Fraunhofer IME

Fraunhofer Institute for Molecular Biology and Applied Ecology IME

Annual report 2023/24

Preface

The year 2023 was marked by the reorganization of the management of the Fraunhofer-Gesellschaft as well as Fraunhofer IME. The new Fraunhofer President, Prof. Holger Hanselka, is dedicating his presidency to the goal of returning the Fraunhofer-Gesellschaft to its primary objective of applied research for industry, combined with a consolidation of size and a simultaneous focus on the quality of work processes and results. In order to reflect the thematic and strategic orientation of the Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Prof. Dr. Christoph Schäfers, who has been head of the division for many years, was appointed to the institute management of Fraunhofer IME at the beginning of 2024. Together with Prof. Dr. Stefan Schillberg, who is primarily responsible for the Molecular Biotechnology division in Aachen and Münster as well as the institute branch Bioresources in Giessen, he will lead the positioning of the institute within the Fraunhofer-Gesellschaft and on the market for research services.

In 2023, the junior research groups "Cultured Meat" and "Single Cell Protein" were created in Aachen to strengthen the "New Agricultural Systems" department. The focus of these groups is on establishing processes to provide alternative protein sources for human nutrition. Recombinant proteins are also increasingly in demand in the agricultural and food industry and the site has been able to produce several protein candidates on a larger scale in different expression systems and make them available to industry. The activities of the junior research groups were also presented by the group leaders at the "Food ingredients Europe" exhibition in Frankfurt am Main last year.

An important event was the visit of the new President of the Fraunhofer-Gesellschaft, Prof. Holger Hanselka, to the Fraunhofer IME in Aachen in December 2023. During a tour of the institute, the President was given numerous insights into our research activities, including the field of vertical farming. Our location in Münster with the "Functional and Applied Genomics" department presented the commercially available bicycle tires produced from the Russian dandelion. The focus of Prof. Hanselka's visit, however, was the dialogue with the employees and their questions on scientific and organizational topics of the Fraunhofer-Gesellschaft, which the President responded to very openly.

The challenges posed by the energy crisis and the conversion of the ERP system continued in 2023 and led to a negative annual result for the second year in a row. The new laboratory building in Giessen is not yet fully functional, nor is the large laboratory building in Schmallenberg, which was ceremoniously opened by the Prime Minister of the Federal State of North Rhine-Westphalia, Hendrik Wüst, in June 2023. While employees were able to move into the office floor, the commissioning of the laboratory floors is still ongoing and is contributing to the annual result due to the significant delay. However, the structural and strategic foundations have been laid to return to a budget in 2025 that follows the Fraunhofer rules consolidated under the new presidency; the 2024 budget plan already shows a clear recovery. Volatilization studies and ecotoxicogenomic tests to determine the molecular threshold value of a hazard have been successfully established as new service offerings.

Fraunhofer IME's strategy process 2028 is in a dynamic phase and, with the development of the method platform called "Agri'n'Omics", has achieved an important initial output for the strategic orientation and cooperative collaboration of all sites for the future viability of the institute. Read more about this on the following pages: "Agri'n'Omics: Joint method platform for a strategic orientation of the Fraunhofer IME".

Prof. Dr. Stefan Schillberg

Prof. Dr. Christoph Schäfers

Content

Agri'n'Omics: Joint method platform for a strategic direction of Fraunhofer IME

by Prof. Dr. Christoph Schäfers & Prof. Dr. Stefan Schillberg

The Fraunhofer Institute for Molecular Biology and Applied Ecology IME is divided into the "Applied Ecology" division in Schmallenberg and the "Molecular Biotechnology" division in Aachen and Münster, including the institute branch "Bioresources" in Giessen. Following the spin-off of the "Translational Medicine" division as an independent Fraunhofer Institute (Fraunhofer ITMP) in 2021, the "Molecular Biotechnology" and "Bioresources" research areas focused more strongly on bioeconomic topics, while the "Applied Ecology" division further expanded its leading position in the development of methods for the substance-related environmental risk assessment of synthetic and biogenic substances throughout Europe. This development has resulted in two key guidelines for the future strategic direction of Fraunhofer IME:

1. the institute's focal points have different business models and transfer paths, which in the future, will continue to be managed independently:
    a. Product and process development with protection and utilisation of IP rights (Molecular Biotechnology and Bioresources)
    b. Development of guidelines and regulatory substance testing (Applied Ecology)
2. at the same time, it must be ensured that a common profile is visible in the thematic and methodological overlap area of the agricultural and food industry, which promotes the integration of the four locations.

The term **Agri'n'Omics** was coined for this purpose as part of the development of the institute's 2028 strategy. We understand this to mean the observation/investigation of the entirety of molecular processes in agricultural production, with the aim of understanding, evaluating, utilising and improving these processes - both from the perspective of plant and animal production, as well as from the perspective of agroecology.

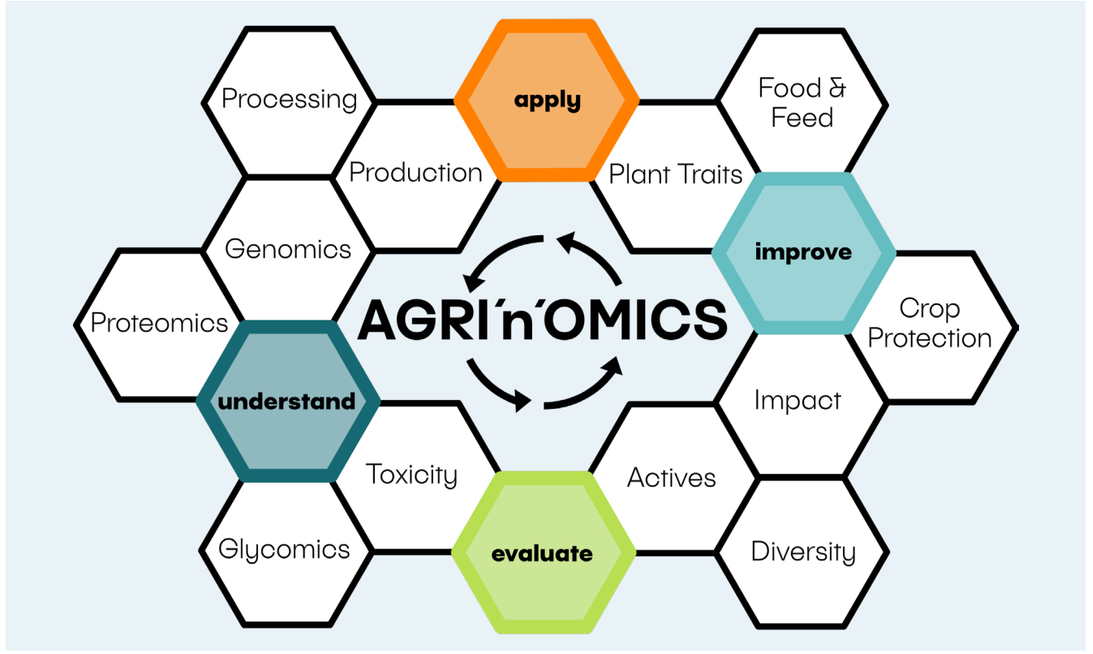
Through Agri'n'Omics, the very different focal points of the institute form a common method platform. This enables genome, transcriptome and proteome analyses as well as dependent metabolome and lipidome analyses and the processing of topics from the research areas of (eco-) toxicogenomics and nutrigenomics. This complements the research of the other, more process-engineering orientated institutes of the Fraunhofer Group Resource Technologies and Bioeconomy VRB.

In order to establish, expand and holistically utilise the joint Agri'n'Omics method platform, more intensive coordination of the research activities of the four Fraunhofer IME locations will be essential in the future.

The aim is to elevate Fraunhofer to a globally leading role both in the research field of bioeconomy and in regulatory substance assessment. Fraunhofer IME works on molecular interactions with regard to bioeconomic benefits (molecular biotechnology and bioresources) and ecological "adverse outcome" (applied ecology) in order to provide benchmarks and solutions for healthy, sustainable, climate-friendly, resource-conserving agriculture and resilient agricultural systems.

There are three main topics:

- **Plant cultivation:** The molecular expertise of plant breeding research in the "Molecular Biotechnology" (MB) department and the Environmental Microbiology department of the "Applied Ecology" (AE) department at the Münster site lays the foundations for questions of plant cultivation (optimisation of plant and seed properties for the bioeconomy, MB) and soil evaluation (AE). The crop metabolism established at the Schmallenberg site (AE) to assess the side effects of fertilisers and pesticides on the consumer can be used in cooperation with plant biotechnology at the Aachen site to record and optimise qualitative aspects of food and feed. At the same time, the Schmallenberg site continues to record and evaluate the impact of plant cultivation and plant protection measures on water and soil, which is supplemented by biodiversity research at the Giessen site.
- **Closed agricultural systems:** Closed systems are characterised by their controllability, their independence of climate and season and their resource efficiency in terms of nutrients, water, space and transport routes. Vertical or contained farming of food crops at the Aachen site could be supplemented by concepts for the nutritional optimisation of the products with the help of the Agri'n'Omics platform. For the production of cultured meat with a typical meat texture, there are interesting approaches to reducing the harmful properties of red meat, which are complemented by the nutritional science expertise at



the Giessen site. Researchers in Giessen are testing the co-cultivation of insects, fish and plants, whose protein production could be analysed for undesirable side effects at the same time. This expertise is supplemented by technology (RAS systems in the 14C application area) and knowledge in the field of aquaculture at the Schmallenberg site. Closed systems are also indispensable in the production of high-quality non-food products. This applies to microbiological expression systems as well as to plants optimised for specific properties.

- **New/biological pesticides:** Researchers at the Giessen site have developed numerous approaches for controlling pest and vector insects, for example using the sterile male method, RNAi or the use of parasites. The use of animal toxins and antimicrobial peptides is also being trialled. At the Münster site, scientists are identifying secondary plant substances with defence potential. Researchers in Schmallenberg can provide analytical support for these approaches and for validating them as standard methods so that they can be offered to industry as GLP studies for novel efficacy tests of biopesticides.

The Agri'n'Omics method platform thus offers numerous opportunities to link the research activities of the four sites, utilise synergies and jointly develop new subject areas.

Cooperation with universities and colleges

Fraunhofer IME maintains a close dialogue with various universities and colleges. The cornerstone of the cooperation is the close personal interweaving of Fraunhofer IME managers as chair holders and other professorships at the cooperating universities in Aachen, Münster and Giessen. A large number of university research focuses can be linked to the Agri'n'Omics platform in a targeted manner: For example, synergy effects can be expected through the interaction of plant biotechnology (University of Münster), molecular biotechnology (RWTH Aachen University) and the focus areas of agricultural sciences and food research at Justus Liebig University Giessen with the core topics of plant cultivation/soil science and animal production/aquaculture at the four Fraunhofer IME locations.

The institute

Fraunhofer IME profile

The Fraunhofer Institute for Molecular Biology and Applied Ecology comprises the "Molecular Biotechnology" Division and its Branch for "Bioresources" as well as the "Applied Ecology" Division. Prof. Dr. Stefan Schillberg has been the executive director of the institute since 2022, Prof. Dr. Christoph Schäfers was appointed into the institute's management in early 2024.

The 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 and on the public sector. In 2023, Fraunhofer IME collaborated with more than 150 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 2023, the institute employed about 424 people at the locations in Aachen, Münster, Schmallenberg and Gießen. We have close ties with the Institute of Molecular Biotechnology at RWTH Aachen University, the Department of Biology and Biotechnology of Plants at the University of Münster, the Department of Insect Biotechnology at the Justus-Liebig University Giessen. 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 feed as well as 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.

Bioresources

We exploit groups of organisms with a large biodiversity such as insects, bacteria and fungi as bioresources by using innovative technologies and established platforms to isolate and characterize naturally occuring substances. We evaluate them with regard to their application potential in medicine, plant protection and industrial biotechnology. Thus, new molecules will be identified in order to develop antibiotics or substances for the food and feed industry, like aromatics, preservatives and enzymes, as well as to open up new applications and to form a basis for the creation of value-added chains. Moreover, we develop insect models for toxicological studies and deploy biotechnological methods to control pest and vector insects, for example RNA inference in plant protection or sterile insect technology.

Applied Ecology

Our objective is the risk assessment of synthetic and biogenetic substances for the environment and consumers. We develop experimental and model-based methods for the analysis and prediction of the environmental concentration and the hazaroudness of substances with regards to the environment as well as for the analysis of consumer exposition to substances in th environment. We often act as scientific mediators between commercial producers and the regulatory authorities and are involved in the new and further development of international test guidelines. We conduct contract research for industry and the public and use our analytical expertise to increase food safety and quality.

Fraunhofer IME within the Fraunhofer-Gesellschaft

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 76 institutes and research institutions throughout Germany. More than 30,800 employees are qualified scientists and engineers, who work with an annual research budget of 3.0 billion euros. Of this sum, 2.6 billion euros is generated through contract research.

