Fraunhofer

IME

FRAUNHOFER INSTITUTE FOR MOLECULAR BIOLOGY AND APPLIED ECOLOGY IME

CHANGE OF PERSPECTIVE

ANNUAL REPORT 2017/18

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Molecular Biotechnology

Molecular Biotechnology is the basis of a modern bioeconomy and contributes sustainably to the knowledge-based production and industrial use of renewable raw materials. On behalf of our customers, the Molecular Biotechnology Division develops 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. In recent years, we have established ourselves successfully in the research landscape and on the market due to our synergistic activities in the fields of green, red and white biotechnology. We offer our partners in academia, industry and the regulatory authorities a comprehensive research and service portfolio.

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 development of concepts for the sustainable agricultural production of active substances from plants. We also develop biological and biotechnological methods for the control of pest and vector insects and utilize insects to generate protein from organic waste.

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.

Symbol used in the annual report

MB Department
Molecular Biotechnology Division

Symbol used in the annual report

AE BR Department
Applied Ecology and Bioresources Division

Symbol used in the annual report

TM Department
Translational Medicine Division

SEEING THROUGH OTHER EYES

As researchers, we are accustomed to looking at problems from different perspectives: we are "seeing through other eyes" in order to achieve our goals. As members of the Fraunhofer-Gesellschaft, we value interdisciplinary cooperation between institutes, and build synergies through productive collaborations to maximize our potential. At the Fraunhofer IME, this principle applies not only to joint projects with other institutes, but also to teamwork across our three institute divisions of Molecular Biotechnology, Applied Ecology and Bioresources, and Translational Medicine, whose core competences cover a wide range of fields within the life sciences.

The strength of Fraunhofer IME lies in this broad spectrum of scientific and methodological expertise, enabling us to develop innovative and comprehensive solutions to the enormous challenges confronting society in areas such as sustainable agriculture, health and the bioeconomy. Our dedication to this approach has been validated again this year by the continued high-level funding received from public bodies and industry. For example, two new LOEWE centers have been funded by the state of Hesse, involving the Fraunhofer IME locations in Frankfurt and Gießen, focusing on biodiversity and neglected tropical diseases. Our locations in Aachen, Münster and Schmallenberg have secured funding for the conception phase of a group of projects in the framework of the national research strategy "BioEconomy" of the Federal Ministry of Education and Research (BMBF). And as an example of cooperation with industry, we have the new alliance between the Branch Lab ScreeningPort of the Fraunhofer IME in Hamburg and Evotec, where the aim is to push forward the development of new therapeutic agents by using pluripotent stem cells. We are very excited to see how these various projects unfold in 2018.

Our report section provides insights into selected research topics representing all six Fraunhofer IME locations. For example, we consider the cross-species aging research currently underway in the "Longaevitas" junior research group at our Münster location, page 41, and the analysis of nanoparticles in the environment, highlighting the importance of adequate detection methods for the assessment of environmental risks, as an example of current research at our Schmallenberg location, page 29. On page 37, we consider the search for alternatives to the frequently used but controversial chemical compound bisphenol A as an example of research currently underway at Fraunhofer IME Hamburg. Johannes Buyel from Fraunhofer IME Aachen explains, in the interview on page 45, the advantages of plants for the production of recombinant protein pharmaceuticals, and new research at Fraunhofer IME Gießen, aiming to tap the immense potential of insects as a source of protein, is discussed on page 33. Our special focus article on page 51 introduces the world of machine learning and explains how researchers at our Frankfurt location are advancing pain research.

Finally, we wish to thank all those who, through their continued commitment and support, have contributed to our success in 2017. We are most grateful to our business and research partners for their excellent and dependable cooperation, and to our staff for their dedication. We wish everyone involved an equally successful year in 2018.

Frankfurt, Schmallenberg and Aachen, March 2018

Prof. Dr. Dr. Gerd Geisslinger Prof. Dr. Christoph Schäfers Prof. Dr. Stefan Schillberg

THE INSTITUTE

»1«

CHANGE OF PERSPECTIVE

Links between the six Fraunhofer IME locations are growing ever closer. This Kanizsa Figure highlights our ability to fill in the gaps and see an object as a whole.

FRAUNHOFER IME PROFILE

Since the beginning of 2017, the Fraunhofer IME has comprised the three major divisions of Molecular Biotechnology, Applied Ecology and Bioresources, and Translational Medicine under the lead of Prof. Stefan Schillberg, Prof. Christoph Schäfers and Prof. Gerd Geisslinger. Prof. Geisslinger is the managing director of the institute in the three-member interim management team.

The Fraunhofer IME is a strong partner for contract research in the areas of pharmaceuticals, medicine, chemicals, the bioeconomy 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 2017, Fraunhofer IME collaborated with more than 100 national and international industrial clients and several international industrial associations, for whom confidential projects were conducted.

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 work is closely linked with basic research and we benefit from large international networks. 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.

At the end of 2017, the institute employed 527 personnel working at the Aachen, Münster, Schmallenberg, Gießen, Frankfurt and Hamburg locations. We have close ties with the Department of Biology and Biotechnology of Plants at the University of Münster, the Institute for Clinical Pharmacology at Goethe University, Frankfurt, the Department of Applied Entomology at the Justus-Liebig University Gießen, and the world's first Institute for Insect Biotechnology, founded in Gießen in 2016. 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

The Fraunhofer-Gesellschaft is the leading organization for applied research in Europe, conducting research at 72 institutes and research units at locations throughout Germany. The Fraunhofer-Gesellschaft employs about 25,000 personnel working with an annual research budget of 2.3 billion euros, more than two 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 for 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 eight such groups, representing different areas of the research and development market. They contribute to the corporate policy and implementation of the Fraunhofer-Gesellschaft's functional and financing model. Fraunhofer 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 with the business fields Medical Translational Research and Biomedical Technology, Regenerative Medicine, Healthy Foods, The New Potential of Biotechnology, and Process, Chemical, and Pesticide Safety.

The Fraunhofer Group for Life Sciences includes six Fraunhofer Institutes as well as one Fraunhofer research institution. Since February 2017, Prof. Horst-Christian Langowski (Fraunhofer Institute for Process Engineering and Packaging IVV) has been the Chairman with Prof. Krug (Fraunhofer Institute for Toxicology and Experimental Medicine ITEM) serving as deputy.

https://www.lifesciences.fraunhofer.de/en.html

Institutes or institute departments with complementary expertise cooperate in Fraunhofer Alliances to facilitate customer access to the services and research capability of the Fraunhofer-Gesellschaft. 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:
https://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 with 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/corporate-responsibility.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 2017, 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

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

Ministerialrätin 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 20, 2017, at the elbdeck in Hamburg. The Executive Board of the Fraunhofer-Gesellschaft was represented by Dr. Lorenz Kaiser.

BUSINESS FIELDS MOLECULAR BIOTECHNOLOGY

Bioproduction and Industrial Biotechnology

The business field Bioproduction and Industrial Biotechnology 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 microorganisms and animal cells through to plant cells. Here 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. Fraunhofer 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 bulk chemicals and fuels such as isopropanol, isoprene and hexanol, through to plant-based polymers such as 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 and improvement of plant traits, crops and enabling technologies to increase 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 such as genome editing and TILLING. The departments and project groups involved in this business field focus on precision breeding techniques, the discovery and 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 agribusiness companies.

Production of Recombinant Proteins

The Fraunhofer 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 microorganisms, 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, agriculture and cosmetic sectors, and for technological applications. In addition, the institute 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.

MB

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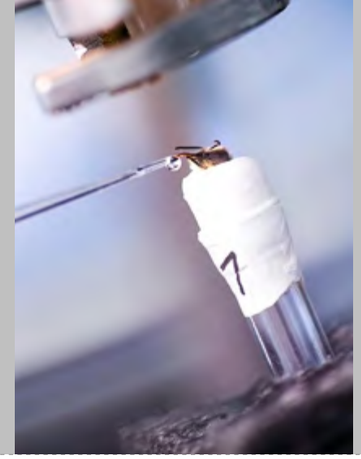
Molecular Biotechnology: Research, Development and Services

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



BUSINESS FIELDS APPLIED ECOLOGY AND BIORESOURCES

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.

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 take existing methods used to analyze the metabolism of plant protection products in crops and farm animals and adapt 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.

Sustainable Agricultural Production of Substances

We use local factors such as soil quality, microclimate and infrastructure to assess the potential of agricultural areas for specific uses. We consider both structural and material determinants in such evaluations, combining species range maps from nature protection agencies with probabilistic risk assessments for plant protection products 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.

Bioresources for the Bioeconomy

We use groups of organisms with great biodiversity as bioresources, including insects, bacteria and fungi. We combine innovative technologies and established platforms to isolate and characterize natural substances, and to evaluate their potential for use in medicine, plant protection and industrial biotechnology. In this way, novel molecules are identified to develop as antibiotics or ingredients for the food and feed industry, such as flavoring agents, preservatives and enzymes, leading to 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.

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 and 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, for example RNA interference and the sterile insect technique. We also use insects for the conversion of organic waste into proteins and fats for the food and feed industry.

Applied Ecology: Research, Development and Services

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

Bioresources: Research, Development and Services

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

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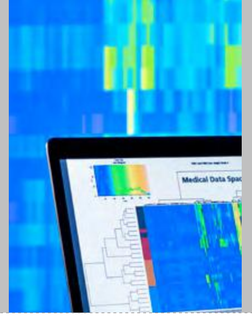

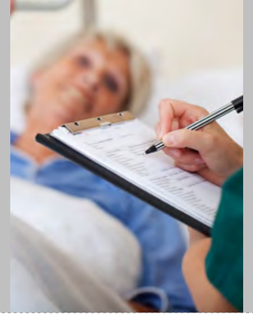

BUSINESS FIELDS TRANSLATIONAL MEDICINE

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.

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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.

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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 Fraunhofer ScreeningPort in Hamburg has applied this expertise in bioinformatics and has set up the DataScientist 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.

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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 and subgroups to be treated, combined with an individual, adaptive study design, employing the latest statistical and biomedical analysis. The new Quality by Design approach implemented at our Frankfurt location 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 characteristic of this group.

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Translational Medicine: Research, Development and Services

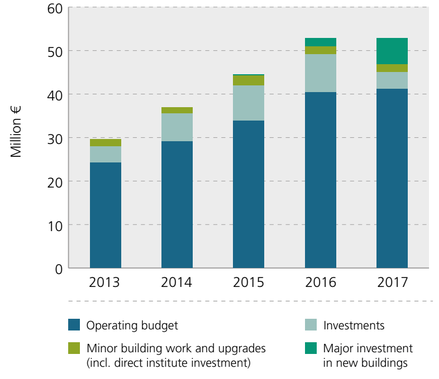
http://www.ime.fraunhofer.de/content/dam/ime/de/documents/Publikationen/Research-Development-Services_Translational-Medicine.pdf

INSTITUTE DATA

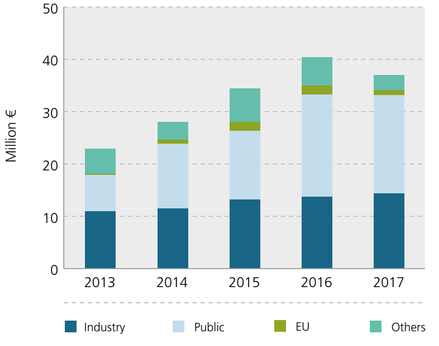
Budget

In 2017, the Fraunhofer IME operating budget increased by 2% compared to 2016, reaching 41.1 million euros. A further 4 million euros was invested in equipment. There was a marked increase in Fraunhofer IME building activity (7.7 million euros), the main project being preliminary construction work on the new institute facilities in Gießen. The budget included 77.1% from external revenues, equivalent to 89.7% when the largely state-funded locations in Gießen and Frankfurt are taken into account. The industry revenues rose again to a current level of 14.2 million euros. This represents 45.6% of total revenues or 34.6% when Gießen and Frankfurt are included. Fraunhofer IME has thus achieved an excellent outcome for the year 2017 in terms of key performance figures for the Fraunhofer-Gesellschaft.

