Fraunhofer
IME

FRAUNHOFER INSTITUTE FOR MOLECULAR BIOLOGY AND APPLIED ECOLOGY IME

ANNUAL REPORT 2019

60 YEARS OF RESEARCH FOR TODAY, TO-MORROW AND THE DAY AFTER TOMORROW

60 YEARS: TEMPORA MUTANTUR, NOS ET MUTAMUR IN ILLIS

70 years of the Fraunhofer-Gesellschaft, 60 years of Fraunhofer at Schmallenberg, two good reasons to celebrate. On December 1, 1959, the Fraunhofer-Gesellschaft integrated the research laboratory founded two years earlier by Dr. Karl Bisa in Schmallenberg into the Fraunhofer Institute for Aerobiology IAe.

In 2019, the division "Applied Ecology and Bioresources" celebrated the 60th anniversary of the founding of the Fraunhofer site Schmallenberg. Initially with a focus on inhalation toxicology, it can be regarded as the origin of Fraunhofer health research. As the Institute for toxicology and aerosol research ITA moved to Hannover in 1985 (today Fraunhofer ITEM), in Schmallenberg environmental risk assessment of substances became the dominant issue (Institute for Environmental Chemistry and Ecotoxicology IUCT). Today, the branch of Applied Ecology holds a leading position in Europe regarding research for and development of substance-related test methods (OECD, EU, DIN/ISO), test strategies and evaluation concepts for environmental risk and consumer exposure assessment. It is acknowledged as scientific mediator between regulatory authorities and industry. Our success is reflected by the steady growth in business volume and staff. Both were doubled in the last 11 years at routinely high industry yields of more than 50 percent, triggering the current construction of new laboratory capacities and meeting rooms.
The branch Bioresources, funded by the LOEWE programme in Gießen, developed to become the leading research centre for insect biotechnology and will move into its new building in 2020. A core business is the valorization of biodiversity as a resource for the bioeconomy. Example platforms are the microbial strain collection taken over from Sanofi and a library of animal toxins. The division Bioresources develops innovative technologies for the sustainable control of detrimental and vector insects, for the industrial use of insects (insect farming) and the conservation of biodiversity.

The "Molecular Biotechnology" division was established 20 years ago and has further expanded its activities in white and green biotechnology. Together with industrial partners, a number of bio-economic processes and products have been transferred to commercial application, such as plant stem cells for the cosmetics industry, a cell-free expression system, an amylose-free potato variety and tires with natural rubber from alternative plant sources. A further focus at the Aachen location is the utilization of anaerobic bacteria to produce various alcohols and jet fuel from off-gases from the steel industry. Another focus is the High Performance Center "Networked, Adaptive Production" which has the aim to enable a much more flexible and efficient design of demanding value-added chains for the manufacture of technical and biological products. After three successful years, the three Fraunhofer Institutes IME, ILT and IPT in Aachen were granted a project extension of initially one more year with a planned consolidation from 2021 onwards, in order to exploit the opportunities offered by digitization for sustainable (bio)production. A further highlight is the market launch of a bicycle tire made from latex of the Russian dandelion - the optimization of the plant and the process for extracting the valuable material were established at Fraunhofer IME in Münster.

In cooperation with other Fraunhofer Institutes, the Translational Medicine division located in Frankfurt am Main and Hamburg fosters medical progress through transdisciplinary cutting-edge research. The so-called 4D concept plays a significant role in this regard. In order to optimally address the 4D ("Drugs", "Diagnostics", "Data", "Devices") to the benefit of the patient, experts from various scientific disciplines (physicians, natural scientists, computer scientists, engineers) need to work together. Based on the diversity of its constituent institutes, Fraunhofer is the only research organization that, is able to optimally apply all 4D in health research and thus constitutes the ideal partner for innovative development projects. Artificial intelligence and machine learning methods are increasingly being employed, for example, in the development of a digital twin in the Fraunhofer lighthouse project MED²ICIN together with an algorithm for testing biological age. In the course of expansion of a biobank, a strategic cooperation in the field of spondyloarthritides has been established with the German Rheumatism Research Center Berlin. Fraunhofer IME is also the strategic research partner of a US biotech company for the development of a drug for a rare disease. Our efforts to establish an inflammation clinic as an integrative concept for the effective treatment of immune-mediated diseases is of major importance. The aim is to connect excellent transdisciplinary research with interdisciplinary care, in an innovative and cost intelligent way, for the well-being of patients and to contribute to the development of sustainable healthcare in Germany.

Finally, we wish to thank all those who, through their continued commitment and support, have contributed to our success in 2019. 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 2020, stay healthy!

Frankfurt am Main, Schmallenberg and Aachen in March 2020

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

THE INSTITUTE

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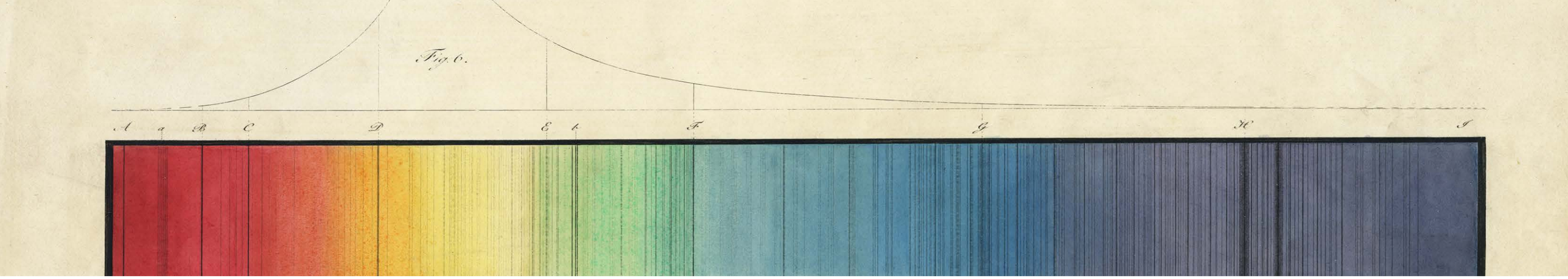
60 years ago, the research laboratory at the Schmallenberg location was integrated into the Fraunhofer-Gesellschaft.



60 YEARS OF HISTORY

The foundation of the Fraunhofer-Gesellschaft on March 26, **1949** laid the groundwork for the leading organization in the field of applied research and development in Europe. Fraunhofer IME is one of the first ten Fraunhofer Institutes.

1959 On December 1, a research laboratory set up by Dr. Bisa in Schmallenberg is integrated into the Fraunhofer-Gesellschaft named Fraunhofer Institute for Aerobiology IAe. Construction of the main building begins in the same year.

1969 The institute has now about 70 employees and is directed by Dr. Oldiges, Dr. Rüterjans and Prof. Stöber. The research focus lies on protecting people from air pollutants. Until 1971, it is financed mainly by the Federal Ministry of Defence.

1972 The German Federal Ministry for Research and Technology takes over the institutional support of the Fraunhofer-Gesellschaft. At Fraunhofer IAe, research questions of general environmental protection become more prominent.

1979 The institute is renamed to Fraunhofer Institute for Toxicology and Aerosol Research ITA and an additional location is added. The research focus "Human Health" under the direction of Prof. Stöber is the focus of toxicological research in Hanover. Dr. Oldiges is in charge of research at Schmallenberg focusing on the protection of the environment.

1982 Dr. Hochrainer, Dr. Oberdörster and their team were awarded the Joseph von Fraunhofer Prize for their research on the carcinogenicity of cadmium aerosols.

1983 Prof. Klein is appointed head at the Schmallenberg branch of the institute, initially together with Dr. Oldiges. The fate of chemicals in the environment and their effects on environmental organisms is now the focus of research.

1985 The Schmallenberg and Hanover locations are split into two independent Fraunhofer Institutes. Renaming the Schmallenberg location Fraunhofer Institute for Environmental Chemistry and Ecotoxicology IUCT reflects the institute's new research priorities.

1992 The Central Institute of Nutrition of the former Academy of Sciences of the German Democratic Republic (GDR) is the origin of the Fraunhofer IUCT branch "Department Biochemical Ecotoxicology" in Potsdam. It is closed seven years later.

1998 To strengthen the biotechnological competence of the Fraunhofer-Gesellschaft, the new department "Molecular Biotechnology" is founded at Fraunhofer IUCT under the direction of Dr. Fischer.
Prof. Klein was awarded the Order of Merit of the Federal Republic of Germany for his achievements in ecological chemistry.

2000 The Federal Environmental Specimen Bank is being set up at Fraunhofer IUCT in Schmallenberg as a long-term archive for documenting the state of the environment in Germany.
Dr. Fischer is appointed Chair of Molecular Biotechnology at the RWTH Aachen University.

2001 At the end of September Prof. Klein took his retirement. Prof. Fischer is appointed the new head of the institute. Dr. Schillberg receives the Joseph von Fraunhofer Special Prize for his research work on molecular farming. Due to the successful work in the department of Molecular Biology, the institute is renamed to Fraunhofer Institute for Molecular Biology and Applied Ecology IME. Fraunhofer IME is a founding member of the Fraunhofer Group for Life Sciences, a body strengthening the role of the biosciences within the Fraunhofer-Gesellschaft.

2006 The division Molecular Biology moves into its own new building near the RWTH Aachen University.

2008 The Fraunhofer Food Chain Management Alliance is founded. Under the leadership of the Fraunhofer IME division "Applied Ecology", several Fraunhofer Institutes are working jointly to improve food safety.

2009 A new Fraunhofer IME project group "Bioresources" headed by Prof. Vilcinskas is established at the Justus Liebig University Gießen (JLU). In the following years insect biotechnology is established at the JLU and Fraunhofer. The location in Gießen is appointed as a LOEWE Center (Hessen State Offensive for Development of Scientific-Economic Excellence).

2010 In cooperation with Prof. Prüfer's Department of Plant Biotechnology, the Fraunhofer IME branch lab "Plant Biopolymers" is launched at the University of Münster (WWU).

2011 Prof. Schillberg, Dr. Rademacher and Dr. Drossard were awarded the Fraunhofer Prize Human-Centered Technology for the development of a production platform for plant-based biopharmaceuticals.

2012 The new Fraunhofer Project Group "Translational Medicine and Pharmacology" starts its work at the Goethe University Frankfurt am Main with the help of LOEWE funding from the state of Hessen. Under the direction of Prof. Geißlinger, a LOEWE Center is being established in the following years, bringing together drug research, preclinical and clinical model development, and clinical research.

2014 With the integration of the European ScreeningPort GmbH in Hamburg into Fraunhofer IME, the institute is further expanding its strength in pharmaceutical drug research. The work of the cooperation project on natural rubber from Russian dandelion is rewarded with the GreenTec Award.

2015 Prof. Prüfer and Dr. Schulze Gronover, both Fraunhofer IME, together with Dr. Recker from Continental Reifen Deutschland GmbH are awarded the Joseph von Fraunhofer Prize for their research on the Russian dandelion and the development of its application.

2017 Prof. Fischer leaves Fraunhofer IME and hands over the acting management to the head of the locations in Frankfurt am Main, Schmallenberg und Aachen: Prof. Geißlinger, Prof. Schäfers and Prof. Schillberg. Prof. Geißlinger is executive director of Fraunhofer IME as well as Health Research Officer of the Fraunhofer-Gesellschaft. The institute is restructured into three divisions: Molecular Biotechnology, Translational Medicine, Applied Ecology and Bioresources.

2018 Fraunhofer IME, together with the other core institutes IZI and ITEM, establishes the Fraunhofer Cluster of Excellence for Immune-Mediated Diseases CIMD. The central aim is the translation of innovative ideas and identified targets into individualized therapies for immune diseases. Fraunhofer IME is instrumental in the conception of the PoC initiative of Helmholtz-Fraunhofer-German university medicine and receives one of four funded projects in the pilot phase. The institute is also involved in the MED²ICIN Fraunhofer lighthouse project.

2019 Our sixtieth year is marked by construction projects: In Gießen, the Bioresources branch will move into its new institute building, Translational Medicine is planning a new institute building in Frankfurt am Main and in Schmallenberg, extensive conversion and new building measures are in full swing.

Fraunhofer IME has written its own history over the past 60 years - and it is far from over. With the spirit of scientific inquiry to guide us, we invent the shape of things to come – the world of tomorrow and beyond. The future has always been our driving force for the development of sustainable solutions at the service of people and the environment.

FRAUNHOFER IME PROFILE

Since the beginning of 2017, Fraunhofer IME has comprised the three divisions of Molecular Biotechnology, Applied Ecology and Bioresources, and Translational Medicine. On July 1, 2018, the Executive Board of the Fraunhofer-Gesellschaft appointed Prof. Dr. Dr. Gerd Geißlinger as the Executive Director of Fraunhofer IME. He had been Acting Executive Director since January 2017. Prof. Dr. Schillberg and Prof. Dr. Schäfers are acting members of the institute management.

Fraunhofer IME is a strong partner for contract research in the areas of pharmaceuticals, medicine, chemicals, 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 2019, 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 process complex projects across departments and where appropriate, also focuses on cooperation with external institutes and partners. We work closely with basic research and are internationally networked. Our laboratories with state-of-the-art equipment and complex environmental simulation facilities allow us to offer a wide range of research and services as well as studies according to good laboratory practice (GLP).

At the end of 2019, the institute employed 533 personnel working at the Aachen, Münster, Schmallenberg, Gießen, Frankfurt am Main 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 the Goethe University Frankfurt, Frankfurt am Main, 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.

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, animal cells 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 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.

Symbols used in the annual report

MB Division
Molecular Biotechnology

AE BR Division
Applied Ecology and Bioresources

TM Division
Translational Medicine

70 YEARS OF FUTURE
#WHATSNEXT

FRAUNHOFER IME WITHIN THE FRAUNHOFER-GESELLSCHAFT

Founded 70 years ago, the Fraunhofer-Gesellschaft is the world's leading applied research organization. With its focus on developing key technologies that are vital for the future and enabling the commercial exploitation of this work by business and industry, Fraunhofer plays a central role in the innovation process. As a pioneer and catalyst for groundbreaking developments and scientific excellence, Fraunhofer helps shape society now and in the future. The Fraunhofer-Gesellschaft currently operates 74 institutes and research institutions throughout Germany. The majority of the organization's 28,000 employees are qualified scientists and engineers, who work with an annual research budget of 2.8 billion euros. Of this sum, 2.3 billion euros is generated through contract research.
The Fraunhofer Institutes are organized in eight thematically oriented alliances. Their goals are the technical coordination within the Fraunhofer-Gesellschaft, the bundling of core competencies and a joint appearance on the market. Fraunhofer IME is a member of the Life Sciences Network, a scientific-technological community of highly qualified experts from key areas of modern life sciences from six Fraunhofer Institutes and one Fraunhofer Research Institution.
www.lifesciences.fraunhofer.de/en.html

Institutes or departments of institutes with different competencies cooperate in Fraunhofer alliances to jointly develop and market a business segment. The Fraunhofer Alliances make it easier for customers to access the results and services of the Fraunhofer-Gesellschaft. Fraunhofer IME is involved in two alliances:
Fraunhofer Big Data and Artificial Intelligence Alliance: www.bigdata.fraunhofer.de/en.html
Food Chain Management: www.fcm.fraunhofer.de/en.html

Fraunhofer Clusters of Excellence promote the cooperative development and processing of system-relevant topics through an inter-institute research structure in a "virtual institute". Fraunhofer IME is one of the three core institutes of the Fraunhofer Cluster of Excellence for Immune-Mediated Diseases CIMD.
www.cimd.fraunhofer.de/en.html

High Performance Centers organize the collaboration between university and non-university research with industry. Universities, higher education institutions, Fraunhofer Institutes and further non-university research institutions work together at one location on specific topics in order to quickly transfer innovations to application. Fraunhofer IME in Aachen is involved in the "Networked, adaptive production" High Performance Center.
www.vernetzte-adaptive-produktion.de/en.html

Fraunhofer lighthouse projects put the focus on strategic objectives with a view to developing practical solutions from which economies such as Germany's can benefit. The projects aim to turn original scientific ideas into marketable products as quickly as possible. Fraunhofer IME is contributing its expertise to the lead project MED²ICIN.
https://websites.fraunhofer.de/med2icin/

The Fraunhofer Sustainability Network is an initiative of 20 Fraunhofer Institutes aiming to raise awareness within the Fraunhofer Gesellschaft for the integration of sustainability issues.
www.fraunhofer.de/en/about-fraunhofer/corporate-responsibility/governance/sustainability/fraunhofer-sustainability-network.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 2019, 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 am Main

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

Stefan Lütke Entrup
Gemeinschaft zur Förderung von Pflanzeninnovation e. V., Bonn

Prof. Dr. Heyo Kroemer (Deputy Chairman)
University of Göttingen, Göttingen

Prof. Dr. Joybrato Mukherjee
President of the University of Gießen, Gießen (guest)

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. Ulrich Rüdiger
Rector of RWTH Aachen University, Aachen (guest)

Dr. Karin Schlesier
German Federal Institute for Risk Assessment, Berlin

Prof. Dr. Angelika Vollmar
Ludwig-Maximilians-Universität München, München

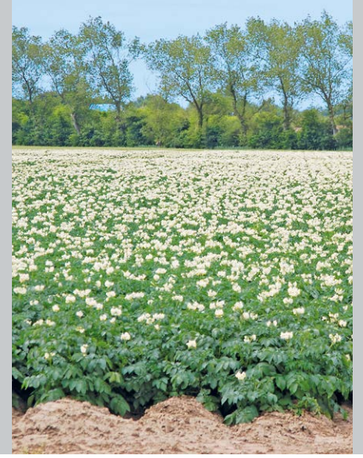
Prof. Dr. Johannes Wessels
Rector of the University of Münster, Münster (guest)

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

Prof. Dr. Birgitta Wolff
President of the Goethe University Frankfurt, Frankfurt am Main (guest)

The annual meeting of the Advisory Board was held on May 16, 2019 at Fraunhofer IME in Schmallenberg. The Executive Board of the Fraunhofer-Gesellschaft was represented by Dr. Johannes Landes, Director R&D-Contracts IPR.

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, bio based fuels, fine chemicals, biomaterials and proteins for industrial applications and consumer products. This can be produced using a diverse array of organisms, from microorganisms and plant cells through to animal cells.
Here the value chain is covered: From target discovery and screening, the development and optimization of production strains and the transfer of laboratory-scale processes to scale up and pilot-scale manufacturing for future industrial production and downstream processes, including the evaluation of economic feasibility.
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 metabolites and 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 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

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 as well as cell-free expression systems. 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.