The Fraunhofer Institutes are organized in nine 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.fraunhofer.de/en/institutes/institutes-and-research-establishments-in-germany/fraunhofer-groups/resource-technologies-and-bioeconomy

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 lead market alliances:
Chemimal Industry: www.chemie.fraunhofer.de/en
Agriculture and Food Industry: www.food.fraunhofer.de/en

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 an associated institute of the Fraunhofer Cluster of Excellence for Immune-Mediated Diseases CIMD. **www.cimd.fraunhofer.de/en.htm**

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

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 coordinates the lighthouse project "FutureProteins" and is involved in the project "ShaPID".
www.ime.fraunhofer.de/en/trends/futureproteins
www.shapid.fraunhofer.de/en

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

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. Members of the Fraunhofer IME Advisory Board:

Dr. Harald Seulberger (Chairman)
BASF SE, Limburgerhof

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

Dr. Dr. h.c. Christian Patermann
formerly director Directorate-General for Research and Innovation, Bonn

Dr. rer nat Thomas Preuss (guest)
Bayer AG, Leverkusen

Dr. Doreen Schachtschabel (guest)
Senior Vice President R&D Seeds and Traits, BASF SE, Gent

Dr. Karin Schlesier
Federal Institute for Risk Assessment, Berlin

Prof. Dr. Wiltrud Treffenfeldt
Life Science & Biotechnology, Oberrieden, Schweiz

Prof. Dr. Johannes Wessels
Rector of University of Münster, Münster

Dr. Hans-Ulrich Wiese
formerly member of the Executive Board of the Fraunhofer-Gesellschaft

Business fields

Molecular Biotechnology

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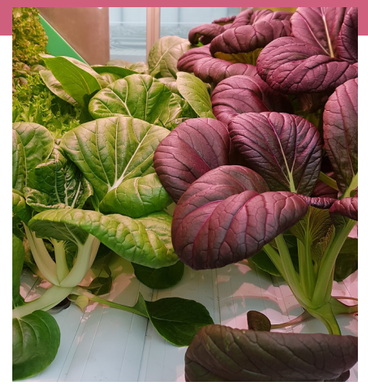
Bioproduction and Industrial Biotechnology

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.

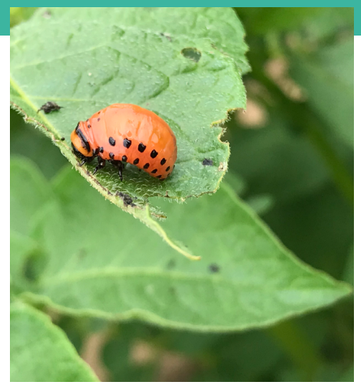
The departments and project groups involved in this business field focus on precision breeding techniques and the development and testing of GM crops. The department "New Agricultural Systems" establishes technologies such as vertical farming, Single Cell Protein and Cultured Meat to provide alternative protein sources for human food. Based on this wide-ranging expertise, Fraunhofer IME acts as a preferred partner for academic laboratories, SMEs and major agribusiness companies.

Protein production

The Fraunhofer IME offers expertise in all aspects of the design, production, purification and characterization of recombinant proteins, including process development and scale-up from a laboratory process to the manufacture in kilograms. 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.

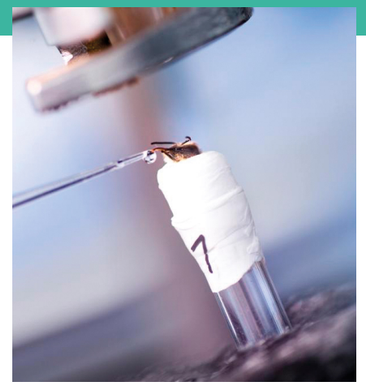
Business fields

Bioresources



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. With the world's largest industrial strain collection of microorgasnisms, taken over from Sanofi, we are also open to 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.

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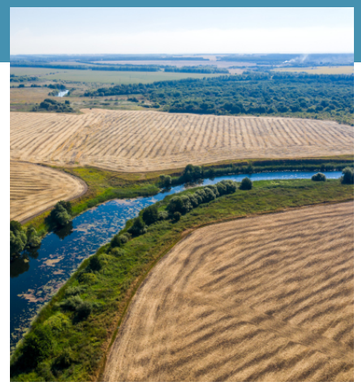
Business fields

Applied Ecology

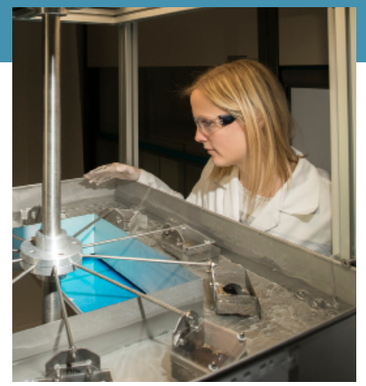
Environmental Risk Assessment of Chemicals

We use our expertise in environmental trace analytics, experimental environmental chemistry and ecotoxicology as well as the modelling of the fate and effects of substances to analyse their risks in the environment. In consultation with the regulatory authorities, we identify issues and develop test guidelines to address them. We are partners to industry for the quality-assured implementation and evaluation of complex experimental and model-based studies with scientific standards and fulfil the relevant requirements of the ECHA (REACH) or EMA. We use the analysis and classification of molecular mechanisms of action in screening tools for environmental effects of product candidates. We host the Federal Environmental Specimen Bank and carry out environmental monitoring projects in order to identify potential new environmental impacts and verify prospective assessments.



Soil and Water Protection

The protection of soil and water requires the characterisation of their quality, the identification of relevant pollution pathways and the most comprehensive possible detection of potentially hazardous components in incoming material flows, such as composts, sewage sludge or wastewater. We are successively expanding our organic and inorganic chemical trace analytics and effect-based analysis to include suspect and non-target methods. Using high-resolution LC-MS/MS, we record the entire mass spectrum of occurring substances. Also, using transcriptomics and proteomics, we record the mechanisms of action of all material loads that are present in effect-relevant concentrations in eluates of soil, compost or sewage sludge, or in water or wastewater samples. The local and regional biodiversity is recorded via e-DNA determinations and can be checked for a correlation with the contaminated material.



Environmental Risk Assessment of Agrochemicals

We test and assess the environmental compatibility of plant protection products in accordance with national and international plant protection legislation (in particular EC 1107/2009). To this end, we develop and implement tailored studies for higher tier risk assessment (HTRA), e.g. life cycle tests with fish, species sensitivity distributions (SSDs) and mesocosm studies including chemical analyses. The experimental work is complemented by statistics, exposure and effect modelling. As a consequence of our experience with in house studies for pesticide manufacturers and our work for and in co-operation with authorities, we can often mediate between notifiers and authorities when it comes to the evaluation of studies or the determination of an optimal test strategy.

Evaluation of Food Safety and Consumer Risk Assessment

Food quality depends on the production, primary processing and further processing of agricultural raw materials. We deal with the quality characteristics of raw materials and foodstuffs and their contamination by harmful substances. For example, we adapt existing protocols for the metabolism of pesticides in crop plants and animals to veterinary drugs, feed additives and new livestock taxa. We are also developing cell-metabolic alternatives to animal experiments. We track degradation and transformation products using radioactive labelling, including during food processing. Within the Fraunhofer Food Industry Alliance, these issues are extended to the entire food chain with a focus on food analyses/processing, microsystems technology and logistics.

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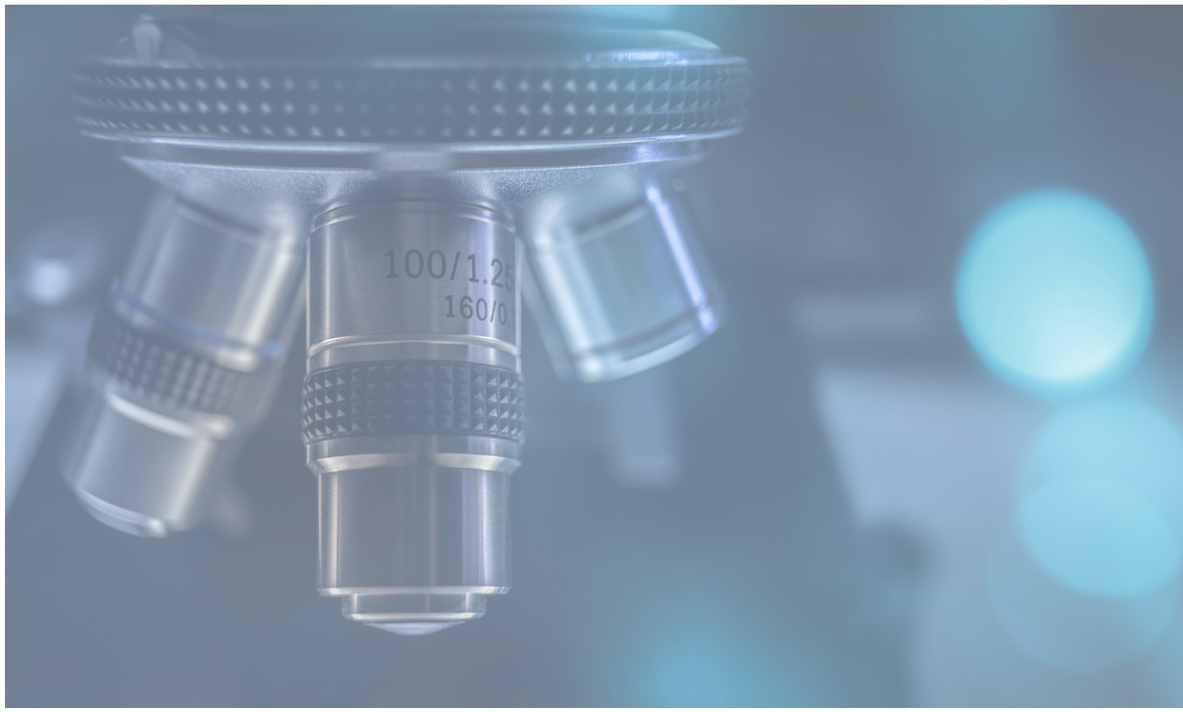


The Fraunhofer President Prof. Holger Hanselka visiting the Fraunhofer IME in Aachen during his dialogue tour.

Hendrik Wüst, Prime Minister of the Federal State of North Rhine-Westphalia, at the opening ceremony of the new laboratory building in Schmallenberg.

Highlight

AlterN'omics: Alternative animal models for biomedical research

by Dr. Anton G. Windfelder

Manduca sexta **is an important model organism for researching inflammatory bowel diseases. The intestinal epithelium (blue) of *Manduca* resembles that of mammals. It is surrounded by a protective, mucous peritrophic matrix (yellow), which protects the epithelium from bacteria (purple), similar to humans. Moreover, *Manduca* has a strong immune system that can effectively fight pathogen bacteria and keep them under control. These characteristics make *Manduca sexta* a very useful model for the examination of inflammatory bowel diseases, while giving insights into possible therapies for similar diseases in humans.**

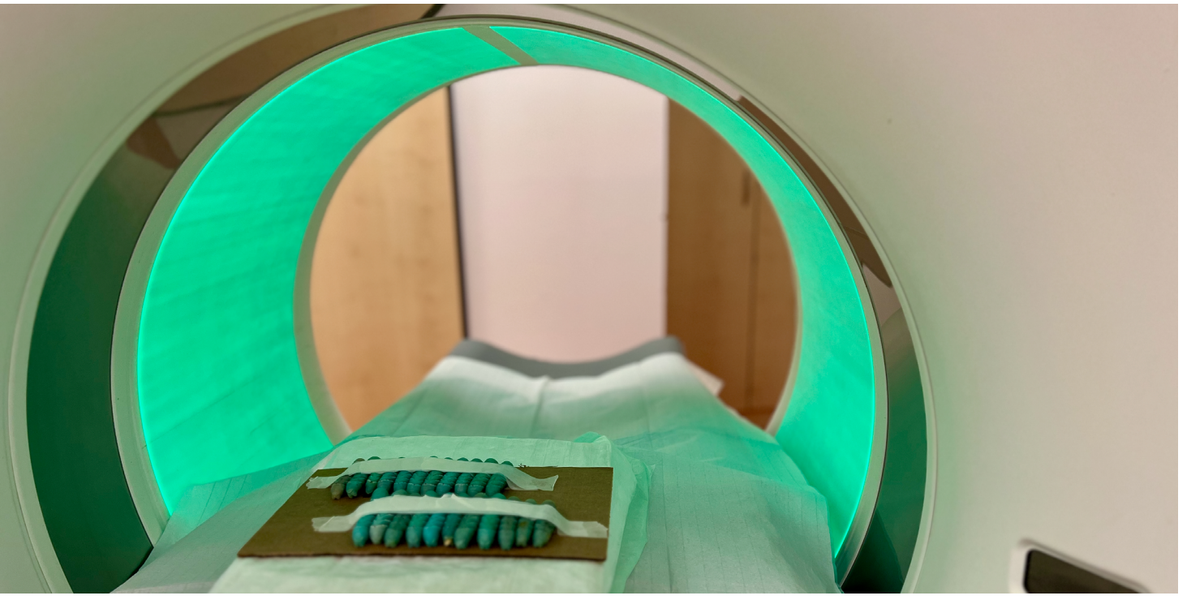
Small mammals such as rats and mice have become an integral part of preclinical research. However, there are increasing ethical and economic concerns about the extensive use of these animals in biomedical research. This is also reflected in funding practices for scientific projects and in legislation. In future, all possibilities for reducing the number of laboratory animals and the use of possible alternatives to vertebrates should be fully exploited. In this context, invertebrates such as insects can play an important role in relieving the burden on classic laboratory animals such as rats or mice. For this reason, the Fraunhofer IME has established a unique technology platform in cooperation with the University of Giessen, the University of Düsseldorf and the Max-Planck Institute Bad Nauheim: **AlterN'omics**. Here, sustainable, efficient and innovative technologies are combined to supplement traditional animal models with alternatives. This approach accelerates and economizes biomedical translational research. The holistic consideration and evaluation ('omics) of alternative models ('alter' for alternative or alternation) is the name of our unbiased technology approach.