Total budget of the Fraunhofer IME, Germany



External financing of the Fraunhofer IME, Germany



INSTITUTE MANAGEMENT AND LOCATIONS

Information as of January 1, 2018

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(interim position)

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Prof. Dr. Stefan Schillberg
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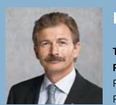
TRANSLATIONAL MEDICINE DIVISION

Head: Prof. Dr. Dr. Gerd Geisslinger

Location Frankfurt



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Fraunhofer Cluster of Excellence "ImmuVision"

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Fraunhofer Foundation Project

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

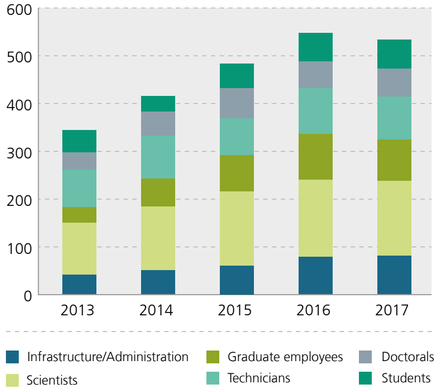
Special promotion of young investigators: Fraunhofer Attract Groups

AM **Molecular Biocontrol**
Prof. Dr. Marc F. Schetelig

MB **Fast Protein Expression and Purification**
Dr. Johannes Buyel

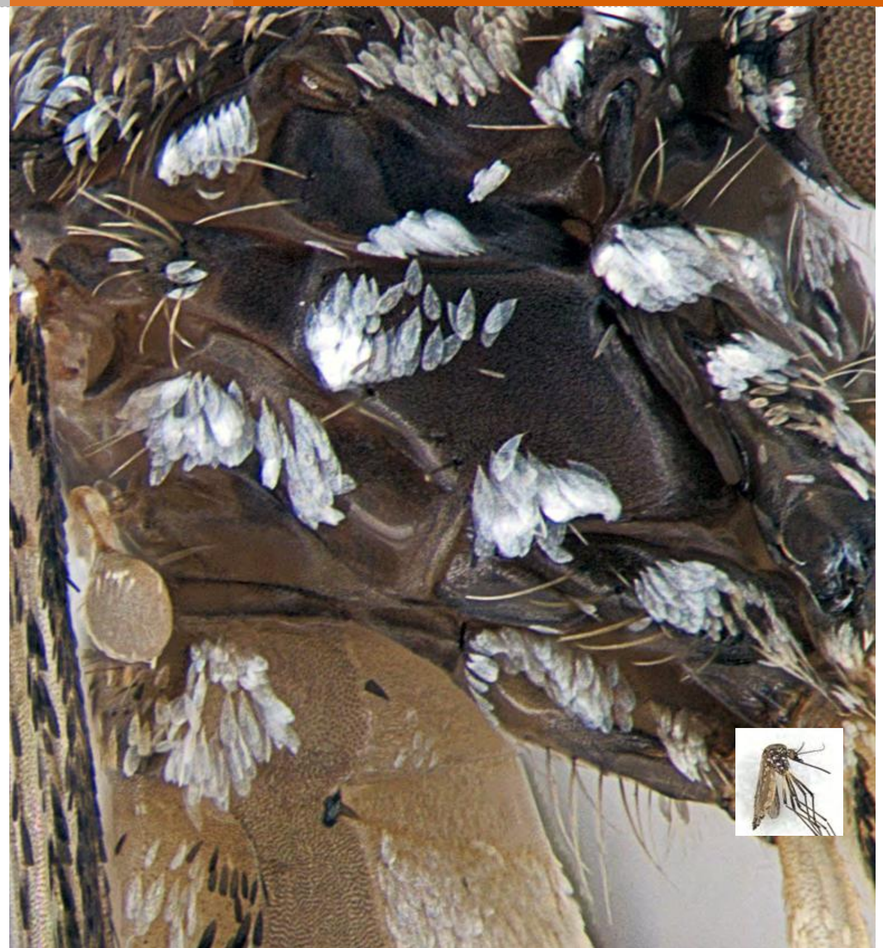
MB **Longaevitas**
Dr. Philip Känel

Employees of the Fraunhofer IME, Germany



Personnel

At the end of 2017, 527 personnel were employed at the Fraunhofer IME locations in Aachen, Münster, Schmallenberg, Gießen, Frankfurt and Hamburg. This slight reduction (2.6% lower than 2016) reflects the restructuring measures implemented in Aachen and Gießen. The number of staff employed in Schmallenberg and Frankfurt rose over the same period. The percentage of women working at the Fraunhofer IME in 2017 was 52.4%.



REPORTS ON IME RESEARCH

Environment:
Tracking down nanomaterials

Insects:
Future suppliers of food and raw materials?

Testing alternatives to bisphenol A:
Assessing the endocrine risk

Applied aging research:
The rewards of aging

»2«
CHANGE OF PERSPECTIVE

What is this? A bird? A designer dress? Is it part of a plant? No – both are shots of a yellow fever mosquito. The technical equipment at the Fraunhofer Institute offers some astonishing insights.

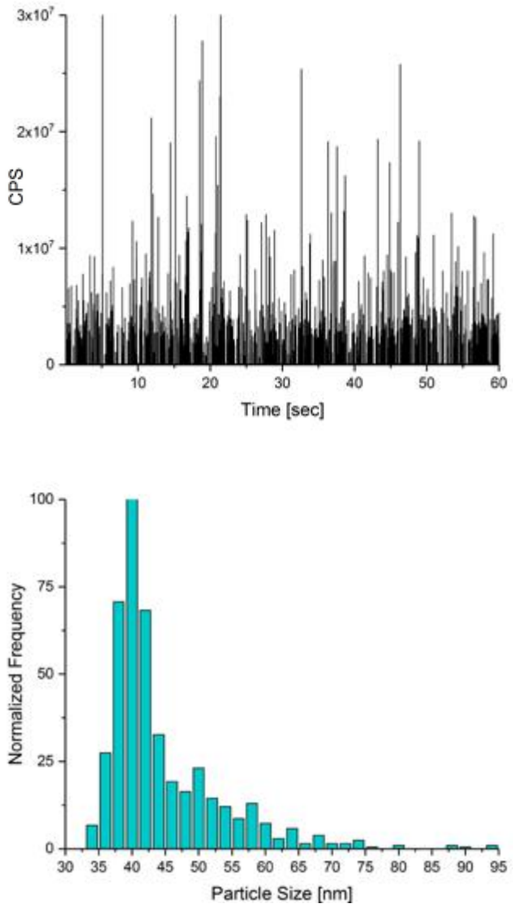
ENVIRONMENT: TRACKING DOWN NANOMATERIALS

Boris Meisterjahn and Nicola Schröder operating the AF4 system (asymmetric flow-field-flow-fractionation method for the analysis of nanoparticles)

Thanks to their special properties, nanomaterials are now an essential feature of everyday life, and they are found in many consumer products, medicines and fuels. However, their widespread application has consequences, particularly due to their potential release into the environment. The detection of environmental nanoparticles is challenging. The Fraunhofer IME is developing innovative methods for the detection of minute amounts of nanomaterials in the environment.

Characterization of nanomaterials: Multiple challenges for science

Nanomaterials find their way into many environmental systems throughout their lifecycle, but especially when they are used and discarded. They can end up in the aquatic environment via wastewater treatment plants and can be spread over the ground in sludge used for agricultural purposes. This exposes animals and plants to potential harm. To assess the potential risk of nanomaterials, methods are needed to detect them in environmental samples. Furthermore, techniques are needed that can be applied in standardized laboratory trials to establish the concentration and size at which nanomaterials have modifying effects on living organisms.



Particle size distribution determined by spICP-MS in a solution of silver-spiked mussel tissue after enzymatic digestion.

Upper chart:
Time-resolved analysis of the silver present in the solution. Visible "intensity spikes" (in counts per second, CPS) are derived from single particles.

Lower chart:
Calculated normalized particle size distribution. The particle size distribution of the spiked silver nanomaterial is preserved.

The comprehensive characterization of nanomaterials on this scale presents a scientific challenge at many levels. As a doctoral student and laboratory manager, Boris Meisterjahn (from the Department of Ecological Chemistry) explains: "It is necessary to determine both the concentration of the particles and also their size distribution. In most cases, the particles must be transferred to an aqueous suspension for this purpose. Samples should be prepared in such a way that the particular properties of the nanoparticles are retained, because, further to their concentration, their size is a key determining characteristic. This can be achieved through the use of gentle procedures such as colloidal extraction. In the case of biological samples and tissues, the targeted enzymatic breakdown of the biological matrix may be suitable. We need very sensitive methods for characterization because we expect the concentrations of these particles in the environment to be very low." For inorganic materials, a promising approach is single-particle inductively-coupled plasma mass spectrometry, which is shortened to spICP-MS. Whereas conventional ICP-MS techniques can be used to distinguish and precisely quantify metals based on their different weights, spiCP-MS can also count and quantify individual particles in aqueous suspensions. Gentle separation techniques such as asymmetrical flow-field-flow fractionation, which allows particles to be separated according to their size, can also be used to analyze suspensions. Coupled to an ICP-MS unit, this allows the particle size distribution to be determined, at the same time revealing the elementary composition.

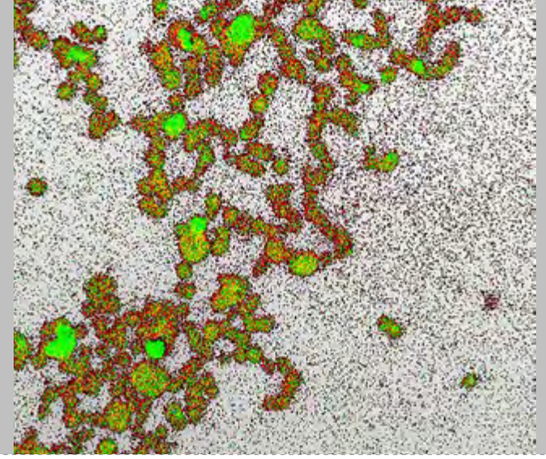
Elemental fingerprinting to detect high background levels of nanomaterials in the environment

A challenge is that soil and sediments contain naturally occurring colloidal particles that appear very similar in composition to synthetic nanomaterials. For example, in order to detect synthetic, nanoscale cerium dioxide in soil, these particles must be distinguished from a natural background of cerium-containing soil particles. One promising approach is to exploit the chemical purity of the synthetic particles, which tends to be higher than that of natural particles. Furthermore, the naturally occurring particles often contain similar ratios of certain elements, described as the "natural element fingerprint". This differs from the ratios found in synthetic nanomaterials. By comparing the two fingerprints, i.e. by measuring the element-to-isotope ratio, conclusions can be drawn about the presence and quantities of synthetic nanomaterials in a sample.

Despite the modification of nanosilver in wastewater treatment plants, harmful effects remain

In wastewater treatment plants and during sewage sludge treatment, silver nanomaterials are transformed into silver sulfide. This transformed silver nanomaterial enters the soil when sludge is applied as agricultural fertilizer, and it is necessary to ask whether the modified material is taken up by soil organisms in the same manner as the original manufactured product. It is also important to know whether this material is harmful

Species such as the common mussel filter water, which enables them to take up substances. Mussels can therefore be used as model organisms to investigate the bioaccumulation of nanoparticles.



TEM image of sulfidized silver nanomaterial.
Green represents silver, red represents sulfur.

to the organisms. To answer these questions, Dr. Marco Kraas, a former doctoral student in the team led by microbiologist Dr. Kerstin Hund-Rinke, conducted experiments on model wastewater treatment plants spiked with silver nanomaterials. After processing, the sludges were spread over the ground and long-term trials in the laboratory were used to investigate their effects on microorganisms in the soil. Another series of long-term laboratory trials was conducted on silver nanomaterials that had already been modified. Further field studies took place in parallel to these trials, aiming to characterize the accumulation and effects of silver nanoparticles under natural conditions. Dr. Hund-Rinke describes the findings as follows: "We found that although the wastewater purification process transforms the silver to silver sulfide, which is almost indissoluble, subsequent use of the sludge on the ground can bring about toxic effects in soil microorganisms over the long term."

Looking back: The presence of nanomaterials in mussels with a lifespan of several decades

The potential accumulation of nanomaterials in aquatic organisms is another issue demanding investigation. "Mussels are particularly interesting animals from our point of view because they are filtering organisms and therefore take substances directly from the water", explains Dr. Burkhard Knopf, Laboratory Manager in the Environmental Specimen Bank and Elemental Analysis Department. The Federal Environmental Specimen Bank, located at Fraunhofer IME in Schmallenberg, has a store of mussel samples, collected systematically over a period of several decades and kept at very low temperatures. These form a valuable archive for retrospective observations. The long-term archive can answer questions such as whether nanomaterials accumulate in mussels and can also reveal certain trends. For example, Fraunhofer IME chemists are investigating the nanomaterials titanium dioxide, silver and cerium dioxide. The biological components of tissue homogenates are broken down mainly by enzymatic hydrolysis, and inorganic components, including the particles under investigation, are retained in the resulting solution. The remaining particles are then analyzed by spICP-MS. "To verify the basic method, we first added synthetic silver, titanium dioxide and cerium dioxide particles to the tissue samples, and the corresponding particles and their size distribution could indeed be determined in most cases", explains Meisterjahn. The methods developed by Fraunhofer researchers are currently being used to study the stored mussel samples. The work is not yet finished, but has already revealed some promising preliminary results.

In addition, newly developed test systems can be applied to mussels or other model organisms to measure bioaccumulation – the build-up of substances in the food chain – over time. A test installation has been set up in the Department of Bioaccumulation and Animal Metabolism in which organisms can be subjected to a constant level of nanoparticle exposure despite the unstable nature of nanomaterials. In the first series of experiments with various types of particle, the new test system was able to measure the accumulation of nanomaterials in the test organisms.

To conclude:

With various well-established analytical procedures, we can now detect the smallest amounts of nanomaterials in the environment, see how they spread, and look at how they behave over time. This allows us to determine the environmental compartments in which nanomaterials accumulate, as well as their stability and their subsequent transport. We can also determine their potential for enrichment in specific environmental media or particular organisms. This will allow us to estimate the potential risk to the environment posed by nanomaterials.

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INSECTS: FUTURE SUPPLIERS OF FOOD AND RAW MATERIALS?

Prof. Vilcinskas is fascinated by the many opportunities of insect biotechnology.

The black soldier fly – a promising candidate for the bioconversion of biological waste.

The world population is growing steadily, and with it, the global demand for protein. Conventional strategies to meet this demand are no longer sufficient: production levels are already reaching their limits, and the production of meat as the classic source of protein is already leaving environmental scars with far-reaching ecological consequences. The time has come to turn to alternative sources of protein.

Proteins are required for human and livestock nutrition. The global increase in meat consumption cannot be addressed sustainably, and vast areas of rainforest are currently being cleared for soya cultivation, chiefly for the production of animal feed. In Brazil alone, about 156,000 square kilometers of rainforest was destroyed between 2002 and 2012 to make way for soya plantations. In the oceans, the growing number of fish species that have been overfished will lead to dwindling yields for fisheries. Prices for fishmeal are already rising. The discrepancy between protein production levels and requirements for the animal feed market is widening and is now described in the literature as the "protein gap". Experts predict that the global demand for nutritional protein will exceed available protein sources by 100 million tonnes in 2025 and by 300 million tonnes in 2050.