MB

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MB

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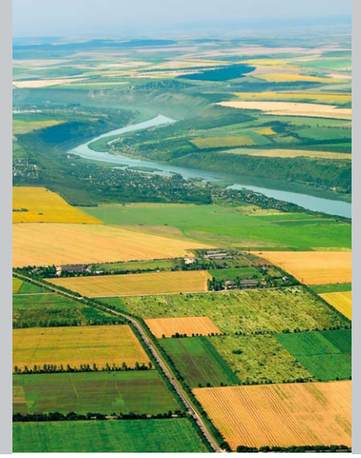
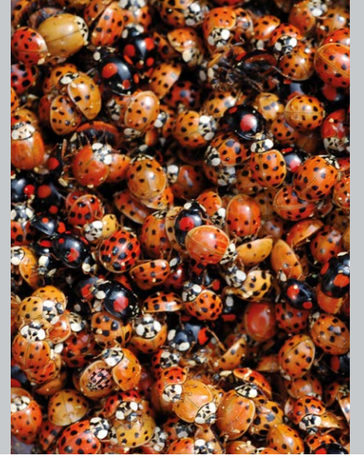
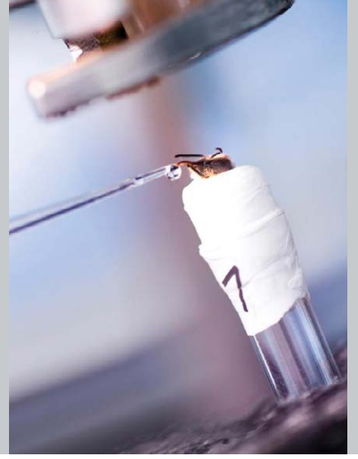
Molecular Biotechnology: Research, Development and Services

www.ime.fraunhofer.de/en/MB/RDS

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 $4C_2 4C$

We develop across divisions concepts for the sustainable agricultural production of substances for a diversified bioeconomy: **C**onnecting niches to **C**hains of bioeconomic value added for **C**ircular flow in a **C**limax economy. To achieve this, amongst other things, we use Fraunhofer technologies of the lead project **C**ognitive Agriculture to meet socio-economic and ecological requirements (**C**ommunity claims) with new **C**rops and changed livestock husbandry (**C**attle/livestock). We take into account differentiated soil and microclimate properties, the use and optimization of plants for the production of valuable and active substances (Aachen and Münster), and waste and insects for obtaining protein (Gießen). Regulatory requirements arising from digital agriculture in the application of plant protection products, veterinary medicines and fertilizers, are also taken into account (Schmallenberg).

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 Fraunhofer Evotec Natural Products Excellence Center for Infectious Diseases (FENPEC ID) with the world's largest industrial Sanofi strain collection of microorganisms is also available for projects with other industrial partners from non-competing fields of application.

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 and Bioresources: Research, Development and Services

www.ime.fraunhofer.de/en/AEBR/RDS

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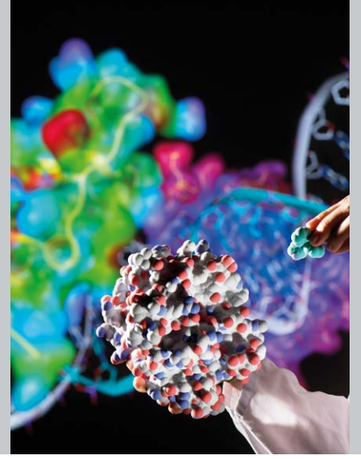
BUSINESS FIELDS TRANSLATIONAL MEDICINE



Assay Platforms and Drug Discovery

Our expertise is in modern drug discovery, enabled by our high quality screening collections totalling over 350,000 lead-like compounds, state of the art automated infrastructure and well-established in-house in silico screening platforms. This allows our partners to realise their projects from target validation through to preclinical studies. We have established an extensive portfolio of target, phenotypic and biophysical based assays, as well as in vitro disease models based on induced pluripotent stem cells. This allows us to investigate target "druggability" and enables mechanism of action studies. The "Fraunhofer IME Repurposing Collection" of over 5,500 small molecules, also offers an alternative path to quick clinical application. As a screening partner site in the EU-OPENSCREEN infrastructure, we provide access to synthetic chemistry, chemical proteomics and structural biology platforms.

TM

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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. 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.

TM

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Digital Health Research

We contribute to the digitalization of the pharmaceutical research by establishing the Fraunhofer "Medical Data Space", a decentralized data management system for the autonomous and secure storage and exchange of medical data between networked databases. For several pan-European projects we provide our expertise in bioinformatics by implementing a Data Scientist to ensure the highest standards in FAIR data management for drug discovery data analysis workflows, which integrate project, public and proprietary data. We further develop algorithms and AI tools for the statistical analysis of patient and virtual patient cohorts in the areas of diabetes, ageing research and - in collaboration with Germany-based cancer registries - in oncology.

TM

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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 am Main 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.

TM

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Translational Medicine: Research, Development and Services

www.ime.fraunhofer.de/en/TM/RDS

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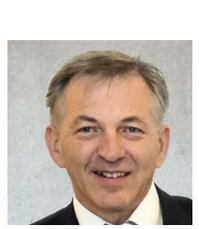

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INSTITUTE DATA

Budget

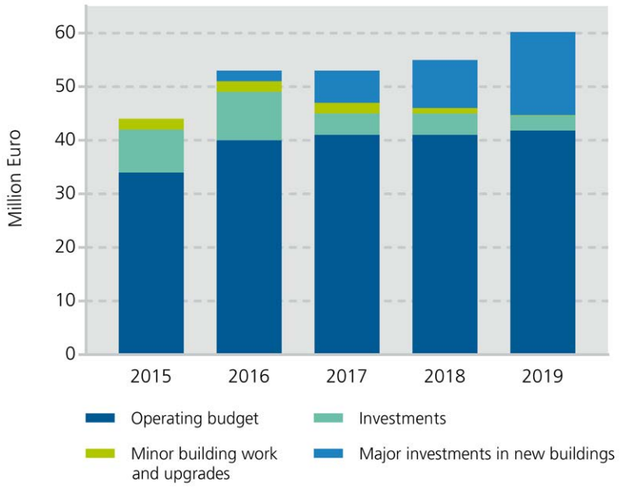
In 2019, the operating budget of Fraunhofer IME increased to a previously unreached level of 41.8 million euros. In addition, about 2.8 million euros were invested in equipment. Fraunhofer IME again recorded a significant increase in construction activities (approx. 15.6 million euros), primarily due to the construction of the new institutes in Gießen and Schmallenberg.

67.5 percent of the budget was financed by external income, or 77.7 percent if the locations in Gießen and Frankfurt am Main, which are mainly financed by the federal state, are included.

Economic earnings of 14.1 million euros remain at a constantly high level. This corresponds to an economic revenue share (Rho Wi) of 41.0 percent and 33.8 percent respectively.

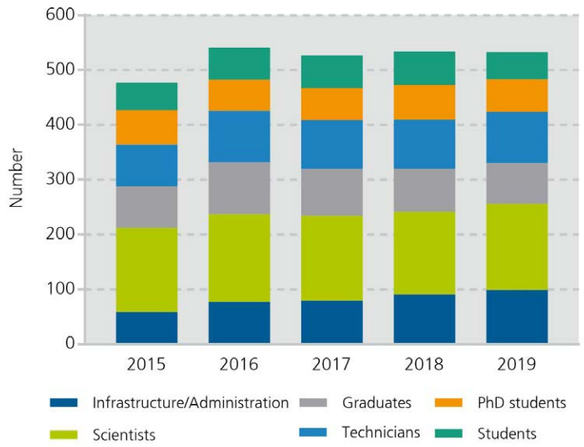
Thus, in 2019, Fraunhofer IME once again achieved excellent results in the key figures of the Fraunhofer-Gesellschaft.

Total budget of Fraunhofer IME



External financing of Fraunhofer IME

Employees of Fraunhofer IME



Personnel

At the end of 2019, 533 personnel were employed at the Fraunhofer IME locations in Aachen, Münster, Schmallenberg, Gießen, Frankfurt am Main and Hamburg.
In 2019, 53.7 percent of Fraunhofer IME personnel were female.

OUR RESEARCH

The radiokitchen – Quo vadis, molecule?

Colorful potatoes

Translation of research into medical applications

Insect virulence inhibitors for the therapy of lung infections

Recycling CO_2 emissions with bacteria

Using artificial intelligence to predict biological age

»2«

Fraunhofer IME is one of the first ten institutes to succeed in the turbulent early days of the Fraunhofer-Gesellschaft.

THE RADIOKITCHEN – QUO VADIS, MOLECULE?

Food processing often comprises many complex steps.

For an authorisation of plant protection products, their fate during food processing is currently simulated only by heating the active substance in water. A new laboratory at Fraunhofer IME now allows the performance of complex studies under realistic food processing conditions. First results show significant differences between current simulation procedures and reality.

A predominant portion of our food is processed prior to consumption. The desired properties of most foodstuffs are only obtained after cooking, baking or roasting steps. Complex chemical reactions occur during food processing and can lead to the formation of desired colouring or aroma components. Also, hazardous substances like acrylamide can be produced during such processes. Due to the enormous complexity of food processing the elucidation of such food chemical reactions often takes several years. A special laboratory kitchen – the radiokitchen – at Fraunhofer IME now allows the performance of complex and realistic food processing procedures using radiolabelled substances. The use of highly specific tracing of radioactivity of a substance and its degradation products can significantly speed up such studies in comparison to current approaches.

Plant protection products and food processing

Almost every conventionally grown agricultural product is treated with plant protection products. These agrochemicals serve as an integral part of modern agriculture. Even after correct application, residues of plant protection products in agricultural raw products cannot be avoided. To assess the potential risks of active substances and their degradation products to humans, animals, and the environment, active substances undergo an extensive registration and approval procedure. This includes complex studies to elucidate the fate and the action of substances in plants, animals, and the environment. As many foodstuffs are processed prior to consumption, the fate of plant protection products during food processing is of high interest for food safety. To investigate this fate the current registration procedure only requires heating of an active substance in water at maximum temperatures of 120 °C. Higher temperatures, as obtained for example during baking or frying processes, or chemical reactions with food ingredients are not considered so far. In a project in cooperation with Fraunhofer IVV we investigated how simulation studies compare to realistic processing steps.

Simulative trials often far from reality

When heating the fungicide prochloraz in rapeseed oil, an extensive degradation of the active substance was already demonstrated in preliminary tests. The radioactive label allowed an insight into the complexity of the degradation process. For the first time, processing-induced chemical reactions between an active ingredient and food ingredients like fatty acids and glycerol were proven. In total, the formation of eleven degradation products was observed. Many of these were described for the first time. The degradation process was found to be highly dependent on temperature, heating time and the type of oil used. In the simulation trials, however, a minor degradation with only a single degradation product was reported. During high-temperature heating of tomato products the insecticide deltamethrin also showed high discrepancies to the results of simulation trials. In the frame of the current procedure a broad degradation of the active substance was described. Despite temperatures of up to 250 °C, deltamethrin was found to be stable during the heating of tomato paste.

In a third trial, potatoes were treated with the sprouting inhibitor chlorpropham and were stored for up to six months. At different points of storage, individual tubers were withdrawn and boiled (100 °C), fried (170 °C) and baked (200 °C). In contrast to the opinion of the European Food Safety Authority no formation of the important compound 3-chloroaniline was observed during potato processing. Chlorpropham residues in edible products were reduced by 73 to 83 percent during the different processing steps.

The results clearly show that complex food chemical reactions during food processing cannot be reduced to simple heating experiments of substances in water. The tests with prochloraz in heated oil show that the reactions can be much more complex. At the same time, tests with deltamethrin and chlorpropham show that an increase in temperature and the presence of a matrix do not necessarily constitute a worst case scenario. Future tests are planned to investigate how the complexity of food processing for the authorization of plant protection products can be simplified to a few model tests. The identification of worst case scenarios can further increase food safety and consumer protection.

Tracing radioactivity as a shortcut

Furthermore, the results show enormous advantages of radioanalytical methods compared to normal techniques. The tracing of radioactivity allows the ability to obtain a full balance of the residues of the active substance and its degradation products. Also, this technique facilitates and accelerates the identification of potentially relevant new degradation products. Radioanalytical methods will be further used to better understand chemical reactions during food processing. For example, in a current project in cooperation with the Monash University in Australia we aim to elucidate the fate of nutrients during food processing. In this project, potential effects of processing-induced degradation products on human health are investigated.

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COLORFUL POTATOES

Anthocyanin-rich potatoes in the field and on the market.

Colorful potatoes are not only beautiful to look at, but also health-promoting, since they contain larger quantities of colored, secondary plant substances, so-called anthocyanins, than their pale counterparts. In order to make these anthocyanins accessible to many people, the project "MoMaPo" (Molecular markers for the generation of potatoes with enhanced anthocyanin content) is developing molecular tools for the targeted breeding of such potatoes.

Secondary plant compounds in human nutrition

Even in industrial nations with an excellent food supply and variety, fruit and vegetable consumption is often relatively low and well below internationally recommended levels. We cover the majority of our diet with a few basic foods such as rice, corn, wheat and potatoes. A human diet based predominantly on plants can make a valuable contribution to human health, especially if it is based on fruit and vegetables, since plant-based food always contains secondary plant substances in addition to the classic macronutrients carbohydrates, proteins and fats.

Secondary plant compounds are organic compounds that are mostly found in specialized cells, where they play an important role for the entire plant, e.g. in protection against predators or through their attractive coloring. Many of the secondary plant compounds also have positive effects on human health, which scientists know they can use. For example, most pharmaceuticals are based on plant secondary metabolites. But even today, the mechanisms of action of some secondary plant metabolites are still unknown. A large group of secondary plant substances are the water-soluble anthocyanins, which belong to the group of flavonoids. They are found in cell sap of almost all higher plants. They mostly also occur in the flowers and fruits, where they are responsible for the partly intensive red, violet or blue coloring. Hence, their name. It consists of two parts: Ánthos, the ancient Greek word for flower, and kyáneos, the ancient Greek word for dark blue or dark color. Anthocyanins have three main functions in plants: They absorb the short wavelength UV light of the sun and give the radiant energy as heat. This is how proteins and DNA molecules in the cells are protected from the harmful effect of the UV rays. In addition, the intense coloring attracts insects and other animals. They ensure the propagation and distribution of the plant. The anthocyanins also have a strong antioxidant effect. If the plant is exposed to oxidative stress, free radicals are produced, which react with oxygen molecules to form reactive oxygen radicals and exert a negative influence on the metabolism of the plant. Free radicals are also suspected to be associated with various diseases in humans. Anthocyanins are able to render free radicals harmless and are therefore said to have health-promoting effects. Studies in humans and animals have shown that anthocyanins have anti-inflammatory, anti-viral and anti-carcinogenic properties. In addition, positive effects on cardiovascular disease, obesity, increased cholesterol levels and memory performance were observed.

Most staple foods, such as wheat or rice, are relatively poor in anthocyanins, so fruit and vegetables are currently the main source of anthocyanins in human nutrition. Potatoes are an exception, as old, lesser-known blue- and red-fleshed potato varieties whose color is due to the presence of anthocyanins exist, in addition to the yellow- and white-fleshed ones. Especially in South America there are still many colored old landraces to be found, which can be used for the breeding of modern efficient potato varieties with a high content of anthocyanins.

Potato breeding with molecular tools

Potato breeding is a complex process and in particular the genetics of quantitative traits such as the anthocyanin content in tuber flesh is difficult to resolve. New varieties are developed by combination breeding by crossing two varieties or clones with desired properties. The crossing and selection processes for the generation of a new potato variety in the classical way takes about ten years.

By the use of molecular markers for different characteristics, this process can be significantly shortened. Early in the selection process, those offspring can be selected that will develop the desired characteristics. For example, plants could be selected that are resistant to certain diseases without the necessity to carry out very complex resistance tests in the field or greenhouse. Such an approach is known as marker-assisted selection or "smart breeding". The use of such markers is indispensable for certain characteristics. If, for example, colored landraces are crossed with uncolored elite varieties, uncolored offspring can develop because important alleles for anthocyanin production split off. In order to restore the characteristic high anthocyanin content, lines containing different complementary alleles must be combined in further crosses. Therefore, such advantageous alleles must be identified at the molecular level in order to provide the necessary tools for such breeding, which is the primary goal of the binational cooperation project "MoMaPo". The participating partners Universidad Austral de Chile, Fraunhofer Chile Research and Fraunhofer IME were able to use the potato gene bank of the Universidad Austral de Chile, which represents the extraordinary biodiversity of Chilean potatoes. An important part of this gene bank are the potatoes collected in the area of Chiloe Island, which are characterized by a particularly high diversity in the characteristic of colored mark tubers. 290 of these plants were analysed for potential markers of increased anthocyanin content. The results obtained were then bioinformatically associated with the anthocyanin content determined, so that molecular markers could be identified which may be used in the future for breeding new potato varieties with coloured tuber flesh.

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TRANSLATION OF RESEARCH INTO MEDICAL APPLICATIONS

Drug development is closely linked with the identification of endogenous molecules as targets for therapeutic agents. However, the relevance of these molecular targets for the treatment of the specific disease must first be proven. This target validation process requires standardized, robust, reproducible and high quality testing procedures. Fraunhofer IME is part of a consortium that for the first time has developed guidelines for optimizing such a process.

The "Critical Path Concept" is designed to support researchers in developing a validation process for their project.

The challenge in biomedical research

Despite the diversity of medicines, the effective treatment of many diseases is either inadequate or impossible. Although the medical demand is very high, no new drugs for the treatment of diseases like Alzheimer's have reached the market for years. The medical community is also desperately searching for new antibiotics, yet the big pharmaceutical companies recently announced their withdrawal from this research area.

In the scientific world and even in society, the "reproducibility crisis" in biomedical research has been an intensively discussed issue for a long time. This unsatisfactory situation is at least partially responsible for the deficit in the implementation of potential targets for drug development.

The discovery of such biological targets is the basis for the development of novel drugs. Knowledge about new targets originates mainly from basic research at universities and non-university research institutions. This is where discoveries are made that shed light on fundamental pathological processes leading to the development of diseases. In order to be able to translate this knowledge into clinically applicable therapeutic approaches, validation of the target according to industrial standards is mandatory. Such validation processes must be robust, reproducible and well documented. They must be carried out under defined quality conditions and be backed up by sufficient statistical evidence. A major reason for the lack of application of suitable approaches from basic research is lack of knowledge of these industrial requirements and standards in target validation within the academic environment.

The GOT-IT guidelines

At the level of funding bodies, the message has also been heard that the translation of academic research results into medical applications must be improved and promoted.