Around 75 percent of the genes that can trigger a disorder in humans are also present in insects. This also applies to the core components of the innate immune system, which are highly conserved in insects and mammals. For this reason, we were able to successfully establish the insect larvae of the tobacco hornworm (*Manduca sexta*) as an alternative animal model for intestinal inflammation and inflammatory bowel disease[1]. Compared to traditional laboratory animals such as rats or mice, however, insects such as *Manduca* offer several crucial advantages: Their use in research is faster and more cost-efficient than animal experiments with mammals and, moreover, is fraught with fewer ethical concerns.

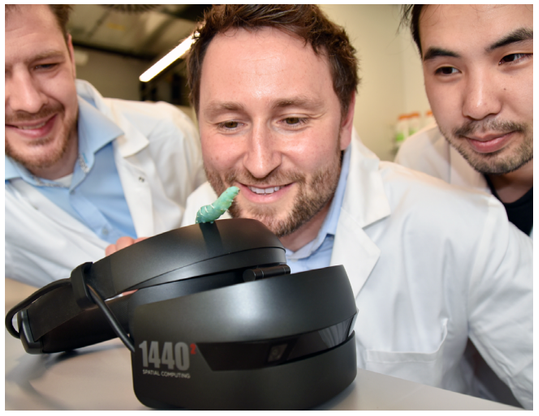
AlterN'omics: innovative, sustainable and efficient

One of the distinctive features of the larvae of the tobacco hornworm is its size. In contrast to other insects such as the fruit fly *Drosophila*, the caterpillars of the tobacco hornworm are about the size of a small mouse and therefore large enough for medical imaging. Using our AlterN'omics technology platform, we show that inflammatory changes in the larvae's intestines can be precisely characterized using computed tomography (CT), magnetic resonance imaging (MRI) or positron emission tomography (PET).

In order to better understand and predict the accumulation of contrast agents in the insect gut, we have created an elaborate 3D atlas using micro-computed tomography and electron microscopy.[2, 3] Using this atlas, we can show that the larval gut runs in a straight line through the animal and that it is particularly easy to quantify contrast agents or tracers that are deposited in the gut wall during inflammation. In general, the more contrast agent is deposited in the intestinal wall, the more severe the inflammation. Due to the enormous size of the animals, clinical CT and MRI equipment can be used to characterize the gut of tobacco hornworms. This enables high-throughput imaging, which can be used to answer preclinical questions *in vivo*.



The tobacco hornworm's intestine can be characterized using CT, MRT and PET devices. A great advantage of clinical devices over special scanners for small animals is the bigger examination capacity. Thus, clinical CT allows for several hundred larvae to be effortlessly examined at the same time, while new pharmaceutics and contrast agents can be tested in vivo.



Our 3D atlas enables us to explore the tobacco hornworm's intestine in virtual reality (VR) or augmented reality (AR). Our 3D models help us to predict the distribution of the contrast agent in the intestine.

The eye of the needle in research

New active substances are usually investigated in cell culture experiments. Research using mammalian cells is simple and inexpensive, but often provides only limited information about how a substance behaves in vivo, i.e. in the complex network of effects of a living organism. In fact, this is a bottleneck in the research of new active substances and therapies, as experiments in cell culture often cannot be reproduced in murine models. This is precisely where experiments with insects such as *Manduca sexta* can help: Substances that have been positively evaluated in cell culture can be tested in vivo in the insect model. If the positive effect can be replicated in the insect, further trials with mammals and finally clinical studies can follow. Unnecessary experiments with mice can thus be avoided, saving resources and making research more ethical overall.

Possible applications

The alternative insect platform presented can be used, for example, to test new antibiotic substances. Using animals fed with bacteria that trigger gut inflammation, we were able to show that an antibiotic prevented inflammation in a concentration-dependent manner. The severity of the intestinal inflammation can be precisely quantified using the aforementioned imaging methods. The method can also be used to characterize and classify bacteria in terms of their gastrointestinal pathogenicity.

Another area of application is the discovery of new anti-inflammatory drugs and the testing of preclinical hypotheses on intestinal inflammation. It has long been suspected that chronic inflammatory bowel diseases such as Crohn's disease and ulcerative colitis are partly caused by so-called reactive oxygen species (ROS). In the intestine, these reactive molecules are produced by the protein DUOX (short for dual oxidase). This protein is equally upregulated in humans and insects during intestinal inflammation. Consequently, the activation of DUOX in the caterpillar model led to intestinal inflammation, which could be characterized by imaging. Interestingly, the intestinal inflammation in the tobacco hawkmoth could also be treated with cortisone - in analogy to humans. Inhibitors of DUOX also resulted in remission. This demonstrates the transferability of the results to the mammalian model and shows that new anti-inflammatory substances can also be tested in the caterpillar model. Further studies will now follow to test the role of DUOX in chronic inflammatory bowel diseases in humans.

Other exciting areas of application are the development and evaluation of new contrast agents and tracers for radiology or nuclear medicine. Together with cooperation partners from the University of Twente in the Netherlands and the University of

Düsseldorf, we were able to establish the larvae of *Manduca sexta* as an alternative animal model for the in-vivo testing of new and innovative MRI contrast agents as part of the AlterN'omics joint project[3].

Most current MRI contrast agents are based on the toxic element gadolinium. Instead, our cooperation partners are investigating biodegradable phosphorus contrast agents as a more environmentally friendly alternative. Phosphorus is a promising alternative for MR imaging due to its natural stability. The only naturally occurring stable isotope, ^{31}P, is both spin-active and extremely biocompatible.

In vivo tests were carried out with the insect larvae of *Manduca sexta* as part of the AlterN'omics technology platform in Giessen and Düsseldorf. The new compound stood out clearly and distinctly from the background and remained in the hemolymph for over 24 hours, indicating its potential for targeted imaging. Furthermore, degradation products of the polymer could be detected in the feces of the caterpillars, confirming the natural in vivo degradation of the polymer.

Overall, we were able to demonstrate the use of insect larvae such as *M. sexta* as an alternative animal model for the in vivo research of new contrast agents and show the great potential of AlterN'omics for our customers. Comparable studies can also be carried out under GLP conditions.

Of course, the insect model is also limited in some areas. The most important difference to mammals is the absence of the B- and T-cell-based adaptive immune response. Other differences include the open circulatory system, disparities in respiration, which in insects occurs via tracheae, and differences in the transport of glucose in the blood or hemolymph of the animals.

Despite these differences, evolutionarily very ancient genes in particular are highly conserved between insects and mammals. It is precisely these primordial genes that are disproportionately often associated with human diseases. For this reason, insect models are excellently suited for understanding human diseases and can replace mice in certain research questions.

The larva of the tobacco hornworm is about the size of a small mouse and thus big enough for medical imaging.

Publication:

[1] Windfelder, A.G., Müller, F.H.H., Mc Larney, B., Hentschel, M., Böhringer, A.C., von Bredow, C.-R., Leinberger, F.H., Kampschulte, M., Maier, L., von Bredow, Y.M., et al. (2022). High-throughput screening of caterpillars as a platform to study host–microbe interactions and enteric immunity. Nature Communications 13. 10.1038/s41467-022-34865-7.

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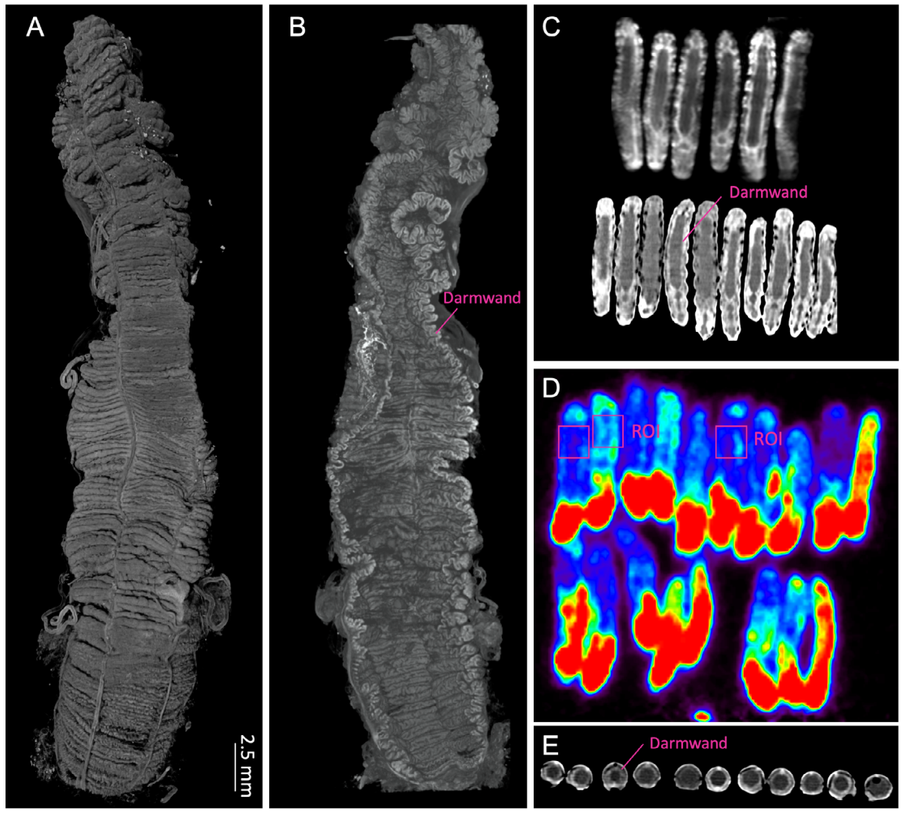
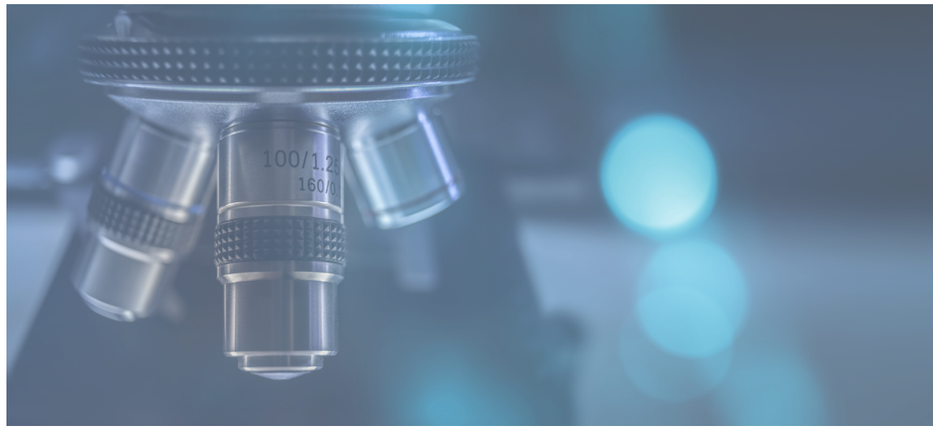


Medical imaging of the tobacco hornworm larvae. A and B: 3D image of the larvae's intestine in the micro CT, C: MRT and CT scans of the larvae, D: 3F desoxyglukcose PET scan, E: CT scans of the larvae.

