinary pharmaceuticals and feed supplements, and we develop cell-based alternatives to animal testing. We track breakdown and conversion products by radioactive labeling throughout the food production cycle. As part of the Fraunhofer Food Chain Management Alliance, we are developing rapid analytical techniques to monitor the food chain. Aroma research combined with geographical information systems has highlighted links between cultivation conditions and the quality of raw foodstuffs.

Dr. Mark Bücking
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Applied Ecology and Bioresources
Research, Development and Services

http://www.ime.fraunhofer.de/content/dam/ime/de/documents/Publikationen/Research-Development-Services_Applied-Ecology.pdf

Sustainable Agricultural Production of Substances

We use local factors such as soil quality, microclimate and infrastructure to determine whether regions can support sustainable agriculture. We consider both structural and material determinants in such evaluations, combining species range maps from nature protection agencies with risk assessments for plant-protection agents and veterinary pharmaceuticals based on geographical information systems (see our business area "Environmental Risk Assessment of Substances"). We compare the economic potential of different value chains in order to achieve a sustainable bioeconomy. Ecological and social considerations can be reinforced through differentiated and targeted subsidies. Our main goal is to achieve the agricultural production of useful active substances.

Prof. Dr. Christoph Schäfers
christoph.schaefers@ime.fraunhofer.de

Bioresources for the Bioeconomy

We use diverse organisms as bioresources, including insects, bacteria and fungi. We combine innovative technologies and established platforms to isolate and characterize natural substances and evaluate their potential for use in medicine, plant protection and industrial biotechnology. These new substances may include antibiotics or food/feed ingredients such as flavoring agents, preservatives and enzymes, allowing the development of novel applications and value chains. The Sanofi-Fraunhofer Natural Product Research Center, which houses the world's largest industrial collection of microbial strains, is available for projects with other industrial partners in pre-competitive areas of research.

Prof. Dr. Andreas Vilcinskas
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Insect Biotechnology

The development and application of insect biotechnology allows us to use insects, insect-derived molecules, cells or organs, and insect-associated microbes as products or systems for diverse applications in medicine, industrial biotechnology, and the food/feed industry. We also exploit insect cells as protein expression systems and insect antennae as biosensors for drugs and explosives. Furthermore, we develop insect models for toxicology studies and use biotechnology to control pest and vector insects, based on techniques such as RNA interference and sterile insect technology. We also use insects for the conversion of organic waste into proteins and fats for the food/feed industry.

Prof. Dr.-Ing. Peter Czermak
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Institute data

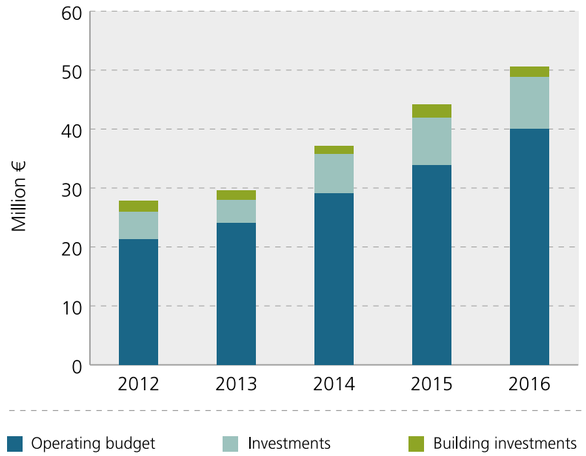
Budget

In 2016, the Fraunhofer IME operating budget was 40.3 million euros, an increase of 6.5 million euros over 2015 representing a growth rate from operations of 19.1%. This growth reflected increased activity at all the IME locations: Schmallenberg, Aachen, Münster, Giessen, Frankfurt/Main and Hamburg. The total external revenue (operating budget plus capital budget) increased by 6 million euros (17.3%) to 40.3 million euros and the overall budget increased by 7.1 million euros (17.1%) to 49.1 million euros. Third party revenue (total rho) amounted to 87.4% and industry revenue to 44.6%, confirming the healthy business profile of the institute. New and replacement investments amounted to 8.7 million euros. Expenditure on construction works in 2016 amounted to nearly 1.8 million euros.

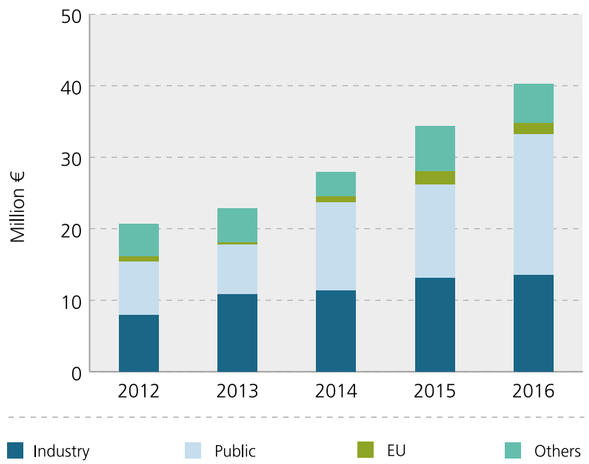
Personnel

At the end of 2016, the Fraunhofer IME employed 541 personnel at its sites in Aachen, Schmallenberg, Giessen, Münster, Frankfurt/Main and Hamburg, representing a 13.4% increase over 2015 (51.2% of these employees were female).

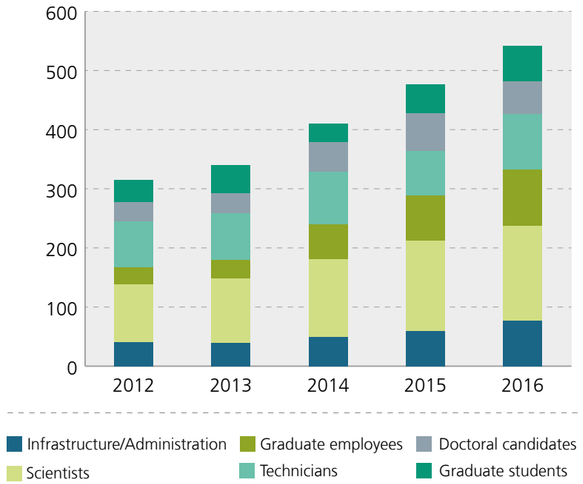
Total budget of the Fraunhofer IME, Germany



External financing of the Fraunhofer IME, Germany



Employees of the Fraunhofer IME, Germany



Locations

Institute Management
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Members of the Institute Management
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Prof. Dr. Christoph Schäfers
(provisional, as of January 2017)
Prof. Dr. Rainer Fischer
(until March 31, 2017)

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Location Frankfurt/Main

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Location Hamburg

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Fraunhofer Foundation Project

- **Malaria Vaccine Development, Diagnostics and Vertical Farming**
  Dipl.-Biol. Andreas Reimann

Special promotion of young investigators: Fraunhofer Attract Groups

- **Molecular Biocontrol**
  Prof. Dr. Marc F. Schetelig
- **Fast Protein Expression and Purification**
  Dr. Johannes Buyel
- **Longaevitas – Cross-species Aging Research**
  Dr. Philip Känel

Santiago de Chile, Chile

FCR – Center for Systems Biotechnology
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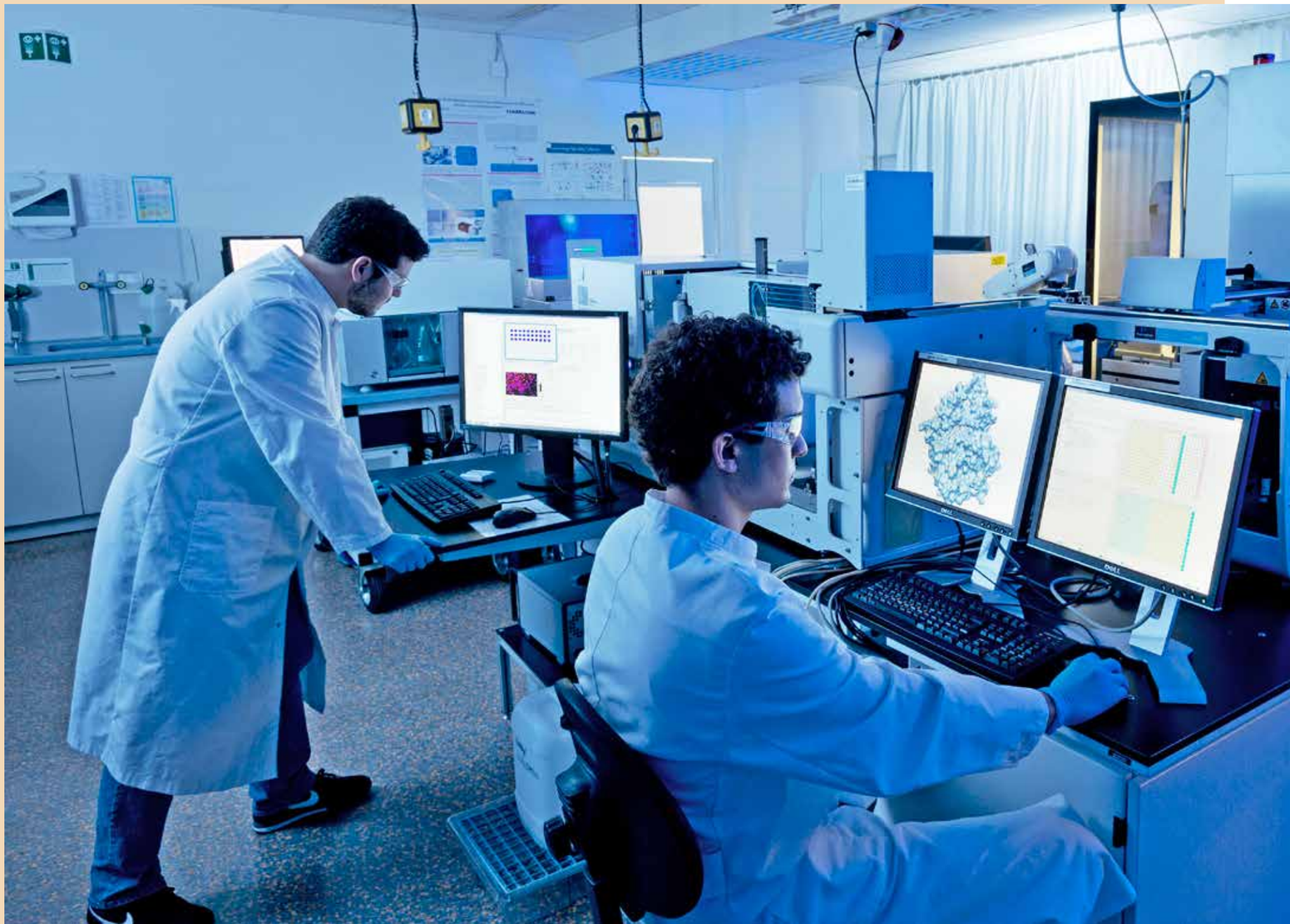
Reports on IME Research

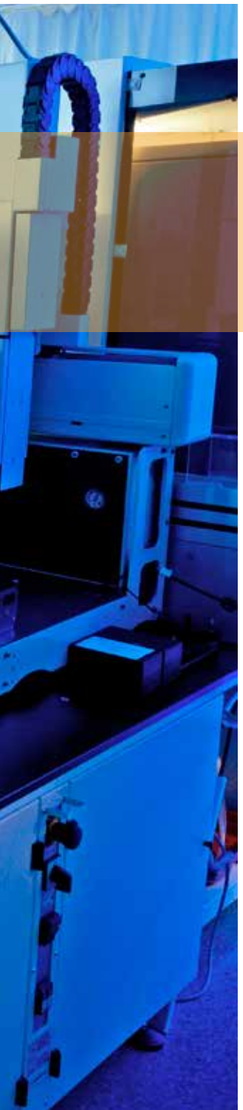
Protecting harvests, curbing diseases:
New strategies for the sterile insect technique

Multiple sclerosis and neuropathic pain:
Novel concepts for diagnosis and treatment

Surface waters:
Measuring background levels of free cyanide



Protecting harvests, curbing diseases: New strategies for the sterile insect technique



Insects are small but they have huge potential: the molecules they produce can facilitate the development of new drugs and plant protection products. However, the world of insects is also dangerous: insect pests can destroy crops and transmit diseases to humans. Molecular biologist Marc F. Schetelig is carrying out research on mosquitoes and flies, aiming to minimize their harmful effects and thus protect human lives and crops.