Intensive farming causes massive ecological damage

Ensuring global food supplies is an urgent humanitarian need, and is also a geopolitical challenge requiring investment on a huge scale. For example, meat production in Germany is booming in response to the need to guarantee protein supplies, and Germany is now one of the top exporters of meat worldwide. But growing animal stocks have a massive impact on the environment: the spreading of slurry and manure over fields increases the nitrate load in the soil and groundwater. In November 2016, Germany was sued by the EU for groundwater pollution with nitrates, which have been steadily accumulating for many years. If the allegation is upheld, Germany will face daily fines of hundreds of thousands of euros.

A similar nutritional gap is expected to arise with the future demand for oils and fats. In the case of plant fats, the key source is the oil palm tree. From 2014 to 2015, 61 million tonnes of palm oil were produced worldwide. The extensive oil palm plantations in Indonesia, Malaysia and other countries are primarily to blame for the shrinking rainforests there. The demand for palm oil is on the rise, and its use for the production of biodiesel and as an ingredient of foods and cosmetics is steadily increasing. Destruction of rainforests to make way for oil palm plantations has already come under strong public criticism, not only due to its impact on climate change but also the threat to biodiversity.

Bioconversion: Insects in the life cycle of the bioeconomy

Insects offer enormous potential for the bioconversion of biological waste and as a source of proteins, fats and other industrially valuable substances. In this regard, companies that harness the benefits of insects could help to close the nutrition gaps and also create value from other products. The Branch for Bioresources of the Fraunhofer IME in Gießen is working intensively on the development of new technologies to use insects for bioconversion, and to exploit them as a resource for the bioeconomy. The translational research strategy of the Gießen group headed by Prof. Andreas Vilcinskas is to explore the potential of diverse insect species for bioconversion. Their main focus is *Hermetia illucens*, the black soldier fly. This species is particularly well suited for the production of valuable products such as proteins and fats from organic waste such as manure from livestock farming. These in turn can be used as animal feed for livestock and in aquaculture. Insects therefore support the concept of a circular bioeconomy.

The use of insects for the production of animal protein via bioconversion is not only energy efficient and inexpensive, it is also truly sustainable. Tonnes of insects can be bred in so called insect reactors. The enormous potential of insect farming has been recognized and the insect breeding business is developing into one of the global markets of the future.

Insect-based production processes are more efficient and better for the environment

Compared to conventional livestock farming, insects offer a number of economic and ecological advantages. They require little space. The production of one tonne of soya protein requires about one hectare of arable land. The same area of land could yield up to 150 tonnes of insect protein from black soldier flies. Another advantage is that insect farming is remarkably scalable, being equally well suited to the small farm scale all the way up to an industrial production plant.

This sustainable approach helps to protect the environment and the climate: insects need far less water than livestock, they

Rain forests are under severe threat worldwide to provide land for soya cultivation and feed production.

Larva of the black soldier fly *Hermetia illucens* – already used as animal feed.

produce no climate endangering methane and, compared to animal husbandry, they generate a thousand times less CO_2. Insects can be bred on an industrial scale without the use of antibiotics, thus slowing the development of resistant pathogens. The insect species used by industry do not transmit diseases to humans or to livestock, and pose no threat to biodiversity.

This approach is particularly sustainable because insects make closed-loop recycling possible. They efficiently transform organic agricultural waste from farming or the food industry back into recyclable materials. In addition, the production of proteins and fats from insects releases other raw materials that are of value for industrial applications, such as chitin and chitosan for use in the food and cosmetics industries. The innovative processes open up new value chains. Even excrement can be put to use, as an excellent organic fertilizer or as raw material for biogas plants. The energy-neutral production of insect proteins is therefore a real possibility. Conventional livestock farming can also benefit from insect farming, because feeding animals on insect proteins has a positive effect on livestock health.

Branch for Bioresources – well positioned for future markets

The benefits discussed above have promoted interest in the industrial use of insects worldwide, leading to increasing acceptance and investment. The Branch for Bioresources of the Fraunhofer IME is working closely with many global players in this new branch of industry.

Since 2017, when the EU granted authorization for the use of insect proteins in aquaculture, the Fraunhofer IME Branch for Bioresources has been collaborating with the French company Ynsect and with Prof. Klaus Eder, Head of Animal Nutrition at the Justus-Liebig University in Gießen. The academic partners and the French company specializing in the production of proteins from mealworms are together investigating the suitability of insect proteins for animal feed.

Given the leading role played by the Branch for Bioresources in the field of insect biotechnology in Germany, the INSECTA 2018 conference will be held in Gießen. This is one of the most important conferences focusing on "Insects for Food and Feed" and the Fraunhofer IME in Gießen is one of the organizers.

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TESTING ALTERNATIVES TO BISPHENOL A: ASSESSING THE ENDOCRINE RISK

A cell-based reporter gene assay is carried out to investigate the hormone-like potential of BPA alternatives.

Bisphenol A (BPA) is a chemical with a dubious reputation. As a feedstock for the synthesis of plastics, BPA is found in many everyday products such as food packaging and medical devices. BPA is structurally similar to certain hormones, and therefore causes adverse effects in humans and poses a risk to other species in the environment. The search for alternatives has begun, but more detailed investigations are needed.

Most water bottles are BPA-free because suppliers use alternatives. However, the harmlessness of these replacements has not always been confirmed.

BPA is a diphenyl-methane derivative which is used as a feedstock for the production of plastics, including polyesters and epoxy resins. Its widespread use in the polymer industry means that humans and other species are exposed to high levels of this compound. Its use as a color developer in thermal paper is one of the most important exposure risks because in this context BPA occurs in its non-polymerized form and is released directly.

Living organisms take up BPA via their food or from soil and water, allowing the chemical to accumulate in many tissues and body fluids. In humans, BPA has been detected in serum, urine, placental tissue, blood from the umbilical cord, and breast milk.

BPA: like a hormone, and with no real substitute

Due to its chemical structure, BPA behaves like a hormone, causing harm to humans and other species in the environment. The negative effects in humans can include neuronal damage, adverse effects on the circulatory and immune systems, reproductive dysfunction and developmental disorders. BPA also has negative effects in many other species. Its harmful influence on the hypothalamus-pituitary-thyroid and hypothalamus-pituitary-gonad systems in vertebrates has been confirmed in numerous studies.

Given the high levels of BPA in certain materials, the numerous pathways by which it can be released into the environment, and its proven harmful effects on reproduction and development, restrictions have already been imposed on the production and application of BPA in North America and the EU. It is now classified by the European Chemicals Agency (ECHA) as a substance of "very high concern".

Growing public concern and restrictions imposed by the regulatory authorities have lent urgency to the development and production of BPA alternatives. Substances with structures similar to BPA are already used in the production of polycarbonate plastics and epoxy resins. For example, the BPA analog bisphenol S (BPS) is used in epoxy adhesives, metal coatings and thermal paper. It differs only slightly from BPA, the central dimethyl-methylene group being replaced by a sulfone group, and for this reason there is concern that BPS may also have endocrine effects. For many other BPA alternatives, some of which are released into the environment in large quantities, there is still no convincing evidence that they have no impact on the endocrine system. No absolutely harmless alternative to BPA has yet been identified.

The German Environment Agency takes a closer look at the potential endocrine risk

The Applied Ecology division of Fraunhofer IME in Schmallenberg has been working for many years with the German Environment Agency (UBA), but the current joint project is the first UBA collaboration involving the Branch Lab ScreeningPort of the Fraunhofer IME in Hamburg. The Hamburg researchers were commissioned by the UBA to investigate the endocrine activity of potential BPA substitutes using a series of biochemical and cellular test systems. The aim was to identify and analyze substances with potentially harmful endocrine effects that are known to be released into the environment in large quantities.

The first step was a wide and comprehensive search for potential BPA substitutes, covering not only the scientific literature but also the patent register. An additional semi-automated literature search method, developed by the IME ScreeningPort, was also applied. These techniques allowed the researches to trawl through several public databanks for publications on BPA and its potential replacements. The combination of these search methods finally led to the identification of around 35 candidate BPA substitutes used in environmentally relevant products.

Every day we hold sales slips in our hands. The thermal paper they are made of is processed using unpolymerized BPA, a substance of “very high concern”. Innocuous alternatives are not yet available.

The German Federal Environment Agency keeps an eye on BPA. The Fraunhofer IME studies assess the risk of BPA alternatives.

Analytical cascades to determine the endocrine risk of BPA substitutesn

The hormonal potency of the selected BPA substitutes was determined by receptor binding analysis. The investigations focused on the human nuclear receptors, androgen receptor and the estrogen receptors α and β. Nuclear receptors are ligand-modulated transcription factors that regulate the expression of receptor-specific genes. When an activated substance binds to a nuclear receptor, it promotes the binding of so-called coactivator proteins, thereby triggering gene expression. On the other hand, the binding of an inhibitory substance to the nuclear receptor prevents its interaction with coactivator proteins and the expression of target genes normally activated by that nuclear receptor is no longer possible.

The IME ScreeningPort devised experimental tests on the selected BPA substitutes to establish their regulatory effects. This involved sequential cascades of biochemical and cell-based assays, including fluorescence polarization, time-resolved fluorescence resonance energy transfer (TR-FRET) and reporter gene assays, to measure the binding of substances to the nuclear receptors and to evaluate their impact on receptor-mediated gene expression.

Binding to nuclear receptors does not necessarily affect gene expression

The Hamburg research team was able to show that many BPA substitutes can bind with high affinity to the nuclear receptors, but in all cases the affinity was lower than that of the natural ligands, such as estrogen. Interestingly, several test substances displayed a stronger affinity for the three receptors than BPA. The investigations also revealed that not all high-affinity ligands promoted coactivator binding and subsequent gene expression. One of the BPA substitutes caused a strong induction of gene expression at very low concentrations, but only when interacting with estrogen receptor α, whereas all the others were required in high concentrations to trigger gene expression via this receptor. In contrast, several of the substances triggered gene activation via estrogen receptor β at concentrations up to 20 times lower than BPA. The EC50 values, i.e. the average effective concentrations of these substances, were still several orders of magnitude higher than those of the natural ligands.

The study identified several BPA substitutes that, unlike BPA itself, appear to have no adverse effects on the three human nuclear receptors, and could therefore be suitable as BPA replacements. Amphibians and fish are highly sensitive to chemicals, particularly endocrine disruptors, and the endocrine effects of the BPA replacements will now be investigated using suitable test organisms. A paper presenting the results of this study is in preparation.

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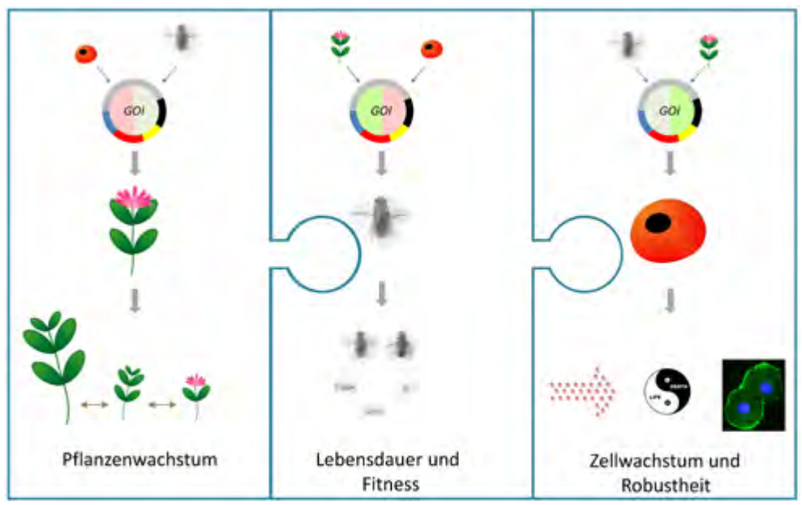
APPLIED AGING RESEARCH: THE REWARDS OF AGING

Dr. Philip Känel takes a new perspective on aging by investigating how foreign genes influence the aging process.

Aging refers to the changes that take place in an organism over time, including the visual signs of aging and the underlying cellular and molecular changes. Dr. Philip Känel and his junior research team "Longaevitas" in Münster are getting to the heart of the matter. Taking investigations a step beyond standard biomedical lines of enquiry, they are investigating the effects of foreign genes relevant to the aging process.

The molecular basis of biological aging is one of today's hottest research topics, especially the identification and functional characterization of genes that are causally linked to a long and healthy life. The corresponding gene products can increase the yields of our crops and minimize age-related diseases in humans.

In plant biology and biomedicine, researchers focus on unraveling the molecular functions of such genes. However, true to the old adage "Let the cobbler stick to his last", this research has been almost entirely confined to specific model organisms in each specialist field.



Genes from flowering plants, insects and mammals have been expressed in a mutually heterologous manner in order to investigate their specific effects on plant growth, the lifespan and fitness of flies, and the growth and robustness of mammalian cell cultures.

Looking at aging in a more holistic manner can reveal some unexpected similarities in diverse species. At the molecular and cellular levels, parallels appear between the simplest unicellular life forms such as yeasts, and more complex organisms such as mammals and higher plants. This is the cutting edge at which the researchers in Münster are working. Their aim is to find out whether aging processes can be directly influenced by the integration and expression of related but foreign genes.

Aging research crossing species boundaries

Why is the aging process in diverse species a topic of such burning interest? The Münster researchers have the answer: Whether microorganism, plant or animal, every organism is subject to continuous regulation to ensure the correct functioning of its specialized cells, tissues and organs. Signaling proteins activate this control mechanism and bring about the specific reactions that are necessary. By substituting one of the organism's own signaling proteins with a similar protein from another species, the functionality and specificity of that protein family can be investigated. For applied research, this opens up the possibility of discovering novel and precise target structures, although in many cases, the host organism recognizes alien proteins as foreign and breaks them down.