Insights into our research



"NovelSweets": New protein-based sugar substitutes

Multipurpose seed coating to safeguard and increase crop yields by protecting and nourishing the seedling - SeedPlus

The RobustNature Excellence network investigates the connection between chemical pollution and biodiversity

Next Generation Steroid hormones – Tailored testing strategies to identify endocrine disrupting substances

Antimicrobial peptides from *Hermetia illucens* for food and feed preservation

Development of a holistic biological plant production

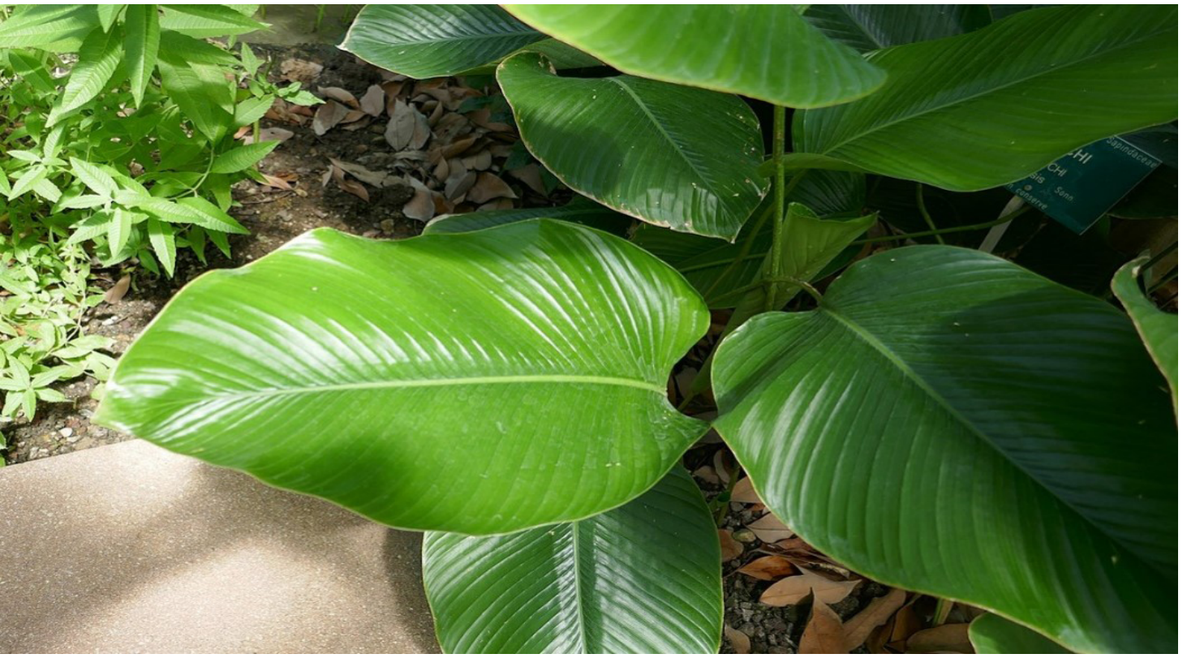
»NovelSweets«: New protein-based sugar substitutes

by Dr. Stefan Rasche

In the past few decades, not only has there been an increase in sugar consumption worldwide, but also an increase in sugar-related chronic illnesses. Health issues such as caries, high blood pressure, cardiovascular diseases (strokes and heart attacks), type 2 diabetes as well as both adult and child obesity are either caused or promoted by excessive sugar consumption. In order to counteract the rising health problems owed to the wrong diet, the Federal Ministry of Food and Agriculture (BMEL) aims to reduce the sugar content in instant food and drinks, thus minimizing the direct in indirect costs for the national economy and society. As part of the BMEL's innovation funding, Fraunhofer IME – along with its partners, the metaX Institute for Dietetics and candidum GmbH – researched innovative sweeteners based on protein in the project "NovelSweet".

Sweet proteins (SP), which were first isolated from tropical and African plants, can be a basis for the development of healthier sugar alternatives. Currently, the five best known SPs are monellin, thaumatin, brazzein, curculin and mabinlin. Their sweetness is owed to their special structures, which allow them to adhere particularly well to the respsonible receptors on our tongue and thereby signify: "This tastes sweet!" In contrast to household sugar, SPs have a number of health benefits: they are practically calorie-free, don't cause caries and don't affect the blood sugar level, making them perfectly suitable for diabetics.

The aim of our project was to optimize the naturally occurring SPs and to manufacture them biotechnologically. To do so, we looked at the 3D structure of the five proteins mentioned above and used bioinformatics processes to identify the areas



Bottom left: The West African plant Thaumatococcus daniellii *that naturally contains thaumatin.*
Top right: Sugar.
Bottom right: Bioreactor for microbial fermentation.

relevant for the proteins to adhere to our sweet taste receptors as well as to optimize further protein characteristics. Those areas where then specifically modified in order to enhance sweetness as well as stability and both chemical and process technological properties of the SPs. This includes an increased temperature stability, enhanced pH stability and optimized sensorics without any unwanted flavors or aftertastes. The optimized product candidates were then manufactured recombinantly through a biotechnological process using microbial fermentation. Afterwards, they were purified, tested for safety and, ultimately, diluted with water so that they could be tasted in order to evaluate the success of the modification.

Sweets proteins that taste like honey

Together with our partners, we were able to develop and produce a SP that is 10,000 times sweeter than household sugar (related to weight). With its honey- and slightly umami-like notes, the SP displays positive taste attributes, which make it an ideal product candidate for a sweetening system. As such, it can substitute sugar and existing sugar alternatives, particularly in beverages, or to optimize their flavor profile in formulations with sweeteners. In order to further develop the SP and get it ready for the market, the current production process has to be optimized in terms of yield and efficiency and a food-compatible process has to be established. As a next step, we will apply for the approval of the SP, which is a central requirement for a timely market introduction, in cooperation with further partners.

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Multipurpose seed coating to safeguard and increase crop yields by protecting and nourishing the seedling - SeedPlus

by Dr. Philip Känel, Dr. Michael Hüben & Dr. Karsten Schlich

In the context of a growing world population and complex challenges such as climate change and the shortage of arable land and water resources, it is essential for agricultural production to achieve high-quality crop yields. In addition, the use of frequently applied herbicides is becoming increasingly restricted. To ensure future food supply these factors require the optimization of existing, and the development of completely new, cultivation methods. Multifunctional, environmentally friendly seed coatings that facilitate the first critical phase of crop establishment can contribute to achieve this goal.

All beginnings are difficult – we make them easier

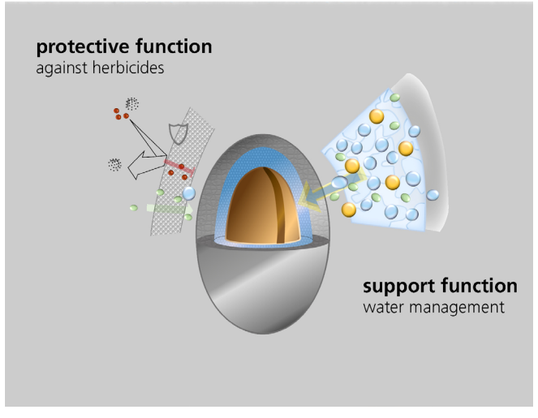
Sowing high-quality seeds is an important factor in establishing successful plant populations, but it is no guarantee. The period between sowing and crop establishment is a crucial, critical phase. The seed can be exposed to a variety of biotic and abiotic stress factors, which individually or in combination can result in reduced plant performance. In order to establish high-yielding plant populations, it is essential to provide the germinating seed with sufficient water during the emergence phase and to protect it from competing weeds.

The Fraunhofer PREPARE project SeedPlus aims to develope complex seed coatings that offer integrated water management and plant protection. This enables effective field emergence, even under unfavorable environmental conditions. The coatings consist of a functional layer to improve water management (water absorption, storage and supply; supportive function) and a selective barrier to protect the seedling from applied herbicides (protective function). At the same time, the existing regulatory gap in soil protection for such coating materials will be filled by developing new testing and evaluation strategies for the safety of the developed product with respect to soil health.

An innovative coating with a combined protective and supportive function not only paves the way for the reduced use of crop protection products, but also for improved cultivation in dry regions with low rainfall. Conventional seed pills were previously developed mainly to protect the growing seedling from pests by adding active ingredients as well as to enable automated sowing thanks to the uniform shape. Integrated fillers also enable absorption of water and support the germination phase, but water uptake is very limited. To make matters worse, the water-retainig components are often based on highly cross-linked, potentially environmentally hazardous synthetic polymers. Regulation 2023/2055 has been in force in the European Union since October 2023. It prohibits the use of microplastics (synthetic polymer particles smaller than or equal to 5 mm) unless their biodegradability can be demonstrated.

Such microplastic particles are also used in seed coatings. In 2019, researchers calculated that coated seeds in Germany are responsible for 87 tons of plastic entering the soil and environment each year. A transition period of five years has been set for the use of microplastics, by which time microplastics from seed coatings must have been replaced by readily degradable substances.

In the SeedPlus project we are developing multifunctional seed coatings together with the Fraunhofer Institutes for Microtechnology and Microsystems IMM and for Chemical Technology ICT. These are produced from ecologically safe formulations in a scalable process, allowing the coating to be adapted to the requirements of the seed at the same time. By combining two opposing coating properties - water management with simultaneous absorption of hydrophobic herbicides - and using new materials in technically scalable processes, the Fraunhofer consortium is creating a new technology base. This makes it possible to customize individual coatings for a wide variety of crops, to make the encapsulation technology directly available for agro-industrial trials, and to continuously optimize the developed coating structure by adding complementary functions. It will also enable subsequent integration and combination with more sustainable chemical and biological pesticides, as well as the targeted use of plant-enhancing biostimulants.



At Fraunhofer IME, we are contributing the expertise of two locations to the SeedPlus project: in Münster, the focus is the functional evaluation of the seed coatings and in Schmallenberg the establishment of new testing and evaluation strategies as part of the environmental risk assessment of the developed product.

Functional evaluation of the seed coating

In order to provide the crop with an advantage over competing weeds, active components play an increasingly important role in new seed formulations. In addition to structural components, e.g., binders or fillers, protective agents like pesticides and repellents, nutrients, as well as germination and growth stimulants, symbiotic soil microbes and soil conditioners (water absorbers) are being integrated into seed coatings. Even though the integration of chemical pesticides in seed coatings has reduced their use during cultivation, further rethinking is required here as well. The alternative to synthetic components lies primarily in the use of natural (biological) starting materials. However, their integration in a coating and effectiveness in the field must first be established and proven on a crop-specific basis.

For the development of innovative, multifunctional seed coatings, we -at the department "Functional and Applied Genomics"- examine the influence of individual components on the respective seed in different formulations. In a first evaluation step we test the material, process and mechanical compatibility of the various compounds. We examine these on the basis of the germination capability of the treated seed under standardized conditions. We record the germination as the sum of the events that begin with the hydration of the seed and end with the formation of the cotyledons.

Figure 1 depicts an example of the influence of a selected coating technology on the germination capacity of the Russian dandelion (*Taraxacum koksaghyz*). When coated with two different materials, the relative germination rate

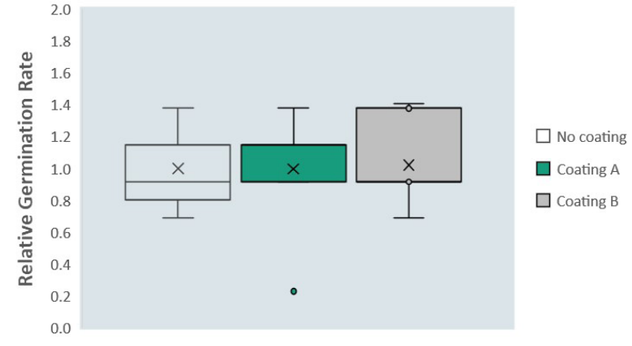


Fig. 1: Germination capability under standard conditions of dandelion seeds coated with material A or B in process X and untreated seeds as control.

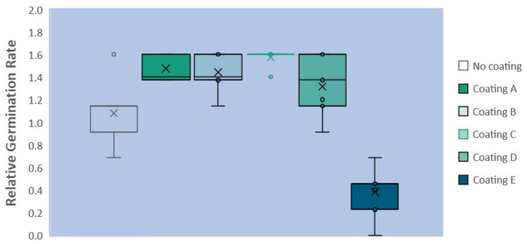


Fig.2: Germination capability under standard conditions of dandelion seeds coated with different materials (C to G) in process Y and of untreated seeds as control.

increased by two percent (material B) and twelve percent (material A) compared to untreated seeds.

Using an alternative coating technology as well as changing the formulations (Fig. 2) led to a significant increase in the germination rates of coated seeds by up to 58 percent compared to untreated seeds for formulations C to F, while coating with formulation G drastically reduced the relative germination rate by 61 percent.

Based on the results of the germination capability, we decide which of the formulations are suitable as binder, filler or active substance for our multifunctional coatings and which technical process should be used to optimally apply the material to the seeds.

In the next step of the evaluation, we examine the performance of the crop through variations and combinations of the coatings in comparison to untreated seed. The performance of the seed and the crop can be investigated using various parameters in the greenhouse and under field conditions. Functional evaluations include herbicide and water uptake by the coating, early seedling development with limited water availability, biomass development after plant emergence, shelf life of the coated seed, and compatibility with conventional seeding techniques. At this stage, crop-specific functional enhancements are made in collaboration with our partners by adding to the formulation or changing the structural composition.