Insect pests are a global issue. In South America, tiger mosquitoes transmit yellow fever, dengue fever and the Zika virus. Wine and fruit growers in Central Europe fear massive crop failures caused by the vinegar fly. Marc F. Schetelig and his

Free from environmental toxins: Targeted strategies to combat agricultural pests

research team have developed new targeted strategies to control insect pests without resorting to environmentally damaging toxins. Schetelig is an expert in the sterile insect technique (SIT) in which sterile males, greatly outnumbering the fertile members of their sex, are dispersed on a massive scale to radically reduce insect pest populations. Millions of sterile males are released over the target area and they mate with most of the females, which subsequently produce no offspring. The SIT was developed in the USA in the late 1930s by Raymond C. Bushland and Edward F. Knipling to combat the New World screw-worm fly, a skin parasite attacking cattle, sheep and humans. The technique targets one insect species directly and therefore protects the environment by avoiding any impact on other species.

To increase the effectiveness of the SIT, Marc F. Schetelig and his research team are developing diverse approaches. These methods should allow the targeting of new invasive pests, for example non-indigenous species. Such biological invaders can transform whole ecosystems and drive out native species. Schetelig is focusing particularly on the spotted-wing drosophila *(Drosophila suzukii)* an invasive agricultural pest. The fly originated in Southeast Asia and has spread across the world. The females lay their eggs in ripe fruit shortly

before harvesting, when farmers are generally no longer allowed to spray their crops. "In this way, the fly evades even the most effective insecticides. And there are currently no successful control strategies available," explains the 36-year-old researcher. He has therefore set about developing a genetic system, whereby the fly's offspring die at the embryonic stage. No larvae emerge from eggs fertilized by the modified males. "We also sterilize the males by irradiation before their release, and can therefore be absolutely certain that they will not reproduce."

Prof. Marc F. Schetelig is an expert in the sterile insect technique. Together with his research team, he works to increase the efficiency of this method.

With his research group, Schetelig has also optimized the breeding and propagation of sterile males in the laboratory. The mechanism causing sterility in the genetically modified males can be switched off by feeding them with the antibiotic tetracycline. "However, no antibiotic is released into the environment," says Schetelig, "because, in contrast to other available genetic systems, we need only minimal amounts of antibiotic for the adult flies." He and his team have inserted an additional genetic system into the fly genome to bypass the time-consuming and laborious task of manually weeding out females before mass release. These new systems ensure that no females survive the embryonic stage. "This hugely increases the effectiveness of mass breeding, because we are only raising males," explains the molecular biologist.

More effective breeding and propagation of sterile males through new genetic systems

Now, Schetelig's team are applying the systems they developed for the flies to tiger mosquitoes, which transmit many dangerous pathogens including the dengue, Zika, yellow fever, Chikungunya

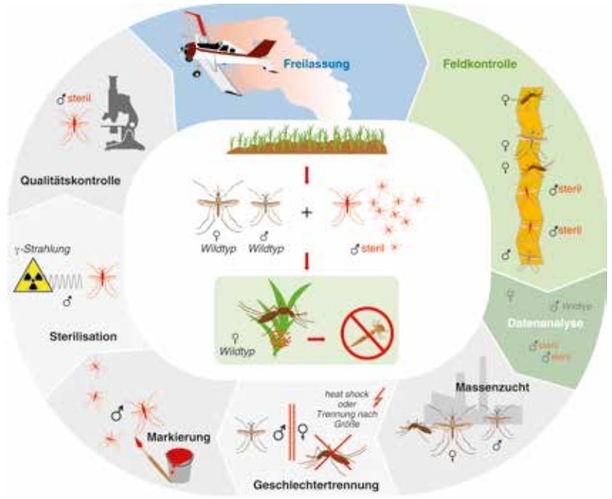
A crop pest that threatens harvests of cherries, raspberries, plums and grapes in Central Europe: the vinegar fly *Drosophila suzukii*.

fever and Rift-Valley fever viruses. This insect originated in the tropics but has since spread around the world, even to Germany. Tiger mosquitoes have already survived the German winter and have bred in an area near Freiburg-im-Breisgau.

Although Schetelig has great confidence in this new technology, he is also aware that releasing transgenic insects into the environment requires careful risk assessment. He also investigates what will happen, for example, when other animals eat the genetically modified flies. Will their new genetic information be transferred to other organisms? "We are taking two approaches here: on the one hand, we are conducting tests to determine whether any DNA transfer takes place, but on the other hand, we are developing systems to anchor the additional DNA more stably within the genome." So far, the researchers have conducted broad studies over several years and have found no evidence of transfer. That is good news, indicating that the modified DNA is not transferred to other organisms. For Schetelig himself, this is an important but not unexpected result: "All organisms, including humans, feed on animals, plants and fungi containing DNA. If transfer occurred frequently then, during our evolution, we could have incorporated countless genes from other living organisms, some of which would have changed us radically." Risk evaluation on such issues forms an integral part of all projects and is used to define and understand the potential dangers of any new system.

A further goal: Combating dangerous pathogens such as dengue and Zika viruses

The Schetelig group is also developing non-transgenic systems. "We can apply these techniques in many ways for safe, targeted pest control," Schetelig explains. "They allow us to assess the comparative advantages and disadvantages of new systems, and to try out various techniques developed for the same purpose, as back-up systems to meet the challenge of emerging pest resistance. In the end, alternative solutions will be necessary if the range of permitted procedures is limited by the regulations and authorization procedures imposed in different countries. This," Schetelig believes, "will ensure that we are equipped with a broad spectrum of integrated and optimal pest control solutions so that even the most resilient pests, such as the spotted-wing drosophila, can be successfully controlled. In Schetelig's opinion, transgenic SIT technology will initially be applied in regions such as South America, where regulations for the release of genetically modified organisms are already in place. He is convinced that the acceptance of such techniques is determined partially by the severity of the threat posed by such pests. As he puts it, "If we in Germany had the same problems with dengue fever and the Zika virus that they have in Brazil, or if our farmers were at risk of losing the basis of their economic existence due to the destructive action of the spotted-wing drosophila, then the widest possible range of solutions would be evaluated in Germany too. And the sterile insect technique with modified insects would certainly be one of the options considered."



The sterile insect technique involves the mass-release of sterile males, thereby decimating populations of harmful insects. With new methods, it should now be possible to apply the technique to other pests.

At the LOEWE Center for Insect Biotechnology & Bioresources, funded by the Hesse Ministry for Science and Art, Marc F. Schetelig supervises a group of junior scientists. He also leads the Emmy-Noether Group "Development and Risk Assessment of Transgenic Environmentally Friendly Insect Pest Control Methods for Fruit Flies and Mosquitoes", funded by the DFG (German Research Foundation) and holds a Professorship for Insect Biotechnology in Plant Protection at the Justus-Liebig University Giessen. Fraunhofer provides further support for Schetelig's research in the field of molecular biocontrol through the Attract research program.

Combining different systems: Successful management of pests that are hard to control

AE BR Bioresources, Attract Group Molecular Biocontrol

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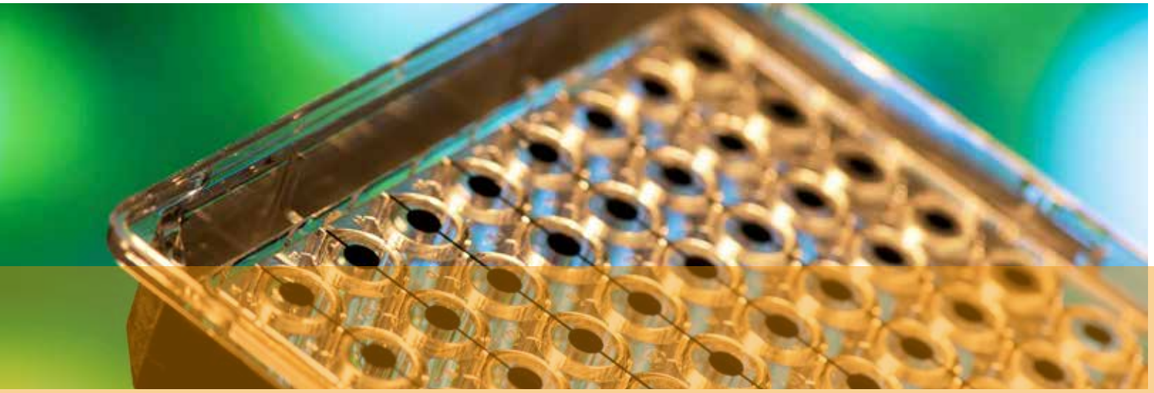
Multiple sclerosis and neuropathic pain: Novel concepts for diagnosis and treatment



Plates for the high-throughput screening of potential active agents: Researchers at the IME Hamburg and Frankfurt/Main locations are working intensively on several translational projects focusing on MS.

Scientists at the Fraunhofer IME ScreeningPort and the IME project group Translational Medicine and Pharmacology are working closely together to develop new strategies for the diagnosis and treatment of disorders of the nervous system, including multiple sclerosis and chronic pain.

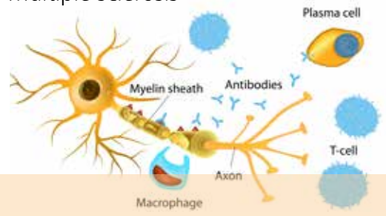
Multiple sclerosis (MS) is a chronic, disabling disease that affects 2.5 million people worldwide and is typically diagnosed between the ages of 20 and 40. MS is the most common inflammatory and neurodegenerative disease of the central nervous system (CNS). It can substantially and adversely affect the quality of life and is associated with high costs for MS patients, their families, and society as a whole. There are approximately 130,000 MS patients in Germany. Current therapeutic approaches target the immune system and reduce relapses which reflect intermittent deterioration of MS symptoms. To date, there are no available treatment options that prevent the underlying neurodegenerative component of the disease, which causes the destruction of nerve cells in the CNS. Therefore, Fraunhofer IME has initiated several programs to develop novel, orally available MS treatments that aim to prevent neurodegeneration and promote neuroprotection and neuroregeneration.