Even so, the Münster team has successfully identified some key determinants of aging, including those responsible for growth, maturation and longevity. The researchers have achieved this by the cross-species expression of a strongly conserved protein family. In their modified form, foreign proteins steer known signaling pathways in a new direction and thereby influence the specific molecular and cellular changes that underlie the process of aging.

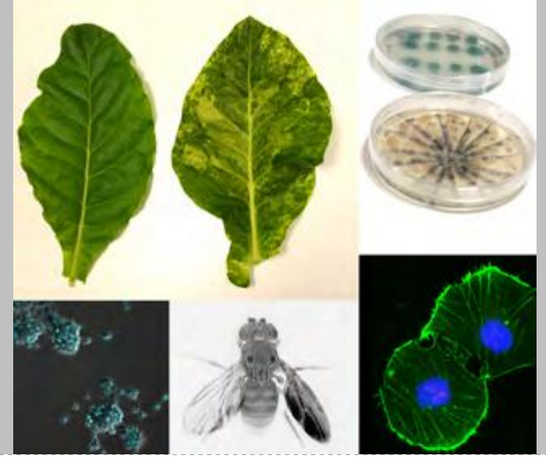
Foreign signaling proteins optimize growth and robustness in mammalian cells

The research group in Münster has expressed certain signaling proteins from the model tobacco plant *Nicotiana tabacum* and the fruit fly *Drosophila melanogaster* in mammalian cells. Not only do the foreign proteins induce a response, they also set off other molecular processes that the native proteins do not trigger. In some cell lines, the heterologous expression of signaling proteins leads to changes in growth, whereas in others the cells become more robust by developing greater resistance to programmed cell death.

This control of growth and longevity can be put to commercial use. Unlike microbial cells, which are remarkably scalable, gene expression in mammalian cells is often limited when the process is scaled up. Cell line development aims not only to optimize product expression but also to achieve rapid growth and increased robustness, which now seems possible.

The researchers aim to transfer the greater robustness and growth capacity of the Münster cell lines to the mammalian expression systems most widely used in industry, namely the Chinese hamster ovary (CHO) and human embryonic kidney

Heterologous gene expression in tobacco plants involves a commonly used technique for the regeneration of plants from undifferentiated callus cells. The emerging plant shoots are nurtured for several weeks in sterile culture in order to obtain regenerated plants for analysis.



The diverging effects of the various signaling proteins obtained from the tobacco plant or from flies are manifested in a range of experimental models – not only at the molecular level but also in modified growth or morphology.

(HEK-293) lines. As soon as the most effective signaling proteins for these cell lines have been identified, the corresponding genes will be stably integrated into the genome of the new target cells to generate high-performance lines with reproducible characteristics.

With plant genes, you can live longer – at least if you're a fly!

The aging process has been investigated using diverse model organisms, ranging from simple unicellular microbes, which are particularly suitable for observing cellular changes, to short-lived model organisms such as the roundworm or fruit fly. The Longaevitas research team in Münster has extended the lifespan of the fruit fly significantly by expressing a signaling protein native to plants. The effects already noticeable in mammalian cell lines are seen much more clearly in the fruit fly: Not only does the heterologous protein extend the lifespan of the fly, but the effect is far more marked than the expression of the fly's native version of that protein.

Now the research group is looking for an explanation for this phenomenon. Foreign signaling proteins can set different downstream mechanisms in motion compared to those triggered by native proteins. These signaling proteins usually activate signal cascades by binding to enzymes and other protein complexes in the cell. In the long-lived flies, several specific binding partners and target genes for the heterologous signaling proteins have been identified. The task is now to assess their potential as target structures for therapeutic intervention against age-related, degenerative diseases in humans.

New factors for optimizing crop yields

Higher crop yields are commercially beneficial because they increase productivity without expanding the area under cultivation. Aging, and developmental processes such as senescence, provide starting points from which to increase growth in plants. The blossoming of certain flowering plants has already been mechanically or genetically delayed in order to lengthen their growth phase and produce more biomass. In this field of research, the point of interest is not the aging of the plant but the regulatory mechanisms involved in switching from the growth phase to the reproductive phase. This is another line of research for the team in Münster. Here, the goal is to find out which regulatory mechanisms are responsible for producing the non-flowering and thereby longer-living phenotype in their model tobacco plants. Knowledge from the work on mammalian cells and fruit flies is useful because many genes and proteins that control growth and development in animals also play similar roles in plants, but despite their potential they have hardly been investigated at all. Using databank searches, the Münster researchers have already identified plant versions of the animal proteins found to interact with the heterologous plant signaling proteins in mammalian cell lines and the fruit fly. The Münster team is currently establishing the role of these proteins in plant growth and development. One newly discovered protein family in plants is highly promising and may provide a strategy to influence the growth of crops.

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IN DIALOG

An interview with Dr. Johannes Buyel

Background

Johannes Buyel has a doctorate in biotechnology and is a bioprocess engineer. He has maintained close ties with the Fraunhofer IME since his student days. His work focuses on the development and optimization of processes for the production of biopharmaceuticals. He leads the junior research group FAST-PEP at the Fraunhofer IME in Aachen and, together with Jürgen Drossard, also heads the Department of Integrated Production Platforms. His aim is to develop computer simulations of complex production processes. These theoretical models allow the better characterization of processes, so they can be controlled more effectively.

»3«
CHANGE OF PERSPECTIVE

The classic image: Two people talking, either side of a vase. Wait a minute – isn't that Dr. Johannes Buyel?

PLANTS ARE THE BEST BET: NEW MEDICINES FROM COMPUTER MODELS AND TOBACCO

For the production of complex substances, Dr. Johannes Buyel is placing his bets on plants. His team's work on a mistletoe toxin illustrates the point. They first isolated the toxic protein in its active form from tobacco plants. The same toxin produced in bacteria is initially inactive and needs to be activated in a series of further steps. In developing production processes, Dr. Buyel takes a comprehensive approach that considers both the theory and the practice. He is not satisfied with establishing the optimal experimental conditions for the synthesis of a substance by trial and error in the laboratory. With his computational models, he aims to determine the best conditions for the highly complex processes in advance.

Dr. Johannes Buyel combines bioinformatics with traditional molecular biology. By doing so he develops optimized production processes in plants.

Dr. Buyel, you are working on the production of biopharmaceuticals – what does that mean exactly?

Pharmaceuticals do not usually spring up from nowhere – they have to be produced. There are various approaches. Some substances can be synthesized chemically – this is described as in vitro, which means "in the test tube". But with more complex molecules such as proteins, that's not possible. Their production requires too many interdependent, consecutive synthesis steps. Such processes cannot easily be reproduced in a test tube, so complex proteins can only be produced in vivo, which means in living, biological systems. To this end, the genetic information for the protein is inserted into the production organism allowing us to utilize its protein production capacity. Pharmaceuticals produced in this way are described as biopharmaceuticals. We use a variety of organisms: bacteria, yeast, mammalian and plant cells, and also whole plants. In comparison to chemical synthesis, the processes in these organisms are of course very much more complex, and involve thousands of reactions taking place in parallel. It is therefore difficult to develop production processes and run them in a controlled manner.

What's your strategy for mastering this level of complexity?

In my team, we are taking a two-pronged approach to the challenge of developing production processes for biopharmaceutical proteins. We are not simply going into the laboratory and testing different parameters such as pH or temperature, but first setting up a model that describes these frequently complex connections. This model will allow us to select process conditions and parameters that will make our development work more efficient. Ultimately, we'll reach our goal faster: to come up with an easily implementable process delivering high yields of a high-quality product. Our previous modeling has already enabled us to reduce our experimental expenses and so cut costs. Everything that we develop on a small, laboratory scale at IME is designed to be scaled up and implemented in a much larger, industrial context. What works for us here in microliters will need to function commercially with volumes of several hundred liters.

What are the benefits of biopharmaceuticals and what are they used for in medicine?

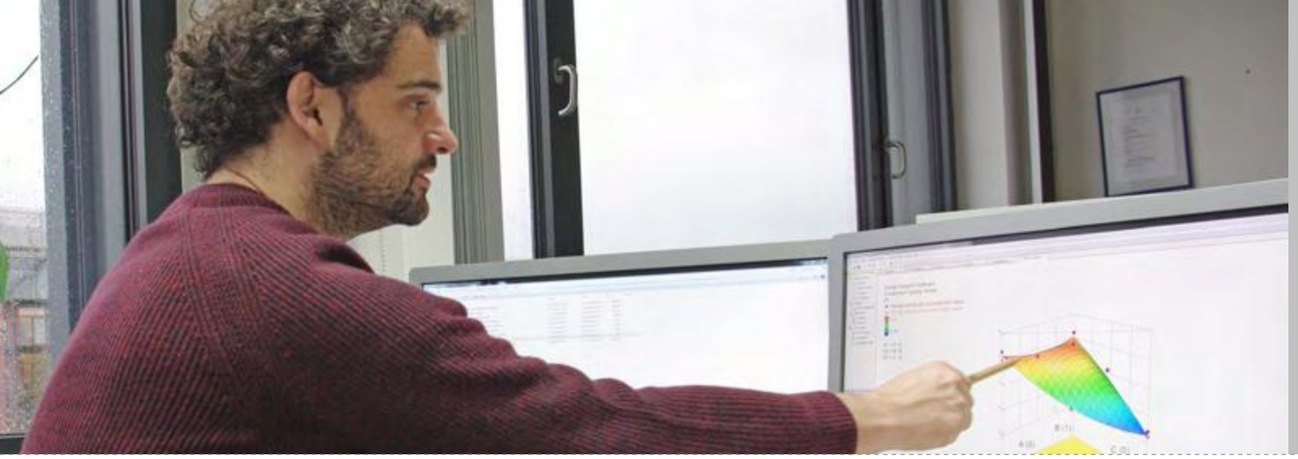
In a word: complexity. Due to their structure, biopharmaceuticals can take part in complex interactions and trigger mechanisms that simple molecules, such as aspirin, cannot affect. Furthermore, the complexity of a substance also increases its specificity, which markedly reduces the risk of side-effects. On the other hand, this advantage has a downside: complex molecules require more complex production processes involving living cells or parts of cells and this is a costly and time-consuming process. One important area of application for biopharmaceuticals is cancer treatment, where we need agents that have a toxic effect only against cancer cells, which is achieved by binding to tumor cells specifically.

Isn't it problematic, producing toxic substances in biological systems?

Yes, that's an excellent point. If the product we're making is toxic to humans, then it will often be toxic to other mammalian cells. We can get around this in many cases by using bacteria or yeasts instead, but because they are simpler they have limitations for the production of the most complex proteins. We encountered that just recently in a development project with one client. However, using plants was a good alternative and they have proved to be the best system – I think this will be confirmed in more cases in the future.

Fascinating – can you tell us more?

Sure. Our aim was to produce a toxic protein from mistletoe which selectively binds tumor cells, meaning it could potentially be used for cancer treatment. We had taken the process develop-



Computational models allow us to visualize the quality of production processes.

Plants, such as these tobacco seedlings, are the most efficient expression system for some proteins. An example is the mistletoe toxin, for which Johannes Buyel has developed an optimized production process.

ment further for our client in an established bacterial system. We then scaled it up far enough to obtain sufficient material for clinical studies. However, that was relatively costly and inefficient. And after production, the protein remained undissolved and inactive. It needed to go through several stages of purification and then it had to be dissolved and activated by refolding it into its natural form. This refolding is very inefficient under artificial conditions and so finally we had a yield of just 10%. The basic problem was the primitiveness of the bacteria. In the plant, the mistletoe toxin undergoes a number of modifications that bacterial cells are unable to carry out, and these extra refolding steps were unnecessary.

So, is that why you decided to use plants for the production of the toxin?

Exactly. The preparation was a bit more complicated because we predicted that the toxin would by synthesized in its active form and therefore had to take some safety precautions for our staff and the environment. But it was worth it. In the tobacco plant, we managed to produce the protein directly in its active form, which simplified the preparation and purification considerably. We increased the yield by almost 20% in comparison to the bacterial system, and at the same time more or less halved the amount of work involved. So, as I see it, plants offer distinct advantages.

What's your opinion: will the biopharmaceuticals of the future be produced in plants?

No, that can't be said in all cases – many medicines are produced successfully and economically in microbial and animal systems and there is no need to change that. But for some substances, plants offer a good alternative, or even a fundamentally more efficient production system. However, it is not easy to convince potential clients, particularly those from larger companies, that plants are a relevant, exciting and effective production system for biopharmaceuticals. That's because the utilization of plants involves extra costs from the start and this raises a barrier. Many millions are currently being invested in large fermenters for the cultivation of bacterial and mammalian cells, but this kind of infrastructure is not used in production processes involving plants. Plants need a glasshouse or a vertical farm and that means further investment. A further challenge, as I see it, will be getting licensing for biopharmaceuticals from plants. Relatively few plant-based processes have been utilized thus far, so authorization may take longer than it does for established production processes.

If an investor offered you 10 million euros, what would you do with it?

I would take on more staff specialized in computer modeling. I'm interested to know how well these models can perform and what advantages they offer over brute force in the form of a high-throughput experimental screening. I see huge potential there. Computational models improve our understanding of processes and interactions. This allows us to influence ongoing processes in a targeted manner at any point in time, because we know in advance which key parameters need to be adjusted to achieve a certain result.

To finish, what part of your work gives you the most pleasure?

The planning, implementation – though that should go in parentheses, because I'm no longer strictly involved there – and evaluation of experiments. It's a real pleasure for me to look at complex connections and try to understand them. And the question of applications, which the Fraunhofer-Gesellschaft emphasizes so strongly, is important to me, too. We have a clear idea of what we want to achieve through our research and we work consistently towards that goal. At the same time, we enjoy a certain degree of freedom that allows us to try things out, such as the mistletoe toxin in tobacco plants. It's that blend that I value so much.