With the "National Drug Initiative", the Federal Government has set itself the goal of strengthening drug research and promoting the development of new drugs. As part of this initiative, the Federal Ministry of Education and Research (BMBF) has already provided various funding measures dealing with the topic of target validation. The project "Guidelines On Target Validation for Innovative Therapeutics", or GOT-IT for short, was developed as part of these extensive funding measures. A consortium consisting of scientists from the Charité in Berlin, the consulting firm PAASP in Heidelberg and Fraunhofer IME in Frankfurt am Main has developed guidelines for robust target validation that can be used and implemented in the academic environment.

Initially, the consortium carried out a comprehensive analysis of the scientific literature on target validation. In this process, different priorities were set, such as the relevance of the model organism used, the number of test systems and evaluation methods employed, and the application of various quality criteria. The results show that, among other things, quality aspects such as the blinding of studies and the calculation of the sample size have been taken into account in only a very few studies. Based on the results of the literature analysis, guidelines were developed in dialogue with other scientists together with experts from industry and transfer societies. These guidelines are already being taken into account for the evaluation of project proposals for new BMBF funding measures.

The guidelines were designed to be applicable to as many clinical indications as possible - from infection to neuroscientific research. The GOT-IT consortium has defined "validation blocks" for the guidelines, which should be taken into account when developing a project. They address the link between target and disease, safety aspects, innovation and technical feasibility. For each of these validation blocks critical questions are suggested, the answers to which should help the researcher to identify the most relevant aspects of the validation process to address for a specific project. With these tools, the researcher should be able to develop an individual project-related critical path.

Online tools

Currently, online tools are being designed to develop structured plans for a target validation project. In addition, the GOT-IT consortium is creating a learning application for young academics involved in target validation and an online networking platform where academic and industrial scientists can interact with each other (www.got-it.app). With these tools, the GOT-IT recommendations should be made available to a broad user group. They should support academics in implementing industry-like processes for target validation and make an important contribution to improving the quality and applicability of academic research results.

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INSECT VIRULENCE INHIBITORS FOR THE THERAPY OF LUNG INFECTIONS

The larvae of the greater wax moth produce a large repertoire of antimicrobial peptides.

The researchers used bioreactors to produce larger quantities of IMPI.

Thermolysin-like metalloproteases such as pseudolysin (*Pseudomonas aeruginosa*) are highly toxic and are considered important virulence factors, since humans do not have any endogenous inhibitors against these bacterial enzymes. So far, the only selective virulence blocker has been discovered in the larvae of the greater wax moth, *Galleria mellonella* - the Insect Metalloprotease Inhibitor (IMPI). IMPI is used to develop a new therapeutic approach against lung infections.

Alternative therapeutic approach for the treatment of lung infections

In Europe, more than 33,000 people die each year from infections with resistant pathogens. The identification of new active ingredients with antibacterial activity and their development into antibiotics is very costly and involves a high risk. Effective new strategies to combat resistant pathogens are urgently needed - especially in lung infections, which are among the leading causes of death according to the World Health Organization (WHO). One of the most common pathogens in hospitals that develop resistance to antibiotics used in hospitals is the gram-negative bacterium *Pseudomonas aeruginosa*. This bacterium initially attaches itself to a region where the host's defence mechanism is already weakened (e.g. by trauma, burns, surgery, etc.). Extracellular virulence factors are then released, causing further damage to host tissue until the bacterium enters the host's bloodstream and spreads throughout the body. As the infection progresses, the attached colonies form a biofilm that provides effective protection against the host's immune response.

Virulence factors are essential for infection and their persistence and the selective inhibition of these factors is an attractive new strategy in the fight against emerging antimicrobial resistance. This approach of an alternative treatment strategy does not focus on the immediate killing of the pathogens, but on the neutralization of their pathogenicity or virulence factors. Pseudolysin, one of the crucial virulence factors of *P. aeruginosa*, is an M4 metalloprotease. Among the bacterial exotoxins, metalloproteases belonging to the M4 family play a prominent role. These are not only essential as virulence factors, they also cause symptoms associated with infections such as haemorrhagic bleeding, necrosis and sepsis. However, the inhibitors of M4 metalloproteases that have been tested so far are not suitable for the development of new anti-infectives, as they also inhibit human matrix metalloproteases and can therefore cause serious side effects. The search for innovative virulence blockers is thus focused on molecules that act highly specifically against thermolysin-like metalloproteases without inhibiting human enzymes. The only selective inhibitor of microbial M4 metalloproteases described so far is a peptide derived from insects, the Insect Metalloprotease Inhibitor (IMPI). Within the BMBF-funded project "Inhalable Virulence Inhibitors from Insects for the Therapy of Lung Infections" (4-IN), the optimization of IMPI and its preclinical testing with regard to its potential as a novel agent for the prevention and treatment of lung infections is addressed.

IMPI - antimicrobial peptide from *Galleria mellonella*

IMPI is an isolate from the larvae of the greater wax moth, *Galleria mellonella*, which are capable of producing a large repertoire of antimicrobial peptides. As part of the humoral immune response to an infection caused by bacterial or fungal pathogens, IMPI was isolated from the larval hemolymph. The characterization of the IMPI revealed a peptide stabilized by five disulfide bridges and about 8 kDa in size, its mode of action is based on its binding to the active site of the metalloprotease. Due to the five disulfide bridges and molecular interactions with the protease, IMPI retains its structure after cleavage, between amino acids N56 and I57, by the protease and reversibly inhibits protease activity.

Biotechnological production of antimicrobial peptide

With the development of a new therapeutic approach against lung infections, based on the IMPI molecule, the excessive use of broad-spectrum antibiotics will be simultaneously reduced. In order to investigate the potential effect of IMPI in more detail, a suitable manufacturing process had to be developed first. For this purpose, the bacterial expression system *Escherichia coli* was chosen. Due to the complex folding of the peptide, only selected strains are suitable for production - these strains are capable of forming the five disulfide bridges, which are crucial for the successful inhibition of M4 metalloproteases.

With regard to the development of a production process for biopharmaceuticals, the media development for the fermentation was exclusively carried out using chemically defined substances. An optimization of the media formulation as well as the process parameters by means of statistical design of experiments led to the development of a fed-batch process with high cell densities during IMPI production. The transferability of the fermentation process was demonstrated after establishing suitable scale-up criteria from 0.5 L to 7.5 L and 20 L scale. In addition to recombinant production, the focus of process development was also on the establishment of a suitable purification method. In the course of this DSP development, a chromatographic purification strategy was successfully implemented to obtain a pure product and remove endotoxins.

Efficacy and toxicity studies of the IMPI are performed by the cooperation partner, the Fraunhofer Institute for Toxicology and Experimental Medicine ITEM in Hannover. Once suitable cell infection models have been established, the effectiveness of optimized IMPI variants against the pathogen *P. aeruginosa* can also be investigated in the form of a combination therapy with antibiotics or other potential antimicrobial peptides. This allows a further extension of the efficacy range for evaluation in in vitro and in vivo models of pneumonia with antibiotic-resistant pathogens.

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RECYCLING CO_2 EMISSIONS WITH BACTERIA

Steel plants emit tons of CO, CO_2 and H_2 as off-gas, a valuable substrate for some bacteria.

The number of passengers is constantly increasing - the goal is a sustainable production of jet fuel.

Microorganisms are tiny all-rounders. They are able to produce numerous substances from a wide variety of chemical substance classes. Even when using different substrates, they are not picky. It is therefore possible to use them as microbial cell factories in order to produce useful basic chemicals and fuels from exhaust gases using biotechnology.

The vast majority of scientists worldwide agree - climate change is man-made. The use of fossil resources for the production of basic chemicals and fuels releases large amounts of carbon dioxide (CO_2). As a result, fossil resources are depleting and the concentration of CO_2 in the air rises continuously, accelerating climate change with all its negative effects. In 2018 alone, around 4.4 billion passengers were transported by aircraft and 359 billion liters of jet fuel were consumed, and the numbers are increasing. But what can we do if society does not want to do without everyday things and travel? One option is to use alternative sustainable biotechnological production processes. Bacteria possess biosynthetic pathways for a large number of chemical substances. For example, bacteria of the genus Clostridium can produce solvents such as acetone, but also acids such as acetic acid and a number of alcohols such as ethanol, butanol and hexanol. Traditionally, sugar extracted from plants is used as the substrate in this process. In order to feed a growing world population, industrial raw materials must not compete with the production of food. Furthermore, they must be cheap and available in large quantities. One part of the solution could be the recycling of off-gases from the steel industry. Large quantities are generated during steel production - around 1.4 tons of CO_2 are emitted per ton of steel. These gases also consist of carbon monoxide (CO) and hydrogen (H_2). Certain bacteria such as *Clostridium ljungdahlii* are able to use CO_2 and CO as a source of carbon for their growth and the production of various metabolic products. CO and H_2 serve as an energy source. How do you get the bacteria to synthesize specific substances and furthermore to produce large quantities of these?

Stable integration of non-native biosynthetic pathways into the genome of *Clostridium ljungdahlii*

Not all desirable products can be produced by the bacteria recycling the gas. By introducing genes of known biosynthetic pathways, the product spectrum can be considerably expanded. An intermediate product common to all organisms serves as the starting substrate for these "imported" biosynthetic pathways: Acetyl-CoA. It can then be enzymatically converted into a product in several steps. The basic chemicals obtained in this way need to be extracted and can subsequently be processed chemically for manufacturing everyday products. Acetone is converted into plexiglass, isoprene into rubber, and ethanol, butanol and hexanol into fuel.

In order to establish the somethimes very complex biosynthetic pathways in the cells, the genes of the biosynthetic pathway are introduced as DNA fragments and integrated into the genome in order to obtain a stable production strain. In this way, the use of antibiotics as selection markers for cultivation are not necessary. The development of methods for the transfer and integration of large biosynthetic pathways in *C. ljungdahlii* was established at Fraunhofer IME and was recently published in the journal "Biotechnology for Biofuels".

Proof-of-concept: From off-gases to jet fuel

A fermentation system was optimized for the utilization of the toxic and potentially explosive gases CO, CO_2 and H_2 by the gas-fermenting clostridia. A gas mixing system for the testing of different gas compositions was installed. Furthermore, first process parameters were improved. As part of a Fraunhofer-Gesellschaft funded MAVO project, the products resulting from gas fermentation with clostridia were purified and chemically processed in collaboration with Fraunhofer ICT and Fraunhofer UMSICHT. After oligomerization of acetone, butanol and hexanol, it is now feasible to obtain a complex high-molecular mixture that can serve as drop-in fuel for aviation fuel.

Metabolic engineering and optimization in current projects

Based on the promising results of the MAVO project on the targeted genetic modification of bacteria for the production of specific basic chemicals and their further processing, additional projects in this field are underway. Following proof-of-concept, the cells are now being optimized to increase product yields. Possible bottlenecks in the biosynthetic pathway no longer remain a black box, but can be identified by transcriptome, proteome and metabolite analyses. In addition to the identification of more efficient enzymes for the biosynthetic pathway used, alternative competing biosynthetic pathways can be eliminated by using methods employed at Fraunhofer IME for these organisms, such as random chemical mutagenesis or directed mutagenesis using CRISPR/Cas9. The product quantities are analyzed by GC-MS-MS to screen for the best strains. The aim is to identify production strains that are suitable to ensure an economical and sustainable production of the desired molecules on an industrial scale. In addition to the extraction of chemicals for the production of jet fuels, there are numerous other industrial applications. We are currently working on several projects with different objectives: The EU-funded H2020 project BIOCON-CO_2 focuses, among other topics, on the utilization of CO_2 to produce isopropanol, butanol and hexanol, and the BioCOnversion project coordinated by CLIB and funded by the BMBF pursues the utilization of CO from steel plants to produce a plastic precursor.

MB

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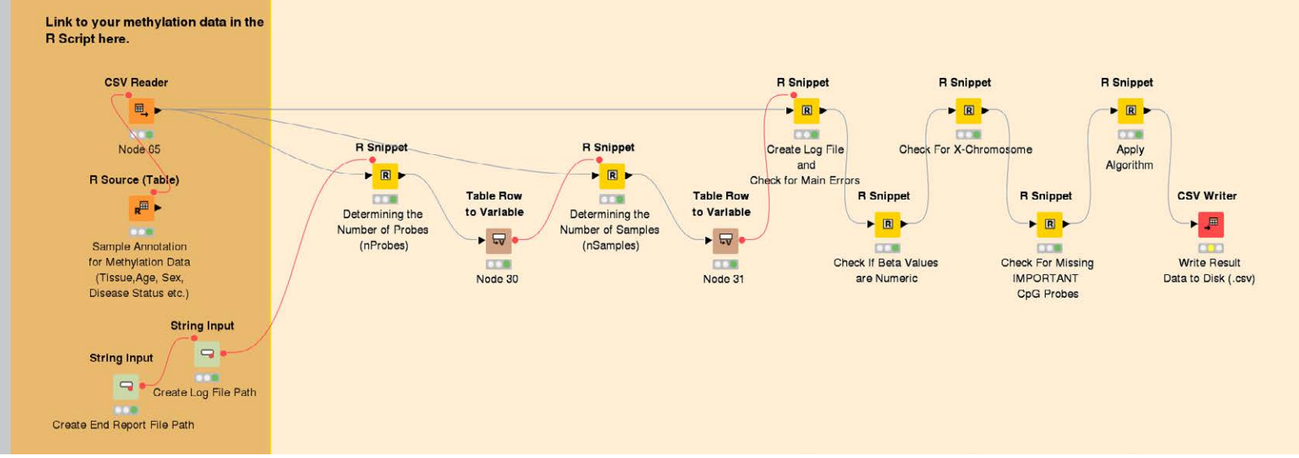
USING ARTIFICIAL INTELLIGENCE TO PREDICT BIOLOGICAL AGE



KNIME workflow for analysing provided epigenetic data.

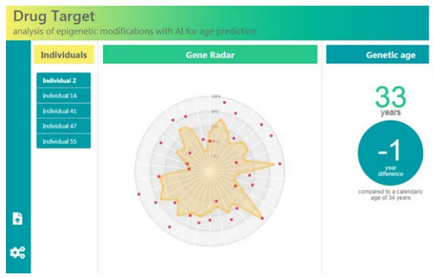
The global average life expectancy is currently at its highest, which has largely been driven by medical advancements. In ageing populations, the quality of life may be compromised and measures can be taken which will reduce the risk of being afflicted by diseases through diet and exercise. One relatively new addition in determining the health of an individual at the cellular level makes use of advanced sequencing technologies and artificial intelligence. Our cutting edge research is presented herein.

Correlating epigenetic changes with the ageing process enabled by advanced sequencing technologies

The genetic code is largely constant throughout life. However, in the epigenetic code, significant changes do occur, which encompass heritable changes in gene expression that do not involve changes to the underlying genetic code. Epigenetic changes are now known to be a regular occurrence influenced by many variables such as age, lifestyle, disease and environmental factors. One of the most widely studied epigenetic changes is methylation of the genetic code. This process involves the transfer of a methyl group (CH_3) to the C5 position of cytosine, forming 5-methylcytosine (5mC), which are also known as CpG sites. Methylation of genes has a direct impact on gene expression and there is growing evidence that it correlates with the biological age of an individual and may not correspond to the number of years a person has been alive, namely their chronological age. We have worked in collaboration with Cerascreen GmbH and developed an algorithm that can successfully predict an individual's biological age from the epigenetic profile of the DNA extracted from a saliva sample. The biological age can be used as a surrogate for the health of an individual in a broad sense. Below is a description of the Biological Age test developed in a collaboration between Fraunhofer IME and Cerascreen GmbH.

The Biological Age Test workflow and output

Following extraction of DNA from each saliva sample, we use the Illumina sequencing platform to determine the CpG profile of an individual. Our algorithm is subsequently utilized to analyze the CpG data and predict the biological age of an individual. Overall, the methylation of 800,000 sites are measured and our algorithm has been refined such that we only require CpG sites of 130 genes to reliably predict the biological age. It is to be noted that 30 of these genes code for proteins for which assays are available to monitor their functional activity. In addition, small molecule modulators for these 30 proteins have been reported in the literature, which demonstrates their druggability. These proteins are currently being evaluated as drug targets with the aim of identifying chemical modulators which may halt or even reverse biological aging.

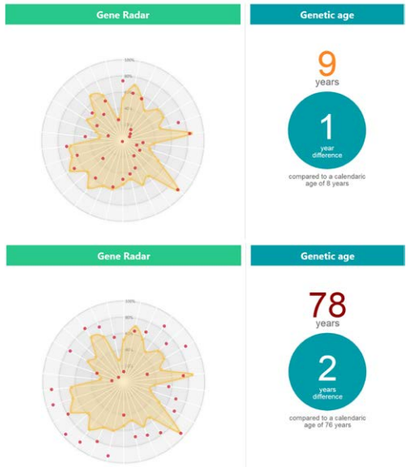


Graphic User Interface for the Biological Age Test. The Gene Radar plot indicates the extent of methylation for each of the 30 genes correlating with ageing.

Fraunhofer IME has developed a Graphical User Interface (GUI), which provides a visual representation of the epigenetic profile of an individual. The capabilities of the GUI will be expanded to include analysis of additional health related information.

Modulation of the ageing process – making this a reality using in vitro techniques and artificial intelligence

The above research has led to the identification of 30 genes whose profiles alter during ageing. This is exemplified by the Gene Radar plots for a 9 year old and a 78 year old individual.



Comparison of the methylation (red dots) of 30 genes for a 9 (above) and 78 year old (below) individual. Orange area: Average methylation across all ages.

In a Proof-of-Concept study, five druggable protein targets (from the above mentioned 30 genes) were prioritized and miniaturized screening compatible assays were developed. These were subsequently screened against a library of 800 chemical compounds with known safety properties. The outputs of the Proof-of-Concept screening have successfully yielded compounds which are modulators of the targets of interest. As these have been shown to be linked to biological ageing, we propose to initiate screening campaigns for each target using larger compound libraries in order to identify novel compounds. Fraunhofer IME is currently working closely with Cerascreen GmbH to secure funding for this work and hope to identify new compounds that offer the potential to halt or even reverse the ageing process. In order to protect the intellectual property that has been generated from this project, a PCT patent application has been submitted.