Neuroprotective effects in MS patients – an ion channel is a promising molecular target

The IME project group Translational Medicine and Pharmacology (TMP) in Frankfurt/Main is studying the potential of circulating lipids, particularly ceramides and lysophosphatides, as early diagnostic biomarkers in both MS patients and experimental models. At the tissue and cellular levels, chronic inflammatory processes that continuously disturb neuro-axonal homeostasis are implicated in the neurodegeneration observed in MS. Therefore, the course of the disease in a patient depends on the balance between stressor load and inflammation on one hand, and the intrinsic capacity for neuronal self-protection on the other. Ion channels, which allow charged molecules to pass through cell membranes, are partially responsible for maintaining this balance. Signalling via the neuronal calcium-activated sodium ion channel TRPM4 has recently been shown to play a key role in the process of neuro-axonal injury in the inflamed CNS. The pharmacological inhibition of TRPM4 therefore represents a highly promising therapeutic strategy with the potential to promote neuroprotective effects in MS patients. Scientists at the IME ScreeningPort in Hamburg have worked intensively with clinical and academic groups at the University Medical Center Hamburg-Eppendorf and medicinal chemistry experts at Evotec AG over the past 3 years to identify and validate small molecules which partly block the function of TRPM4. The endpoint of this BMBF funded NEU2 BioPharma project was the identification of a potent and selective compound lead series. Following on from the successful first TRPM4 project, further funding has been approved under the prestigious translational BMBF VIP+ program. This follow-on project was launched in January 2017, and its goal is to reach early pre-clinical proof-of-concept with leading TRPM4 inhibitors by 2019. IME ScreeningPort continues to be involved in a number of additional translational projects related to MS under the NEU2 BioPharma portfolio, including studies to identify specific neuronal proteins, circulating microRNAs and metabolites in human blood as markers of disease activity and progression. No such markers are currently available, but they are absolutely necessary for the reliable assessment of drug efficacy in the prevention of neurodegeneration during clinical trials and also for the subsequent rapid development of new drugs for the market.

A further TMP project which has been funded by the BMBF is the development of TMP-001 as a repurposed drug for the treatment of MS. This drug has been extensively studied in preclinical models in

Multiple sclerosis

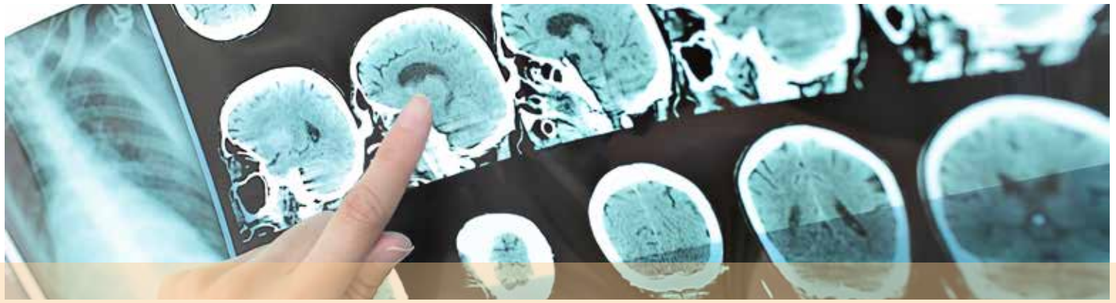


MS involves an increase in the migration of pathogenic immune cells into the central nervous system. Changes in the inflammatory milieu then cause chronic-progressive neural damage.

A repurposed drug may offer an inexpensive and orally active alternative for MS patients

Frankfurt/Main and can reduce the frequency of both early and subsequent disease relapses, resulting in less CNS damage and the promotion of regulatory immune cells. The mechanism appears to be multifactorial, involving effects on T lymphocyte regulation, oxidative tissue injury and altered neurotransmitter production. Having successfully completed a phase 1 study in human volunteers, a phase 2 multicenter clinical trial of TMP-001 is currently underway in MS patients at several European hospitals. As a repurposed drug, the demonstration of clinical efficacy could provide MS patients with an inexpensive, orally available alternative treatment.

Currently, imaging procedures are used to diagnose MS and monitor its progression, because key molecular biomarkers remain to be identified. Fraunhofer IME researchers are working to find such markers, which could facilitate the development of new therapeutic agents.



Chemotherapy-induced peripheral neuropathic pain (CIPNP) is a severe debilitating side effect of widely used cytostatics during cancer therapy. CIPNP affects up to 70% of chemotherapy patients and can cause the delay or even the discontinuation of chemotherapy. It may even persist in patients after chemotherapy has stopped, thus massively reducing their quality of life. Substances that cause CIPNP include taxanes such as paclitaxel, which is widely used for the treatment of breast cancer, and platinum derivatives such as oxaliplatin, which is mainly used for the treatment of colorectal cancer. But other cytostatics, such as vincristine and bortezomib, also cause severe CIPNP. Currently, there is no approved pharmacological treatment for CIPNP. However, the number of cancer survivors who suffer from chemotherapy side effects will increase substantially in the near future, so there is an emerging need for treatment options for CIPNP.

Researchers in the project group TMP have identified a mouse protein known as CYP2J6 that is involved in CIPNP caused by paclitaxel. This protein generates a signaling lipid (9,10-EpOME) that sensitizes peripheral sensory neurons when injected into mice and thus causes mechanical and thermal pain. In humans, the corresponding protein is known as CYP2J2 and it has the same expression pattern and function.

Chemotherapy-induced pain – potential preventative treatment in cancer patients

In a drug repurposing screen at IME ScreeningPort in Hamburg involving 615 already approved pharmaceutical compounds, several potent inhibitors of the human CYP2J2 protein were found. Among the top screening hits was T-10010, a well-tolerated drug that has been used for many years to reduce blood pressure. T-10010 proved to be a potent inhibitor of CYP2J2 and CYP2J6, reducing the synthesis of 9,10-EpOME in neuronal tissue and also in the plasma of treated mice. It reduces mechanical pain hypersensitivity when injected into mice with CIPNP, and can even prevent the development of CIPNP when administered before paclitaxel treatment. These results indicate that T-10010 offers a promising novel pharmacological approach for the treatment, and potentially also the prevention, of CIPNP in cancer patients.

TM Translational Medicine and Pharmacology

TM ScreeningPort

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Surface waters: Measuring background levels of free cyanide

Free cyanide is highly toxic towards aquatic organisms. Environmental quality standards for free cyanide were recently proposed under the European Water Framework Directive. However, current detection methods are not sensitive enough to measure the proposed levels accurately. Fraunhofer IME researchers have adapted an existing analytical method for free cyanide and investigated background concentrations in surface waters to facilitate compliance testing.

Cyanide is a naturally occuring compound which is cycled in the environment by cyanide degrading organisms and those which assimilate cyanide. Natural background concentrations of cyanide can originate from the degradation of plants and microbes such as algae. For cyanide in waters, a distinction is made between "total cyanides", defined as all simple cyanide compounds and complex structures containing cyanide, and "easily liberated / weak and dissociable cyanides", comprising hydrogen cyanide and all compounds that release hydrogen cyanide at pH ~4. The latter is the highly toxic "free cyanide".

"We currently lack reliable data on the background concentrations of free cyanide in surface waters," says project coordinator Burkhard Knopf. "However, the scientific literature indicates that background levels derived from plant and microbial processes should be half a microgram to ten micrograms per liter." Recently, the UK Environmental Protection Agency proposed an environmental quality standard (EQS) of 0.26 µg/L free cyanide under the Water Framework Directive, to avoid long-term adverse effects in freshwater systems. The European Union Joint Research Centre (JRC) has proposed an annual average EQS of 0.5 µg/L free cyanide. The Water Framework Directive mandates that analytical methods used to determine compliance with EQS levels must have a limit of quantification (LOQ), defined as the quantity of analyte in a sample that can be measured reliably, of at least 30% of the EQS concentration. "But current methods for the measurement of free cyanide in waters only achieve LOQs of approximately one microgram per liter, so more sensitive methods are required," explains Knopf. "A consortium of industry associations therefore initiated an investigation by Fraunhofer IME to implement and test a fit-for-purpose method that provides reliable data for free cyanide background concentrations in surface waters."

The Water Framework Directive of the EU aims at assuring a good status of all water bodies – toxic compounds have to be tested for exceeding potential effect levels

As method Knopf and his team selected continuous flow analysis where samples are directly injected into a constant flow of reagents and are transported, after different chemical reactions in the system, to the detector.

This approach was selected because the technical requirements are ideal for the optimization of sensitivity. Photometric detection is needed to detect low concentrations of cyanide, so the IME researchers selected a continuous flow photometric analysis system with a special cuvette installation. The target LOQ was approximately 30% of the proposed EQS concentration (i.e. ~0.15 µg/L) to ensure compliance testing with the proposed JRC EQS concentration of 0.5 µg/L. Knopf: "We determined the LOQ and the limit of detection, in short LOD, the latter defined as the concentration at which an analyte can be qualitatively detected in a sample, in two separate measurement series at a 95% confidence level according to the German standard DIN 32645." Under optimal test conditions the LODs were below 0.04 µg/L and the LOQs were below 0.14 µg/L. The researchers predict that routine test conditions should achieve LOQs about 0.3 µg/L. During the validation process, the analytical precision, selectivity, robustness and measurement uncertainty of the improved method were found to be sufficient. However, the investigations of Knopf and his team showed that all reagent solutions have to be free of any gas to reduce disturbances of the measurements by interfering influences and the used reagent solutions have to be prepared freshly.

The selected method was implemented and validated according to ISO 17025 accreditation requirements

Free forms of cyanide occur naturally in the environment and are highly toxic. Cyanide levels are influenced by a combination of different parameters.

"We carried out tests to confirm that the improved method was suitable for testing field samples and also investigated whether samples can be

To measure concentrations of cyanide, researchers took water samples from different positions along the course of the River Lenne and stabilized them before transfer to the laboratory.

Dr. Burkhard Knopf: "Previous techniques for measuring free cyanide in lakes and rivers achieved a limit of quantification of approximately one microgram per liter. Our modification of an existing method now achieves measurements of far greater sensitivity."

stabilized for at least 24 hours before testing. In February and March 2016, we therefore collected several sets of samples from along the River Lenne near Schmallenberg for analysis according to Water Framework Directive requirements," says Burkhard Knopf. Samples were collected from the river's spring and from downstream locations. For transport and storage, the samples were stabilized by adjusting to pH 12 and keeping them in the dark at 4°C. Lenne water samples spiked with cyanide standard were used a positive controls. This approach was sufficient to stabilize the samples and the field validation results were satisfactory, confirming that the protocol is fit for purpose.

The suitability of the improved protocol for the measurement of free cyanide was demonstrated using field samples

Analysis of the samples from the River Lenne confirmed the expected low levels of free cyanide in natural waters, with mean concentrations from both sampling campaigns in the range of the LODs (up to 0.36 µg/L). There were significant differences in free cyanide concentrations between the spring, with levels mostly below the LODs, and four downstream sampling points, with free cyanide concentrations at least 50% higher, possibly due to degraded plant biomass in the water.

The concentration of free cyanide can be influenced by physicochemical parameters such as pH, oxygen concentration, conductivity, non-purgeable organic carbon, metals, and water hardness. Surface water samples were therefore taken at four different locations differentiated by parameters such as the level of solar radiation and water velocity. In one campaign, samples were also taken at different times of day. The Fraunhofer IME team chose sampling sites at the River Lenne and the Esmecke Barrier Lake.

Background levels of free cyanide in uncontaminated surface waters were below the proposed environmental quality standard of half a microgram per liter

Free cyanide concentrations were generally low, ranging from below the LOQ to ~0.24 µg/L. There were significant differences between stagnant and flowing water, with concentrations of free cyanide at the river sites 23–30% lower than the cyanide levels in the lake. The lake and river samples also differed in terms of their copper, sulfur, phosphor and potassium concentrations, which were higher in river water, whereas non-purgeable organic carbon concentrations were higher in the lake. The stagnant water samples had consistently lower oxygen concentrations and were more acidic. The time of day had no significant impact on free cyanide levels. There does not appear to be a single major parameter that influences free cyanide concentrations in surface waters. The cyanide levels were influenced by combinations of parameters, although it is important to note that the overall differences between cyanide concentrations were small.

"Our investigation showed that background concentrations of free cyanide in the waters we tested were below the EQS of half a microgram per liter proposed by the JRC. However, the analysis of further river and lake waters from different geographical regions is necessary to create a reliable database and to identify possible influencing factors," says Burkhard Knopf.

The project was funded by CEFIC (European Chemical Industry Council), Euromines (European Association of Mining Industries), the European Petroleum Refiners (Concawe Division) and EUROFER (European Steel Association).