Interview: Ruth Hausmann

MB

Dr. Johannes Buyel
johannes.buyel @ime.fraunhofer.de

IN FOCUS

Machine learning in pain research
An article by Dr. Carmen Walter and
Prof. Dr. Jörn Lötsch

»4«
CHANGE OF PERSPECTIVE

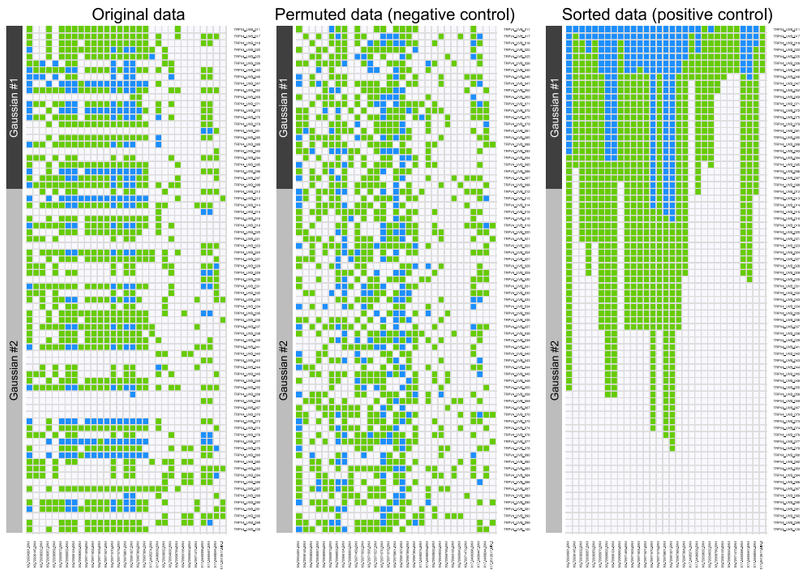
Which way round is reality? How do images form in our heads? Tilting and turning often help us to see and understand.

MACHINE LEARNING IN PAIN RESEARCH

Chronic pain is a condition that demands serious attention, but it is not yet fully understood. At the Branch for Translational Medicine and Pharmacology of the Fraunhofer IME in Frankfurt, we combine classic forms of experimental pain research with bioinformatics. The goal is to produce larger amounts of data in order to understand pain better, allowing the development of innovative therapies and new therapeutic agents.

Every fifth person suffers from chronic pain. The Fraunhofer IME in Frankfurt develops computer-based methods to accelerate pain research.

Pain functions as a physiological warning signal and is essential for survival. However, longer-lasting pain is one of the main reasons for visits to the doctor. Having fulfilled its warning function, pain can become a medical problem, e.g. as a persistent or residual symptom of an acute or former painful disorder. About 20% of the European population suffers from chronic pain – almost 80 million people – and the socio-economic costs of treatment, and the resulting absences from work, are correspondingly high. To this day, many individuals can be relieved of pain only to a limited extent, and there is an urgent need for more research to improve what we know about this condition. A better understanding of pain is the first step towards the development of analgesics with innovative mechanisms of action.



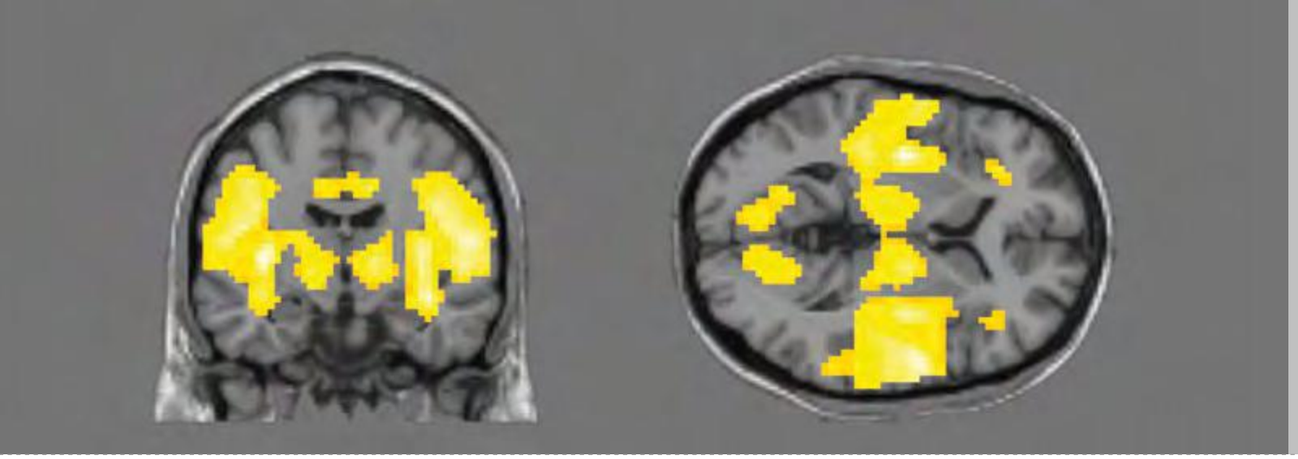
Phenotype prediction by machine learning algorithms based on next-generation sequencing data.

Pain is a complex phenomenon at both the molecular and phenotype-clinical levels. Laboratory and clinical research generates increasing quantities of complex, highly-dimensional data. Methods have been developed with the help of bioinformatics to evaluate these data efficiently and comprehensively. Using classic procedures such as imaging or modeling, raw data can be converted into useful information. This information can be analyzed in more detail to create correlation networks, which in turn can yield new knowledge. At the IME location in Frankfurt, we apply exactly this kind of DIKW approach to pain research: data – information – knowledge – wisdom.

Human pain models generate complex data

Research involving patients suffering from chronic pain is expensive, making it unfeasible during the early phases of drug development. Models have therefore been developed for pain and analgesic research allowing scientific hypotheses to be tested under controlled conditions with relatively small study populations. A model such as this has two main components: a direct pain stimulus and the measurement of the corresponding response. In practice, this can be a heat stimulus to which the subject reacts by twitching or by announcing that the stimulation is beginning to hurt. Such tests can be performed on healthy subjects, considerably reducing the variance in the collected data and thereby the number of subjects required. The costs are much lower compared to clinical studies involving patients suffering from chronic pain. However, a model can only imitate reality and it is not always possible to draw general conclusions from the results.

In our laboratory, we have established models that allow us to induce pain experimentally using chemical, mechanical, thermal or electrical stimuli. We record the responses to these stimuli as various biological signals or reactions. Pain assessment scales and questionnaires are evaluated, and brain responses are recorded by electroencephalography (EEG) or functional magnetic resonance imaging (fMRI). In this way, we can see which areas of the brain are involved in the perception and processing of pain, generating a visual map of the differential actions of analgesic substances on specific parts of the brain. Imaging procedures allow us to detect peripheral, pain-associated signals and measure localized increases in blood flow in the area around a focus of induced pain. In a comparative analysis, we have identified and ranked a set of four pain models that are particularly good at predicting the efficacy of painkillers. Some of these methods form part of the standardized quantitative sensory testing (QST) procedure. The test was developed with patients suffering from neuropathic pain but could be applied without modification in laboratory tests on healthy volunteers. This approach may provide a way to test pharmaceuticals that have direct clinical relevance.



Brain regions activated by intranasal pain stimuli.

Pain is not yet fully understood. Novel bioinformatics and machine learning methods offer new strategies for pain research.

Data exploration generates information

Modern, data-science-based methods of analysis can be applied to broaden and supplement classic, hypothesis-driven approaches to pain research. For example, exploratory data analysis is a highly creative, iterative process. Logical questions are generated from given sets of data. Broad assumptions are first derived through data transformation, modeling and visualization, and these are used, via feedback processes, to refine the original questions and thus find the answers in the corresponding datasets. Tenable hypotheses can then be formulated.
Furthermore, relevant pathophysiological processes can also be recognized through groupings and patterns in the data. This can facilitate the development of innovative analgesic drugs, the identification of new applications for known drugs, or the selection of individualized treatment options.

Machine learning recognizes data structures and generates knowledge

Our understanding of the complexity of pain and the factors contributing to it can be facilitated and extended through the use of modern, computer-based technologies. Machine learning, or the use of self-learning algorithms, is one aspect of artificial intelligence which is currently attracting substantial interest. Machine learning methods can automatically recognize patterns in data and these patterns can be used to predict future outcomes.

In order to test the potential of innovative approaches such as machine learning, we posed the following question: If a machine with artificial intelligence can be trained by providing it with complex genetic information in the form of next-generation sequencing data, would it be possible to predict a phenotype better than we can through simple estimates? To answer this, we took a defined dataset and passed it through a series of data-processing procedures. Two-thirds of the dataset was used in each case to train the system, while the remaining third was used for subsequent prognosis of the phenotype. After repeating the process 1000 times with an increasingly random selection of data subsets, the phenotype could be predicted more precisely through machine learning than by using the principle of coincidence.
Using topographical projection procedures based on machine learning, it is possible to assimilate the information incorporated in an entire experimental study without needing to test specific hypotheses. This is illustrated in our investigation of sensitivity to pain caused by heat stimuli, tested under three different sets of conditions. After the projection of this high-dimensional data onto a self-organized map, we observed the appearance of distance-based and density-based structures that overlapped with the various test conditions. Furthermore, we detected a gender difference: women are more sensitive to pain than men.

Artificial intelligence boosts research into pain and analgesia

With modern pharmacological data science techniques, the complex and highly-dimensional data encountered in human pain and analgesia research can be transformed from units of experimental data into generalized knowledge. This could usefully supplement hypothesis-based research strategies. To combine data from evidence-based pain models and complex biological responses such as pain-associated brain activation or changes in levels of individual biomarkers, the emerging discipline of computer-aided pain research has some powerful new tools to offer. These tools will help us to understand pain better and to discover new treatment options. Machine learning and related techniques thus have the potential to fundamentally alter the study and treatment of pain.

TM
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SELECTED PUBLICATIONS

Bioaccumulation & Animal Metabolism

Industrial Biotechnology

Bioresources

Translational Medicine and Pharmacology

Environmental Specimen Bank and Elemental Analysis

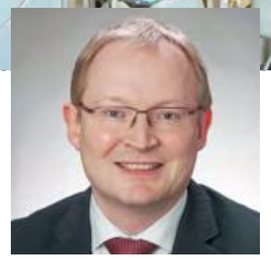
Functional and Applied Genomics

ScreeningPort

»5«

CHANGE OF PERSPECTIVE

Do you want to see these images undistorted? Then change the perspective by tilting this page away from you. Viewing the images at an angle gives an undistorted view.



PROF. DR. CHRISTIAN SCHLECHTRIEM,
BIOACCUMULATION &
ANIMAL METABOLISM

“Test solutions containing highly lipophilic substances can be generated using a column-elution technique.”

BIOCONCONCENTRATION STUDIES WITH HIGHLY LIPOPHILIC SUBSTANCES

The enrichment of substances in the food web (bioaccumulation) is an important factor when assessing their environmental risk. Highly-lipophilic test substances (HLS) are only sparingly soluble in water and are easily absorbed, so fish flow-through studies involving these substances require specific methods for the preparation of test media. The use of solvents and solubilizing agents is not recommended because they might cause test artifacts. As part of a study funded by the German Environment Agency, we investigated whether stable concentrations of HLS can be generated and maintained over periods of several weeks using a column-elution technique. Glass columns were filled with a carrier material loaded with HLS such as hexachlorobenzol, *o*-terphenyl, PCB congener 153 or dibenz[*a,h*]anthracene. We found that the column-elution technique delivered constant concentrations of HLS over an uptake period of 8 weeks without the need for solvents or solubilizing agents. After further dilution, the eluates were applied in flow-through bioconcentration studies with rainbow trout for 8 weeks according to OECD 305. The deviations from the estimated time-weighted average concentration of the test media were always below 20%. We found that the column-elution technique can deliver constant concentrations of HLS in flow-through tests according to OECD 305 to determine the bioconcentration in fish.

AE BR Bioaccumulation & Animal Metabolism

Schlechtriem, C., Böhm, L., Bebon, R., Bruckert, H.-J., Düring, R.-A.: Fish bioconcentration studies with column-generated analyte concentrations of highly hydrophobic organic chemicals. Environmental Toxicology and Chemistry 36 (2017) 906-916 (DOI:10.1002/etc.3635)

STEFAN GAIDA,
INDUSTRIAL BIOTECHNOLOGY

“The next generation of biofuels will still be used in the era of CO_2-neutral electro-mobility.”

PROMOTING SUSTAINABILITY: BIOFUELS FROM PLANT WASTE

Butanol is a key intermediate in the chemical industry and can also be used without major obstacles in modern combustion engines as an alternative to fossil fuels. By focusing on sustainability, we aim to obtain bio-butanol from plant waste as a next-generation biofuel.

For this purpose, we are using the anaerobic bacterium *Clostridium cellulolyticum*. As its name suggests, this microorganism can break down cellulose, thus recovering raw materials from cellulose-rich straw and wood waste for the chemical industry. However, the bacterium lacks the genetic machinery to produce butanol. We have therefore isolated the genes for butanol synthesis from the related species *Clostridium acetobutylicum* and inserted them into our cellulose-degrading strain. As anticipated, the genetically modified strain of *Clostridium cellulolyticum* produced butanol when provided with cellulose and cellobiose as a sole carbon and energy source. Thus far, we have achieved yields of about 120 mg butanol per liter of fermentation culture, which is excellent in terms of process verification but still far too little for commercial processes. Our next goal was therefore to identify potential bottlenecks in the biosynthesis pathway using targeted proteomic and metabolic analysis to measure the levels of the relevant proteins and intermediates during fermentation. We were able to detect all the proteins and the two key metabolic intermediates in the engineered butanol biosynthesis pathway. This information will enable us to achieve more targeted metabolic engineering.