Assessment strategy and methodology for the sustainability and safety of the developed product

Components of conventional seed coatings, especially the active ingredients they contain, are absorbed by the seedling/plant. However, uptake is not complete and residues of the coatings, including the active ingredients, remain in the soil and pose a potential risk to the environment.

Therefore, in addition to the development of formulations and coating technologies, a testing and assessment strategy is being established at the Schmallenberg location in the "Applied Ecology" department to assess the environmental risk of coating materials in terms of ecotoxicity and degradability. To this end, alternative endpoints for assessing the degradability of polymers in the environment are being researched and established. The development of screening methods for the environmental fate and impact of polymeric coating materials will enable rapid and cost-effective control through early identification of risks in relation to regulatory acceptance in the development phase of the subsequent product.

Testing and assessment methodology

Based on the materials used in the project, a two-step testing strategy is followed: First, a broad range of degradability and toxicity tests are performed using the screening method. The materials are tested as individual components. The degradation pattern of the components is evaluated by examining biodegradation in miniaturized approaches using sewage sludge (Fig. 3).

Fig. 3: Modified screening approach for the investigation of biodegradation in sewage sludge based on OECD 301B

A decisive factor in this analysis is a general statement on degradability (yes/no) with the possibility of a basic characterization of degradation and the identification of degradation products. This will lead to feedback to ecotoxicology if studies on the environmental impact of degradation products become relevant.

The tracking and identification of degradation products in complex environmental matrices is made possible by the use of radioactive 14C isotope labeling. The aim is to transfer these methods to unlabeled materials. Figure 4 shows the identification of sodium alginate in the sewage sludge matrix from the OECD 301 test using pyrolysis GC/MS.

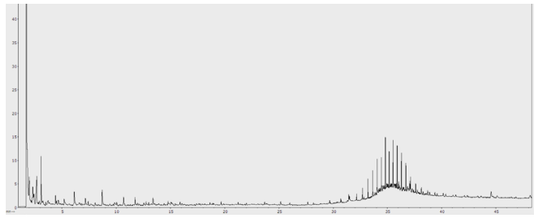


Fig. 4: Identification of sodium alginate in sewage sludge matrix with pyrolysis-GC/MS.

To evaluate the reliability of the sludge screening data, they are then compared with the results of the OECD 307 soil simulation test.

The environmental effect is initially investigated on aquatic and terrestrial model organisms. using solutions or aqueous eluates of the materials. Miniaturized algae, daphnia and fish embryo tests will be established to cover all trophic levels. By combining these tests with OMICs methods, adverse mechanisms of action will also be captured at the molecular level, allowing assessment of long-term, chronic effects.

In addition, miniaturized rapid tests are used to observe the effect on soil microorganisms. The results are compared with the results of accepted OECD registration tests, ideally supported by literature data or self-generated experimental results. Before the final product (encapsulated seed) is manufactured, components identified as non-toxic and degradable will be re-tested for their effect on soil (micro) organisms to confirm their safety.

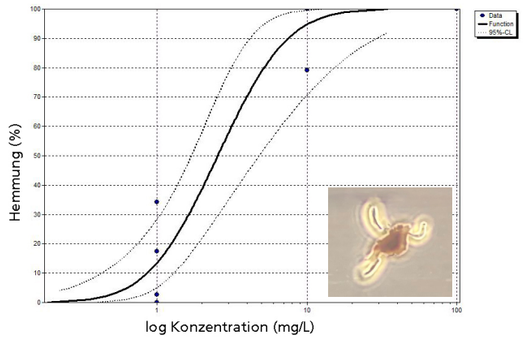


Fig. 5: Microscopic image of the interaction of a particulate polymer with algal cells (OECD 201 growth inhibition test with the freshwater alga (Raphidocelis subcapitata)) and corresponding dose-response relationship (plotted with ToxRat®).

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The RobustNature Excellence network investigates the connection between chemical pollution and biodiversity

by Dr. Dr. Henner Hollert, Dr. Sarah Johann & Dr. Andreas Schiwy

We are facing three interlinked crises: global warming, biodiversity loss and chemical pollution. The RobustNature Excellence network, led by Goethe University Frankfurt, is investigating the connection between chemical pollution and biodiversity loss in an interdisciplinary and transdisciplinary approach. Frankfurt University Professor Dr. Dr. Henner Hollert, who also heads a new department at Fraunhofer IME, is one of the two spokespersons for RobustNature.

The starting point

Currently, more than 350,000 chemicals are listed for production and use, and this number is constantly increasing. The annual production of substances such as agrochemicals, industrial chemicals, pharmaceuticals, cosmetics and plastics is increasing and - despite major advances in substance assessment and regulation - poses a significant risk to both human health and the global environment. According to the *Lancet Commission on pollution and health*, chemical pollution is the most important cause of premature death in humans worldwide. It was responsible for 9 million premature deaths in 2015 (Landrigan et al. 2017). This figure is three times higher than the total number of deaths caused by HIV, tuberculosis and malaria. Biodiversity is also severely threatened by human activities today. The causes of biodiversity decline are manifold and include habitat loss and fragmentation, invasive species and climate change. In a recent meta-analysis, chemical pollution was identified as one of the three main causes of global biodiversity loss. In the last two years, there have been groundbreaking developments regarding the global significance of chemicals and their release into the environment, which can play an important role in the decline of biodiversity. For example, Persson et al. (2022) were able to show for the first time that the planetary boundaries for novel pollutants are located outside the Safe Operating Space of the planetary boundary. A little later, the potentially massive link between biodiversity loss and chemical pollution was pointed out (Groh et al. 2022). Both phenomena have often been studied within individual disciplines, but rarely together and across disciplines (Sylvester et al. 2023). However, a comprehensive scientific research concept that addresses these complex interrelationships is still lacking and the complex interactions between chemical pollution and the dynamics of large-scale biodiversity are still largely unexplored in quantitative terms.

The RobustNature network

Although the harmful effects of chemical pollution on humans and the environment have been known for a long time, many problems were only recognized incidentally and *a posterori*, i.e. only after the pollution events. It could be DDT and the identified endocrine effects on bald eagles in the 1970s or the (current) mortality of silver salmon in North America, which could be traced back to the chemical 6PPD-quinone released from tyre rubber. A comprehensive understanding of the interactions between chemical pollution and biodiversity decline is necessary to achieve a forward-looking assessment of the interactions between these components of ecosystem degradation and to derive options for action and levers for societal change.

RobustNature was founded as an Excellence network with start-up funding from Goethe University (GU) with the aim of investigating the connection between chemical pollution and biodiversity loss in an interdisciplinary and transdisciplinary manner. The spokespersons are the two Frankfurt University professors Henner Hollert and Ernst Stelzer. Hollert also heads the new Department of Environmental Media Related Ecotoxicology at Fraunhofer IME. The network is supported by Dr Sarah Johann (GU) as coordinator and Dr Andreas Schiwy (GU and Fraunhofer IME).

The RobustNature network consists of university partners and non-university research institutions. In addition to the Sustainability & Biodiversity profile area and various departments of the Goethe University Frankfurt, the network also includes the TU Darmstadt, the Justus Liebig University Giessen, the RWTH Aachen University and Fraunhofer IME with locations in Schmallenberg and Giessen. The Senckenberg Research Institute and Nature Museum in Frankfurt (SGN), the Helmholtz Centre for Environmental Research (UFZ), the Institute for Social-Ecological Research (ISOE), the Leibniz Institute for Financial Market Research (SAFE) and selected international partners (e.g. University of Saskatchewan in Canada and ETH Zurich) are also involved. An important role is played by a total of 17 SynergyFund projects, which are investigating issues focusing on chemical pollution and biodiversity loss, as well as organismal interactions, in an interdisciplinary and transdisciplinary manner. In recent years, the network has published several important studies (e.g. Sylvester et al. 2023, Eastwood et al. 2023, Müller et al. 2023, Brack et al. 2022, Crawford et al. 2022), organised workshops (e.g. Earth4All, NORMAN network Innovative approaches for environmental monitoring of chemical pollution and biodiversity) and successfully applied for collaborative projects. The network is also currently preparing two large coordinated joint projects, both of which involve Fraunhofer IME. In order to define the research questions in a transdisciplinary manner (in the sense of a co-design), for example, a stakeholder workshop was held with members of RobustNature, representatives from authorities (e.g. Federal Environment Agency, Federal Institute for Hydrology and Hessian Ministry of the Environment), industry and science. Also, the BLAC congress "Chemicals Policy in Dialogue" was actively organised and presentations were made. The website www.robustnature.de and a YouTube channel provide an overview of the network.

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One planet: one health. A call to support the initiative on a global science–policy body on chemicals and waste. (2022) Environ Sciences Europe 34. doi.org/10.1186/s12302-022-00602-6

Crawford, S. E., et al.
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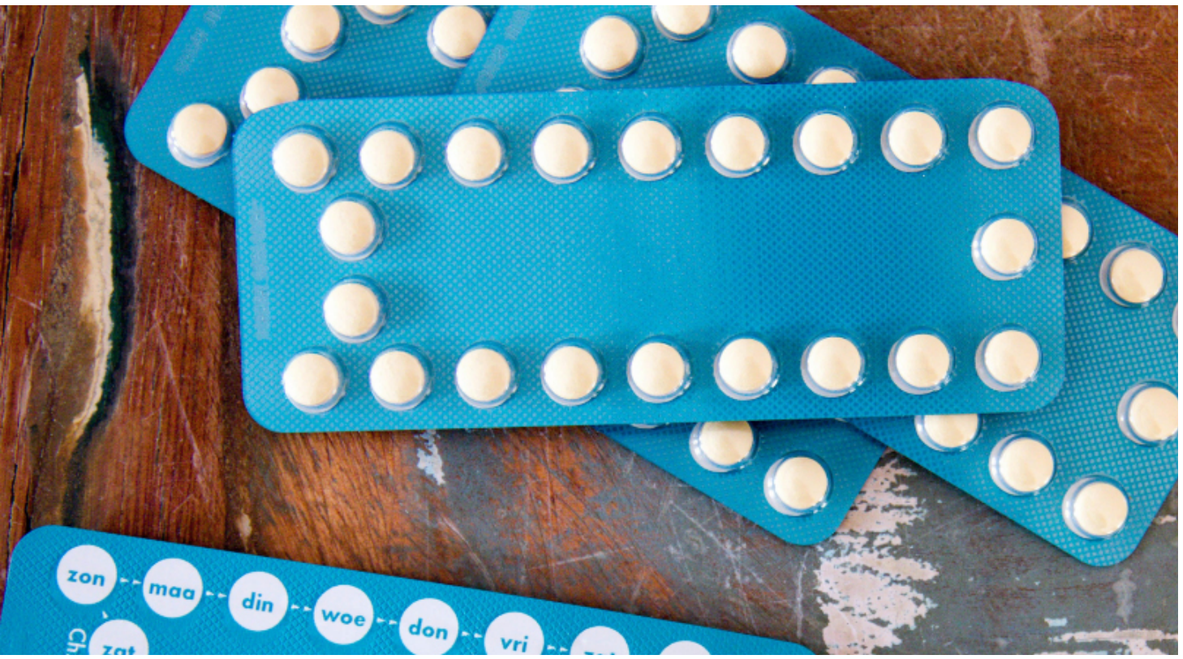
Next Generation Steroid hormones – Tailored testing strategies to identify endocrine disrupting substances

by Dr. Matthias Teigeler

The entry of pharmaceuticals into the aquatic environment has become an important topic in environmental research and is attracting increasing public interest. Human and veterinary pharmaceuticals enter the aquatic environment via various routes and pose a risk to aquatic organisms. It is known that pharmaceutical residues remain in the environment and can have harmful effects on non-target organisms. Endocrine disruptors in particular, which can act like natural hormones in the organism, have been identified as a potential threat, as they can cause damage even at low concentrations in water.

The aim of this research project, which is in close cooperation with the Federal Environment Agency of Germany, was to develop a customised testing strategy to assess the environmental risk of novel endocrine active substances, in particular synthetic progestins and glucocorticoids. In the first phase of the project, a comprehensive literature review was carried out to collect and evaluate existing knowledge on the effects of these substances. On this basis, two representative substances for the drug classes named were identified for further investigation. Dienogest, a substance used in the treatment of endometriosis and for contraception, was selected as a candidate for the progestogens. The glucocorticoids were represented by the active substance dexamethasone, which is used – among other things – to treat allergic and inflammatory processes due to its immunosuppressive effect. This is used to treat allergies and inflammation by suppressing immune reactions. In our research study, two long-term laboratory experiments with fish and an additional study with an aquatic invertebrate, were conducted. The results of the laboratory experiments were collated, compared with the results from the literature and discussed. An assessment strategy was then developed on the basis of the two reference substances with the aim of creating a tailored risk assessment.

A zebrafish one-generation reproduction test (ZEOGRT) was carried out for dienogest as well as a life cycle test with midges (chironomids). For dexamethasone, only the zebrafish study was conducted. In the experiments, the organisms were exposed to different concentrations of the test substances and various biological parameters relating to growth, reproduction and survival were measured.