AE BR Environmental Specimen Bank and Elemental Analysis

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In Dialog with Christian Schlechtriem

Christian Schlechtriem has specialist knowledge in the areas of agricultural production, animal metabolism and bioaccumulation, particularly the buildup of harmful substances in living organisms. He puts this combination of expertise to excellent use when assessing the potential risks to the environment and to consumers posed by chemicals such as pesticides or feed supplements, before these products are launched onto the market. He acts as an intermediary between manufacturers and regulatory authorities, and is closely involved in the development of guidelines for studies concerning the accumulation of environmentally harmful substances. Overall, his work contributes to environmental and consumer protection – his overarching aim is to prevent that such threats to animals and humans arise.

Personal background

Prof. Dr. Christian Schlechtriem is a qualified agricultural scientist focusing on animal nutrition with expertise in fish physiology and aquatic ecology. He heads the IME Bioaccumulation and Animal Metabolism department and holds an honorary professorship, conferred by the University of Siegen. He has conducted research, including environmental studies, in Israel, Canada, Scotland and Sweden, and has developed new concepts for fish nutrition. The various stages in his career have enabled Prof. Schlechtriem to see the broader picture and think outside the box, from an interdisciplinary angle.

Trout, carp and tiny crabs: Valuable helpers in environmental and consumer protection

Professor Schlechtriem, are fish and fish feed the connecting thread running through your research career?
Yes, since my student days. I carried out a fishpond study as a doctoral student of agricultural sciences in Israel, and since then fish have been a constant feature in my research. Fish nutrition and animal metabolism interest me from many different angles. So much is involved here: sustainable farming, environmental and consumer protection, and the effects of new products such as feedstuffs, pesticides, antibiotics and sunscreens on the environment.

And how can fish tell us whether chemical product residues are accumulating in our environment?
Fish are often used as model organisms to measure the accumulation of environmentally damaging substances. This so-called bioaccumulation is measured in the lab and recorded as the bioconcentration factor. Fish absorb substances very efficiently through their gills. A few micrograms of a substance in a liter of water can become concentrated a thousand-fold in the fish and so become a burden on the food chain. We take a proactive approach in this evaluation process by aiming to prevent harmful substances finding their way into the environment in the first place.

You act as an intermediary between product manufacturers and regulatory authorities, which require tests to be carried out on chemicals before they are launched on the market. That must be challenging.
It certainly is. We have to be very careful and work with great precision. It is a balancing act. On one hand, we want to protect the environment, animals and consumers. On the other hand, the results of our tests can determine the fate of a product and thereby the economic success of a company. We always need to keep a clear overall picture of our position within the jungle of regulations.

How does that work in concrete terms?
Say, for example, a pesticide manufacturer needs to investigate whether a new product leaves any chemical residues in aquaculture products, and if so, the nature of those residues. In the past, there was no suitable test system available. Now, in cooperation with the regulatory authorities and industry, we have developed a test system for fish metabolism studies. Another example is a test system designed to investigate the bioaccumulation of strongly hydrophobic substances that are almost insoluble in water. We confirmed this is possible and got a system up and running.

Rainbow trout at feeding time – fish can take up and accumulate environmental pollutants via the water or fish feed.

That's "typical Fraunhofer" isn't it?
Exactly. We always have a specific application in mind, so we need to be creative and we need to devise solutions that work reliably. We develop prototypes as potential test systems to be incorporated into standard evaluation procedures, often in cooperation with national and international partners. We aim to simplify testing procedures while improving the quality of the results – and to achieve this using as few test animals as possible.

Alternative test systems can minimize the number of animals we use for testing?
Yes, and as far as possible we try to avoid using fish altogether. So we also use *in silico* and *in vitro* methods, which means computer simulations and test-tube experiments. We can make predictions about the bioaccumulation of a certain substance from models based on empirical results. However, these models never tell the whole story and can lead to erroneous assessments. This is where metabolism comes in. Using fish liver cells, we can measure the conversion of chemicals in the test tube. For these tests we use trout and carp, the latter playing an important role in Asia. We then develop computer simulations based on our laboratory data to refine our results even further. My vision is not simply to predict how much of a substance accumulates in animals in nature, but to predict the levels of these substances in our food too, for instance in filleted fish.

Are there invertebrate organisms that could be used for testing instead of fish?
This is a hot topic right now, and we are in the midst of preparing a publication on that very subject! *Hyalella azteca*, a crab only a few

millimeters in length, lives at the bottom of rivers and lakes in Northern and Central America. We have found a close correlation between bioaccumulation in fish and *Hyalella* when the measurements are adjusted for the relative fat content of the animals. We took data available from fish studies and compared it with results obtained with *Hyalella*. It was impressive how well they matched!

“We strive to prevent the accumulation of chemicals in the environment, reducing the likelihood that consumers will finally ingest them. Our goal is to ensure that foods of animal origin contain no environmentally damaging substances.”

Could that also be an option for the testing of cosmetics?

Yes. As vertebrates, fish are legally protected and cannot be used to test cosmetics. However, we need to find out what residues, if any, are accumulating in the environment and to what extent, and to determine whether they could possibly enter the food chain. *In silico* and *in vitro* experiments in combination with *Hyalella* studies could offer a solution.

Bioaccumulation studies on the freshwater amphipod or scud *Hyalella azteca*, measuring just a few millimeters in length, offers an alternative to standard studies on fish.

Another focus of your work is sustainable aquaculture. What is the meaning of ‘sustainable’ in this context?

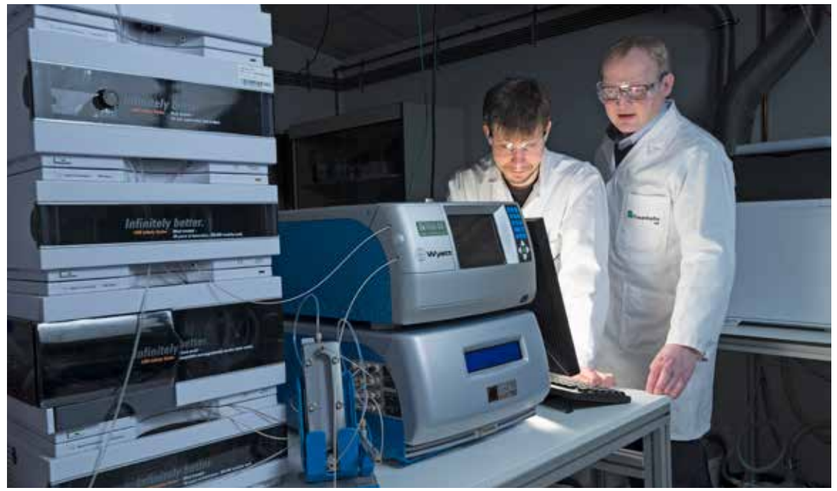
We are concerned with the effect of aquaculture on the environment and issues surrounding fish diets. An example of sustainability in this context could be substituting components of fish feed, such as fish oil and fishmeal from the overfished seas, with plant-derived materials. Again we have to keep bioaccumulation in mind here: are there pesticide residues in plant-derived feedstuffs? Harmful substances should not be allowed to get into fish feed and enter the food chain by that route.

You have devised a calculator for work on fish nutrition in aquaculture. What does it do exactly?

Our “Dietary Burden Calculator” can provide a realistic estimate of pesticide residues in fish feed containing plant-derived constituents. We use it when assessing the levels of plant protection products. Data from field studies is entered, followed by various scenarios for feed formulations. Then we just press a button and we can read off the potential concentration of a certain chemical in the fish feed and that tells us whether we need to run further studies on metabolism and accumulation in the animal. In the meantime, the calculator has become a fixed component of regulatory assessment work.

The potential impact of nanomaterial residues is causing considerable headaches for researchers. Why?

It is particularly difficult to test for nanomaterials. They transform, shrink and dissolve, making it very difficult to establish the risks they pose to the environment, animals and humans, and at



Boris Meisterjahn and Prof. Dr. Christian Schlechtriem in the laboratory with the AF4 system (used to fractionate nanoparticles). Fraunhofer IME offers state-of-the-art techniques for the characterization of nanomaterials.

what stage. Nanoparticles occur in many everyday products: titanium dioxide in sunscreen and antibacterial nanosilver in socks, to mention just two examples. Sunscreen gets rinsed off in the shower, socks get washed, and so the nanoparticles get into the wastewater.

What approach are you currently taking vis-à-vis nanoparticles?

In the BMBF project FENOMENO we are studying nanoparticles in the effluent from municipal wastewater treatment plants. What happens when the effluent from these treatment plants drains into a lake? Can the nanoparticles carried in them build up in the aquatic food chain? We hope to establish this through field and laboratory studies.

Finally, will you tell us what you love most about your work as a scientist, Professor Schlechtriem?

For me, using innovative approaches to extend our capabilities in substance evaluation is a continuous motivation. It is a very meaningful task. The environment and the consumer both benefit. I want us to have the assurance that our food is safe.

Interview: Sabine Dzuck

AE BR Bioaccumulation and Animal Metabolism

Prof. Dr. Christian Schlechtriem
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In Focus

An article by Prof. Dr. Stefan Schillberg
and Prof. Dr. Dirk Prüfer

Plants as raw materials and production systems
for diverse applications in biotechnology

Plants as raw materials and production systems for diverse applications in biotechnology

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Plants not only supply us with food and feed but also play a key role in the "biologizing" of industry: They provide industrial raw materials such as cellulose, starch and rubber, and also serve as production systems for the active ingredients in pharmaceutical and cosmetic products. Fraunhofer IME is conducting projects focusing on these diverse areas of plant biotechnology.

For the human race, plants represent the largest natural resource for sustainable development, and as such, they form a cornerstone of the bioeconomy. As well as their key roles in the provision of food and animal feed, plants also produce renewable raw materials such as starch and oils, and their biomass is a starting material for the production of biofuels such as bioethanol. Against the background of a steadily increasing global population and the loss of agricultural land, the main goal of modern cultivation programs is to increase biomass production and improve the quality of new and established crops.

Crop optimization to increase agronomic traits, biomass yields and processing efficiency

The core expertise of the plant biotechnology departments in Aachen and Münster is the improvement of crops to achieve added value. We focus on the development of improved plant systems and efficient downstream processing to yield valuable plant-derived raw materials. Furthermore, we consider the need to meet industrial demands in terms of scaling-up and economic process management from the very start.

By applying modern biotechnological procedures in a series of joint projects with industrial partners, Fraunhofer IME researchers have developed new plant varieties and plant-based processes that are ready for commercialization or already on the market. In collaboration with the biotechnology company BioPlant and the starch supplier Emsland-Stärke, a new potato variety has been produced with a high content of amylopectin and little or no amylose. We used mutation breeding, a standard procedure in modern plant breeding, to switch off a gene required for amylose biosynthesis so that only the amylopectin form of starch accumulates in the potato tubers. This can be made into glue or used as a thickening agent in the food and paper manufacturing industries. Normally, amylopectin must be separated from amylose in an energy-demanding process, so the availability of amylopectin-rich potatoes makes starch production less expensive and more environmentally friendly.

Modern plant breeding methods: New varieties of potato producing only one form of starch simplify industrial exploitation and help to protect the environment

In collaboration with the University of Münster, North Rhine-Westphalia, the plant breeding association ESKUSA, and the Julius Kühn Institute, we have used modern breeding techniques to exploit the Russian dandelion as a sustainable alternative source of rubber. Sustainable cultivation of the robust dandelion has been established in a temperate climate and even on ground unsuitable for food and feed crops. By increasing the root biomass and developing a simple, resource-saving extraction process, large quantities of dandelion rubber can now be produced. Together with the tire manufacturer Continental, we have manufactured and successfully tested the first prototype tires for passenger cars, trucks and buses, as well as engine mountings to reduce vibrations.