MB Industrial Biotechnology

Gaida, S. M., Liedtke, A., Jentges, A. H. W., Engels, B., Jennewein, S.: Metabolic engineering of Clostridium cellulolyticum for the production of n-butanol from crystalline cellulose. Microbial cell factories (2016) No. 15(1):6. (DOI: 10.1186/s12934-015-0406-2)

PROF. DR. ANDREAS VILCINSKAS,
BIORESOURCES

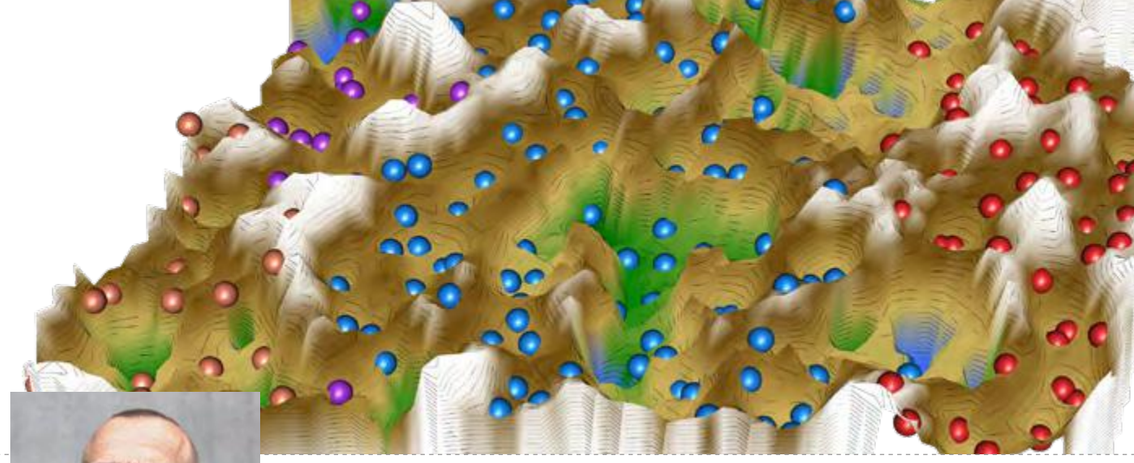
"Insects can adapt to highly specialized diets thanks to their gut flora. We can utilize these microorganisms for biotechnological applications."

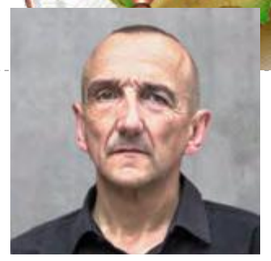
THE BURYING BEETLE AS A TREASURE TROVE FOR BIOTECHNOLOGY

The booming field of insect biotechnology includes the development and commercial application of biotechnological processes based on insects, their molecules, cells and organs, and their microorganisms. The resulting products can be used in medicine, plant protection or industry. We are focusing on insects as a bioresource for the bioeconomy because this taxonomic group comprises the greatest number of species and the highest level of biodiversity on earth. The evolutionary success of insects in part reflects their ability to use symbiotic microorganisms to tap unusual sources of nutrition. An interesting example is the burying beetle *Nicrophorus vespilloides*, which feeds on the carcasses of small mammals and birds, and also breeds on them. In cooperation with the Max Planck Society, we are exploring the potential of insect-associated microbes for applications in industrial biotechnology. The AIM-Biotech project (Application of Insect-associated Microbes in Industrial Biotechnology) has received 1.5 million euros in funding. We are the first to investigate how the burying beetle uses specialized intestinal microorganisms to digest a mouse carcass more than a hundred times heavier than itself. The gut flora of the burying beetle is a treasure trove for biotechnology and opens a whole new value chain. Our discoveries have set the course for future research and have been published in "Nature Communications".

AE BR Bioresources

Vogel, H., Shukla, S., Engl, T., Weiss, B., Fischer, R., Steiger, S., Heckel, D., Kaltenpoth, M., Vilcinskas, A.: The digestive and defensive basis of carcass utilization by the burying beetle and its microbiota. Nature Communications (2017) No. 8:15186. (DOI:10.1038/ncomms15186)





PROF. DR. JÖRN LÖTSCH,
TRANSLATIONAL MEDICINE
AND PHARMACOLOGY

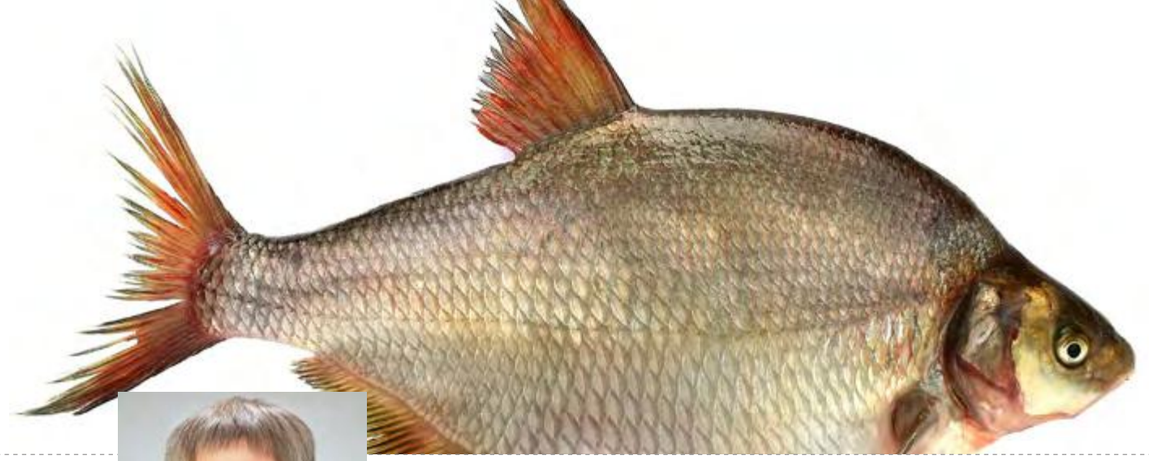
"Complex pain data can be structured through machine learning "

UNDERSTANDING PAIN BETTER

Everyone one knows what pain is, but for the pain researcher the phenomenon is difficult to understand due to its complexity. In a cover article in the top-ranking international journal "Pain", we present a new methodological approach involving the collection of masses of pain-related measures from healthy subjects in which structures can be revealed by machine learning.
These data-driven techniques allow us to identify groups of people in terms of individual pain sensitivity, who, where needed, would benefit from pain therapy individually tailored to their specific profile. As an interdisciplinary team, we have developed an experimental human pain model: sensitivity to stimuli such as pressure, heat or cold is measured in healthy subjects in order to build up a close-to individual pain profile. These measurements and data are then analyzed and structured in cooperation with the University of Marburg. The methods used are those of machine learning, which is particularly well suited to the recognition of structures in complex data. The end result is a three-dimensional representation of the formerly highly-dimensional data, showing group structures of subjects with similar or different pain sensitivities. As an example, men and women differed markedly in their sensitivity to pressure pain. The illustration above was selected for the cover of the "Pain" issue in which our article was published.

TM Translational Medicine and Pharmacology

Lötsch J., Geisslinger G., Heinemann S., Lerch F., Oertel B.G., Ultsch A.: QST response patterns to capsaicin- and UV-B-induced local skin hypersensitization in healthy subjects: a machine-learned analysis. Pain (2018) No. 159(1):11-24 (DOI: 10.1097/j.pain.0000000000001008)



DR. HEINZ RÜDEL,
ENVIRONMENTAL SPECIMEN BANK
AND ELEMENTAL ANALYSIS

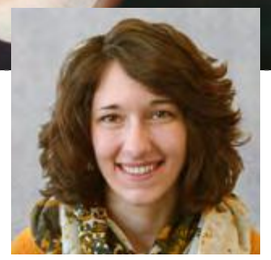
"Our study shows that environmental HBCD levels have declined following the introduction of voluntary emission reduction measures."

MONITORING HEXABROMOCYCLODODECANE (HBCD) LEVELS IN EUROPEAN WATERS

In 2007, Fraunhofer IME was contracted by the industry association CEFIC to run a multi-year monitoring study on the brominated flame retardant hexabromocyclododecane (HBCD). At that time, HBCD was a major flame retardant applied to insulation material for buildings, and the regulatory authorities were concerned about its potential harmful properties. The aim of the study was to investigate the impact of reduction measures implemented by HBCD producers and users in Europe. To this end, we monitored HBCD in fish as well as in parallel sampled sediment from one lake in Germany and suspended particulate matter (SPM) from five European rivers. We chose a common fish (bream) as an indicator species and collected samples between 2007 and 2013 from the rivers Götaälv (SE), Rhône (FR), Western Scheldt (NL), Mersey (UK) and Tees (UK), and also from Lake Belau (DE). Sediment and SPM were collected every second year between 2008 and 2014. HBCD was analyzed by coupling liquid chromatography and tandem mass spectrometry.
For most sites, we observed a decline in HBCD levels in fish. For example, in the rivers Rhône and Western Scheldt, the levels dropped significantly by about 80 and 60%, respectively. In the River Rhône, HBCD levels also decreased in the SPM. High HBCD levels were detected in the River Tees, where the sampling site was affected by a former HBCD production plant upstream. Here, HBCD levels decreased only after a major flood in 2013. Although the SPM monitoring data were not completely consistent, the fish data clearly indicate the anticipated decline in environmental HBCD concentrations at most sites with diffuse emissions.

AEBR Environmental Specimen Bank and Elemental Analysis

Rüdel, H., Müller, J., Nowak, J., Ricking, M., Klein, R., Kotthoff, M.: Hexabromocyclododecane diastereomers in fish and suspended particulate matter from selected European waters – trend monitoring and environmental quality standard compliance. Environ Sci Pollut Res 24 (2017) 18048-18062 (DOI: 10.1007/s11356-017-9469-4)



KATHARINA PÜTTER,
FUNCTIONAL AND APPLIED
GENOMICS

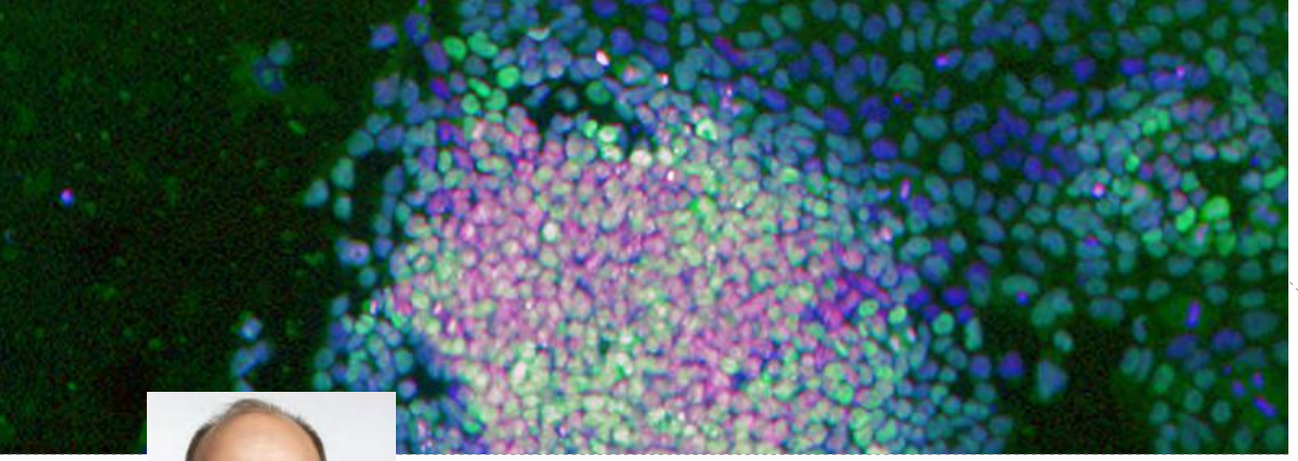
"The worldwide demand for natural rubber is growing. Through our research, we aim to establish the dandelion as an alternative rubber-producing crop."

MORE RUBBER FROM DANDELIONS: UNDERSTANDING THE GENES

Latex, the white sap of the dandelion, contains many different terpenes, which are highly valuable industrial chemicals. The polyterpene poly(cis-1,4-isoprene) is the main component of natural rubber and is used in more than 40,000 everyday products. To use dandelions as an alternative production crop for rubber, we need to understand the natural process of rubber biosynthesis and the corresponding regulatory mechanisms. This will help us develop methods to increase the rubber content of dandelion latex.
During our research, we have generated transgenic dandelion lines overexpressing various genes from thale cress and therefore producing the corresponding proteins. This approach identified three Arabidopsis genes whose simultaneous and tissue-specific overexpression appears promising. The genes encode pacemaker enzymes that are switched on prior to rubber biosynthesis. Tissue-specific expression does not appear to affect other aspects of dandelion metabolism. We have therefore set up a prototype for tissue-specific metabolic engineering in dandelion, and we have increased the poly(cis-1,4-isoprene) content by 2.3-fold. The sterol content is five times higher and the levels of industrially relevant triterpenes are 2.2-fold higher. These results show that genetic engineering can be used to enhance terpene levels directly.

MB Functional and Applied Genomics

Pütter, K.M., van Deenen, N., Unland, K., Prüfer, D., Schulze Gronover, C.: Isoprenoid biosynthesis in dandelion latex is enhanced by the overexpression of three key enzymes involved in the mevalonate pathway. BMC Plant Biology (2017) No. 17:88 (DOI: https://doi.org/10.1186/s12870-017-1036-0)



OLIVER KEMINER,
SCREENINGPORT

“Using image-based high-throughput screening, we can identify substances for the optimization of cell therapy.”