TM

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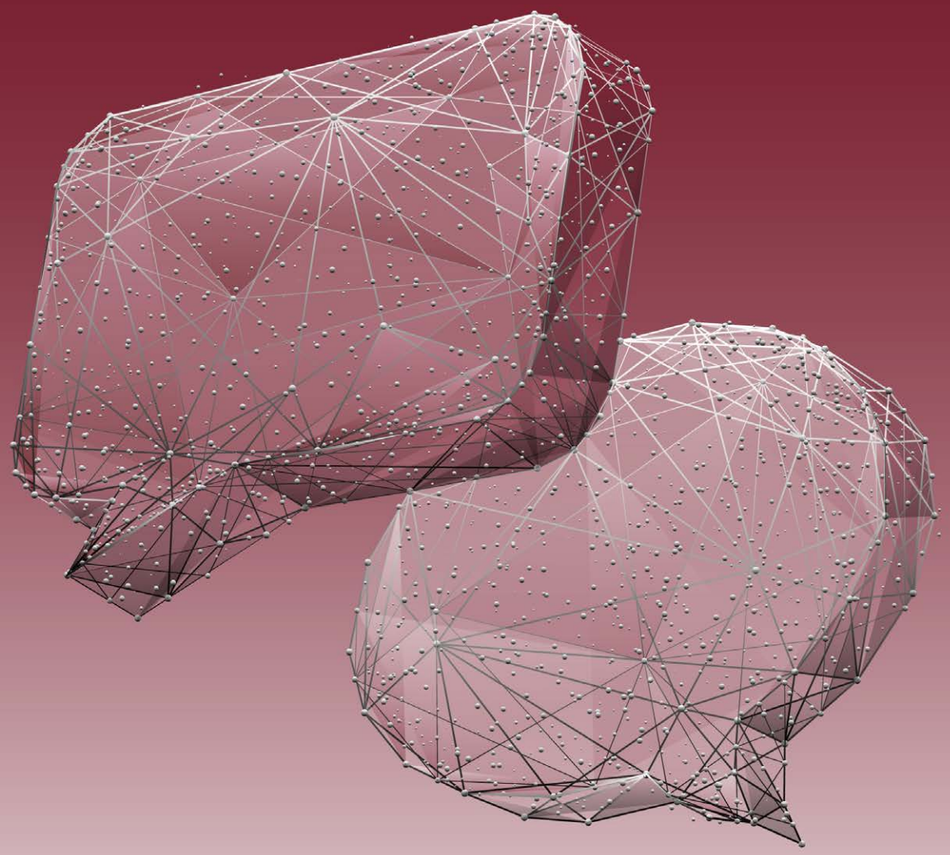

IN DIALOG

An Interview with Dr. Kwang-Zin Lee

Background

Dr. Kwang-Zin Lee studied biology at the Eberhard Karls University in Tübingen. After his doctoral thesis at the Max Planck Institute for Developmental Biology, he conducted several research stays abroad, including at the University of Western Ontario in Canada, the Centre d'Immunologie de Marseille-Luminy and the Insitut de biologie moléculaire et cellulaire in Strasbourg, France. Since 2016 he is working at the Branch for Bioresources at the Fraunhofer Institute for Molecular Biology and Applied Ecology IME in Gießen, Germany. There he established the research group for insect pathogens. In 2017, he took over as head of the Biodiversity department and established the new department of Biological Plant Protection at Fraunhofer IME in Gießen, of which he is head since 2018. His goal is to develop customized solutions for biological plant protection from natural insect pathogens such as bacteria, fungi and viruses.

»3«
Bioresources

In 2009, the Fraunhofer IME project group "Bioresources" was established in Gießen under the leadership of Prof. Dr. Andreas Vilcinskas.

BIOLOGICAL PLANT PROTECTION: WITH MICROBES AGAINST INSECT PESTS

The spotted wing drosophila originates from Asia and has also been common in Germany since 2011. It infests fruit crops such as cherries.

To develop biologically safe crop protection products, Dr. Kwang-Zin Lee and his team focus on isolating and developing natural antagonists of insect pests. One of the model systems used in his research is the invasive spotted wing drosophila *Drosophila suzukii*, which is currently responsible for major agricultural damage in fruit growing both nationally and internationally. Natural viruses and bacteria are isolated from the fly as microbial antagonists and tested for their suitability in biological plant protection. Dr. Lee and his colleagues are testing whether these viruses and bacteria can be used directly as biologicals or the effective natural substances extracted from them in modern crop protection. At the same time, innovative methods for the large-scale production of the candidates in the bioprocess area are being developed together with partners from science and industry.

Dr. Lee, you studied biology. What appealed to you in this subject and your future career? What does your everyday working life look like today?

I have to go a bit further, since my childhood I have a strong interest in animals, especially insects, according to my mother one of my first words was “ant”. Everything living possessed a special attraction for me. It was already clear to me as a child that I wanted to become a biologist. As my career progressed, my everyday work gradually shifted from the laboratory to more office work. At the beginning as a research assistant I was still actively involved in the laboratory. The tasks as a group leader can be envisaged in such a way that more time is invested in the planning and design of projects and the resulting work packages. In addition, there are teaching activities for the new master's course in “Insect Biotechnology and Bioresources” at Justus Liebig University and various administrative tasks.

How do classical and “modern“ pest management differ? How do you estimate the potential?

Until today, classical pest management has been based mainly on chemical insecticides. Unfortunately, these are accompanied by not inconsiderable undesirable side effects, such as negative effects on human health and the environment, the development of resistance of harmful organisms to these insecticides and collateral damage to non-target organisms such as bees and bumblebees. One promising approach is biological pest management. Biological plant protection involves the use of various macro- and microorganisms. The macro-organisms are generally predators or parasites of the harmful organisms. These are mainly insects, spiders and nematodes, which are also commercially available and are actively used as beneficial insects. The majority of beneficial insects are used for greenhouse cultivation. Ladybirds, for example, are known to be important aphid antagonists. We study microorganisms such as bacteria, fungi and viruses. These insect pathogens generally have a high host specificity and can be specifically applied against certain insect pests. The public opposition to chemical insecticides has also led to a rethink in the crop protection industry, so I believe that the future potential for biological crop protection is very high.

Your team is dedicated to biological plant protection using insects. Why insects of all things? What specific research approaches do you pursue?

Insects are one of the most evolutionarily successful and by far the most species-rich class of animals of all. Over a million species have been described, each of which represents a large reservoir of insect-pathogenic microorganisms. An insect pathologist therefore has an almost unlimited number of insect-pathogenic candidates and combinations for the application of insect pathogens. As mentioned above, many insect pathogens are very host-specific, i.e. ideal for the development of tailor-made insect control if only a defined pest is to be controlled.
We need an environmentally sound method to control insect pests, our strategy is based on the use of natural insect pathogens.

We are currently isolating insect-pathogenic microorganisms regionally from harmful insects. For this purpose, we specifically collect sickly, so-called moribund, insects and isolate their pathogens from them. The samples are prepared using two different methods. After homogenization, one sample is spread directly onto culture plates and incubated to enrich bacteria or fungi.
The other sample is sieved through a 0.22 µm fine filter to specifically isolate viruses. The results obtained with natural viruses from the spotted wing drosophila *Drosophila suzukii*, an invasive insect that is highly damaging to ripe fruit, should be highlighted. There we succeeded in isolating and identifying a virus that has an insecticidal effect against the fly. This virus is quite new and has not yet been characterised in detail. We are working to extract from this virus with different methods by optimizing the efficacy, establishing mass production and developing suitable formulations, to ultimately be able to bring a biologically safe agent against the spotted wing drosophila to market maturity.

The spotted wing drosophila infests soft-skinned fruits. It lays its eggs inside intact fruits and causes enormous harvest losses.

In Germany, the first infestation by the spotted wing drosophila was observed on wine in 2011.

Why do you think Fraunhofer IME in Gießen is the ideal environment for this type of research?

The environment at Fraunhofer IME is particularly stimulating because we have many colleagues with excellent expertise in a wide range of fields such as applied entomology, microbiology, molecular biology, microbial genomics, bioinformatics, analytics and bioprocess technology, and we have established excellent interdisciplinary networks to solve research questions and develop products. This means that we are able to map closed project cycles within Fraunhofer IME, in which every area benefits. A small example: If we isolate and identify microorganisms in our department that have no direct effects on the respective harmful insects, this is of course a pity for our research and development. But, if the microorganisms produce interesting natural substances, they might be of interest to colleagues in other departments focusing on bioresources. We can then for example pass them on to our colleagues in the Department of Natural Products Research. It is particularly important for us to work closely with colleagues who integrate our new microorganisms into Fraunhofer IME's own strain bank using state-of-the-art technology, who carry out analyses of the transcriptome and genome data for strain characterisation, who assist in the necessary tests and data acquisition for risk assessment and who are indispensable partners in the identification of new lead structures. In addition, through close cooperation with the Justus Liebig University and its Institute of Insect Biotechnology, as well as the THM (Technische Hochschule Mittelhessen - University of Applied Sciences), we also have strong local partners with whom we have a centre in Central Hessen in the translational life sciences that is unique in this form, both nationally and internationally. Through the international master's degree program “Insect Biotechnology and Bioresources“, we also inspire young scientists to pursue this field of research. In addition, I find direct contact with industrial partners, associations and farmers very important, which gives us a sharper focus on the development of required products and services. Fraunhofer IME is thus a mediator between basic research and industrial research, and I personally enjoy being involved in this interdisciplinary field of conflict.

What are the advantages of biological pest management? Will we soon be able to dispense completely with chemical pest control agents?

The advantage of biological pest management processes based on microbial antagonists over conventional pest control is the generally high selectivity and thus the low risk to humans and the environment. Of course, there are also disadvantages; the production of biological pesticides is usually associated with higher costs compared to chemical substances. Since we cooperate with internal partners and experts in bioprocess optimization, I believe that we can find solutions that make the processes more economical.

No, in the short term I don't see any possibility of completely dispensing with chemical pest control. I would see biological plant protection with insect pathogens as part of an integrative pest control measure in which at least the proportion of chemical pesticides can be significantly reduced.

Finally: What do you enjoy most about your work?

Honestly: Everything! I enjoy planning, conducting and evaluating studies, interacting with partners from industry, agriculture, associations and university research institutions, and exchanging scientific information with colleagues from the various sub-areas of insect biotechnology. When, after planning and carrying out the projects, the final result is a patent application or a specialist publication, this gives me great satisfaction. But I also enjoy the administrative activities and staff management extraordinarily.

Dr. Kwang-Zin Lee
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IN FOCUS

Understanding flower development - Targeted increase of plant biomass!
PD Dr. Gundula Noll

»4«

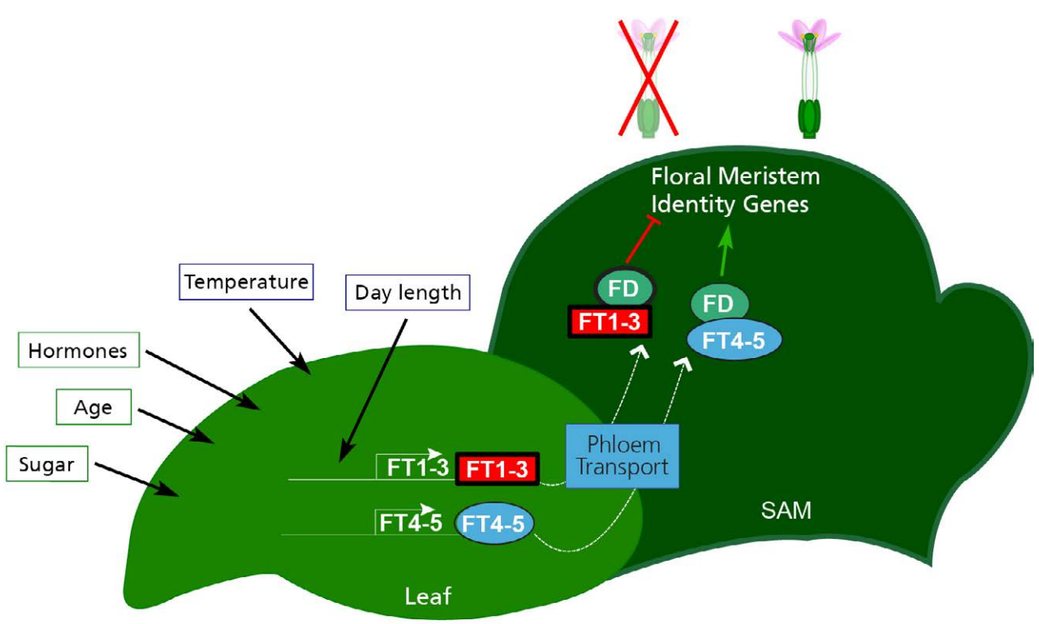
Plant Biopolymers

In December 2010, a branch lab was opened at the University of Münster under the direction of Prof. Dr. Dirk Prüfer. One research focus is flower development.

UNDERSTANDING FLOWER DEVELOPMENT – TARGETED INCREASE OF PLANT BIOMASS!

Left: The targeted suppression of flowering leads to an enormous increase in biomass - not only under greenhouse conditions.
Middle: The modulation of the flowering time is a key objective of our research.
Right: To flower, or not to flower, that is the question!

In times of a rapidly growing world population and a shortage of arable land, securing global food supplies is one of the greatest global challenges facing humanity. In order to meet this challenge, a drastic increase in agricultural production is an outstanding goal, in addition to a fairer distribution of food. Increasing plant biomass, i.e. increasing the yield of crops, is of fundamental importance in this context and is consequently the focus of modern plant breeding. In the "Functional and Applied Genomics" department of Fraunhofer IME at the locations Aachen and Münster, we investigate the floral induction mechanisms of plants. Based on this knowledge, we can increase biomass and yield of plants using modern breeding methods.



External environmental factors and internal plant processes determine the timing of flowering.
This process is strictly regulated, as it is essential to ensure the existence of the respective species. At the molecular level, all these factors target the expression of FLOWERING LOCUS T (FT), a central mobile stimulus of flower induction described in many species. For our model species tobacco we could identify a special case of FTs: In addition to flower-activating FTs (FT4-5), tobacco also possesses flower-inhibiting FTs (FT1-3), which are transported via the phloem into the shoot apical meristem (SAM) where they compete for FD and thus determine the optimal flowering time.

The timing of flower induction in plants is a tightly regulated process, as it determines the reproductive success of the respective species. Both external environmental stimuli (exogenous factors), such as the day length or a mandatory exposure to cold, as well as internal (endogenous) factors, such as the age of the plant, play important roles in this regulation. Even though the basic factors of flower induction are similar in many plants, this is a species-specific process, since the architecture of the plant body, the habitat and the age entering the flowering stage are often very different. Thus, a basic understanding of the decisive factors and processes is of fundamental importance, especially for conventional, but also for alternative, novel crops, as they directly influence the yield. The rapidly growing world population and the effects of climate change, such as prolonged periods of drought or flooding, are the driving forces behind modern plant breeding in terms of increasing yields and producing more adaptive plants.

The central factor of flower induction of almost all plants studied to date is responsible for triggering the entire cascade of flower formation and development: This so-called Flowering Locus T (FT) is within the focus of our research group. We aim to understand how FT is regulated, along with its downstream genes. Ultimately, we hope to be able to increase the biomass and thus the yield of crops by specifically modulating FT.

Flowering Locus T (FT) – the key regulator of flower development

As early as the 1930s, botanists in pioneering studies on floral induction concluded that there must be a mobile flowering stimulus - a so-called florigen - which is formed in the leaves and then transported to the tip of the shoot. Here it terminates the vegetative growth of the plant by mediating the transition from a vegetative to a reproductive meristem. Many decades later, this mobile stimulus of floral induction was described on a molecular level as Flowering Locus T (FT).

In innumerable plants, his regulator is formed in the conductive tissues of the leaves and then transported via the phloem from the leaves to the apical meristem of the shoot tip(s). Here FT interacts with its partner, the so-called FD, and subsequently activates all processes necessary for floral induction and flower development. Although FT is the central module of floral induction across species, it is regulated by diverse factors in different plant species. Depending on the location of the plant, day length plays a decisive role in the availability of FT, while other plants need a period of cold (winter) to activate FT and initiate their flowering process. Our research group is working on elucidating the mode of action of FT in plants of the Solanaceae family. This includes our model plant tobacco as well as important crop species such as potato and tomato.

Leaf biomass of an unmodified tobacco plant cultivated at 15 °C increased temperature and normal irrigation.

Significantly increased leaf biomass of an FT-optimized tobacco plant cultivated at 15 °C elevated temperature and normal irrigation.

Yield increase by targeted modulation of activators and repressors of flower induction

Our research already resulted in the identification and characterization of several FTs. In addition to the FTs that activate floral induction, we also identified a special case of FTs in these plant species: These are FTs preventing the formation of flowers, i.e. repressing them. This is in a similar form only described for a few other crops like sugar beet or sunflower. Based on the molecular characterization of FTs that have a repressive effect on floral induction, a special focus of our current work is on the use of genetic engineering to achieve a remarkable increase in plant biomass.

By specifically modulating the plant, we have succeeded in providing larger quantities of this repressive factor and thereby keeping the plant in the vegetative growth stage. The inhibition of flowering prolongs the vegetative growth, which enables us to control the morphology and thus the yield and biomass of the plant. Such optimized tobacco plants reached heights of around five meters and thus an increase in biomass of up to 60 percent due to the leaf size alone, further increased enormously by the formation of up to 10 times more leaves. The elucidation of the mode of action of activating versus repressing FTs now allows us to precisely regulate plant architecture, flowering time and seed quantity and thus the yield realized by use of modern breeding methods such as CRISPR/Cas. In this way, we achieve economically relevant and, above all, field applicable breeding objectives.

Even under stress, FT-optimized plants still maintain their positive agronomic traits

In view of global climate change and the steadily increasing world population, plants that are more resistant or tolerant to changing environmental conditions such as heat and drought will be indispensable for securing the food supply.
Our latest studies show that plants in which we have reduced the levels of activating FTs using modern breeding methods maintain their positive agronomic traits such as increased biomass and seed production even under various abiotic stress conditions. Normally, tobacco plants exposed to temperatures only 5 °C higher than normal conditions are significantly retarded and leaf biomass is substantially lower. FT-optimized plants generated with our technique, even when grown at 15 °C higher temperatures, produced biomass similar to that of wild type plants cultivated under normal conditions.

Thus, FTs acting as floral inducers are promising candidates for breeding programs aiming at adapting various crops to the effects of climate change. For example, it would be interesting to test this breeding strategy in vegetative plants such as potatoes, sugar beet or lettuce, where carbon and energy distribution into the vegetative organs is desirable and a prolonged vegetative growth phase by modulating the activity of FTs could be beneficial. In the case of potato, research on the specific functions of the different FTs is of particular interest. In this plant, tuber formation is also dependent on the availability of certain FTs and a targeted modulation of FT levels could further increase the yield of potato plants even under changing environmental conditions.
This project again shows that the combination of basic research to elucidate the function of various key factors in flower development with the goals of applied research, such as the targeted breeding-based optimization of these key factors, is a central, successful and effective approach. In terms of modern plant breeding, this represents a particular incentive and a major challenge.