Plants provide an important source of ingredients for the cosmetics industry. "Plant stem cells", which can be isolated from plant tissue and cultivated in a liquid culture medium, can be part of cosmetic creams and lotions. Together with the cosmetic company Babor in Aachen, we have established stem cell cultures from the berries of the wild service tree and the European pear, and have optimized their cultivation to such an extent that cells of consistently high quality can be supplied in sufficient quantity the whole year round. And all that, without resorting to the use of pesticides or the gathering of plant material from the wild. Since 2013, Babor has used extracts from these plant stem cell lines for their cosmetic products.

Fraunhofer IME researchers have cultivated a potato producing only the amylopectin form of starch – a raw material for the manufacture of glues and food thickeners.

The dandelion as a source of rubber: Prototypes for truck and car tires as well as engine mounts to reduce vibration have already been tested successfully.

As well as the three examples above, Fraunhofer IME researchers are working on several other projects in the field of plant biotechnology. One important aim is to increase plant biomass. This can be done, for instance, by boosting the intake

Using plants to make tires and cosmetics: Rubber from dandelions and cosmetic ingredients from plant stem cells

of carbon dioxide and thereby stepping up the rate of photosynthesis, resulting in potato tubers that grow to twice the normal size. In other experiments, we have identified a mutation that causes plants to grow continuously. The plants show no sign of aging, have permanently green leaves, and produce considerably more biomass in a given time period than plants with a functional gene.

Finally, we are using plants and plant cell cultures as green factories for the production of pharmaceutical ingredients. As part of a project to produce antibodies in tobacco against the human immunodeficiency virus (HIV), we established a procedure to produce clinical-grade recombinant proteins for testing in humans. This was the first procedure of its kind in Europe. Having successfully developed some innovative malaria vaccine candidates in Aachen, we are now working on their production in tobacco plants. This year, a new form of plant cultivation including "vertical farming" will go into operation, which will facilitate the automated cultivation and harvesting of plants producing recombinant proteins using a system of stacked platforms. The plants will be grown under controlled conditions in an artificial substrate without soil and will be illuminated by specially adapted LEDs. The malaria vaccine candidates will be extracted and purified in an integrated downstream processing unit to ensure

they meet strict quality criteria. Once production is complete, our vertical farm will be available for other lines of research such as the production of secondary metabolites in medicinal plants. Vertical farms could also be used as new sites for

Plants as production systems for active biopharmaceutical ingredients: Production of malaria vaccine candidates in tobacco plants

food production in previously inaccessible areas. The vertical farming of vegetables or herbs in urban areas offers the added benefits of a low carbon footprint, the use of less space, energy and water, and the exclusion of pollutants and pesticides.

Our wide-ranging technology portfolio, modern equipment and comprehensive and long-established expertise enable us to address diverse questions raised by our partners and customers, resulting in appropriate solutions for a range of applications. We use the latest advances in plant biotechnology, such as targeted gene knock-out by genome editing, or the phenotyping of plants or the selection of individual cells by flow cytometry, and we benefit from the latest research findings of our medical, industrial and insect biotechnology departments, highlighting new targets for the improvement of crops and the production of valuable raw materials and active ingredients.

MB Plant Biotechnology

MB Functional and Applied Genomics

A novel plant cultivation unit is under construction at the Fraunhofer IME in Aachen, offering a vertical farm on eight levels. The cultivation and harvesting of the plants is fully automated.

Six Selected Publications from 2016

ScreeningPort

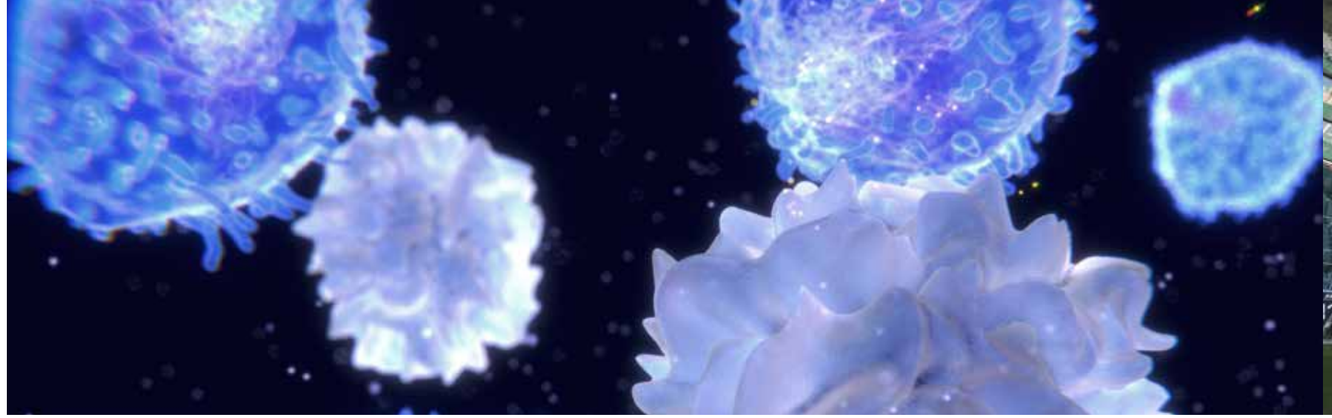
Plant Biotechnology

Functional and Applied Genomics

Environmental Specimen Bank and Elemental Analysis

Integrated Production Platforms

Ecological Chemistry



Modifying the immune response in autoimmune diseases and cancer

Ole Pless, ScreeningPort
Together with our academic partners, we have opened up an avenue for the development of novel strategies in immunotherapy.

Migratory dendritic cells facilitate the immune response by transporting antigens from sites of inflammation to the lymphoid organs, which act as central hubs for immune system activation. During an interdisciplinary joint project, our partners at the University Medical Center Hamburg-Eppendorf found that migratory dendritic cells express the molecule regulatory protein Arc/Arg3.1, which was previously thought to be expressed solely in the central nervous system. The strictly confined expression of Arc/Arg3.1 in migratory dendritic cells allows us to use this protein as a highly specific marker. Using high-throughput imaging, we were able to show that Arc/Arg3.1 regulates cytoskeletal changes that are necessary to accelerate the migration of dendritic cells in response to inflammation. Blocking the function of Arc/Arg3.1 in migratory dendritic cells reduces T cell reactions and thereby slows down disease progression in preclinical models of multiple sclerosis and allergic contact dermatitis. These results provide the basis for new therapeutic strategies because we can now identify rapidly-migrating dendritic cells suitable for immunotherapy in the context of autoimmunity or tumor immunology. This study won special recognition, being selected as "Paper of the Month" by the University Medical Center Hamburg-Eppendorf.

TM ScreeningPort

Ufer, F., Vargas, P., Broder Engler, J., Tintelnot, J., Schattling, B., Winkler, H., Bauer, S., Kursawe, N., Willing, A., Keminer, O., Ohana, O., Salinas-Riester, G., Pless, O., Kuhl, D., Friese, M.A.:
Arc/Arg3.1 governs inflammatory dendritic cell migration from the skin and thereby controls T cell activation. Science Immunology (2016)
(DOI 10.1126/sciimmunol.aaf8665)

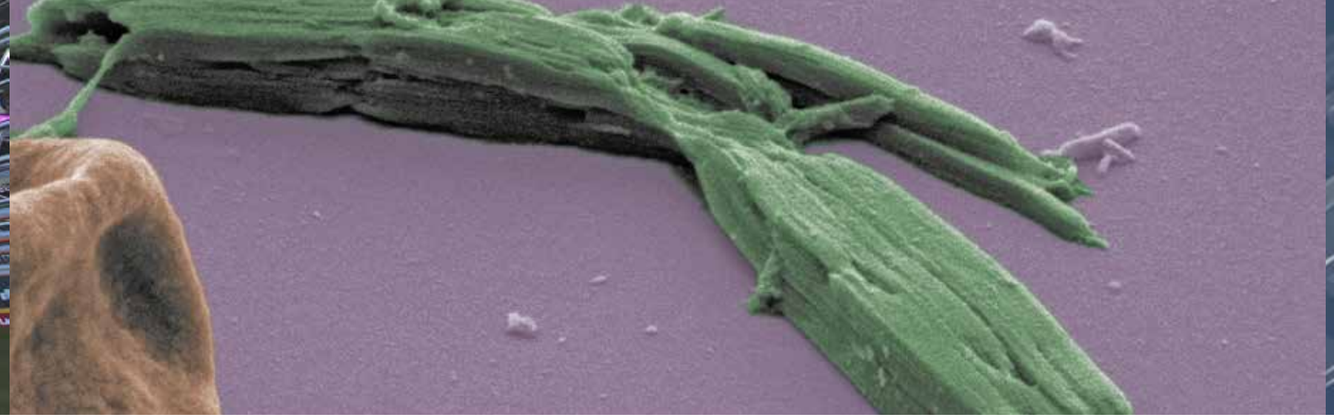
LED illumination for soccer turf – getting the ball rolling

Stefan Rasche, Plant Biotechnology
LED illumination for biological applications is on the rise, but we have yet to realize its full potential.

In modern soccer stadiums, the turf must be artificially illuminated because natural sunlight is shielded by the high and overhanging external walls. Typically, this artificial illumination is provided by sodium-vapor lamps. However, recent developments in LED technology offer economical alternatives.
We investigated the illumination of soccer turf with LED modules provided by a medium sized engineering company. The turf was cultivated under controlled conditions at 10°C with illumination provided by the LED modules. We measured the biomass growth trend at different intervening distances between turf and light source. We also evaluated the effect of long-term light stress on the growth characteristics of the turf, as well as the germination rate of seven lawn seed combinations. Overall, we found that growth could be stimulated under the selected conditions for at least 6 weeks. Moreover, all the seed combinations we tested germinated after incubation for 6 to 7 days and vigorous growth was observed throughout the experiment. Our data showed that current LED technology is suitable for the artificial illumination of soccer turf. However, the full potential of this lighting method has not yet been assessed, providing plenty of room for further optimization.

MB Plant Biotechnology

Rasche, S., Schmitz, C., Jablonka, N., Schillberg, S.:
LED-Beleuchtung von Fußballrasen – Möglichkeiten, Chancen und Grenzen. European Journal of Turfgrass Science, Ausgabe 4-2016



Forizymes: New ways to immobilize enzymes

Gundula Noll, Functional and Applied Genomics
The ability to immobilize enzymes is important for industrial applications. Our technology platform can contribute significantly to the development of improved carrier materials.

The immobilization of enzymes on carrier materials is an important industrial strategy because it increases enzyme stability and allows continuous recycling by separating the enzyme from the reaction solution. However, many carrier materials are technically unsuitable because immobilization causes a dramatic loss of enzyme activity. Forisomes are unusual macromolecular protein complexes found in the phloem of some plants. They respond to certain chemical and physical stimuli by changing their structure, allowing them to block the phloem and prevent fluid loss when the plant is injured. These same properties can be replicated *in vitro*. Recombinant forisomes display remarkable structural and functional stability and can be used to reversibly block artificial microchannels over many cycles. Recombinant forisomes can also be functionalized into forizymes by expressing the forisome subunits as fusion proteins such that the enzymes are presented on the exterior of the assembled complex. We demonstrated this principle by preparing functionalized and reactive forizymes presenting the enzymes glucose-6-phosphate dehydrogenase and/or hexokinase 2. When both enzymes were presented on the same forizyme, the reaction cascade was found to be ~30% faster than the reaction catalyzed by the individual forizymes or the corresponding enzymes in solution. Our novel immobilization platform thus not only combines the sensory properties of forisomes with the catalytic function of enzymes for the first time, but also provides a basis for the targeted development of controllable multi-enzyme complexes on technical devices such as lab-on-a-chip systems.