HIGH-CONTENT SCREENING: DISCOVERING INDUCERS OF BETA-CELL REGENERATION

Diabetes mellitus is one of the most prevalent metabolic disorders in Western society. In diabetes, the insulin-producing beta-cells die or lose their ability to produce sufficient insulin. As a potential strategy for cell-replacement therapy, beta-cells could be replaced by Langerhans islet transplantation. However, there are only a few organ donors, and heterologous transplants are risky. New approaches are geared towards the regeneration of progenitor cells. In principle, induced pluripotent stem cells from patients offer an unlimited resource for the production of the body’s own beta-cells. Growth factors play an important role here, but they are also in short supply, frequently unstable, and potentially infectious due to their animal origin.

The aim of our screening campaign was to identify new and stable substances that induce the differentiation of stem cells into early endodermal progenitor cells of the pancreas. Together with our cooperation partner Prof. H. Lickert of the Helmholtz Center in Munich we have developed an image-based high-content screening assay to detect the differentiation marker FOXA2 and the pluripotency factor Oct-3/4. An image analysis procedure, specially developed for the purpose, allows the simultaneous morphological characterization of cells and stem-cell colonies in a 384-well format.

As many as 23,406 molecules have passed through this high-throughput screening process, and have been narrowed down through multi-stage exclusion analysis to a selection of 84 positive substances. The most potent of these are the ROCK inhibitors, which promote the differentiation of human stem cell systems into insulin-secreting beta-cells.

ScreeningPort

Korostylev, A., Pallavi U. Mahaddalka, Keminer, O., Hadian K., Schorpp J., Gribbon, P., Lickert H.: A high-content small molecule screen identifies novel inducers of definitive endoderm. Molecular metabolism (2017) No. 6:640-650 (DOI: 10.1016/j.molmet.2017.04.009)

PEOPLE AND EVENTS

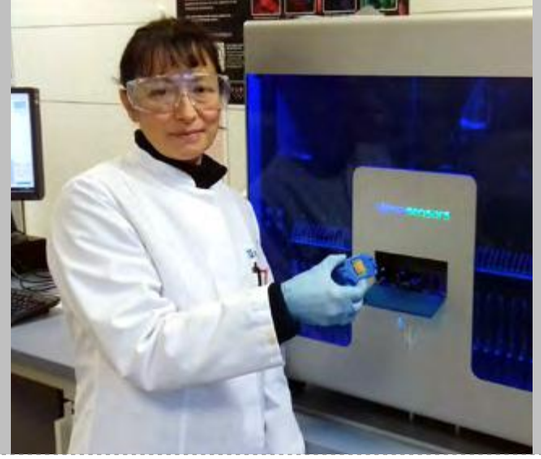
Brief reports
Employees, encounters, successes and new perspectives at the Fraunhofer IME

»6«
CHANGE OF PERSPECTIVE

Portrait or profile? Can you have both together? Fraunhofer IME's Holger Spiegel leaves us wondering.

DECHEMA forum at the Fraunhofer IME in Aachen

The regular meeting of the DECHEMA Zukunftsforum Biotechnologie was held at the Fraunhofer IME Aachen location in November 2017. DECHEMA is a non-profit organization operating at the national and international levels to promote biotechnology and chemical technology. The interdisciplinary exchange of expertise ranges across all aspects of biotechnology, from DNA analysis through to the production of biotechnological products in stainless steel reactors. The Zukunftsforum (Future Forum) of experts in biotechnology brings together young scientists from academia and industry. It represents a cross-section of the next generation of researchers in German biotechnology. The Zukunftsforum sees itself as a catalyst for innovative thinking, while critically appraising the current status of research and teaching, not only within the field of biotechnology but also across the whole spectrum of the natural and engineering sciences. A key issue discussed at this year's meeting in Aachen was the unclear status of young researchers, such as group and project leaders who have neither yet qualified as lecturers nor been granted professorships. The focus was on university lecturing and the supervision of final dissertations, as well as the responsibility for budgeting and personnel. In this context, Fraunhofer IME is currently drawing up a position paper for future orientation in research and teaching. MB



Marine Fungi: EU project forges collaboration between Fraunhofer IME and EMBL

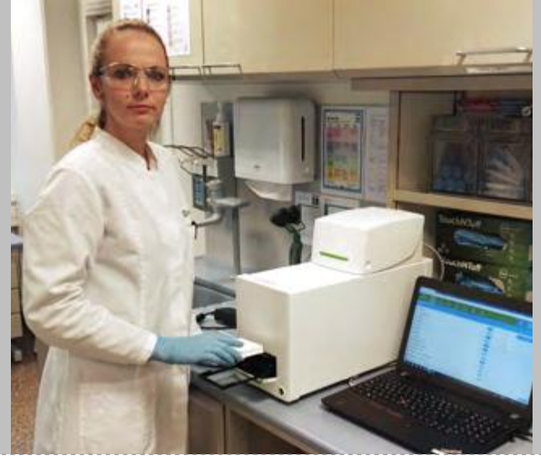
In the EU-funded project "Marine Fungi", Fraunhofer IME has been working together with 10 international partners to identify natural anti-cancer substances in marine fungi. Dr. Adelia Razeto at Fraunhofer IME ScreeningPort is now exploring the mechanisms of action of the natural compounds in depth. She is also using the infrastructure of the European Molecular Biology Laboratory (EMBL) at the German Electron Synchrotron (DESY) for her structural biology and biophysics investigations, which will facilitate the development of novel anti-cancer treatments. Various funding bodies have been approached for follow-on financing to push forward this translational research. The work involves collaboration with the research group led by Dr. Christian Loew at EMBL Hamburg. The plan is to extend the cooperation between Fraunhofer IME, EMBL and the recently founded Center for Structural Systems Biology (CSSB), to further strengthen structural biology research projects in the future. TM

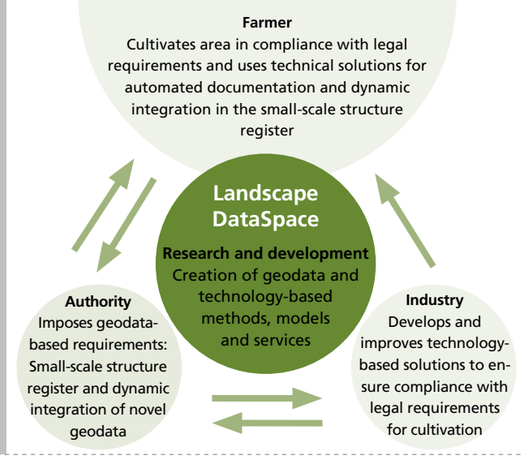
Mark Bücking appointed Associate Professor at Monash University Melbourne

Fraunhofer IME and Monash University in Melbourne, Australia, have been collaborating since 2016. In March 2017, as part of this collaboration, Prof. Mark Bücking received an adjunct appointment as Associate Professor in the School of Chemistry. Monash University is spread over five locations in Melbourne and has more than 70,000 students. With further branches in Malaysia, South Africa, China, Italy and India, it is one of most famous universities in the world, being most renowned in the fields of chemistry, pharmacology, biomedicine and medicine, engineering, and technological sciences. In the field of food research, the School of Chemistry has recently joined forces with the Food Innovation Center. The combined strengths of Fraunhofer IME and Monash School of Chemistry will thus be channeled into joint initiatives making use of Monash University's extensive research and business network throughout Asia combined with Fraunhofer's network within the fields of food and environmental research. The joint supervision of doctoral students is planned, including lectures and presentations in Melbourne. Monash University signed a memorandum of understanding with Fraunhofer Food Chain Management Alliance back in January 2017. An initial collaborative project with Monash, funded by the Fraunhofer-Gesellschaft, is scheduled to begin in 2018. Under the heading "Health Kitchen", the aim is to study the retention and transformation of food ingredients in the human body. AE BR

Fraunhofer IME develops new technologies for the world's largest insect farm

Insects are set to play an important role as an alternative source of protein for food and animal feed. The increasing demand for proteins, particularly in Asia, is becoming difficult to fulfil via traditional farming and fisheries. Asia is already taking a leading role in the establishment of an insect-based industry. Over the next three years, the world's largest insect farm will be built on the Indonesian island of Java. The Branch for Bioresources of the Fraunhofer IME in Gießen has been contracted by Alternative Protein Corporation, a British company, to develop new technologies for the large-scale breeding of the black soldier fly *Hermetia illucens*. Mixing business with pleasure, the flies recycle huge amounts of plant waste generated by the Indonesian palm oil industry and thereby produce sustainable quantities of proteins, oils and other raw materials on an industrial scale. Prof. Andreas Vilcinskas signed a contract for the planned research work with Director David Carew and their Indonesian partners in Jakarta in January 2018. AE BR





Food Systems – Fit for the Future?

On November 13, 2017, the Fraunhofer Food Chain Management Alliance celebrated its 10th anniversary with the Symposium "Food Systems – Fit for the Future?" at the Fraunhofer Headquarters in Munich. Prof. Mark Bücking, Head of the Environmental and Food Analysis Department and Managing Director of the Alliance, commented: "Numerous guests from industry, the regulatory authorities and academia took the opportunity to meet with our experts and discuss global trends, opportunities and challenges around the food value chain, and to initiate potential co-operations." The discussions focused on consumer access to safe and high-quality foods, the improvement of resource efficiency by process optimization and the minimization of losses, and approaches to strengthen consumer trust by ensuring transparency and providing comprehensive information to enable better decision making. AE BR

Market launch support: Cooperation with PerkinElmer

The Branch Lab ScreeningPort of the Fraunhofer IME has been supporting preparations for the market launch of a new multi-modal microtiter plate reader developed by the multinational corporation PerkinElmer, a global leader in biotechnology. With this product, PerkinElmer is launching a new generation of microtiter-format analyzers. The special feature of the VICTOR Nivo™ System is its small size, yet it still supports all the standard detection technologies.
Even before the first official presentation of the world's smallest multimodal reader in July 2017, the instrument had been put through extensive benchmark tests at the IME Hamburg location. The aim of the long-term collaboration is to carry out test runs in the many different application areas used in modern laboratory routine practice, and to evaluate the results in application reports. Several joint application notes on various topics have already been published, including methods for DNA and protein quantification, the evaluation of cellular proliferation and cytotoxicity, as well as ELISA and enzyme activity assays, which can all be measured using the VICTOR Nivo™ System. The current focus is on the validation of common assay techniques, such as the *twinlite* Firefly and Renilla luciferase reporter gene assay, and the DELFIA® cell proliferation assay. TM

Landscape Data Space – data-based sustainable rural land use for a regional value creation

The Industrial Data Space has been set up by Fraunhofer and is sponsored by the German Federal Ministry of Education and Research. It aims to provide a safe and mutually accessible data space for diverse companies. Agriculture is not addressed in this system so far. Prof. Christoph Schäfers, ecologist and institute director at Fraunhofer IME, and Dr. Matthias Trapp, agricultural scientist at the Institute for Agroecology of RLP AgroScience GmbH, intend to use the Industrial Data Space architecture and its data protection concept to create an area-related (georeferenced) communication infrastructure for agriculture. The Landscape Data Space will encompass a spatio-temporally defined area including all economic and ecological properties and functions required to implement landscape-related measures thus improving resilience, minimizing risks, and linking local and regional value-creation chains. Public bodies will share their extensive geodata resources with the Landscape Data Space, including basic as well as functional data. This will allow the pinpoint implementation of legal requirements and policies for the improvement of regional structures using a spatiotemporally explicit financial support model for agriculture and nature conservation. Farmers will use the system to fulfil their legal requirements, to make use of available financial support, and to integrate the sensor data generated by their agricultural machines. The public can also be interactively engaged. For all stakeholders, the Landscape Data Space will provide a safe, anonymous and reciprocally accessible data space. Fraunhofer IME, as a public research organization with high credibility in industry and society, is the ideal organization to operate the Landscape Data Space. AE BR

Successful acquisition of funding for bioeconomy research

Finite fossil fuel resources combined with climate and environmental protection policies make the transformation from an oil-based industry to biobased enterprises a necessity. The concept of a bioeconomy sets the stage for a new style of economy based on the efficient and sustainable utilization of biological resources. The German government has recognized the importance of this transformation for the future, and has therefore allocated BMBF funding within the framework of the national research initiative "BioEconomy". In 2017, the Fraunhofer IME successfully secured some of this funding, with five projects at the Aachen and Schmallenberg locations already receiving support for the initial conception phase. This funding will be used to develop a comprehensive funding application. The aim of the proposed research projects in the areas "Agricultural Systems of the Future" and "Innovation Areas – Bioeconomy" is to develop and explore innovative platforms and processes for sustainable production. The spectrum of biobased products ranges from foods through to pharmaceuticals and biomaterials. Fingers crossed for the second phase – the approval of funding for the launch of our projects! MB

Fraunhofer IME ScreeningPort selected as an EU-OPENSCREEN partner site

EU-OPENSCREEN is the European Research Infrastructure in the area of chemical biology, supported by the European Strategy Forum for Research Infrastructures (ESFRI). The Branch Lab ScreeningPort of the Fraunhofer IME in Hamburg is one of the three German sites nominated and now selected by the German Federal Government as partner sites. The ScreeningPort thereby contributes to a pan-European series of 20 similar screening and chemical research facilities. The central office of EU OPENSCREEN is located in the Leibniz Institute for Molecular Pharmacology in Berlin. The current coordinator is Dr. Philip Gribbon from ScreeningPort, highlighting the Fraunhofer IME's support for this important pan-European program. All high-capacity screening platforms in the EU OPENSCREEN network have access to a shared collection of chemical substances. This will include up to 140,000 commercial and proprietary compounds, brought together by European chemists. Together with external users from various life sciences disciplines, EU-OPENSCREEN will develop novel compounds as molecular tools. All the substances and data generated will be made available in an open-access database. In November 2017, 26 members of the German Society for Chemical Biology from 22 different institutions met together in Berlin to discuss future collaborations and joint research priorities. TM