MB

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SELECTED PUBLICATIONS

Plant cell packs named cookies

Characterization of protein interactions in living cells

Deciphering the mechanisms of rubber biosynthesis in dandelions

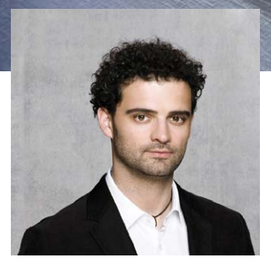
Impact of insect meal on fat metabolism

Novel insights into the mechanism of caspase-6

Bioconcentration studies with the crustacean *Hyalella azteca*

»5«

In 2019, Fraunhofer IME researchers published about 150 articles in peer-reviewed journals.



Dr. Dr.-Ing. Johannes Buyel
Head of Department
Bioprocess Engineering

Plant cell packs in 96-well format.

PLANT CELL PACKS NAMED COOKIES

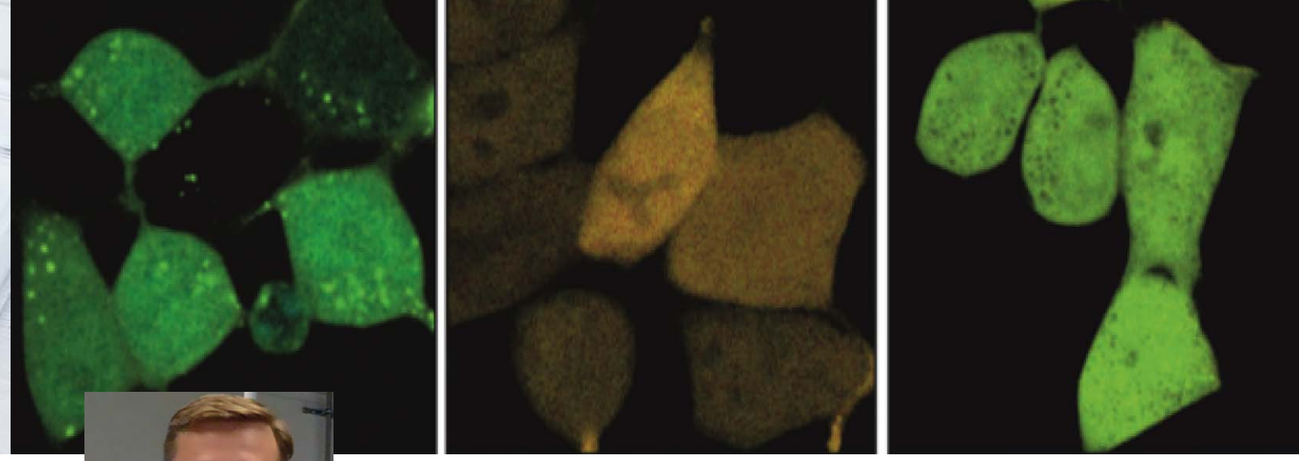
»THE NEW TECHNIQUE ENABLES RAPID, REPRODUCIBLE AND PARALLEL SCREENING OF RECOMBINANT PROTEINS«

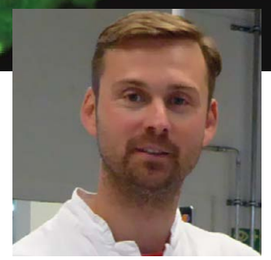
Protein expression in plants offers several advantages in terms of production costs and safety compared to mammalian cell cultures. However, until now there has been no reliable way for plants to test large numbers of different product candidates, e.g. with regard to their accumulation, at a reasonable cost.

In the Department Bioprocess Engineering (formerly Integrated Production Platforms), we have now developed and patented an innovative technology that impressively solves this problem: Plant cell packs (PCPs), also known as "cookies" due to their flat, light form. PCPs are plant cells that we first keep in cell culture and which we then deprive of liquid medium. The remaining cake can then be treated with *Agrobacterium tumefaciens*: A mere drop of the bacterial solution is sufficient. The soil-borne bacterium has the natural ability to transfer DNA into plant cells and we have modified this DNA to contain the information for the product candidates we are interested in. The result of the treatment is the accumulation of the candidates in the plant cells within three to five days. Our method is several times more efficient than a similar treatment of plant cells in liquid culture. Since PCPs can be cast into various formats, including 96-well plates, we can use the method for both screening and scale-up to supply initial activity tests. The costs are around 25 cents per sample. To date, we have successfully tested the method with a wide variety of plant cells and products: From carrots to tobacco and from antibodies to toxins. But we're moving on. We are currently working to automate all steps of the protocol in order to fully exploit the potential of the technology. We are also establishing correlation factors with which we can transfer PCP results to whole plants and thus to many hundreds of kilograms of biomass.

MB Molecular Biotechnology

Rademacher, T., Sack, M., Blessing, D., Fischer, R., Holland, T., **Buyel, J.**
Plant cell packs: A scalable platform for recombinant protein production and metabolic engineering (2019) Plant Biotechnology Journal, 17 (8), 1560-1566. DOI: 10.1111/pbi.13081





Dr. Tilo Knape
Research fellow
Translational Drug Validation | Biochemical Pathology

Protein-interaction-dependent FRET signals in living cells.

CHARACTERIZATION OF PROTEIN INTERACTIONS IN LIVING CELLS

»DETAILED KNOWLEDGE ABOUT PROTEIN INTERACTIONS HELPS TO UNDERSTAND THE CAUSES OF DISEASES AND TO TREAT THEM THERAPEUTICALLY«

The detailed identification and characterization of protein-protein interactions is of fundamental importance to investigate the causes and development of diseases, to identify new molecular and pharmacological targets, to detect subtle changes in protein interactions in drug treatment, and to verify the pharmacological and toxicological potential of new and existing drugs.

In order to further minimize the disadvantages of current preclinical in vitro test systems such as high costs, low throughput and limitations in terms of selectivity, specificity and sensitivity, we have developed a systematically improved, innovative, flow cytometry-based Förster Resonance Energy Transfer (FRET) test system for the molecular verification of specific protein-protein interactions. With a special focus on the human nuclear hormone receptor peroxisome proliferator-activated receptor gamma (PPARγ), we were able to demonstrate for the first time that our in vitro test system provides detailed, reliable and reproducible data for the identification and characterization of binding intensity and affinity of direct protein-protein interactions from PPARγ with its co-factors in a high-throughput test system in living cells. By improving the sensitivity of our in vitro test system, it can be used to identify new therapeutic targets for the treatment of human diseases and to characterize in detail the binding profile of drugs.

TM Translational Medicine and Pharmacology

Trümper, V., von Knethen, A., Preuß, A., Ermilov, E., Hackbarth, S., Kuchler, L., Gunne, S., Schäfer, A., Bornhütter, T, Vereb, G., Ujlaky-Nagy, L., Brüne, B., Röder, B., Schindler, M., Parnham, M.J., **Knape, T.**
Flow cytometry-based FRET identifies binding intensities in PPARγ1 protein-protein interactions in living cells (2019) Theranostics, 9(19), 5444-5463. DOI: 10.7150/thno.29367

Eva Niephaus
PhD student
Functional and Applied Genomics

The Russian dandelion, a natural rubber source.

DECIPHERING THE MECHANISMS OF RUBBER BIOSYNTHESIS IN DANDELIONS

»ESTABLISHMENT AS A RUBBER CROP REQUIRES FUNDAMENTAL KNOWLEDGE ABOUT THE RUBBER METABOLISM IN DANDELION«

The demand for natural rubber is growing steadily: Car tires, rubber gloves and pacifiers are just three examples of about 40,000 products containing the plant biopolymer. Natural rubber can often not be replaced by synthetic, petroleum-based polymers due to its unique properties. For this reason, the economic importance of alternative sources other than the rubber tree, as the only commercially used source to date, is increasing. The development of the Russian dandelion (*Taraxacum koksaghyz*) into a natural rubber crop has made considerable progress in recent years. Nevertheless, not all individual components and metabolic links of rubber biosynthesis are fully known yet. However, it is crucial to understand these in detail in order to produce plants with a high production capacity.

As part of our study, we identified a protein (TkCPTL1) that is essential for dandelion rubber biosynthesis. TkCPTL1 forms a complex through its interaction with a catalytically active protein. It is located on the surface of particles found in the latex of dandelion. There, the complex synthesizes the long polymer chains that are stored inside the particles. The targeted reduction of *TkCPTL1* gene expression prevents the formation of a functional complex. As the interaction partner is missing, the plant can no longer produce rubber. Alternatively, other secondary plant compounds, whose synthesis is closely linked to that of rubber, are increasingly formed. As part of our experiments, we were able to show that these are now increasingly found in the latex particles in place of rubber. Extensive proteome analyses of rubber-deficient dandelion plants enabled us to derive further potential factors, different metabolic pathways associated with rubber biosynthesis, as new starting points for future research.

MB Molecular Biotechnology

Niephaus, E., Müller, B., Deenen, N., Lassowskat, I., Bonin, M., Finkemeier, I., Prüfer, D., Schulze Gronover, C.
Uncovering mechanisms of rubber biosynthesis in *Taraxacum koksaghyz* – role of cis-prenyltransferase-like 1 protein (2019)
The Plant Journal, 100 (3), 591-600. DOI: 10.1111/tpj.14471

Prof. Dr. Holger Zorn
Head of Department
Food- and Feed Improvement Agents

Mealworms are considered as a source of high quality protein.

IMPACT OF INSECT MEAL ON FAT METABOLISM

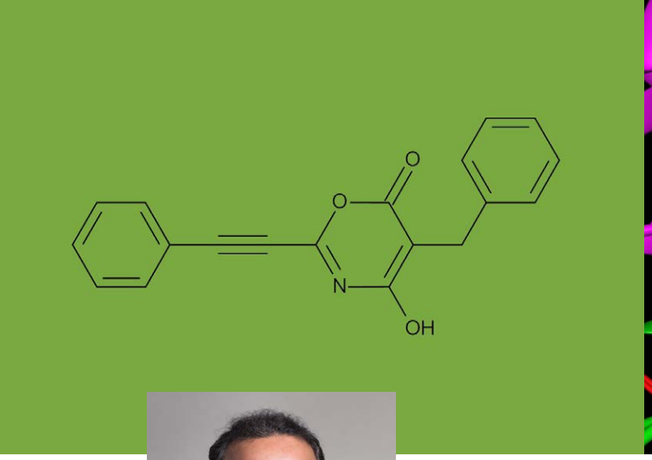
»OUR INVESTIGATIONS SHOW THAT INSECT MEAL HAS BENEFICIAL EFFECTS IN THE CASE OF FAT METABOLISM DISORDERS«

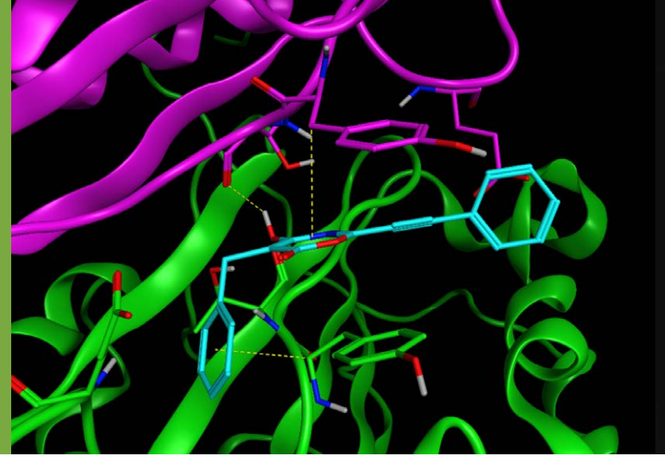
In our studies we investigated the hypothesis that insect meal as a protein source has a beneficial effect on fat metabolism. To this end, we conducted two experiments with obese rats, which are considered a model for obesity and metabolic syndrome in humans. Two groups of rats received either casein or insect meal as a protein source. In both experiments, we found that rats fed insect meal had drastically reduced cholesterol and triglyceride levels in blood plasma and liver by up to 60 percent. The livers of the rats in the group receiving insect meal were also significantly smaller and already externally visibly showed a lower fat content than those of the control groups with casein as a protein source. Extensive investigations using complex analytical methods showed that the reduced cholesterol and triglyceride levels in blood plasma and liver were the result of inhibition of cholesterol and triglyceride synthesis in the liver. The rats fed insect meal also had lower levels of homocysteine, a substance closely related to cholesterol metabolism and also considered a risk factor for arteriosclerosis (hardening of the blood vessels). We also found that insect meal diets lead to changes in the composition of cell membranes, with the proportion of certain phospholipids (phosphatidylethanolamine) increasing and the proportion of other phospholipids (phosphatidylcholine) decreasing. These changes are also very significant, since the contents of individual phospholipids can strongly influence membrane properties (enzyme activities, activities of transport proteins). Overall, our investigations show that feeding insect meal to obese rats has very positive effects on fat metabolism.

These studies give reason for hope that similar beneficial effects could also occur in overweight persons. Since insect meal is a complex mixture of different bioactive substances, our current studies focus on identifying the ingredients of insect meal that are responsible for the beneficial effects.

AE BR Bioresources

Meyer S, Gessner DK, Wen G, Most E, Liebisch G, **Zorn H,** Ringseis R, Eder K.
The antisteatotic and hypolipidemic effect of insect meal in obese zucker rats is accompanied by profound changes in hepatic phospholipid and 1-carbon metabolism. Molecular Nutrition & Food Research, 63 (8), e1801305. DOI: 10.1002/mnfr.201801305





Dr. Sheraz Gul
Research fellow
Drug Discovery

Docking pose of the allosteric inhibitor and caspase-6.

NOVEL INSIGHTS INTO THE MECHANISM OF CASPASE-6

»A COLLABORATION WITH THE MOST CITED AUTHOR FOR HUNTINGTON'S DISEASE BRINGS US ONE STEP CLOSER TO DISCOVERING A TREATMENT FOR HD«

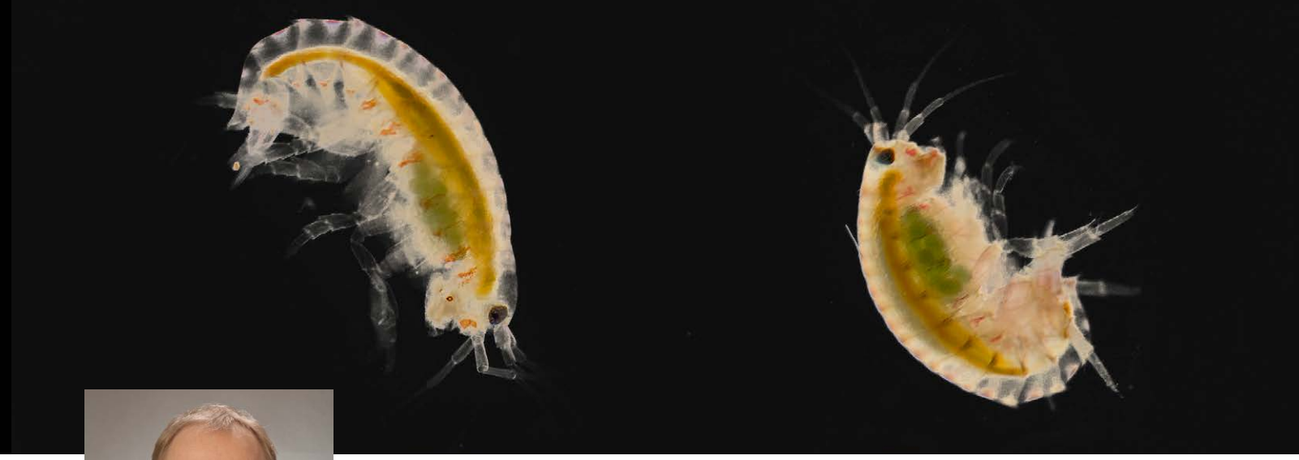
Fraunhofer IME has been collaborating with Dr. Michael Hayden of the University of British Columbia who is the most cited author in the world for Huntington's disease. The focus of the research project has been to identify inhibitors of the caspase-6 enzyme which processes huntingtin protein. This is considered a crucial event in Huntington's disease pathogenesis.

During the research project, Fraunhofer IME developed a novel assay to measure caspase-6 mediated processing of huntingtin protein. This assay was successfully miniaturized and screened against 22,644 compounds, and one specific compound series was shown to inhibit caspase-6 with high efficiency. This initial exciting result led to a further collaboration between the partners in order to progress the most promising compounds in the drug discovery value chain. The research teams performed a comprehensive study of the caspase-6 inhibitors and the most significant finding from this work was the identification of inhibitors which block the interaction between caspase-6 and huntingtin protein. Molecular docking studies suggested that the inhibitor binds an allosteric site in the caspase-6 and this can explain the highly selective nature of the inhibitors.

In conclusion, we have identified a compound series with a novel mode of action with high fidelity for caspase-6. The most optimal compounds were evaluated in preclinical in vitro pharmacology and absorption, distribution, metabolism, excretion and toxicity studies and showed to meet industry standard "Lead Compound" criteria. As this is a major milestone in the drug discovery value chain, a patent entitled "Modulators of Caspase-6" was granted (PCT/IB2015/000144). Once the intellectual property relating to the compounds was secured, the research team published a paper in Cell Chemical Biology which describes in detail the results of the collaboration.

TM ScreeningPort

Ehrnhoefer, D.E., Skotte, N.H., Reinshagen, J., Qiu, X., Windshügel, B., Jaishankar, P., Ladha, S., Petina, O., Khankischpur, M., Nguyen, Y.T.N., Caron, N.S., Razeto, A., Meyer Zu Rheda, M., Deng, Y., Huynh, K.T., Wittig, I., Gribbon, P., Renslo, A.R., Geffken, D., **Gul, S.**, Hayden, M.R.
Activation of caspase-6 is promoted by a mutant Huntingtin fragment and blocked by an allosteric inhibitor compound (2019) Cell Chemical Biology 26 (9), 1295-1305. DOI: 10.1016/j.chembiol.2019.07.001



Prof. Dr. Christian Schlechtriem
Head of the Department
Bioaccumulation and Animal Metabolism

Hyalella azteca, an epibenthic amphipod, under the microscope.