MB Functional and Applied Genomics

Visser, F., Müller, B., Rose, J., Prüfer, D., Noll, G.A.: Forizymes – functionalised artificial forisomes as a platform for the production and immobilisation of single enzymes and multi-enzyme complexes. Scientific Reports (2016) 6:30839
(DOI 10.1038/srep30839)

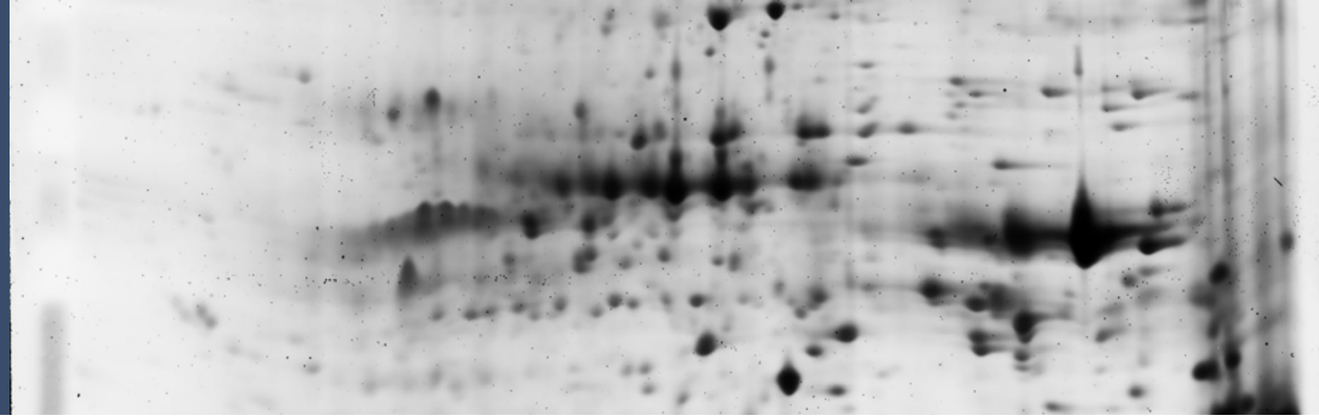
How can we detect potential endocrine activity?

Martin Müller, Environmental Specimen Bank and Elemental Analysis
Our screening method based on structural alerts helps to identify substances with potential endocrine effects

Experimental tests that reliably detect the potential endocrine effects of substances are expensive and involve the use of large numbers of vertebrates, and therefore tend to be reserved for substances considered as particularly suspect. Further evidence can be gathered from the results of previous experiments, theoretical predictions based on structural analogy to known endocrine agents, and the analysis of structure-activity relationships where available. Using this computer-assisted approach, we have developed an *in silico* screening model and have tested and refined known structural alerts on the basis of data from *in vitro* studies. These structural alerts enable us to identify potential endocrine disruptors with estrogen or androgen receptor-mediated modes of action. The application of structural alerts to organic compounds listed in the European Inventory of Existing Commercial Chemical Substances (EINECS) identified ~11% of these substances as candidates likely to exert strong estrogenic and androgenic effects, thus warranting further investigation. Although it is not possible to exclude the possibility of endocrine effects in the remaining substances, with lower disruptive potential, it is likely that the most hazardous candidates have been identified given the excellent agreement between the activities predicted by the structural alerts and those measured *in vitro* in the case of substances with particularly high endocrine activities. The combined structural alerts used in our screening method therefore appear suitable for the purpose of highlighting probable androgen and estrogen receptor interactions.

AE BR Environmental Specimen Bank and Elemental Analysis

Nendza, M., Wenzel, A., Müller, M., Lewin, G., Simetska, N., Stock, F., Arning, J.: Screening for potential endocrine disrupters in fish: evidence from structural alerts and *in vitro* and *in vivo* toxicological assays. Environmental Sciences Europe (2016) 28:26
(DOI: http://dx.doi.org/10.1186/s12302-016-0094-5)



Production of recombinant proteins in plants: Antibodies can detect minute amounts of protein impurities

Johannes Buyel,
Integrated Production Platforms
New antibodies will help to further our understanding of expression systems based on plants.

Plants can be used as an alternative to microbes and animal cells for the production of valuable recombinant proteins. The key advantages of plants include the ease of cultivation and the ability to scale up production rapidly and without great cost, to match the demand for the final product. In contrast to fermentation processes, plants are not widely used in the industrial sector. We therefore lack the analytical procedures that are commercially available for other production systems, but these procedures are important for the development and authorization of manufacturing processes. In this project, we established an antibody-based method for the specific detection of small quantities of host plant proteins. This is necessary because host plant proteins must be separated from the desired recombinant protein during the production process. The effectiveness of separation can be demonstrated clearly to the regulatory authorities if no traces of host plant proteins can be detected in the final preparation containing the recombinant protein, and this is precisely what we can now reliably achieve using our new antibodies. Furthermore, the same antibodies can also be used to compare the efficiency of different purification steps, helping us to identify the procedures that remove the most host plant proteins in one go. Our new analytical method will therefore allow us to develop more cost-effective manufacturing processes in a shorter time.

MB Integrated Production Platforms

Arfi, Z.A., Hellwig, S., Drossard, J., Fischer, R., Buyel, J.F.:
Polyclonal antibodies for specific detection of tobacco host cell proteins can be efficiently generated following RuBisCO depletion and the removal of endotoxins.
Biotechnology Journal, 11 (2016) 507-518
(DOI:10.1002/biot.201500271)

Biodegradation of chemicals: Tests in water-sediment systems

Prasit Shrestha, Ecological Chemistry
Together with our partners, we have developed methods to improve the robustness of chemical risk assessment.

Simulation tests are used to explore the degradation of chemicals in ponds and rivers, and standard test guidelines such as OECD 308 and 309 have been established to ensure that test results from different laboratories are comparable. OECD 308 has attracted criticism since its adoption in 2002 due to various drawbacks including the static test system, the water/sediment ratio and the neglect of phase transfer processes, ultimately resulting in less robust degradation data.
We therefore compared the two standard methods and two modified methods which should bridge the gap between the standard methods. The tests were run using four radiolabeled test compounds with different degradation and sorption properties, and were accompanied by sorption tests to monitor phase transfer. This was the first systematic comparison of the standard methods at this level. Experiments were supported by our partner ECT Ecotoxicology, enabling us to conduct 34 simulation studies in 2 years. We also investigated the impact of different OECD 309 test setups, allowing us to offer best practice recommendations for the generation of robust data.
Our experimental data were used by partners in the Swiss Federal Institute of Aquatic Science and Technology (EAWAG) and the University of Budapest to develop a computer model that describes degradation processes and calculates the degradation rate constant, which is independent of the test system. The project results were presented at an EAWAG workshop for discussion with industry representatives and the regulatory authorities. The overall work was acknowledged as a significant step towards the generation of robust data for chemical risk assessment.

AE BR Ecological Chemistry

Shrestha, P., Junker, T., Fenner, K., Hahn, S., Honti, M., Bakkour, R., Diaz, C., Hennecke, D.: Simulation studies to explore biodegradation in water-sediment systems: From OECD 308 to OECD 309. Environmental Science & Technology 50 (2016) No. 13: 6856–6864
(DOI:10.1021/acs.est.6b01095) and second part of the paper, same issue: 6865-6872

People and Events

Brief reports: Employees, encounters, successes, and new perspectives at the Fraunhofer IME

The German government think-tank on health policy presents its results

Meeting the challenges facing the pharmaceutical industry – Prof. Dr. Rainer Fischer, Senior Executive Director of the Fraunhofer IME until the end of 2016 (2nd from left) participated in the "Pharmadialog".

The German Ministry of Health has urged participants in the "Pharmadialog" – a federal think-tank on health policy – to focus for 18 months on challenges facing the pharmaceuticals industry, particularly research and development, production and supply issues. The key aims of this high-level board are to promote rapid access to high-quality and affordable medicines and the development of new antibiotics. In the spring of 2016, Federal Ministers Hermann Gröhe (Health), Johanna Wanka (Education and Research) and State Secretary Rainer Sontowski, together with representatives from the pharmaceuticals industry, the scientific research community, and the trade union IG BCE, presented their findings.

As an advisory member of the "Pharmadialog", Rainer Fischer (Senior Executive Director of the Fraunhofer IME until the end of 2016) helped to draw up a list of proposed measures, and he summarizes their overarching goals as follows: "Academic research, the economic sector and politicians must work together more effectively to ensure that Germany maintains its strong reputation as an industrial base for pharmaceutical development and that our health system remains one of the best in the world." Among other things, the BMBF (Federal Ministry of Education and Research) will increase funding for novel approaches to the treatment and diagnosis of bacterial infections. The Natural Product Center of Excellence, founded jointly by Fraunhofer and Sanofi in 2014, is a prime example of improved collaboration between research teams within industrial organizations and academic research institutes. This is knowledge transfer for real – through joint teams and laboratories. MB

Agricultural Economics 4.0: Sustainable agriculture and significant value creation

In March 2016, a symposium was held in Schmallenberg to set up the new Fraunhofer IME business field "Sustainable Agricultural Production of Raw Materials". Among those invited were members of the Fraunhofer Sustainability Network, South Westphalia University of Applied Sciences, and representatives of key national institutions such as the Julius-Kühn Institute, the Agricultural Institute of the State of Thüringen, the Leibniz Center for Agricultural Landscape Research, and RLP AgroScience. Within an initiative of the Fraunhofer-Gesellschaft the IME also develops concepts for sustainable agriculture: In April, while drawing up their agenda, the Fraunhofer Sustainability Network chose "Multidimensional optimization of the use of restricted agricultural areas" as one of three topics for specific attention. The white paper "Agricultural Economics 4.0" grew from these two initiatives and was presented on June 15 within the framework of the initiative "Smart Agriculture/Forestry" in Dresden. The President of the Fraunhofer-Gesellschaft and the Minister for Environment and Agriculture of the State of Saxony were the driving force behind this initiative. Because the concept of agro-business and restrictions on land available for agriculture are central to future developments, Christoph Schäfers, Head of the Fraunhofer IME Applied Ecology Division, will play a coordinating role in the area "Bio-Economy". AE BR

Opening of the first European stem cell bank

EBiSC
European Bank for induced pluripotent Stem Cells

Induced pluripotent stem cells are a source of huge potential for research, regenerative medicine and the development of new drugs. The catalog of the first European bank of induced pluripotent stem cells (EBiSC) went online in 2016, making these cells available for research. "The stem-cell bank is an accessible resource for partners from the academic research community and the pharmaceuticals industry. The EBiSC makes applied stem-cell research possible, and offers a wide range of quality-controlled cell lines from healthy donors as well as patients with particular diseases," explains Ole Pless of the Fraunhofer IME ScreeningPort. The IME brings many years of experience working with image-based cell analysis to this consortium, and is cooperating with both small and medium-sized pharmaceutical companies as well as academic partners in order to obtain cells of the best possible quality. TM

IAA Commercial Vehicles 2016: First use of dandelion rubber in trucks and buses

Together with the technology company Continental, the Julius-Kühn Institute and ESKUSA, Fraunhofer IME researchers are tapping the potential of dandelions as a sustainable source of raw material for the rubber processing industry. Dandelions offer an ecologically and economically attractive alternative to the tropical rubber tree. After successful performance tests in car tires and engine mounts, natural rubber from the robust weed with golden-yellow flowers is now being put to use in commercial vehicles. At the 2016 IAA Commercial Vehicles exhibition in Hanover, Continental displayed its prototype tires, engine mounts and driveshaft bearings made from dandelion rubber and used in trucks and buses. MB