Medical Data Space: IDSA working group set up under Fraunhofer IME directorship

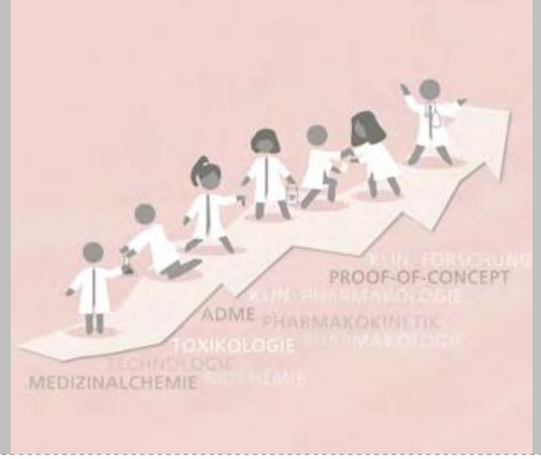
The International DATA Space Association e.V. (IDSA) links players from different branches of the digital transformation initiative, bringing together academic research and industry. The working group Medical Data Space was set up in January 2018 under Fraunhofer IME directorship. The group will engage healthcare personnel who wish to improve and develop patient care and research through digitalized solutions and services. The reference architecture of the Industrial Data Space provides a foundation that will be adapted for healthcare specifications. The goal is to create a platform for the safe, structured and systematic exchange of data, metadata and algorithms from independent, decentralized data sources. The various connectors, brokers, services and securities defined in the Industrial Data Space and adapted for specific use cases will be modified for applications in the Medical Data Space. The plan is to combine and supplement existing solutions in medicine, industry and research for further development. TM

New Heads of Department in Ecotoxicology

Since April 1, 2017, Dr. Elke Eilebrecht and Matthias Teigeler have worked as joint directors of the Department of Ecotoxicology, one of the largest and most economically productive departments at the Fraunhofer IME site in Schmallenberg. They took over this role from Prof. Christoph Schäfers who, as Director of the Division Applied Ecology and Bioresources, focuses on his institute management role. The Department of Ecotoxicology develops and runs ecotoxicological studies and strategies as well as models to assess the environmental risks posed by chemicals, plant protection agents and pharmaceuticals. By optimal use of facilities and expertise, the department offers a broad range of testing models. Higher tier-studies under complex conditions, mimicking those in the real environment, form a key component of the work. Dr. Elke Eilebrecht and Matthias Teigeler use their long-term experience in the development and adaptation of testing systems that comply with new regulatory requirements. By incorporating the outcomes of current research, they conform to increasingly rigorous scientific standards. Matthias Teigeler's principal aim is to identify risks to aquatic life stages, particularly those posed by hormonally active substances, using fish life cycle studies. Dr. Elke Eilebrecht's research focuses on the development and optimization of animal-protection-compliant testing procedures, e.g. through the inclusion of molecular endpoints. As experts in their respective fields, both researchers play an active role on OECD committees. AE BR

"Men only" at the Aachen Corporate Marathon 2017

As in previous years, a team from the Fraunhofer IME took part in the 6th Corporate Marathon around Campus Melaten in Aachen. The demand for the 3500 starting places in the 4.8 km race was very high, and all places were taken two months before the event. The IME runners were eager to compete in the 9.6 km marathon and met this challenge with élan! The four IME runners – Holger Spiegel, Jonas Glawe, Philipp Heuter and Sebastian Barrenstein – took 50th place in a total of 435 men's teams. Congratulations to them! For Philipp Heuter, who was taking part in the Corporate Marathon for the first time, the whole atmosphere spurred him on. "During my last training session, I only managed two laps, whereas in the real race, I ran all four with no problem." There was no women's team at the start this year but that may change in the future. The aim for next year is to get even more IME participants on and along the route. MB



Successful rating: LOEWE Center TMP

The Federal State of Hesse is providing financial backing for the LOEWE Center for Translational Medicine and Pharmacology (TMP), together with the Fraunhofer IME branch of the same name, for a second funding period of three years starting from January 1, 2018. The amount of funding is approximately 19.4 million euros, and a further 22 million euros has been set aside for the building of the new Fraunhofer research facilities on the campus of the University Hospital in Frankfurt Niederrad. This is an important step forward in the steady development of Frankfurt as a center for research. Universities and research institutes will benefit, as well as commercial enterprises in the Hesse region. The LOEWE Center TMP brings together partners from Fraunhofer IME, the Goethe University Frankfurt, and the Max-Planck Institute for Heart and Lung Research in Bad Nauheim. Together, these institutes are working on innovative diagnostic and therapeutic approaches in the indication areas of pain, rheumatoid arthritis, sepsis and multiple sclerosis. As Prof. Gerd Geisslinger, spokesman for the LOEWE Center TMP, observes: "The renewed funding is an important milestone on the road to establishing the first Fraunhofer Institute in Frankfurt, and the LOEWE program of the State of Hesse is therefore the ideal instrument for this funding". TM

Phoenix Award for Matthias G. Wacker

The Phoenix Pharmaceutics Science Award for innovative and outstanding work in the field of pharmaceutical research and development was presented this year for the 21st time by the PHOENIX Group. The 40,000 euro award is one of the most prestigious research awards in German-speaking countries, and winners are selected by an independent jury. Dr. Matthias G. Wacker, Head of the Pharmaceutical Technology and Nanosciences at the Branch for Translational Medicine and Pharmacology of the Fraunhofer IME, received this year's award for his work on the development of innovative prolonged-release formulations for therapeutic agents.
Wacker's team used novel nanocapsules to protect the therapeutic agent interferon β from premature degradation. They also simulated its release from subcutaneous tissue using a specialized hydrogel. In order to compare the release of interferon β from the capsules in living animals and in an in vitro model, they used various approaches including an imaging procedure to predict its bioavailability. In the future, this approach could help to improve the performance of prolonged-release formulations. The interdisciplinary research has been published in "The Journal of Controlled Release" and was carried out in conjunction with preclinical research groups at Fraunhofer IME in Frankfurt as well as the University Hospital and Institute for Biophysics of the Goethe University Frankfurt. TM

ImmuVision: Fraunhofer Research Cluster of Excellence

Since January 1, 2018, the Fraunhofer-Gesellschaft has provided funding for a research cluster of excellence focusing on immunological disorders, led by Fraunhofer IME's Prof. Gerd Geisslinger. Three Fraunhofer Institutes – IME, IZI and ITEM – with prominence in this field and with complementary expertise, form the inner core of this strategically linked cluster, working together with other collaborating Fraunhofer institutes.
The long-term aim of the ImmuVision Cluster of Excellence is to close the research gaps hindering the development of pharmaceutical agents and treatments for immunological disorders, and to improve patient care. This will be achieved by formulating scientific hypotheses, identifying potential target molecules and developing efficient, sustainable therapies.
The ImmuVision Cluster of Excellence has additional strategic goals. A virtual institute will be established to combine the interdisciplinary competences of the three core institutes, with the aim of improving the visibility, profile and competitiveness of the Fraunhofer-Gesellschaft in the area of health research and promoting cooperation with industrial partners.
A joint strategy for furthering the careers of junior scientists in translational research is also on the agenda.
The ImmuVision Cluster of Excellence will thus underpin the biomedical expertise of the Fraunhofer-Gesellschaft as a whole, raising its international profile even further. TM

FACTS 2017/18

Publications

Patents

Doctoral and Master's Theses,
State Examinations
and Bachelor's Theses

Networks in Science and Industry

PUBLICATIONS

- Molecular Biotechnology
- Applied Ecology and Bioresources
- Translational Medicine

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DOCTORAL AND MASTER'S THESES, STATE EXAMINATIONS AND BACHELOR'S THESES

DOCTORAL AND MASTER'S THESES, STATE EXAMINATIONS AND BACHELOR'S THESES

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RWTH Aachen University

Baumann, Linda
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Justus-Liebig-Universität Giessen

Beiß, Véronique
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Justus-Liebig-Universität Giessen

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Technische Universität Berlin

Büttner, Dominik
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Goethe-Universität Frankfurt

Cremer, Christian
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RWTH Aachen University

Daniel (geb. Homann), Julia
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Goethe-Universität Frankfurt

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Goethe-Universität Frankfurt

Druzinec, Damir
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Technische Universität Berlin

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Jacobs University Bremen

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Grieger, Elena
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RWTH Aachen University

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Hohmann, Stephan
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Kampe, Sebastian
Porcellio scaber als Testorganismus für Bioakkumulationsstudien.
RWTH Aachen University

Klose, Diana
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RWTH Aachen University

Knothe, Claudia
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Woitok, Mira
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RWTH Aachen University

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Post-transcriptional control of C/EBPalpha and C/EBPbeta proteins.
University of Groningen

Zinn, Sebastian
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Goethe-Universität Frankfurt

Theses at a glance

	Bachelor´s Theses (BSc)	Master´s Theses (MA), State Examinations	Doctoral Theses	Total
IME-MB	12	10	11	33
IME-AE-BR	6	16	10	32
IME-TM	3	7	15	25
IME	21	33	36	90

NETWORKS IN SCIENCE AND INDUSTRY

Networks in Science and Industry

International Activities and Cooperations with Industry

The Fraunhofer IME cooperates with many international research partners and remains in close contact with universities and other research organizations. The aim is to recognize trends and developments as they emerge, and to develop and implement novel research strategies and technologies.

In 2017, the Fraunhofer IME co-operated with around 100 national and international industrial clients and several international industrial associations for whom confidential projects were carried out.

Cooperation with Universities

The Fraunhofer IME has close ties with the Institute of Plant Biology and Biotechnology at the University of Münster, the Institute for Insect Biotechnology at the Justus-Liebig-University in Giessen, as well as the Institute for Clinical Pharmacology at the Goethe-University in Frankfurt.

Lecturing Assignments

Prof. Dr. Mark Bücking holds lectures in the degree program food chemistry at the Bergische Universität Wuppertal and is Associate Professor at Monash University Melbourne, Australia.

Prof. Dr. Harald Burkhardt is Head of the Division of Rheumatology at the University Hospital Frankfurt and Professor of Internal Medicine/ Rheumatology at the Goethe University Frankfurt.

Dr. Natasja de Bruin holds seminars at the Goethe University Hospital Frankfurt and is guest lecturer at the Donders Institute for Brain Cognition and Behavior, MSc Cognitive Neuroscience (Radboud University Nijmegen, the Netherlands).

Prof. Dr. Carsten Claussen is Honorary Professor for Information Systems at the Heinz-Nixdorf Institute of the University of Paderborn.

Dr. Andreas Ernst holds seminars at the Goethe University Hospital Frankfurt.

Prof. Dr. Dr. Gerd Geisslinger is Director of the Institute for Clinical Pharmacology of the University Medical Center Frankfurt.

Dr. Sheraz Gul is Adjunct Lecturer at the NUI Galway, College of Medicine, Nursing & Health Sciences, Ireland and was an invited instructor at "MSc (Toxicology) – Screening Molecular Libraries Module" at the King Abdullah International Medical Research Centre (KAIMRC), Saudi Arabia.

Dr. Matthias Kotthoff holds lectures in the degree program food chemistry at the Bergische Universität Wuppertal.

PD Dr. Bruno Oertel holds seminars at the Goethe University Hospital Frankfurt.

Prof. Dr. Michael Parnham is Professor of Pharmacology and Toxicology in the Faculty of Biochemistry, Chemistry and Pharmacy at Goethe University Frankfurt.

Dr. Ole Pless and Prof. Dr. Carsten Claussen hold lectures, seminars and work placements at the Faculty of Medicine of the University Hamburg (UKE).

Dr. Ole Pless holds seminars at the Goethe University Hospital Frankfurt.

Prof. Dr. Dirk Prüfer is Professor of Plant Biotechnology at the University of Münster.

Prof. Dr. Christoph Schäfers holds an Extraordinary Professorship for Eco(system) toxicology at the University of Münster.

Prof. Dr. Marc F. Schetelig is Professor for Insect Biotechnology in Plant Protection at the Justus-Liebig University Giessen.

Dr. Andreas Schiermeyer and **Holger Spiegel** provide lectures on Plant Biotechnology at the FH Aachen, University of Applied Sciences.

PD Dr. Susanne Schiffmann holds seminars at the Goethe University Hospital Frankfurt.

Prof. Dr. Stefan Schillberg is Honorary Professor at the Justus-Liebig University Giessen.

Prof. Dr. Christian Schlechtriem is Honorary Professor for Ecotoxicology at the University Siegen and holds lectures and courses at the RWTH Aachen University.

Matthias Teigeler holds lectures on Ecotoxicology at the University for Applied Sciences Bingen and the Technical University Braunschweig and is a lecturer for the Module Ecotoxicology, Advanced animal welfare training in fish toxicology, of "Berliner Fortbildungen".

Prof. Dr. Andreas Vilcinskas is Professor for Applied Entomology and Director of the recently established Institute for Insect Biotechnology, both at the Justus-Liebig University Giessen.

Dr. Carmen Walter and **Dr. Miriam Wolters** hold seminars at the Goethe University Hospital Frankfurt.

Memberships of Editorial Boards and Committees

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Editorial Board: Dr. Sheraz Gul

Drug Target Review
Scientific Contributing Editor:
Dr. Sheraz Gul

Environmental Sciences Europe
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Frontiers Media S.A.
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Prof. Dr. Dirk Prüfer

Frontiers in Pharmacology
Frontiers Media S.A.
Editorial Board:
Prof. Dr. Dieter Steinhilber

Handbuch der Bodenuntersuchung
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IMPRINT

Published by
Fraunhofer Institute for Molecular Biology
and Applied Ecology IME
Forckenbeckstraße 6
52074 Aachen
Germany

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Language editing and proofreading
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Concept and Design
Die Medialisten, Aachen

Production
Druckerei Schlömer, Düren

Reporting Period
1 January 2017 until 1 January 2018

Aachen, Münster, Schmallenberg, Gießen,
Frankfurt and Hamburg, March 2018

Photo Acknowledgements
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Facts 2017/18
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