Endocrine acting substances are increasingly being identified as a threat to aquatic organisms.

In the fish studies carried out, possible effects on different generations of the animals were investigated. A parent generation, a complete filial generation and the early embryonic life phase of a second subsequent generation were exposed to the substances.

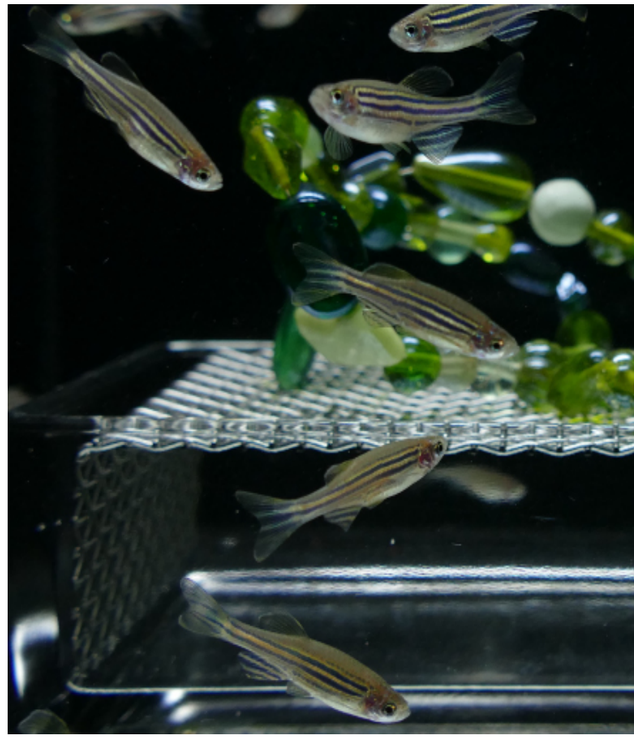
For dienogest, the results showed no effects on the parent generation of zebrafish. The fertilisation ability and survival of the early larvae in the first filial generation were impaired, and the hatching success of the second filial generation was also reduced. In the chironomid study, no effects were observed as a result of substance exposure.

Dexamethasone caused reduced growth in both the parent and the subsequent generation of zebrafish, with the males being more severely affected. However, reproductive ability and other parameters were not negatively affected.

The results suggest that synthetic progestins such as dienogest may have similar effects to other potent endocrine acting substances such as oestrogens and androgens. However, the underlying mechanism remains unclear. On the other hand, exposure to dexamethasone had effects on the growth of fish at different life stages, but did not affect reproductive performance or sex ratio. The studies indicate that fish, as aquatic vertebrates, are more sensitive to endocrine acting substances than aquatic invertebrates. From this it could be concluded that the test design used in the fish test is suitable for detecting the relevant and sensitive population-relevant endpoints.

For a regulatory assessment of an active substance, a further challenge is to determine the cause of the observed effects on the organisms. In the case of progestins, additional methodological approaches that also take molecular mechanisms into consideration are available for this purpose. These include innovative omics methods that can, for example, detect changes in gene expression. The comparison with reference chemicals for which endocrine activity is known allows the identification of mechanisms of action of novel substances. For substances with immunosuppressive effects, such as the glucocorticoid under investigation, further methods to detect immunosuppressive mechanisms (e.g. LPS-Challenge) are available to detect a corresponding pattern of action.

These methods offer the possibility of developing customised test strategies even for less studied classes of active substances. Further research is required to improve the identification of the underlying mechanisms and thus ensure the acceptance of these methods by the evaluating regulatory authorities.



ZEOGRT: Investigation of the reproduction success of zebrafish using spawning trays.

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Antimicrobial peptides from *Hermetia illucens* for food and feed preservation

by Jeanny Jerschow-Schaumann

Hermetia illucens *flies on egg-laying site.*

More than 600 million people worldwide suffer from foodborne infections each year. Antimicrobial peptides (AMPs) from insects, such as *Hermetia illucens*, are a promising way to improve product safety and shelf life of products to reduce this high number. Some structural classes have pronounced activity against Gram-negative foodborne pathogens. Due to the dependency of larval nutrition and AMP expression, promising AMPs can be generated by feeding appropriate side streams of the food industry.

Food spoilage

Food spoilage results in the degradation of food quality due to microbial growth, which is considered unacceptable by consumers. The loss of food due to spoilage has significant environmental and economic consequences, including wasted water and energy resources and CO_2 emissions. In addition, spoiled food can also cause foodborne illness due to microorganisms or their toxin formation. To prevent this, chemical preservatives are currently used to extend shelf life. However, these additives often have a broad spectrum of activity against microorganisms and are therefore not effective against a specific target group. The addition of these mostly chemically synthesized preservatives is viewed critically by consumers, which is why alternative natural compounds are of high interest. In addition, the substitution of petrochemical raw materials in the production of traditional preservatives (such as benzoic acid and parabens) with sustainable biotechnological processes contributes to achieving the goals of the National Research Strategy Bioeconomy 2030.

Cleaned Hermetia illucens *larvae.*

Antimicrobial peptides

Antimicrobial peptides (AMPs) represent an attractive alternative to conventional preservatives. AMPs are a class of natural and synthetic peptides with a broad spectrum of activity against viruses, bacteria, fungi and parasites. Structurally, AMPs are short peptides of less than 50 amino acids. They are mostly cationic, amphipathic and contain many hydrophobic amino acids. They are formed by a variety of animal and plant sources, but can also be produced by bacteria or fungi.

Due to their strong inhibitory effect on Gram-negative foodborne pathogens, AMPs can also help minimize food and feed spoilage and reduce the risk of foodborne infections or poisoning for consumers and livestock. The product safety and shelf life of food and feed can be significantly improved by the addition of natural AMPs. The targeted use of AMPs against Gram-negative hygiene germs such as *Campylobacter*, *EHEC* or *Salmonella*, while leaving Gram-positive beneficial bacteria unaffected, is a unique selling point and represents a real innovation in the field of food safety. In addition to their antimicrobial activity, they can also have antiviral, anticancer, antifungal and antiparasitic effects. For this reason, they are of particular interest in the search for new antimicrobial agents, for example to combat increasing drug resistance.

Antimicrobial peptides from insects

Insects are highly adaptable to their environment and have developed a variety of defense strategies. One of these strategies, as part of the innate immune system of insects, is the production and subsequent secretion of AMPs as a defense mechanism against bacterial infections. Therefore, a variety of natural AMPs are produced in the hemolymph and body tissues of a large number of insect species. The black soldier fly, *Hermetia illucens*, is known to possess a high variety of different classes of AMPs.

One especially promising class of AMPs are the cecropins. Structurally, cecropins are characterized by two α-helical structures without cysteine residues which are connected by a flexible hinge region. They are highly effective against Gram-negative bacteria, such as *Escherichia coli*, *Salmonella enterica* or *Pseudomonas aeruginosa*, while exhibiting low toxicity to mammalian cells. Efficacy is based on interaction with the bacterial cell membrane according to the "carpet" model. The peptides accumulate in a carpet-like structure on the membrane surface, causing the membrane to lose its integrity. As a result, the membrane dissolves, forming micelles. The membrane disintegrates into small areas lined by the peptide units.

Use of side streams as feed

Hermetia illucens larvae produce a varying spectrum of AMPs, depending on the composition of their feed. By feeding the larvae with specific substrates from the food industry, suitable AMPs can be produced that can be integrated into existing food and feed production processes. To take advantage of this, the AMPs are produced by feeding the larvae with various biogenic side streams from the Frankfurt/Rhine-Main area. The larvae are e.g., fed with brewer's spent grains, apple pomace or cocoa bean shells and compared to a standard diet consisting of chicken feed. By comparing the AMP spectra, a targeted diet can be selected that mainly induces AMP classes in the larvae that have bactericidal activity against Gram-negative hygiene germs and at the same time do not affect the (Gram-positive) starter cultures commonly used in the food industry.

To obtain the AMPs from *H. illucens* larvae, an extraction with subsequent purification is performed. The peptides obtained are identified, tested for their preservative effect and then their technological and sensory properties are described. Alternatively, selected peptides will be produced recombinantly in a suitable expression system and analyzed analogously.

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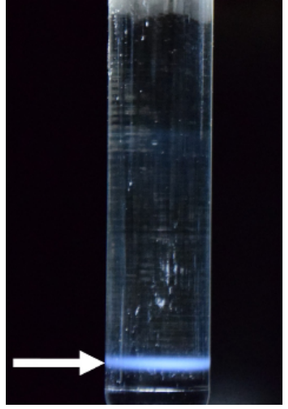
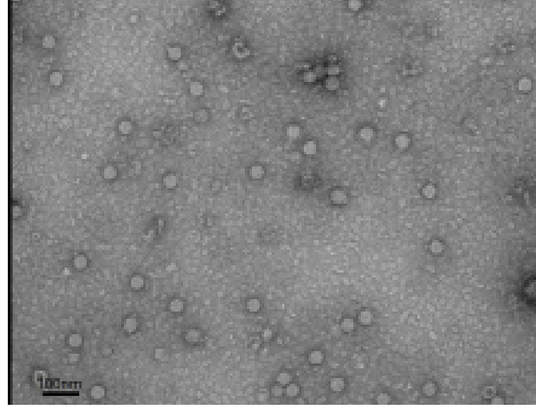
Development of a holistic biological plant production

by Yvonne Linscheid





Left: Image of isolated La Jolla virus particles.

Right: Image of LJV virons in a SEM (scanning electron microscope).

In 2006, the REACH Regulation (Registration, Evaluation, Authorization and Restriction of Chemicals) was drafted by the EU and finally came into force on June 1st, 2007. This regulation aims to protect people and the environment from the devastating effects of excessive use of synthetic chemicals. The use of synthetically produced pesticides is therefore strictly regulated throughout the EU. It also calls for the use of sustainable alternatives. However, no product has yet been approved by the EU for use in agriculture that has the same efficiency and cost-benefit ratio as a chemical pesticide.

Current options of an environmentally friendly pest control

The most common technique for controlling pests is known as "Integrated Pest Management (IPM)". In this application process, different methods are combined and attempts are made to avoid pesticides or to use them only to a limited extent. As the term IPM implies, it is made up of different methods and techniques: e.g. natural predators, plant rotation, seed-planting techniques, use of resistant, standardized seed and plant material, balanced fertilization, liming and irrigation of the plants and continuous cleaning and maintenance of the equipment. With all the methods used, care is taken to ensure that no useful organisms are harmed. Continuous monitoring takes place, which is than analyzed and evaluated. Subsequently, the applied processes have to be optimized and used at the exact time in order to make pest control highly efficient. It can be predicted that a lot of money and manpower will be required to maintain the IPM.

A little miracle weapon: Microbs against pest insects

Entomopathogenic microbs, e.g. fungi, bacteria and viruses, are excellent tools for biological control of pests. Compared to chemical pesticides, with a broad spectrum of activity, target-optimized microbs have several advantages that make them very attractive as an alternative control agent. Due to their host specificity, non-host organisms are not affected by the microb. Furthermore, there is no risk of accumulation in plants or the environment. This holistic approach means that the ecosystem is not affected and can therefore more easily maintain its essential balance. Especially viral entomopathogens, in this case called insect viruses, have a very high host specificity, also in comparison to entomopathogenic bacteria and fungi. Therefore, these microbs in particular could act as a superior tool for insect pest control. Through research and development, they can be developed into an excellent sprayable insecticide that follows the holistic approach.

In Germany, the invasive fruit fly species *Drosophila suzukii* is causing increasing crop losses. Stone fruits (blueberries, raspberries, cherries, etc.) are the preferred fruits of this species. Spraying with synthetic insecticides several times a year is an attempt to protect the fruits. However, this not only destroys the harmful insects, but also the beneficial pollinating insects. This in turn results in higher costs because pollinators have to be bought and released in the field. Furthermore, other invasive species could approach the resulting gap and establish themselves. The use of environmentally harmful insecticides can therefore cause immense damage to the environment and agriculture. With the help of the core competencies of virology, entomology, biotechnology and bioprocess technology, a sprayable product is to be developed within the HOPE project. This should act exclusively on the harmful insect species and can be used at any time during fruit ripening - without harming the environment, agriculture or human health.

First, the pest is examined for viral sequences and then analyses are carried out to match already known viruses of the species *Drosophilidae* with the freshly isolated RNA sequences. Once sequencing has been successfully completed, the newly produced and isolated viral sequences are injected into the insect and the monitoring starts. Are there any morphological changes? Is the lifespan shorter than usually?

If the virus significantly shortens the lifespan, it is fed orally to the adults. The crux is that the virus has to infiltrate the immune system and kill the organism in a very short time. In competition with this are the stable chemical insecticides, which kill within a day or less and can be produced cheaply in large quantities. Previous results with the species Drosophila and insect viruses showed no promising results with oral feeding. A virus that eliminates only 20 to 30 percent of the population or has a negative effect on pollinators when ingested orally cannot be further processed. However, the isolate of the insect virus *La Jolla* Virus (LJV) also achieved a promising result when fed orally. At a concentration of just 10^6 genomic equivalents per milliliter, a mortality rate of 100 percent was recorded after a maximum of five days.