Clinical research at IME's Frankfurt location: a variety of projects

The Clinical Research team at IME's Frankfurt/Main location (Translational Medicine and Pharmacology) once again acquired in 2016 a wide range of clinical studies and research projects. A representative example is the industry-sponsored national multicenter study XTEND, being performed according to §23b of the Law on Medicinal Products. In this study, a fluorescence-optical imaging approach is being used for the detection of blood flow disturbances as a method to predict the development of psoriatic arthritis. In addition, the scientists are currently evaluating the outcome of combination therapy with modern antibody products in a randomized, controlled clinical trial. In this context, the Frankfurt project group is also running three clinical trials for which it is acting as sponsor, following the first step taken in 2014, when Fraunhofer, as represented by the Frankfurt project group, accepted the responsibility to act as a sponsor according to the German Drug Law. This sponsorship role also applies to a Phase IIa trial being carried out with TMP001, a drug candidate developed in-house. The focus of the current clinical activities is on the indications rheumatoid arthritis, psoriatic arthritis and critical care. The Clinical Research team will be expanding in the next year to accommodate sustained data management and biostatistics expertise and to carry out international multi-center studies. TM

Getting fit for big data projects: Fraunhofer FIT and IME ScreeningPort training workshops

Clinical research and drug development produce enormous and rapidly increasing amounts of data. In a joint training program, scientists at the Fraunhofer Institute for Applied Information Technology FIT and the Fraunhofer IME ScreeningPort show how this potential can be put to efficient use. The four-day course for qualification as a Data Manager in Sciences, and particularly in the life sciences, targets specialists and managers handling laboratory and experimental data, including project leaders, laboratory supervisors and other laboratory personnel. Participants are instructed in the sustainable management of data and documents for efficient access and improved transparency. In both theory and practice, the key to success is the organization of laboratory data in the correct way, the optimal use of metadata, and the application of software solutions for data management, data integration and data analysis. Participants are also given the opportunity to discuss specific questions with Fraunhofer experts experienced in the field. TM

Environmental specimen bank at the Festival of the Future

The 30th anniversary of the German Federal Environment Ministry was celebrated on 10/11 September 2016 in Berlin, with the event "Festival of the Future" – Environmental Policy 3.0. More than 100 organizations, associations and environmental initiatives from home and abroad presented their areas of special interest, top priorities and ideas for future environmental policies. A team from the Fraunhofer IME was also there, demonstrating hands-on environmental monitoring at the stand of the German Environment Agency. Staff from the environmental specimen bank in Schmallenberg demonstrated the procedures used at the national environmental specimen bank, an archive of environmental and human specimens used to document environmental quality and to follow changes caused by the action of harmful substances over time. Children, young people and their parents were offered a hands-on opportunity to experiment with liquid nitrogen in a kids' laboratory and to learn how environmental specimens are prepared and archived for environmental research. The activities were mainly geared towards children and young people, to raise awareness of the need to protect the environment and to familiarize them with the potential of science in this endeavor. AB BR

EU program: Young scientists search for new solutions to counter antibiotic resistance

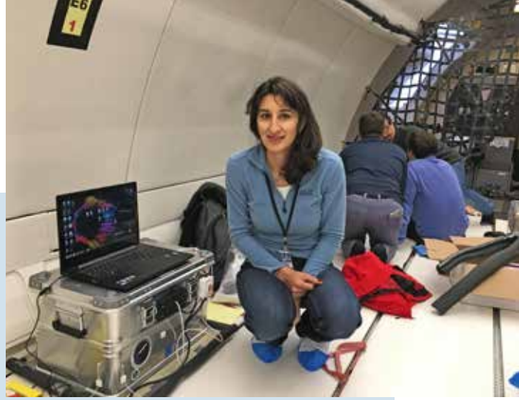
The ITN Translocation project is a highly competitive EU program that promotes cross-disciplinary networking activities among doctoral students and embraces both academia and industry. In 2013, 12 academic groups and 3 small and medium-sized enterprises from across Europe teamed up in the search for solutions to increase antibiotic concentrations inside bacteria. Each academic partner hosted a doctoral candidate from another EU country. Thirty-year-old Alessia Gilardi came from Italy in January 2014 to join the Fraunhofer IME family as a student of the ITN Translocation project, while enrolled at the Jacobs University Bremen for her PhD studies.

Alessia has a Bachelor's degree in Experimental Biology and completed a Master's in Molecular and Cellular Biology at the University of Cagliari, Italy. At the IME ScreeningPort in Hamburg, she worked on the development of adjuvants in antimicrobial therapies, identifying small molecules that can block bacterial efflux systems playing a key role in resistance mechanisms. To complete some parts of the project, valuable collaborations were established between Jacobs University and other research teams within the ITN network, as well as external partners such as the Helmholtz Centre for Infection Research in Braunschweig. Carsten Claussen, Head of the IME ScreeningPort notes that "At the end of these 3 years, after a computational investigation involving large virtual screening campaigns and docking studies, followed by several experimental validations, we were able to identify some promising molecules. And Alessi will become a PhD!" TM

Fraunhofer IME assists Federal Ministry with regulatory issues

In February 2016, Kerstin Hund-Rinke of the Fraunhofer IME together with two other members of the Scientific Advisory Board on Fertilizer Issues, was invited to a meeting with Secretary of State Robert Kloos at the German Federal Ministry of Nutrition and Agriculture (BMEL). Hund-Rinke is also Vice-Chair of the Advisory Board. The purpose of the meeting was to present a Board publication from October 2015 entitled "Views on the use of organic fertilizers and waste material in agriculture" and to discuss their recommendations with representatives of the BMEL. The Scientific Advisory Board assists the Federal Ministry in drawing up recommendations for agricultural, administrative, political and legislatorial organizations on the handling of specific regulatory issues. AE BR

Proteins in parabolic flight: Experiments in microgravity



Experiments conducted in a microgravity environment offer researchers an undistorted view of biological and physical processes by excluding gravity-induced phenomena such as convection, shear forces, or hydrostatic pressure. One way to achieve microgravity conditions is through parabolic flight. Raluca Ostafe of the Fraunhofer IME has studied the effect of microgravity on the kinetics of enzymatic reactions during an Airbus A310 zero-gravity flight. The experiment was conducted remotely using a web application. The results may reveal new catalytic properties and widen the industrial applications of enzymes. MB

The next generations of research scientists at the Fraunhofer IME

"Jugend forscht" is the largest European contest for young people in the field of natural sciences, mathematics and technology. "Girls' Day" and "Boys' Day" allow girls and boys from the fifth grade onwards to explore the possibility of careers in areas generally selected by members of the opposite sex. For several years now, the IME has opened its doors to these initiatives: For the fourth year in a row, Mira Grättinger of the Fraunhofer IME ScreeningPort organized with great dedication the regional "Jugend forscht" contest Hamburg Volkspark, assisted by committed students as well as schoolchildren. The Girls' and Boys'Days have become a regular fixture in the calendar at several IME locations. At IME Schmallenberg, for example, the young participants in 2016 were shown how to freeze environmental samples, measure the hardness of tap water and sort eggs from fish roe. One option for young ladies at the Girls' Day in Aachen was to find out what is hidden in a finely crushed plant extract.

New Head of Department: Jörn Schmitz aims to develop antibody-based therapies

In March 2016, after 20 years of research at Harvard, Jörn Schmitz took up the position as Head of the Fraunhofer IME Immunotherapy department. His goal is to find human antibodies that can be developed as therapeutic agents and, as combination therapies, can be brought quickly from the laboratory to the aid of patients. Improving the quality of life and life expectancy of patients with cancer, or autoimmune diseases is the overarching aim of Schmitz, who for decades has focused on key issues in the fields of virology, immunology and pathology. As he explains, "Whether it is cancer, viruses or bacteria – from an immunological point of view, we are dealing with the same problem. HIV, for instance, mutates and the immune system must follow suit in order to get the virus under control. Tumors on the other hand, are mutations of normal cells. Here the immune system needs to be just as active and the defense mechanisms are the same as those activated to combat infectious diseases." Schmitz is convinced that the antibodies formed by cancer patients hold enormous potential for the development of new immunotherapeutic agents. MB

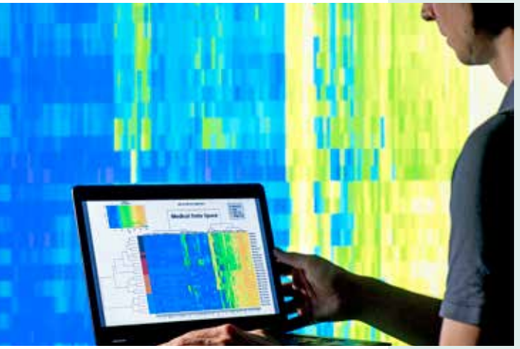
HFSP long-term postdoctoral fellowship for Timurs Maculins

Timurs Maculins has been awarded a long-term postdoctoral fellowship by the Human Frontier Science Program (HFSP). The fellowship enables young researchers to broaden their horizons by switching to a new field of study while simultaneously moving to another country. Tim recently relocated from the High-Throughput Screening Centre in AstraZeneca, Macclesfield, UK to the IME Translational Medicine and Pharmacology project group in Frankfurt/Main, where he is setting up new assays to test for the inhibition of intracellular signaling molecules. The HFSP fellowship will support Tim's research at Fraunhofer and the Institute for Biochemistry II (Goethe University) aiming to understand the fundamental mechanisms by which bacterial pathogens invade human host cells, leading to more insight into the cellular processes triggered by bacterial infection and more effective antibacterial therapy. TM

A course on the environmental risk assessment of plant protection products at the Member State and EU levels

In September 2016, the Wageningen University and Alterra Research offered the first ever training course concerning "Environmental risk assessment of plant protection products at Member State and EU levels". The course targeted personnel representing the regulatory authorities, manufacturers of plant protection products and consultancies. One of the speakers was Udo Hommen from the Fraunhofer IME Applied Ecology Division. Together with Gertie Arts, Ivo Roessink and Theo Brock (all from Wageningen Environmental Research (Alterra)) he was responsible for the course module "Effects" and lectured on the evaluation and grading of studies in aquatic mesocosms and the use of mechanistic effect models for the evaluation of plant protection products. The goal of the two-and-a-half day course was to instruct participants in the correct application of existing guidelines and familiarize them with new approaches to risk assessment for plant protection products. In addition, course participants were instructed in the linking of data on the fate and the effects of pesticides in the environment based on a comprehensive risk assessment. AE BR

Medical Data Space: Huge potential for patients and researchers



At a press conference in Berlin in October, one year into the initiative “Industrial Data Space”, Johanna Wanka, Federal Minister for Education and Research, and Reimund Neugebauer, President of the Fraunhofer Society (FhG), reported on the transformation of the German economy through digitization. The FhG has already prepared a white paper on another Data Space – the “Medical Data Space”, largely drawn up by Carsten Claussen of the Fraunhofer IME, with contributions from many experts inside the FhG and under the moderation of Matthias Jarke and Rainer Fischer, then Institute Directors of the Fraunhofer FIT and IME, respectively. Medical Data Space is a virtual data space allowing interactions among decentralized databases so as to support the secure exchange and linking up of medical and health-related data. Medical Data Space makes synergistic use of elements from the Industrial Data Space but is designed to handle the peculiarities of complex personal data, given that the source of medical data is often an individual person. Particular care must be taken with personal data so as not to infringe privacy rights. The aim is to increase the quality of diagnosis, preventative care and treatment, while devising new and better translational approaches to research. TM