BIOCONCENTRATION STUDIES WITH THE CRUSTACEAN *HYALELLA AZTECA*

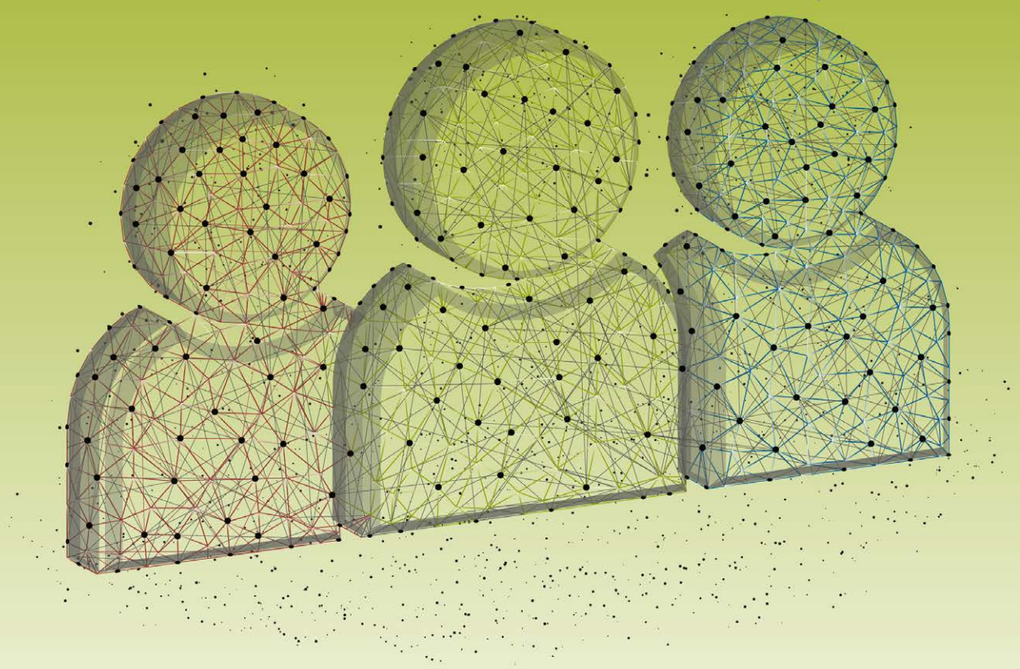
»*HYALELLA AZTECA* HAS A HIGH POTENTIAL TO BE USED AS ALTERNATIVE TEST ORGANISM TO FISH FOR BIOCONCENTRATION STUDIES«

Bioconcentration factors (BCF) for regulatory purposes are usually determined by fish flow-through tests according to technical guidance document OECD 305 (OECD 2012). Fish bioconcentration studies are time consuming, expensive, and use many laboratory organisms in the range of 100–200 organisms per study. Alternative methods that may help to reduce the use of fish for BCF testing would therefore be of value. *Hyalella azteca* is an epibenthic amphipod, which is widespread in North and Middle America and commonly used for ecotoxicity studies with and without sediment. The freshwater amphipods can be easily cultured in the laboratory and are available during the entire year. Due to their high reproduction rate and fast growth, experimental organisms can be raised within a few weeks to adult size to meet the need for a high number of large organisms required for bioconcentration testing.

In this study, we estimated the bioconcentration potential of a wide range of substances in *H. azteca* to allow a comparison with fish BCF data described in the literature. Fourteen substances of different hydrophobicity (log Kow 2.4–7.6) were tested under flowthrough conditions to determine steady state and kinetic bioconcentration factors (BCFss and BCFk). We found that bioconcentration studies with the freshwater amphipod *H. azteca* result in BCF estimates, which show a strong correlation with fish BCF values. Therefore, *H. azteca* has a high potential to be used as alternative test organism to fish for bioconcentration studies. A protocol for bioconcentration tests with *H. azteca* under standardized conditions, including the flow-through and semi-static test design, has been developed as part of project CEFIC-LRI ECO40.

AE BR Applied Ecology

Schlechtriem, C., Kampe, S., Bruckert, H.J., Bischof, I., Ebersbach, I., Kosfeld, V., Kotthoff, M., Schäfers, C., L'Haridon, J. Bioconcentration tests with fish and the freshwater amphipod *Hyalella azteca*. Are the results predictive of bioconcentration in fish? (2019) Environmental Science and Pollution Research 26, 1628–1641. DOI: 10.1007/s11356-018-3677-4

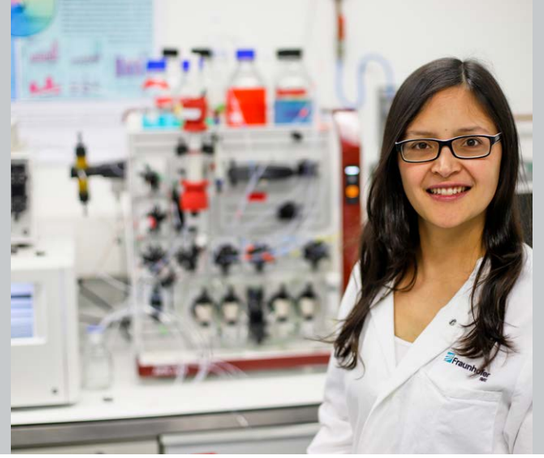


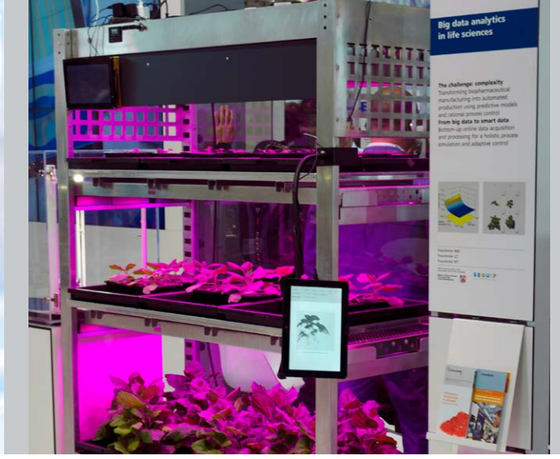
PEOPLE AND EVENTS

Brief reports
Employees, meetings, successes and new perspectives at Fraunhofer IME

»6«

In 2019 533 employees worked at Fraunhofer IME.





Catherine Müschen successful in the Young Research Class

Catherine Müschen, PhD student at Fraunhofer IME in Aachen, has been participating in the two-year Young Research Class program of the Fraunhofer-Gesellschaft since summer 2018. In her team of four, she was happy about the approval of the "In silico-driven bioprocesses" research project, which started on March 1, 2019. The Young Research Class combines the development of original research ideas with networking across hierarchies and disciplines. Scientists who have just completed their doctorate or are in the final phase of their doctorate can take part.

The key topic in 2018 was "Biological transformation". In the Research Camp, which took place in Waischenfeld in June 2018, the 15 participants worked out project ideas. Catherine Müschen and colleagues from Fraunhofer Institutes IBP, ITWM and IIS developed the idea "In silico-driven bioprocesses". The aim of this project is to accelerate biological drug production and process development using plants as an example. The team presented this project idea to the President of the Fraunhofer-Gesellschaft, Prof. Dr.-Ing. Reimund Neugebauer, and the Fraunhofer Think Tank at the project exhibition in September 2018. Subsequently, the project proposal was prepared and submitted for review. In mid-February 2019, the grant was awarded and experimental work at the four Fraunhofer Institutes began on March 1, 2019.
For Catherine Müschen, the "Young Research Class" is an opportunity to apply for projects and carry them out independently. Holding your first funding decision in your hand is an important moment. The highlight of the project will be the presentation at the Fraunhofer Netzwert Symposium 2020 in Munich. MB

Immunology Day of Fraunhofer CIMD

On June 19, 2019, the first "Immunology Day" of the Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD took place in Frankfurt am Main. The field of participants consisted of employes from the core institutes of the research cluster (Fraunhofer IME, ITEM and IZI) and from 38 other Fraunhofer institutes. A total of 170 participants attended the event.

During "Immunology Day", the participants gained insights into the work of the research cluster. The cluster's scientists presented their scientific projects, invited physicians explained what their patients desire most (the "medical need") and representatives from the pharmaceutical industry outlined the requirements and conditions of the market.

Fraunhofer CIMD is dedicated to translational research. It thus transfers basic research into application. Fraunhofer CIMD works in the four areas of health research - Drugs, Diagnostics, Devices and Data, the 4D. These four subject areas are represented by the four professional groups - physicians, scientists, engineers and computational experts. The "Immunology Day" was used to discuss further cooperation possibilities with a focus on how ideas can be applied cost-effectively and transferred into new treatment options.

The "Immunology Day" was a successful kick-off for the promotion of networking, collaboration and cooperation opportunities along the 4D within the entire Fraunhofer-Gesellschaft. TM

With insects on patrol - Bees in action as drug sniffers

Could bees in the future support the police in drug investigation? A 22-year-old inspector from Cologne dealt with this question in her bachelor's thesis and attracted a lot of attention, both in security circles and in the media. In February, she was awarded the "Future Prize of Police Work" for her work.

The idea is based on the research of the LOEWE Center for Insect Biotechnology at the University of Gießen, which has been conducting research on bees and their outstanding sense of smell for years. "It is so accurate that it is all about the recognition of individual molecules" explains Prof. Andreas Vilcinskas, head of the Branch for Bioresources of Fraunhofer IME in Gießen. And since bees are able to remember these odors quickly, they can be conditioned to any odorous substance within a few seconds using weak but unpleasant current pulses.

In practice, this technique could be used for example at airports, where a machine sucks the air from the suitcases into a box of bees. The reaction of the insects can then be used to detect illegal substances in the luggage. Flying missions are also possible. While the classic police dogs have to be trained for months, bees have the additional advantage, apart from the quick conditioning, that they can always be trained for new substances and can be used for a longer period of time. They can work through up to 48 hours. The police union (GdP) sees this research as a "possible revolution for police work". AE BR

High Performance Center "Networked, Adaptive Production" well positioned

On April 16, 2019, the High Performance Center based in Aachen received positive feedback from the five-member expert committee that the Fraunhofer-Gesellschaft had asked to evaluate the project: For almost three years, a team of researchers from the three Aachen-based Fraunhofer Institutes IPT, ILT and IME had been working on the development of a common procedure for processing production data. The evaluators' positive recommendation launches the next funding phase. Dr. Dr.-Ing. Buyel and his team from Fraunhofer IME are contributing their expertise in the field of "Big Data Analytics in complex production environments".

The three Fraunhofer institutes have successfully fulfilled the task of designing an open research platform and test environment for industry in which new concepts of digitized production can be tested and evaluated in a practical manner. Industrial partners including IT system providers, plant manufacturers and manufacturing companies have joined the High Performance Center in an open research community and ensure additional practical relevance.

In each of the four relevant activities "Profile and Implementation", "Location and Impact", "Transfer and Sustainability" and "Strategy and Perspective", the evaluators rated the High Performance Center with top grades. The Aachen-based institutes received special recognition for their excellent cooperation with partners from industry, science and politics as well as the high satisfaction of the industrial partners. The evaluators also highlighted the distinct thematic focus of the High Performance Center and, associated with this, the high visibility as a hot spot and networking hub with outreach beyond the west german region. MB

Equal rights officers at Fraunhofer IME founded network

Gender equality, compatibility of family and career, as well as protection against sexual harassment – these are some topics the equal rights officers (German: *Beauftragte für Chancengleichheit,* BfC) dedicate themselves to. They are bound to discretion, so that all who have concerns or problems in this regard can address their sorrows to them trustfully. To ensure a policy of equal opportunities and as a contact person for the employees each of the Fraunhofer IME locations has its own equal opportunities officer and deputy. However, Fraunhofer IME with its many sites provides the opportunity to connect these small teams to a whole network. This chance was taken by the BfC of the institute locations Aachen (Greta Nölke and Christiane Fischer), Frankfurt am Main (Carmen Walter and Susanne Schiffmann), Gießen (Kirsten Bommersheim and Sabine Schmelzle) and Schmallenberg (Elke Eilebrecht and Jennifer Teigeler). They met for the first time on July 11, 2019 in Gießen in order to found the Fraunhofer IME BfC network. Already during this first meeting, they agreed on topics which will be in the focus of the network.

The first initiative was the presentation of a joint poster at the All-IME Summer Meeting. On this poster, the BfC introduced themselves and provided information about the topic eldercare. In this context, the BfC together with the pme Family Service can support the employees to organize the care of relatives. Furthermore, the BfC informed interested employees about their manifold functions and were available for further questions and discussions.

For the future, the Fraunhofer IME BfC network will continue to work together, because they will achieve more when working together.

Fraunhofer IME organizes stem cell symposium with cooperation partner

On the occasion of the visit of the First Mayor of the Free and Hanseatic City of Hamburg Dr. Peter Tschentscher with a business and science delegation to Japan, Fraunhofer IME and its partner FBRI (Foundation for Biomedical Research and Innovation at Kobe) organized a scientific symposium in Kobe, Japan on August 29, 2019. The symposium on the topic "New opportunities for drug discovery with stem cell technologies" was under the patronage of the director of FBRI, the immune researcher and Nobel Laureate in Medicine 2018 Prof. Dr. Tasuku Honjo, and Dr. Peter Tschentscher, a habilitated physician.

In his welcoming address, Dr. Tschentscher paid special tribute to the international cooperation between Hamburg research institutions, which is expressed in particular in the close partnership between the Kobe Biomedical Innovation Cluster and Life Science North. In his keynote, Prof. Dr. Carsten Claussen reported on exactly such a cooperative research project, in which the disease hypothesis, clinical evidence of stem cell therapy is linked to the Hamburg screening results and his stem cell assays. Prof. Dr. Akihiko Taguchi the PI of this project in the field of dementia disease added impressive clinical data. Other German speakers included Prof. Dr. Heiner Dobner, Director of the Heinrich Pette Institute, who explained the potential of human adult stem cells for infection research. Dr. Peter Fruhstorfer, CEO Eppendorf AG, concluded the industrial discussion with the need for standardized, QC-supported processes and tools. Two Japanese contributions from the Riken Institute and Kobe University dealt with the use of stem cells for regenerative medicine and demonstrated Japan's leading role in stem cells worldwide. TM

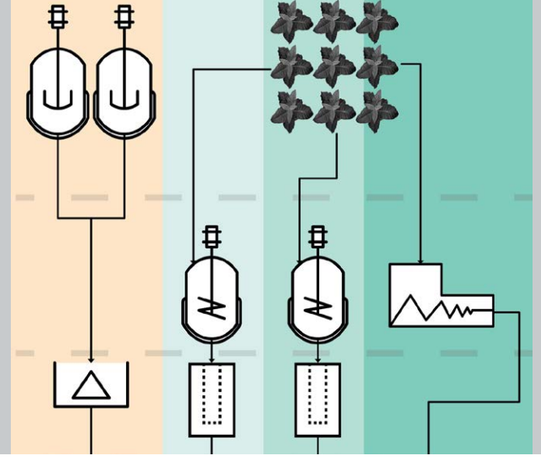
Learning partnership signed and sealed

At the end of June, Rita Hündgen, headmistress of the Cusanus-Gymnasium in Erkelenz and Dr. Dr.-Ing. Johannes Buyel, head of department at Fraunhofer IME in Aachen, signed a cooperation agreement. After a two-year test phase, the learning partnership has now been sealed. During the course of their school curriculum, pupils can visit Fraunhofer IME and will be informed about a "model of the working world in the form of a modern, science oriented research institution with a highly qualified range of services". Key topics of the cooperation are "opening of school and teaching", "action orientation" and "career choice and working world orientation". As a learning partner, Fraunhofer IME offers pupils - especially those in the upper secondary school - the opportunity to gain insights into attractive professional fields, training and study courses, which are opened up to them with the completion of the advanced technical college or general university entrance qualification.

In addition to this basic orientation offer, the following activities are planned: Selective activities by Fraunhofer IME in the field of biology; excursions for the pupils of the advanced biology courses to Fraunhofer IME allowing them to explore the field of research; further training for biology teachers on current topics in molecular biology and applied ecology; creation of an information platform on training opportunities at Fraunhofer IME and in the various institutions of Fraunhofer-Gesellschaft. Johannes Buyel is pleased that the cooperation will be continued: "I am committed to the learning partnership, as pupils have few opportunities to gain insights into the professional life of "research". Personally, I would have gladly accepted such an offer earlier." Obviously, there is also interest today as can be seen by the praise of the participants "that was cool". MB

Federal Environment Minister visits Kids' Lab of the Environmental Specimen Bank

On August, 17-18, 2019, the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety held an open day in Berlin to outline its function. Also present was the Kids' Lab of the Environmental Specimen Bank, supported by Fraunhofer IME. On this occasion, children could experiment with liquid nitrogen at temperatures of minus 196 degrees Celsius, just like real scientists with laboratory coat, gloves and protection goggles. They were able to learn about the different sample types of the Environmental Specimen Bank. Federal Environment Minister Svenja Schulze took the opportunity to learn about the Environmental Specimen Bank at the exhibition stand of Fraunhofer IME. Since the year 2000, Fraunhofer IME operates the German Environmental Specimen Bank as a core element for environmental monitoring in Germany on behalf of the Federal Ministry for the Environment, Nature Conservation and Nuclear Safety. In the course of this program, Fraunhofer IME also conducts retrospective monitoring to examine the content of currently relevant chemicals in specimens from the Specimen Bank. By this means, it can be verified whether substance restrictions by public authorities or voluntary use restrictions of certain substances by the producer, result in a decrease in concentration of those substances in the environment. The results of these studies are compiled in reports and published in international journals. Examples of relevant substances found are organotin compounds in mussels of the North and Baltic Sea, perfluorinated compounds in different organisms of the marine food web or Triclosan and Methyltriclosan in freshwater fish. AE BR



Start of the new department Bioprocess Engineering

In August 2019, the "Bioprocess Engineering" department was established in Aachen. The team, headed by Dr. Johannes Buyel, focuses on various aspects of protein production from the gene to the finished product. Despite great progress in the production of recombinant proteins, there are no generic protocols and process development is necessary on a case-by-case basis. Johannes Buyel, among others, relies on the plant system as a production platform and believes that "for some proteins, plants are a good alternative to established microbial and animal systems or even the much more efficient production system". Contemporary protein production processes consider from the beginning the properties of genes and proteins, the quantity and quality of the products required, downstream processing issues, regulatory requirements and intellectual property issues that might arise. Only then can the most appropriate production strategy be selected. The department has established an automated and integrated platform for the screening of gene variants. This allows translation from the gene to protein production on a pilot scale in less than four weeks and combines parallel chromatographic purification and protein analysis. The experiments are typically based on a design-of-experiments strategy. This strategy provides comprehensive information and descriptive models for the complex influences of different process parameters, enabling rapid process optimization. The approach is complemented by mechanistic models describing expression and chromatographic purification, allowing the investigation of many conditions in silico. By bundling these expertises, the team around Mr. Buyel offers clients the possibility to bring their product to market faster. MB

After mushroom growing, prior to insect breeding

The production of protein from insects is on the rise worldwide. It is considered to be particularly sustainable compared to traditional livestock farming. However, sustainability depends to a large extent on the food used to feed the insects. In the EU there are strict regulations regarding approved food for insects. This is why cereal-based food such as chicken or pig food is often used. If the insects produced in this way are used as animal food, the sustainability of this "detour" is questionable.