Stability tests and formulation of the virus have to be done. Here it is important to test in which pH solutions and temperature ranges the virus remains active. Formulations (coatings of the virus) are necessary for the development of a sprayable product. Different materials (nanoparticles, buffers, surfactants, etc.) must therefore be tested on the flies. The materials that show no negative effect will be combined, the virus is enveloped and tested on the flies. Subsequently, greenhouse tests are carried out. The developed products are applied directly to the fruit and it is observed how the fruit is coated, whether they remain on the surface for some time, how they are affected by air circulation and heat, etc. At the same time, the mortality of the flies is tested.

The end product must be able to be produced in large volumes for commercial use - and at the lowest possible costs. At the moment, virus production is as follows: 1000 flies are injected with 46 nL of virus extract respectively, which is incubated in the flies and extracted after three days. The production time for approx. 1.0 mL of virus extract is therefore four days. Costs and time must be reduced as much as possible. No specific cultivation cell line for LJV is yet available on the market. There are two options for the first approaches: Research is being carried out on a cell line of Drosophila melanogaster, the other would be to establish a new primary cell line of *Drosophila suzukii.* The difficulty here is that insect viruses are very sensitive to the cell type that surrounds them. If the cell type does not correspond to its preferred host organism, there is a possibility that the virus will give up the part of its genome that has the insecticidal effect. This in turn would result in the production of an inactive virus.

If all these processes are successful, a sprayable prototype is created.

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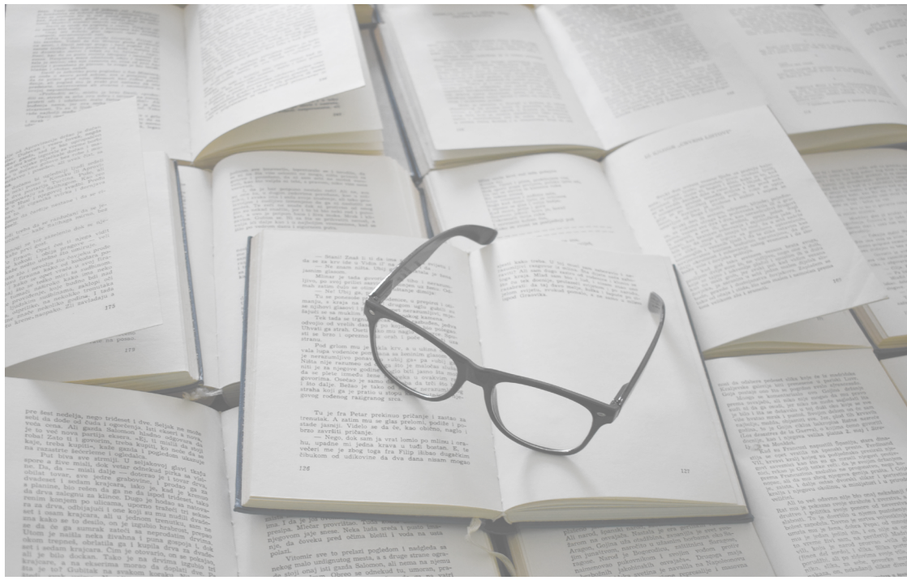
Selected publications



Simulation and optimization of nutrient uptake and biomass formation

Taming the devil's ringlet - flowering time control of *Cuscuta* spp.

Immune challenge analyses in the zebrafish embryo model for human and environmental questions

Chronic toxicity and gene expression analysis in *Cloeon dipterum*

Environmental risk assessment of disinfection by-products

Molecular markers of sexual endocrine disruption in embryonic zebrafish

A new hope against antibiotic-resistant pathogens

Salinity changes threaten the world's oceans and biodiversity

Snake venoms – between challenges and chances

"The biomass yield can be improved with tailored media"

Dr. Henrik Nausch, Fraunhofer IME in Aachen

Iterative models can be used to systematically optimize conditions for bioreactor-based processes.

Simulation and optimization of nutrient uptake and biomass formation

Tobacco (*Nicotiana tabacum*) cv Bright Yellow-2 (BY-2) cell suspension cultures enable the rapid production of complex protein-based biopharmaceuticals but currently achieve low volumetric productivity due to slow biomass formation. The biomass yield can be improved with tailored media, which can be designed either by laborious trial-and-error experiments or systematic, rational design using mechanistic models, linking nutrient consumption and biomass formation. Here we developed an iterative experiment-modeling-optimization workflow to gradually refine such a model and its predictions, based on collected data concerning BY-2 cell macronutrient consumption (sucrose, ammonium, nitrate and phosphate) and biomass formation.

The biomass formation was well predicted by an unstructured segregated mechanistic Monod-type model as long as the nutrient concentrations did not approach zero (we omitted phosphate, which was completely depleted). Multi-criteria optimization for sucrose and biomass formation indicated the best tradeoff (in a Paretian sense) between maximum biomass yield and minimum process time by reducing the initial sucrose concentration, whereas the inoculation biomass could be increased to maximize the biomass yield or minimize the process time, which we confirmed in calibration experiments. Overall, we demonstrated that iterative models can be used to systematically optimize conditions for bioreactor-based processes.

Nausch, H., Baldan, M., Teichert, K., Lutz, J., Claussen, C., Bortz, M., & Buyel, J. F.
Simulation and optimization of nutrient uptake and biomass formation using a multi-parameter Monod-type model of tobacco BY-2 cell suspension cultures in a stirred-tank bioreactor (2023) Frontiers in Plant Science, 14. **DOI**

"When infesting crops, they often cause high yield losses. Understanding the flowering induction of the parasite could be a key to combating it."

PD Dr. Gundula Noll, Fraunhofer IME in Münster

Flowering devil's ringlet, with their thread-like stems they strongly branch out and twine around the host plants.

Taming the devil's ringlet - flowering time control of *Cuscuta* spp.

Devil´s ringlet, also known as *Cuscuta*, are annual holoparasites that ensure their survival by tapping water and nutrients from their host plants. For this purpose, they possess special absorptive organs called haustoria, which enable vascular contact between the host and the parasite. When infesting crops, they often cause high yield losses. The plants also produce large quantities of seeds, which can survive in the soil for several years, making them a double threat to global agriculture.

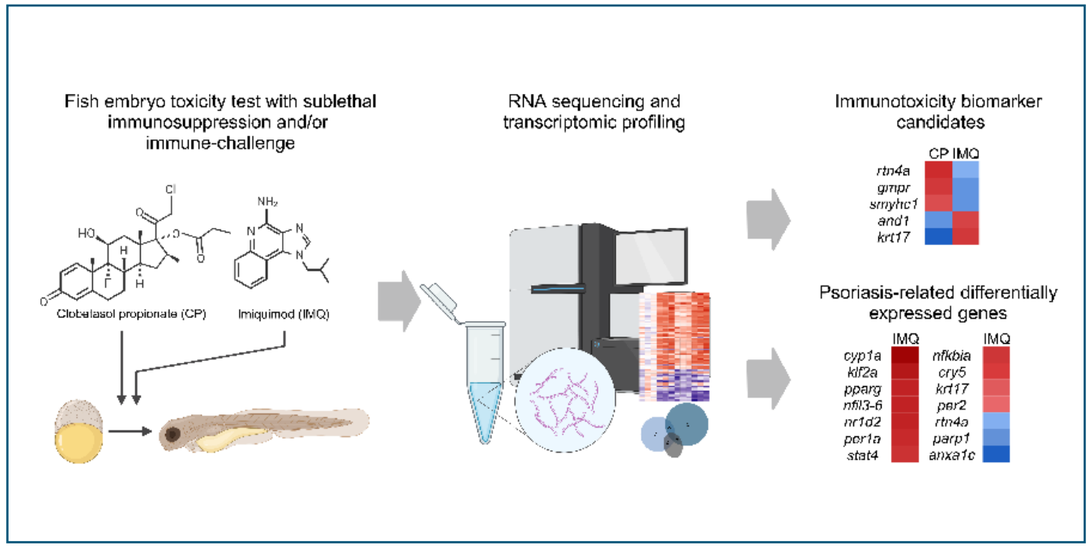
Flower induction in plants is a tightly regulated process that integrates numerous exogenous and endogenous signals. The molecular network differs from species to species, but two conserved proteins act as key regulators: FLOWERING LOCUS T (FT) and FD.

In their recent publication, the scientists at Fraunhofer IME, together with colleagues from the University of Münster and Humboldt University Berlin, identified the endogenous FT-FD floral module in the species *Cuscuta campestris*. They demonstrated the expression of two endogenous *C. campestris* FT genes in the haustoria of the parasitic plant, while the identified FD homolog is ubiquitously expressed. Furthermore, the researchers used genome editing to knock out the essential flowering induction genes NtFT4 and NtFT5 in the host tobacco plants, preventing them from flowering. When these plants were parasitized by *C. campestris*, *C. campestris* flowered just as it did when parasitizing wild-type hosts. This suggests that the host's FT proteins are not necessary for the parasite to initiate the transition from the vegetative to the reproductive phase. The researchers also demonstrated that the FTs of *Cuscuta* were able to induce flowering in the non-flowering tobacco mutant. The results indicate that *Cuscuta* spp. produces a functional endogenous florigen that can induce flowering completely independently of the host FT.

Mäckelmann, S., Känel, A., Kosters, L.M., Lyko, P., Prüfer, D., **Noll, G.A.**, Wicke, S.
Gene complementation analysis suggests that dodder plants (*Cuscuta* spp.) do not depend on the host FT protein for flowering. (2024) Plant Commun **DOI**

"The combination of immune challenge and toxicogenomics allows the identification of marker genes for environmental hazard assessment and the investigation of psoriasis."

Benedikt Luckner, Fraunhofer IME in Schmallenberg



Steps for identifying marker genes for immunosuppression and psoriasis.

Immune challenge analyses in the zebrafish embryo model for human and environmental questions

Although numerous studies indicate a link between chemical contamination and impaired immunocompetence of wildlife populations, the assessment of immunomodulatory modes of action is currently not included in the regulatory requirements for the authorisation of new substances. This is not least due to the complexity of the immune system and a lack of standardised methods and validated biomarkers. To address this issue, we analysed the transcriptomic profiles of zebrafish embryos in response to the immunosuppressive agent clobetasol propionate, a synthetic glucocorticoid, and/or the immunostimulatory agent imiquimod (IMQ). IMQ is an agonist of Toll-like receptor 7 (TLR-7), which is known to induce psoriasis-like effects and symptoms in mice and humans. Psoriasis is a non-contagious autoimmune disease that mainly manifests as an inflammatory skin disease. Research on this disease is mainly conducted using a mouse model. Thus, our study additionally aimed to evaluate the usability of the zebrafish embryo model as an alternative and 3R-compliant system for the IMQ-induced psoriasis mouse model.

We have identified five new candidate biomarkers for immunotoxicity, namely *krt17*, *rtn4a*, *and1*, *smhyc1* and *gmpr*, which will contribute to the increased consideration of immunotoxicity in the environmental risk assessment of new substances in the future. Our results also provide new evidence suggesting that key molecular events of psoriasis may be inducible in the zebrafish embryo. For these reasons, our study supports the zebrafish embryo model as a promising 3R-compliant, cost- and time-saving and reliable alternative model for basic research on the pathogenesis of psoriasis. Also, it can be used as a basis for the future investigation of immunotoxic effects in the context of substance-related environmental hazard assessment.

Luckner, B., Essfeld, F., Ayobahan, S. U., Richling, E., Eilebrecht, E., Eilebrecht, S.
Transcriptomic profiling of TLR-7-mediated immune-challenge in zebrafish embryos in the presence and absence of glucocorticoid-induced immunosuppression (2023) Ecotoxicology and Environmental Safety, 266. **DOI**

"We were able to extensively characterize the effect of fipronil in *Cloeon dipterum* and also validate a suitable test protocol for chronic toxicity testing with this mayfly species."

Kirsten Germing, Fraunhofer IME in Schmallenberg

Cloeon dipterum *larva (left) and Imago (right).*

Chronic toxicity and gene expression analysis in *Cloeon dipterum*

The larvae of mayflies live in various water bodies, where they essentially contribute to ecosystem services. Some studies have shown that representatives of this order are particularly sensitive to various environmental pollutants. However, literature on toxicity tests with mayflies is still sparse to date.

To address this research gap, we decided to investigate the suitability of a test system using mayfly larvae, which was initially developed by the research institute gaiac in Aachen, Germany. In a long-term exposure test over 38 days, we were able to successfully establish a chronic toxicity test with the mayfly species *Cloeon dipterum*. Almost the entire life span of the organism was examined and effects of the insecticide fipronil on larval development, emergence and mortality were observed.