Miniaturized malaria diagnostics: A BMBF-funded validation project

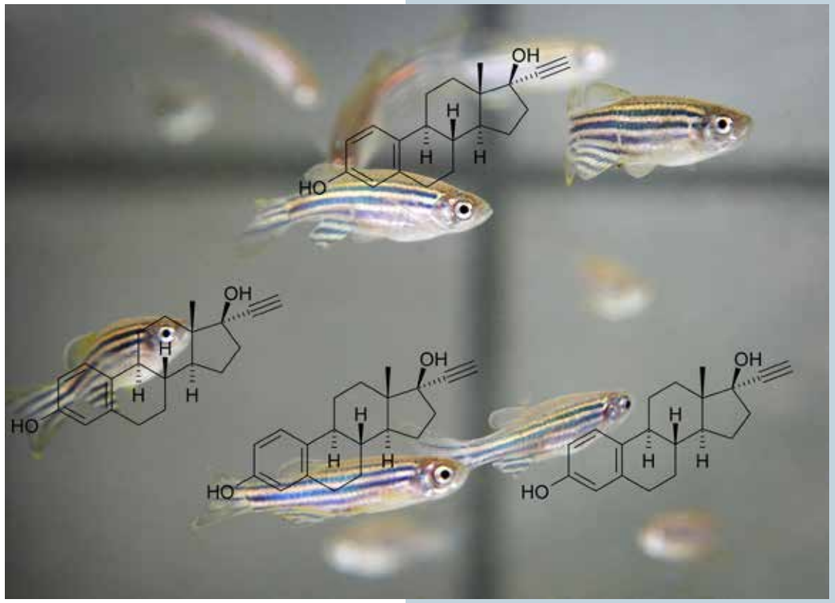
The NanoFRET research consortium coordinated by Rolf Fendel (Fraunhofer IME Immunotherapy department) has received 1.5 million euros in funding under the VIP+ initiative of the Federal Ministry of Education and Research (BMBF). The initiative aims to bridge the gap between academic research and the concrete applications of research findings. The Institute for Tropical Medicine in Tübingen and the Fraunhofer ISC are also members of this consortium. The NanoFRET consortium will use a modular approach that will be trialed for the development of malaria diagnostics, so that tailored diagnostic systems can be established in the future for many other diseases using the same strategy. The aim of the project is to validate a rapid *in vitro* diagnostics assay based on time-resolved fluorescence energy transfer (TR-FRET). A patient’s blood sample is mixed with nanoparticle-coupled antibodies that bind malaria-specific proteins with high specificity and affinity. Europium fluorescence on the nanoparticle produces a specific fluorescent signal when the antibody binds a malaria antigen, and this can be detected without interference from other substances in the sample. This obviates the need for lengthy sample preparation and paves the way for direct measurements using portable devices. This project is a successful follow-up to NAMADI, which received a grant from the Fraunhofer small businesses-oriented internal research program MEF. MB

Harnessing bioresources for the bioeconomy: A new research building and further LOEWE funding

Groundbreaking ceremony (from left to right): Prof. Dr. Alfred Gossner of the Executive Board of the Fraunhofer-Gesellschaft, Dietlind Grabe-Bolz, Mayor of Giessen, Volker Bouffier, Prime Minister of Hesse, Prof. Dr. Andreas Vilcinskas, Head of the Fraunhofer IME Bioresources project group, Prof. Dr. Joybrato Mukherjee, President of the Justus-Liebig University and Prof. Dr. Rainer Fischer, Senior Executive Director of the Fraunhofer IME until the end of 2016.

Insects produce a huge variety of active substances and thus present enormous potential for the diagnosis and treatment of diseases. Under the supervision of Andreas Vilcinskas, Head of the Fraunhofer IME Bioresources project group, Giessen has become a leading center for yellow biotechnology. Now the group is expanding in real terms: In the autumn of 2016, the groundbreaking ceremony for a new Fraunhofer research building was attended by Volker Bouffier, Prime Minister of Hesse. The researchers aim to isolate new active agents from insects, bacteria and fungi, for medicine, plant protection and industry. The 30-million-euro building is to be financed jointly by the Federal State of Hesse and the German Federal Government. The Fraunhofer IME Bioresources project group, set up in 2009 as a division of the Center for Insect Biotechnology (ZIB), enters its second funding period in 2017. The ZIB is supported by the LOEWE research program and during the period 2017-2019 it will receive a total of 18.2 million euros in funding from the State of Hesse. The greater part of this will be allocated to the Fraunhofer project group. Entomologist and Fraunhofer IME researcher Andreas Vilcinskas is also the Coordinator of the ZIB. AE BR

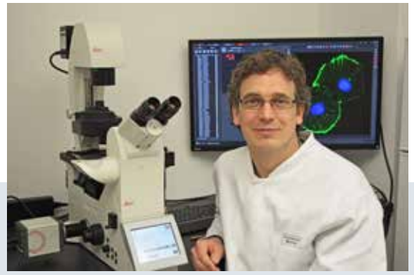
Endocrine disruptors: Strategies for environmental hazard and risk assessment



The Society of Environmental Toxicology and Chemistry (SETAC) Pellston Workshops® bring leading experts together from all over the world to discuss key environmental issues. Christoph Schäfers, Head of the Fraunhofer IME Applied Ecology Division, was invited to the 2016 workshop "Environmental Hazard and Risk Assessment Approaches for Endocrine-Active Substances" as one of 12 principal investigators, alongside 50 consultants and experts from regulatory authorities, universities and industry. The aim of the workshop, held in Pensacola, Florida, USA, from 31 January to 5 February, was to draw up objective recommendations based on current scientific findings for presentation to regulatory bodies and legislators. The hope is that such recommendations will help the authorities to decide whether a hazard-based or risk-based approach is most appropriate for the assessment of particular endocrine disruptors. The panel of experts also performed case studies of hormonally active substances representing a range of endocrine modes of action backed by extensive data at all levels of biological organization. These substances include ethinylestradiol, perchlorate, propiconazole, trenbolone, tributyltin and vinclozolin. The workshop highlighted areas of scientific uncertainty and recommended research and methodological approaches that led to a series of publications. A key conclusion was that an environmental risk assessment of endocrine disruptors is scientifically sound when environmental exposure, or effects (immediate or delayed) on relevant stages of the life cycle or on certain groups of living organisms can be ascertained and a dose/concentration-response relationship can be established, and when the relevant underlying results are available. AE BR

Well-positioned: IME scientists at SETAC Europe 2016

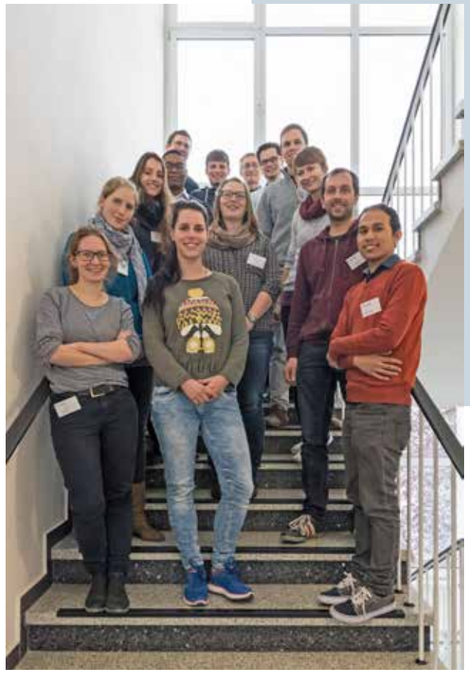
The Fraunhofer IME demonstrated its excellent positioning in the field of ecotoxicological research at the 26th annual meeting of the Society of Environmental Toxicology and Chemistry (SETAC) Europe, held in Nantes in May 2016. IME researchers contributed 30 talks and poster presentations. Udo Hommen sat on the conference scientific committee. He was also invited to present a talk at the meeting of the "Metals Advisory Group" on the potential use of mechanistic effect models for the environmental risk assessment of metals. Given current developments in plant protection product authorization, Hommen pointed out that although population and ecosystem models have been used on many occasions to analyze the effects of metals, they have not yet played a part in regulatory risk assessment. In this context, specific protection targets and relevant ecological scenarios will need to be defined first in order to apply effective models. AE BR



Promotion of young investigators at Fraunhofer: New Attract Group "Longaevitas" in Münster

The Fraunhofer "Attract" program supports young investigators in the development of their research ideas with practical applications in mind. Four new Attract Group Leaders set to work in 2016. The group "Longaevitas", launched at the Fraunhofer IME by 36-year-old Philip Känel, focuses on cross-species aging research. After completing his degree in Biotechnology in Münster, Känel moved to the University of Bern for his doctorate and returned to his home university in 2013. There he carried out research at the Institute of Plant Biology and Biotechnology led by Dirk Prüfer, who brought him to the IME. The focus of Känel's work is a special class of protein – the phosphatidylethanolamine-binding proteins (PEBPs) – that can be used to delay aging in plants, first discovered by IME researchers in tobacco. Certain PEBPs can also prolong the life of fruit flies and increase the division rate of cultured human cells. With his research team, Philip Känel hopes to determine the molecular mechanism of action of PEBPs and harness the potential of these proteins for applications such as the development of high-yielding crops and cell lines. MB

Doctoral Students' Day



Students working for a PhD in environmental sciences have been offered insights into the applied ecology research conducted by the Fraunhofer IME in Schmallenberg. In October, the Environmental Chemistry and Ecotoxicology Division of the German Society of Chemists (GDCh) held their third Doctoral Students' Day. In brief lectures, the young scientists gained an overview of the research fields covered by the Fraunhofer IME Applied Ecology Division. They also attended laboratory demonstrations of methods used for environmental analysis and the implementation of environmental risk assessment studies on potentially hazardous chemicals and plant protection agents. The laboratory tours were combined with presentations of doctoral work completed at the Fraunhofer IME. AE BR

New therapies for healthy aging: Hamburg starts collaboration with researchers from the Netherlands

Forming a strategic alliance for healthy ageing: Hamburg Minister of Science Katharina Fegebank and Vice-Mayor of Groningen Joost van Keulen, in the laboratory of the Fraunhofer IME ScreeningPort in Hamburg.

A strategic alliance has been established between the Fraunhofer IME ScreeningPort in Hamburg and the European Research Institute for the Biology of Ageing (ERIBA) at the University Hospital of Groningen, to accelerate the search for active pharmaceutical ingredients and biomarkers that will help people to age healthily. The German-Dutch research team aims to develop new bioactive substances that influence metabolism to promote healthy aging and combat cancer. "We are very excited about this new strategic alliance. It will allow us to bridge the gap between basic research and the development of pharmaceutical applications, particularly in the field of age-related diseases," says Ole Pless of the Fraunhofer IME ScreeningPort. The cities of Hamburg and Groningen are supporting the initiative financially, and Katharina Fegebank, Vice-Mayor and Minister for Science in Hamburg, has signed an agreement with Joost van Keulen, Vice-ayor of Groningen, to that end. TM

Second "All IME Summer Meeting" in Aachen

In 2016, the Fraunhofer IME employed 541 researchers and other personnel spread across six locations in Germany, making it more difficult than ever to maintain a clear view of the institute as a whole and to foster the lively exchange of ideas between departments. The first "All IME Summer Meeting" in 2014 invited the entire IME team to get together under the same roof in Aachen, and this was such a success that similar meetings are now planned on a regular basis. In September 2016, during a spell of glorious, late-summer weather, staff from Schmallenberg, Münster, Giessen, Frankfurt/Main and Hamburg met in Aachen and were offered a program of lectures, guided tours, an exhibition presenting project highlights, and something completely new: the first ever IME PhD science slam. IME doctoral students took to the stage and showed that well-known presenters of science programs are not the only ones that have what it takes to present complex facts in layman's terms and provide entertaining insights into research. We offer our warmest thanks to the many helping hands who worked to make this "family get-together" possible!

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