It is therefore important to use food sources for insect breeding that comply with EU requirements but do not compete with traditional farm animal food. Dr. Martin Rühl from the Bioresources Division of the Fraunhofer Institute for Molecular Biology and Applied Ecology IME in Gießen, sees potential in the use of harvested fungal substrate from edible mushroom cultivation. This extension of the value chain could open up a previously unused straw- and wood-based by-product stream for the production of valuable animal protein.

After the first promising laboratory-scale experiments developed by Fabiola Neitzel as part of her master's thesis at the Bioresources department of Fraunhofer IME in Gießen, Neitzel and Dr. Rühl have now started an industrial pilot project with the Swiss Mushroom Producers Association (VSP). The insect larvae, which are cultivated on a worn fungal substrate, could in future contribute to the feed supply of fish and poultry farms with regional protein sources. AE BR

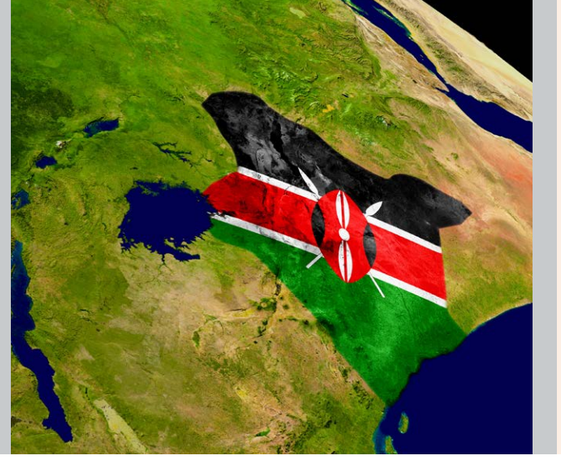
Great success for junior rheumatologist at Frankfurt am Main

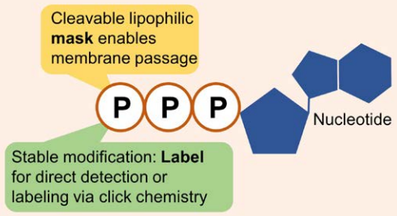
The DGRh Research Initiative 2020, with its idea of person-related support for young physicians in the field of rheumatology, has announced the two prize winners following a nationwide competitive selection process at this year's Rheumatology Congress in Dresden. One of the prize winners is Dr. Sorwe Mojtahed Poor (2nd from right) from the Rheumatology Department of the University Hospital of the Goethe University Frankfurt am Main. The award covers the funding of her position for two years, thus allowing her to devote herself to a patient-oriented research project in cooperation with Fraunhofer IME. The close cooperation between Fraunhofer IME and the Goethe University played a major role in the selection of Dr. Poor, as this ensures that the physician is embedded in a competent translational research environment.

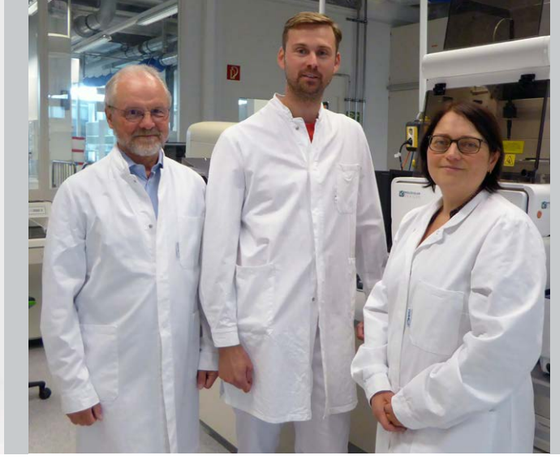
Dr. Poor has already participated in a PhD program at Fraunhofer IME and successfully combined laboratory research with clinical questions. Within the scope of the awarded DGRh funding, Dr. Poor will focus on the research of cardiovascular concomitant diseases in rheumatic disorders and in particular on valid, early detection methods of such manifestations. The aim is not only the timely detection of such concomitant diseases of the cardiovascular system, but also their successful treatment with intensified anti-rheumatic therapy in order to further reduce the mortality of patients with inflammatory rheumatic diseases. This project is again being carried out in close cooperation between Fraunhofer IME in Frankfurt am Main and the University Hospital of the Goethe University. TM

60 years of Fraunhofer in Schmallenberg – globally active, locally rooted

Celebration of a success story: on October 29, as the new center of the institute nears completion, Fraunhofer IME celebrated with 160 guests from science, economy and policy the sixtieth anniversary of the Fraunhofer-site in Schmallenberg-Grafschaft. As well as an overview of the relevant past and present research activities in Schmallenberg, a look ahead to future research topics was given. Investment of almost 30 million euros by the federal government, state and institute funds enable continued future research. A new member of the executive board of Faunhofer-Gesellschaft, Executive Vice President Technology Marketing and Business Models, Prof. Dr. Ralf B. Wehrsporn, emphasized the relevance of the Schmallenberg site as a nucleus of Fraunhofer health research. In their official address, state commissioner Dr. Karl Schneider and parliamentary state secretary of the Ministry for Culture and Science of the state of North Rhine-Westphalia (NRW), Klaus Kaiser, highlighted the relevance as an employer in the region and as an important part in the research landscape of NRW. Environmental spokesperson of the European People's Party (EPP) in the European Parliament and head of CDU-Europe group, MEP Dr. Peter Liese (picture above), praised in his speech the important contribution of Fraunhofer IME to the protection of the environment and consumers and asked for participation in the EU research program Horizon Europe, mission against cancer. Prof. Dr. Adolf Eisenträger, head of the division Pharmaceuticals, Chemicals and Substance Analysis at the German Environment Agency (UBA) outlined the close cooperation between UBA and Fraunhofer IME the Environmental Specimen Bank and gave an example of the development of a guideline. Guests also visited the developing laboratory building. AE BR







Kenyan DAAD-delegation visits Fraunhofer IME in Schmallenberg

A high-level delegation from Kenya visited Germany to become familiar with the German science system and to discuss possibilities to cooperate. Among this delegation were representatives of the National Assembly, of the State Department for Agricultural Research, of the Kenya Agricultural and Livestock Research Organization, of the National Treasury, of the National Research Fund, of Kenya Private Sector Alliance KEPSA, of the University of Eldoret and of the presidential office. Agricultural topics were the focal point of the visit. At first, the delegation visited the German Academic Exchange Service (DAAD) as the host organization and the German Research Foundation (DFG) in Bonn. The next morning, a visit to the Center for Development Research University of Bonn was scheduled. Afterwards the delegation traveled to Schmallenberg, where Fraunhofer-Gesellschaft and Fraunhofer IME with its competences in substance risk assessment for the protection of the environment and consumers were presented by the acting institute director Prof. Dr. Schäfers. Furthermore, DAAD-scholarship holder of the sub-Saharan-Africa program Steve Ayobahan highlighted possibilities of the development and application of methods to identify endocrine effects. After the presentation of the German Environmental Specimen Bank by Sonja Uhlig, the delegation travelled to Braunschweig. Here, the delegation visited the Johann Heinrich von Thünen Institute, Federal Research Institute for Rural Areas, Forestry and Fisheries as well as the Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures GmbH. During the last days of their visit to Germany the delegation spent time in Berlin and visited the Federal Ministry of Food and Agriculture and at the German Federal Institute for Risk Assessment (BfR) as well as the International Green Week. Lastly, the delegation visited the Albrecht Daniel Thaer-Institute of Agricultural and Horticultural Sciences of the Humboldt-University. AE BR

Starting signal for the trilateral cooperation project inCELLphosTAG

With the inCELLphosTAG project, Fraunhofer IME, together with the University of Hamburg and PerkinElmer, has won funding under the new Fraunhofer-DFG cooperation program.

In 2018, the Fraunhofer-Gesellschaft and the Deutsche Forschungsgemeinschaft (DFG, German Research Foundation) launched a cooperation program to effectively transfer basic research into applications. It is based on results from DFG-funded projects that are to be further developed in cooperation with Fraunhofer working groups and an industrial application partner. It offers scientists in basic research the opportunity to further develop their inventions into marketable products and services, as well as companies the opportunity to participate in technological developments at an early stage.

The trilateral cooperation project inCELLphosTAG aims at developing an assay technology that enables investigation of important cellular processes and drug targets in relevant cell systems. It does not use radioactively labelled reagents, which cause health and ecological problems and whose application is subject to strict regulation. Moreover, these reagents are not able to cross intact cell membranes and are therefore not suitable for cell-based high-throughput investigations of the major enzyme classes, such as G-protein coupled receptors (GPCRs) and protein kinases (PKs).

During the 2019-2022 project period, we plan to convert the novel technology into commercial "ready to use" kit formats. This will enable the technology to be widely used and thus advance both basic research and industrial drug research. TM

Urban TaraxaGum - the bicycle tire made of dandelion

After several years of intensive joint development work with Fraunhofer IME, Continental Reifen Deutschland GmbH presented the Urban TARAXAGUM® in 2019, the first serially produced bicycle tire made of dandelion rubber. The natural rubber is obtained from roots of the Russian dandelion *Taraxacum koksaghyz*. Like the tropical rubber tree, the latex of these plants contains large quantities of high-molecular-weight rubber. Prof. Dr. Dirk Prüfer and his team have paved the way for this development in the cycling capital Münster. Together with the WWU Münster, they researched in particular the rubber biosynthesis in dandelions.

Tests conducted by the cooperation partner Continental have shown that not only the car tires but also the bicycle tires are roadworthy in every respect. The first limited edition of the folding tire was quickly sold out, but is now available again. The dandelion for this tire is grown in Mecklenburg-Vorpommern. The tires are manufactured in Korbach, Hessen. Due to the much shorter distances between the cultivation areas located in Germany and the German or European tyre factories, the effort for logistics and transport is drastically reduced and resources can be used more sustainably. MB

Early detection of potential immunotoxicity of immunomodulatory drugs

For many decades pharmaceuticals entering the market either have been derived from traditional, mainly plant-related compounds or consist of small molecular chemicals. In recent years, there has been a marked upswing in the development of biopharmaceuticals, initially therapeutic antibodies, but also cellular therapies, nucleic acids and genes. Such agents not only require different, more complex and often very costly production processes and adapted strategies for testing of experimental and clinical efficacy, they also raise challenges to the testing and prediction of potential adverse effects on the immune system and other organs and tissues.

To address this issue, the European Innovative Medicines Initiative (IMI) announced a call for proposals to develop new approaches to non-clinical predictive testing for immunotoxicity. The winning consortium, led by several Fraunhofer institutes, Fraunhofer IME among them and including about 25 academic and industrial partner institutes from across the EU, is entitled "Immune Safety Avatar: nonclinical mimicking of the immune system effects of immunomodulatory therapies" or imSAVAR. Nearly half of the partners are pharmaceutical companies who guide the planned research to ensure that real world drug development issues are investigated. imSAVAR was officially approved by IMI in September 2019 and initiated in December 2019. Fraunhofer IME will be contributing to several work packages, including the development of novel test models, new biomarkers and the establishment of guidelines for such non-clinical testing. The aim is to define new Adverse Outcome Pathways (AOPs) to assist in the future predictive testing of novel immunomodulatory drugs. TM

"Planet Wissen" with Prof. Andreas Vilcinskas

Andreas Vilcinskas is Professor of Applied Entomology at the University of Gießen and Head of the Branch for Bioresources of Fraunhofer IME. On October 9, he was a studio guest at "Planet Wissen", where this time everything was dealing with the fascinating world of insects.

The lack of habitat and the massive use of environmental toxins are causing more and more species to be threatened by extinction. However, insects have much to offer. Whether as a source for food, as pollinators, or in the removal of carrion, excrement and dead wood, "we depend on them in many ways. We cannot exist without them," Prof. Vilcinskas points out, because "all habitats on land are dependent on insects in one way or another, without them we can not exist at all".

Thanks to their fantastic nature and abilities, insects populate almost all habitats on earth. In the future, we humans could also benefit from the many survival strategies they have developed. Whether as suppliers of antibiotics, in biological crop protection or as a future important source of protein for mankind. Prof. Vilcinskas sees great potential in the young field of research known as "yellow biotechnology". Parallel to the research at the Center for Insect Biotechnology, the world's first international master's degree course in insect biotechnology and bioresources was established at Justus Liebig University in Gießen in 2016. "Learning from insects means learning to win," is the motto of Andreas Vilcinskas. AE BR

Ninth PhD Conference in Aachen

In the doctoral program at Fraunhofer IME in Aachen, the PhD conference is a permanent feature since many years. The aim is the interdepartmental exchange of knowledge and ideas as well as the optimization and consolidation of the PhD students' presentation skills. At the end of November the ninth PhD Conference took place in Aachen. This year, organized by the PhD students themselves, we experienced a day full of exciting lectures and poster contributions. For the first time, we invited bachelor and master students who for example are writing their theses here in Aachen to present a poster. For all of them this was the first opportunity to present their own scientific work to an expert audience. Accordingly, the poster sessions were full of interest and willingness to explain and discuss. In the lectures on topics ranging from metabolic engineering of microorganisms to plants as production systems and bioprocess development, the doctoral candidates presented their latest results. In the lively discussions, they received valuable tips and suggestions for their research.

At the staff meeting in early December, acting director of the institute, Prof. Stefan Schillberg, presented this year's awards. The independent jury selected Patrick Kottenhahn from the Department of Industrial Biotechnology as "Newcomer" of the year with his presentation "Characterization and optimization of 1-hexanol production in CO-utilizing Clostridia". He received a textbook of his choice as the prize. From the group of "Professionals", the jury awarded a prize to the presentation "Chromatographic Model Calibration" by Ronald Jäpel from the Department of Bioprocess Engineering. He approached the challenge of how chromatography can be modelled in a very vivid way. He will use his prize money to attend a conference. MB

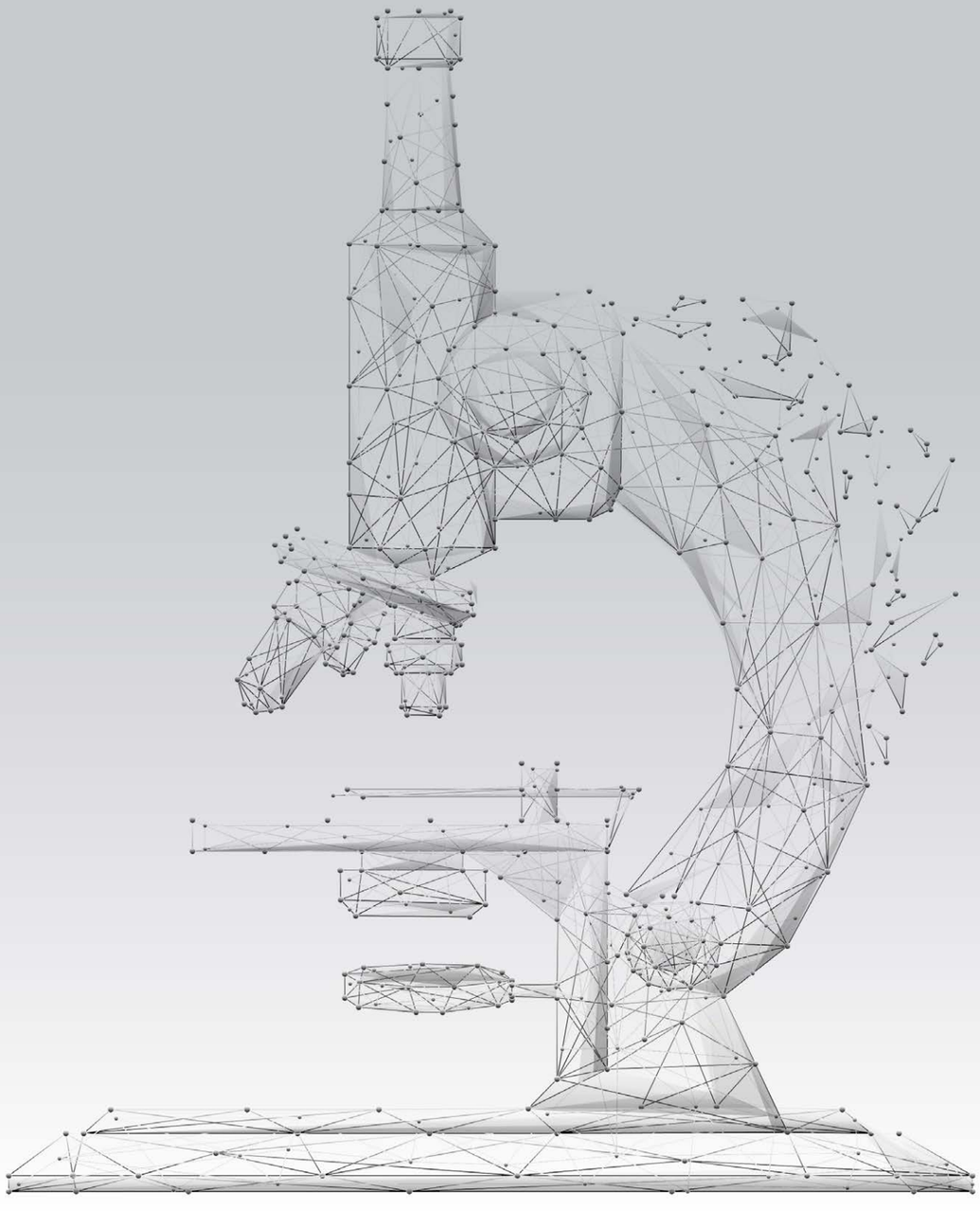
"Jugend Forscht" of secondary school Lennestadt visits Fraunhofer IME

Twenty-seven pupils of the young scientists contest "Jugend Forscht" of the secondary school Lennestadt ("Gymnasium der Stadt Lennestadt, GymSL") came face-to-face with science. Not only did they learn at Fraunhofer IME how Fraunhofer-Gesellschaft is organized in order to conduct applied research but they also had a deep insight into the scientists' work on site. Prof. Dr. Christoph Schäfers, acting director of Fraunhofer IME, committed a whole morning to the 13- to 17-year-old students. After visiting the Environmental Specimen Bank the students discussed with Professor Schäfers their own research projects, which they conduct at the GymSL and received valuable tips first hand. Which organisms should be considered for a specific research question? How do you change conditions of an experiment systematically? The participants came to Fraunhofer IME with fascinating research questions. Some investigated how the leftovers of disposed cigarettes affect the environment, others explored the consequences for animals and plants of exposure to microplastics. Younger pupils try to replace plastic with easily degradable substances, for instance in dishes, and test different materials. "It is great to get support from Fraunhofer IME in our projects when there are hurdles to overcome", a student said after the visit. GymSL is a member of the national Excellence-Network of schools MINT-EC and is particularly focused on supporting explorative learning. AE BR

Fraunhofer IME and Center for Hybrid Nanostructures create nano-bio devices

The Center for Hybrid Nanostructures (CHyN), part of the Institute of Nanostructure- and Solid State Physics of the University of Hamburg, is neighbouring the facilities of the Deutsche Elektronen-Synchrotron (DESY) - and is an integral part of the steadily growing Science City Bahrenfeld which aims at hosting all natural science institutions in Hamburg by 2025, thereby creating synergistic effects between scientific disciplines and basic and applied research.

The team of Prof. Dr. Robert Blick (CHyN) is focusing on the fabrication and application of hybrid nanostructures for integrated nano-bio devices. For the first time now, Jann Harberts and Dr. Robert Zierold of CHyN have generated specialized needle-shaped nanowires which were coated with human neurons differentiated from pluripotent stem cells, generated by Fraunhofer IME (Undine Haferkamp and Dr. Ole Pless). These neurons were well integrated, formed tight interactions with nanowires of different material, size and patterning, and showed similar functionalities as neurons in the human brain, even after weeks of culture. This nanowire set-up allows for the integration of multiple modes of interaction with neurons in a single device and enables bidirectional communication with neural circuits with enhanced spatiotemporal precision. This combination of technologies not only facilitates a greater understanding of the brain in the context of health and disease, but as well aim at impacting the development of novel therapies for neuro-logical, neuro-immune and neuroendocrine conditions. TM



FACTS 2019

Publications

Patents

**Bachelor's, Master's,
State Examination and Doctoral Theses**

Networks in science and industry

PUBLICATIONS

MB Molecular Biotechnology

AEBR Applied Ecology and Bioresources

TM Translational Medicine

PUBLICATIONS

Molecular Biotechnology

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DE 10 2019 133 787.9

Müller, Boje; Prüfer, Dirk; Schulze Gronover, Christian; Benninghaus, Vincent Alexander; Epping, Janina
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DE 10 2019 133 785.2

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US 62/793,234

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EP 3 092 307 B1 (CH, DE, ES, FR, GB, IE, IT, NL, SE)

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EP 2 717 676 B1, 602011055345.3 (DE)

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Artificial forisome body with SEO-F fusion proteins, plant or yeast cells comprising vectors which code for these proteins, as well as vectors which code for SEO-F fusion proteins
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Rademacher, Thomas
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IL 232613A

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N-terminally truncated interleukin-38
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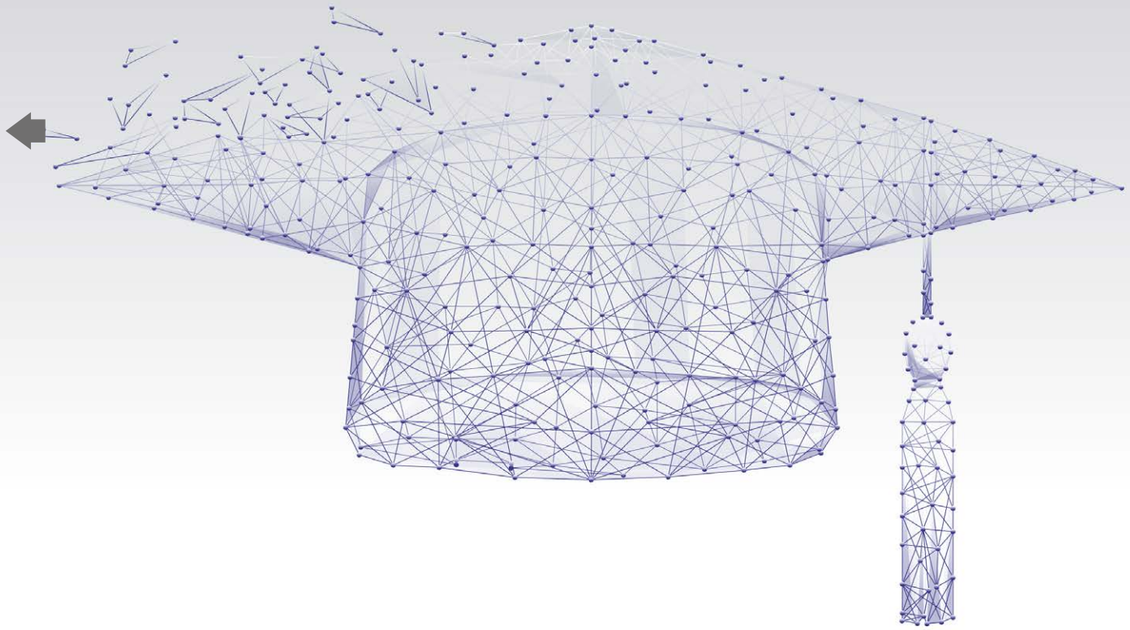
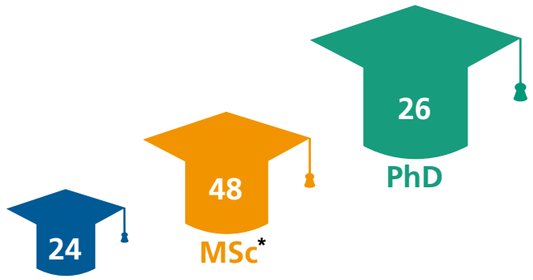


Bachelor’s, Master’s, State Examination and Doctoral Theses

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

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



Theses with the experimental part carried out at Fraunhofer IME (* including 2 state examination theses).

Doctoral Theses

Bröker, Jan-Niklas
Functional characterization of enzymes involved in *Taraxacum koksaghyz* isoprenoid synthesis by metabolic pathway engineering in *Saccharomyces cerevisiae*
Westfälische Wilhelms-Universität Münster

Fracowiak, Jochen
Etablierung eines funktionalen (Meta-)Genomansatzes zur Identifizierung von Klonen mit antibakterieller Aktivität
Justus-Liebig-Universität Gießen

Frank, Ann-Christin
MicroRNA-375 as novel modulator of macrophage migration in the breast cancer microenvironment
Johann Wolfgang Goethe-Universität Frankfurt am Main

Göckener, Bernd
Untersuchung von Pestizidabbauprodukten während der Lebensmittelverarbeitung
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Heise, Philipp
The microbiome of the burying beetle *Nicrophorus vespilloides* as an untapped source for the screening of bioactive small molecules
Justus-Liebig-Universität Gießen

Hoffmann, Daniel
Produktion des Insektenmetalloprotease Inhibitors in *Escherichia coli* - Neuartige Plattformtechnologie für die Inclusion body-basierte Produktaufarbeitung
Justus-Liebig-Universität Gießen

Janas, Christine
Entwicklung einer Apparatur zur in vitro Testung der Wirkstofffreisetzung aus kolloidalen Arzneistoffträgern
Johann Wolfgang Goethe-Universität Frankfurt am Main

Janczi, Thomasz
ADAM15 in apoptosis resistance of synovial fibroblasts: Converting Fas/CD95 death signals into the acvtivation of prosurvival pathways by calmoduin recruitment
Johann Wolfgang Goethe-Universität Frankfurt am Main

Kieselmann, Christopher
Entwicklung und Charakterisierung von Trägersystemen zur dermalen Immuntherapie mit Hymenopterenallergenen
Justus-Liebig-Universität Gießen

Kramer, Jan Sebastian
Biochemische und biophysikalische Untersuchungen der löslichen Epoxidhydrolase und Protein-Arginin-Methyltransferase 6
Johann Wolfgang Goethe-Universität Frankfurt am Main

Kriebs, Katrin
Analysis of the genetic basis, localization and function of PP1 homologs in *Cucumis sativus*
Westfälische Wilhelms-Universität Münster

Kurz, Jennifer
The role of ceramide synthase 2 and 6 in the pathogenesis of multiple sclerosis
Johann Wolfgang Goethe-Universität Frankfurt am Main

Leber, Jasmin
Investigation on the scale-up strategy and harvest for human mesenchymal stromal cell production in a dynamic bioreactor system - Influences of medium, microcarrier choice and new harvest enzymes on the cell quality
Justus-Liebig-Universität Gießen

Nothnagel, Lisa
Entwicklung patientengerechter Arzneistoffformulierungen von R-Flurbiprofen zur Therapie der Multiplen Sklerose
Johann Wolfgang Goethe-Universität Frankfurt am Main

Rosenberger, Julian (geb. Thinnes)
Rationales Design von Entscheidungsbäumen für die pharmazeutisch-technologische Entwicklung
Johann Wolfgang Goethe-Universität Frankfurt am Main

Schäfer, Stefan Martin Gastón Helmut Jonas
Charakterisierung der lipidvermittelten G2A-Aktivierung bei entzündlichen Schmerzen
Johann Wolfgang Goethe-Universität Frankfurt am Main

Shrestha, Prasit
Biodegradation testing of hydrophobic and volatile organic chemicals
Technical University of Denmark

Sprick, Gundula
Transduktion humaner mesenchymaler Stromazellen mit rekombinanten Baculoviren
Justus-Liebig-Universität Gießen

Susen, Rosa Martha
Macrophage HIF-2α regulates tumor-suppressive Spint1 in the tumor microenvironment
Johann Wolfgang Goethe-Universität Frankfurt am Main

Tarighi, Neda
Role of the thromboxane A2 receptor (TP) in peripheral neurons in models for acute inflammation
Johann Wolfgang Goethe-Universität Frankfurt am Main

Treutlein, Elsa-Marie
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Johann Wolfgang Goethe-Universität Frankfurt am Main

Toewe, Andy
Entwicklung einer chiralen Quantifizierungsmethode für entzündungsauflösende Lipidmediatoren in biologischen Matrices mittels Hochleistungsflüssigkeitschromatographie gekoppelt mit Tandemmassenspektrometrie
Johann Wolfgang Goethe-Universität Frankfurt am Main

Visser, Franziska
Molecular and structural characterization of forisome subunits with respect to the development of artificial forisome-based applications
Westfälische Wilhelms-Universität Münster

Wasmuth, Claus
Silbernanopartikel und Silbernitrat in naturnahen Gewässern
Westfälische Wilhelms-Universität Münster

Zimmer, Béla
The oxidized linoleic acid metabolite 12,13-DiHOME mediates thermal hyperalgesia during inflammatory pain
Johann Wolfgang Goethe-Universität Frankfurt am Main

Zitzmann, Jan
Prozessintensivierung für die Produktion von antimikrobiellen Peptiden mit stabil transfizierten *Drosophila melanogaster* S2-Zelllinien
Justus-Liebig-Universität Gießen

NETWORKS IN SCIENCE AND INDUSTRY

NETWORKS IN SCIENCE AND INDUSTRY

Networks in Science and Industry

International activities and cooperations with industry

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 2019, Fraunhofer IME cooperated with around 100 national and international industrial clients and carried out confidential projects for several international industrial associations

Cooperation with universities

Fraunhofer IME has close ties with the Institute of Plant Biology and Biotechnology, the Institute for Evolution and Biodiversity and the Institute for Molecular Microbiology and Biotechnology at the University of Münster. There is also close cooperation with the Institute for Insect Biotechnology at the Justus Liebig University in Gießen, the Institute for Clinical Pharmacology, the Institute for Pathobiochemistry, the Institute for Pharmaceutical Chemistry and the Institute for Pharmaceutical Technology, and several clinics, at the Johann Wolfgang Goethe University in Frankfurt am Main and the RWTH Aachen University. Fraunhofer IME also collaborates with the Aachen-Maastricht Institute for Biobased Materials (AMIBM) at the University of Maastricht, the Institute for Biology V (Environmental Research) at RWTH Aachen University, the Institute for Biology at the University of Siegen, the Center for Fish and Wildlife Medicine at the University of Bern and the School of Chemistry at Monash University in Melbourne.

Lecturing assignments

Dr. Natasja de Bruin holds seminars at the Goethe University Hospital Frankfurt am Main and the Frankfurt International Research School for Translational Biomedicine (FIRST). She participated in the Workshop "Fraunhofer CIMD Young Scientist Program" of Fraunhofer Cluster of Excellence for Immune-Mediated Diseases (CIMD).

Prof. Dr. Mark Bücking holds lectures at the Faculty of Mathematics and Natural Sciences at the University of Wuppertal and is Associate Professor at the School of Chemistry at Monash University, Melbourne, Australia.

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

Dr. Dr.-Ing. Johannes F. Buyel holds lectures in the master program "Molecular and Applied Biotechnology" at the RWTH Aachen University.

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

Prof. Dr.-Ing. Peter Czermak is Professor of Bioprocess Engineering and Pharmazeutical Technology and Managing Director of the Institute of Bioprocess Engineering and Pharmazeutical Technology - IBPT at the Technical University of Central Hessen.

Prof. Dr. Jennifer Dressman is Professor of Pharmaceutical Technology in the Department of Biochemistry, Chemistry and Pharmacy at the Goethe University Frankfurt am Main.

Dr. Jürgen Drossard holds lectures in the master program "Molecular and Applied Biotechnology" at the RWTH Aachen University.

Dr. Bernhard Ellinger holds seminars and internships in the model course in Medicine at the University Medical Center Hamburg-Eppendorf.

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

Prof. Dr. Dr. Gerd Geißlinger is Professor and Director of the Institute for Clinical Pharmacology of the University Medical Center Frankfurt am Main. He lectures in clinical pharmacology and therapy for medical students.

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".

Dr. Kerstin Hund-Rinke holds lectures in ecotoxicology at Hochschule Osnabrück (University of Applied Sciences).

Dr. Michael Klein holds lectures about modelling the environmental fate of chemicals at RWTH Aachen.

Dr. Kwang-Zin Lee lectures at the Institute for Insect Biotechnology in the field of Applied Entomology at the Justus Liebig University of Gießen.

Dr. Martin Müller holds lectures about modelling the environmental fate of chemicals (QSAR) at RWTH Aachen.

Prof. Dr. Michael Parnham is Professor of Pharmacology and Toxicology in the Faculty of Biochemistry, Chemistry and Pharmacy at Goethe University Frankfurt. He offers the module Pharmaceutical Research and Development of the Master of Pharma Business Administration (MPBA) of the Goethe Business School.

Dr. Ole Pless, Dr. Bernhard Elilinger and **Prof. Dr. Carsten Claussen** hold lectures, seminars and internships at the Faculty of Medicine of the University Hamburg (UKE).

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

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

Prof. Dr. Till Schäberle is Professor of Natural Product Research with a focus on insect biotechnology at the Justus Liebig University of Gießen.

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 am Main.

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 established Institute for Insect Biotechnology, both at the Justus Liebig University Gießen.

Dr. Matthias Wacker is Associate Professor in the department of Pharmacy of the National University of Singapore and lectures in Pharmacy and Pharmaceutical Sciences.

Dr. Carmen Walter holds seminars at the Goethe University Hospital Frankfurt am Main.

Dr. Björn Windshügel holds lectures at the Jacobs University Bremen.

Prof. Dr. Holger Zorn is Professor of Food Chemistry and Food Biotechnology and Managing Director of the Institute of Food Chemistry and Food Biotechnology at the Justus Liebig University of Gießen.

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Deutschen Institut für Bautechnik, Projektgruppe »Modellierung«
Dr. Michael Klein

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- NA 119-01-02-02-01 AK Bioverfügbarkeit
Dr. Kerstin Derz

- NA 119-01-02-04 UA Biologische Verfahren
Dr. Kerstin Hund-Rinke

- NA 119-01-02 AA Abfall und Bodenuntersuchung, UA 1 Probenahme
Karlheinz Weinfurtner

- NA 119-01-02-06 UA Bodenschutz, Entsorgung, Altlastensanierung, UA 2 Entsorgung
Karlheinz Weinfurtner

- NA 119-01-03-05-03 AK Marine Biotests
Dr. Karsten Schlich

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Dutch NeuroFederation
Dr. Natasja de Bruin

ECHA/EFSA, Endocrine Disrupting Guidance Consultation Group
Hearing expert:
Prof. Dr. Christoph Schäfers

ECNP, European College of Neuropsychopharmacology & Preclinical Data Forum Network
Dr. Natasja de Bruin

EFSA Working Group Developing an EFSA scientific report for the FOCUS surface water repair action
Dr. Michael Klein

EFSA Working Group on the new guidance document about persistence in soil
Dr. Michael Klein

ETH Review Panel (Department of Chemistry and Applied Biosciences)
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NETWORKS IN SCIENCE AND INDUSTRY

Organization of Scientific Meetings and Courses

3rd Exzellence Course SPA Psoriasis-Arthritis and Axial Spondyloarthritis
Seeheim-Jugenheim, October 24 to 26, 2019, let by PD Dr. med. Frank Behrens in cooperation with House of Pharma & Healthcare

ELRIG Discovery 2019, Looking back to Future
Liverpool, November 4 to 5, 2019, member of the scientific organization committee and session chair Dr. Philip Gribbon

Symposium: New opportunities for drug discovery with stem cell technologies
Kobe, August 29, 2019, organized in cooperation with FBRI (foundation for Biomedical Research and Innovation, Kobe, Japan), Prof. Dr. Carsten Claussen

Immunology Day 2019
Frankfurt am Main, June 19, 2019, organized by the Fraunhofer Cluster of Excellence for Immune-Mediated Diseases CIMD

Workshop »4th MuTaLig COST Action Training School, CA 15135«
Hamburg, March 6 to 8, 2019, organized by the MuTaLig COST Action Committee and Fraunhofer IME, Dr. Sheraz Gul

Workshop: C-CNS Drug Discovery
Kobe, July 11, 2019, organized in cooperation with FBRI (foundation for Biomedical Research and Innovation, Kobe, Japan), Dr. Sheraz Gul

Workshop »Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls«
Maryland, USA, September 23 to 26, 2019, organized by FDA, co-organizer Prof. Dr. Jennifer Dressman

Workshop: Drug Discovery and Development
Hamburg, 17. bis 18. Oktober 2019, organized in cooperation with cisbio, Dr. Sheraz Gul

Workshop: From Molecule to Medicine
Ljubljana, March 18 to 20, 2019, Epichembio COST Action Training School, CM 1406, Dr. Sheraz Gul

Workshop »Nachwuchsförderung des Fraunhofer CIMD«
Frankfurt am Main, June 17 to 18, 2019, organized by the Fraunhofer Cluster of Excellence for Immune-Mediated Diseases CIMD

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