In a second step, we carried out a short-term exposure test over seven days, following changes in the transcriptome of the larvae to supplement the chronic effects with the molecular investigation of mechanisms of action. We found altered gene expression profiles in the substance-exposed larvae compared to the control. We were able to confirm the sublethal effect of fipronil that was recorded in the long-term exposure test after a significantly shorter test duration. Also, we were able to identify potential marker genes in *C. dipterum* for the neurotoxic mechanism of action of fipronil. In combination with the long-term exposure test, we were thus able to extensively characterize the effect of fipronil in *C. dipterum* and also validate a suitable test protocol for chronic toxicity testing with this mayfly species.

Germing, K., Ayobahan, S.U., Reinwald, H., Vogt, M., Ringbeck, B., Göckener, B., Eilebrecht, E., Kosak, L., Eilebrecht, S.
Chronic toxicity testing including transcriptomics-based molecular profling in *Cloeon dipterum* (2023) Environmental Sciences Europe. **DOI**

"We have developed a categorisation for biocidal active substances that enables a more targeted consideration of disinfection by-products in the environmental risk assessment."

Dr. Michael Hüben, Fraunhofer IME in Schmallenberg

Possible entry paths for DBPs into the environment during stable disinfection are direct volatilization or the spreading of manure on fields.

Environmental risk assessment of disinfection by-products

A large variety of biocides, especially disinfectants and preservatives, come into contact with organic matrices during their application and can subsequently be released into the environment. At the same time, biocidal active substances are highly chemically reactive due to different characteristics. Possible reaction products, so-called disinfection by-products (DBP), which are formed during disinfection, must be taken into account in the environmental risk assessment of the biocidal active substance in question.

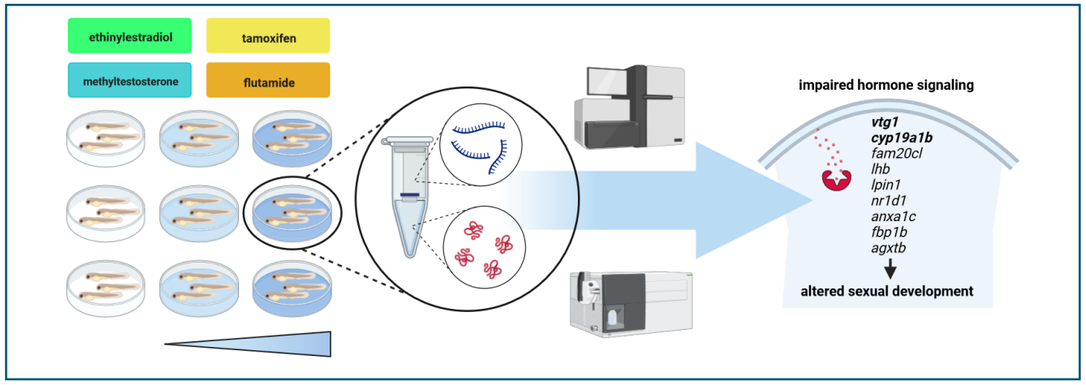
With the chemical structural diversity of the active substances and the varying conditions for the different applications, which include human and animal hygiene as well as the disinfection of swimming pools, hospitals and industrial plants, environmental risk assessment is a very complex issue. Although the existing EU directive provides a sensible framework for this, it does not do justice to the complexity of the issue in detail. Not all relevant active substances and applications are covered. As a result, no EU-wide harmonised, scientifically sound environmental risk assessment of DBPs is currently being carried out.

As part of a research project initiated by the German Environment Agency, we therefore evaluated scientific publications and information from the ECHA substance database. We categorised biocidal active substances according to their DBP formation potential and proposed a scheme for a harmonised and simplified environmental risk assessment of DBPs based on this. At the same time, we were able to identify relevant data gaps regarding DBP formation that should be addressed for further development of the environmental risk assessment of DBPs.

Usman, M., **Hüben, M.**, Hahn, S., Wieck, S., Kehrer-Berger, A., Linnemann, V., Wintgens, T.
Evaluation of the DBP formation potential of biocides and identification of knowledge gaps in environmental risk assessment (2023) Environmental Sciences Europe. **DOI**

"We utilize gene expression profiling to identify screening biomarkers of sexual endocrine disruption. This enables us to priorotise regulatory tests."

Dr. Steve Ayobahan, Fraunhofer IME in Schmallenberg



Toxicogenomic fingerprints in zebrafish embryos reveal promising biomarker candidates for identifying endocrine disrupting hazards of compounds at molecular level.

Molecular markers of sexual endocrine disruption in embryonic zebrafish

Endocrine disruptors (EDs), capable of modulating the sex hormone system of an organism, can exert long-lasting negative effects on reproduction in both humans and the environment. By either mimicking hormones or inhibiting their receptors, these chemicals disrupt the normal processes of hormone production, distribution, metabolism, excretion and activity, which finally leads to adverse effects on populations and entire ecosystems. For these reasons, the properties of EDs prevent a substance from being approved for marketing. The regulatory assessment of EDs properties is challenging due to the complex nature of the endocrine system, the very low effect concentrations and the necessity to test at the population level. This poses a challenge for the development of unified, standardized methodology for studying endocrine disruption in ecotoxicological risk assessment.

This study advocates a transformative approach to screening for endocrine disruption that seeks to overcome the existing hurdles of time-consuming, costly and animal-centred assessments for prioritising substances for regulatory testing. Here, we address this gap by combining sublethal zebrafish embryo assays with transcriptomics and proteomics to identify predictive gene expression biomarkers for sexual endocrine disruption. Using well-characterised reference compounds (ethinylestradiol, tamoxifen, methyltestosterone and flutamide), specific gene expression signatures and associated biological processes were identified at 96 hours post-fertilisation.

Our findings provide a promising set of biomarker candidates capable of discriminating between estrogen and androgen receptor agonism and antagonism. Furthermore, the proposed evaluation of these biomarkers in pre-regulatory zebrafish embryo-based assays has the potential to reveal endocrine disrupting hazards at the molecular level, providing an additional weight of evidence to conventional testing methods. This approach not only provides a robust framework for screening for putative EDs, but also represents a significant step towards reducing reliance on animal testing in higher-tier studies and improving regulatory outcomes.

Ayobahan, S. U., Alvincz, J., Reinwald, H., Strompen, J., Salinas, G., Schäfers, C., Eilebrecht, E., Eilebrecht, S. Comprehensive identification of gene expression fingerprints and biomarkers of sexual endocrine disruption in zebrafish embryo (2023) Ecotoxicology and environmental safety 250. **DOI**

"Only if the development of new antibiotics is accompanied by responsible usage, we will be able to protect ourselves against bacterial infectious diseases in the future."

Dr. Michael Marner, Fraunhofer IME in Giessen

Our research team has optimized a novel antibiotic candidate that attacks antibiotic-resistant Gram-negative pathogens.

A new hope against antibiotic-resistant pathogens

The spread of antibiotic-resistant microorganisms threatens the foundation of modern medicine. In our study, we tested the effectiveness of newly licensed reserve antibiotics against >60 clinical Pseudomonas isolates and found that every second isolate was resistant to at least one of the drugs. This is particularly alarming because most isolates were collected from patients several years before clinical use of the studied reserve antibiotics. Due to similarities in structure and molecular targets compared to already widely used antibiotics, pathogens can protect themselves with "classic" resistance mechanisms against many recently approved reserve antibiotics.

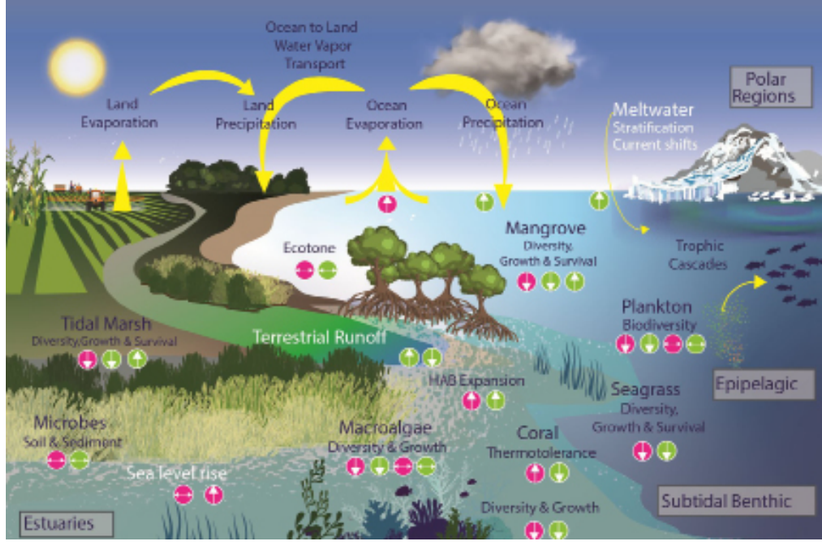
In contrast, in this study we produced two biotechnologically optimized antibiotic agents based on the natural product darobactin A. In general, darobactins are specialized natural products that attack a previously unused pharmaceutical target - the BAM β-barrel assembly machinery) protein complex, which is essential for the survival of Gram-negative bacteria. We were able to provide access to the naturally occurring variant darobactin B and continued to make targeted modifications within the molecular structure. Subsequently, we observed similar and increased potency against the clinical Pseudomonads for our new darobactins compared to the licensed reserve antibiotics. Due to advantageous ADME-Tox properties, we are currently able to investigate the suitability of darobactin B for the treatment of *P. aeruginosa*-induced pneumonia in vivo.

The development of new antibiotics, such as darobactin B, is essential for the healthcare system of the future, but must be combined with widespread measures for responsible use to effectively fight resistant pathogens.

Marner, M., Kolberg, L., Horst, J., Böhringer, N., Hübner, J., Kresna, I.D.M., Liu, Y., Mettal U, Wang, L., Meyer-Bühn, M., Mihajlovic, S., Kappler, M., Schäberle, T.F., von Both, U. Antimicrobial Activity of Ceftazidime-Avibactam, Ceftolozane-Tazobactam, Cefiderocol, and Novel Darobactin Analogs against Multidrug-Resistant Pseudomonas aeruginosa Isolates from Pediatric and Adolescent Cystic Fibrosis Patients. (2023) Microbiology Spectrum, 11 (1). **DOI**

"Our work shows that salinity is an essential climate change topic. While we know quite well how changing temperatures, acidification, and nutrients affect ocean and coastal ecosystems, the effects of human-induced changes in salinity are severely neglected – despite salinity being crucial for all types of organisms, including plants, animals, and microorganismst."

Dr. Till Röthig, Fraunhofer IME in Giessen



Man-made alterations in the hydrological cycle affect the oceans salt content impacting ecosystems and keystone-species

Salinity changes threaten the world's oceans and biodiversity

An international team of researchers unveils the critical yet poorly understood role of salinity, or salt content, in a changing ocean. The study highlights how changes in salinity can potentially have devastating effects on vital ecosystems and the coastal communities dependent on them.

Coastal habitats, known for their high productivity, are particularly susceptible to the impacts of salinity changes. Climate-induced variations in precipitation can lead to extreme flooding and drought events, affecting the availability of freshwater and consequently influencing ecosystems. Furthermore, local human activities such as changes in land use, urbanization, and river regulation exacerbate the challenges for coastal regions.

Marine organisms are adapted to live in salty environments, making salinity a central factor for many metabolic processes. Salinity also interacts with other physical and chemical parameters, such as temperature and oxygen content, shaping the ocean's physical environment and driving global ocean currents, for example. The researchers warn that changes in salinity are expected to increase alongside ocean warming, oxygen depletion, nutrient enrichment, and elevated sediment loads caused by climate change and human activities. Rising sea levels due to warming, freshwater input, and salinity changes lead to the intrusion of saltwater into coastal and low-lying areas, severely impacting the affected ecosystems.

The authors emphasize the urgency of addressing these salinity-related challenges to protect marine and coastal ecosystems and biodiversity. They highlight the vulnerability of selected habitats and their key organisms, such as microorganisms, plankton, corals, mangroves, tidal marshes, macroalgae, and seagrass, illustrating the dependence of humans on these systems.

Röthig, T., Trevathan-Tackett, S.M., Voolstra, C.R., Ross, C., Chaffron, S., Durack, P.J., Warmuth, L.M., Sweet, M. Human-induced salinity changes impact marine organisms and ecosystems. (2023) Global Change Biology, 29 (17).
DOI

"Snake venoms are an important source of new bioresources. Deeper insights into their composition and effects also enable improved bite treatment."

Lennart Schulte, Fraunhofer IME in Giessen

Milos Viper in its natural habitat on Milos.

Snake venoms – between challenges and chances

Snakes evoke fascination and fear in us humans and are implemented into myths and legends all over the world. Reason for that is the potential threat they are posing, especially for residents of the tropics and subtropics, because some species utilize venom for hunting and defense. These venoms are complex mixtures of highly potent biomolecules that can cause severe to leathal damage, but can also be translated into new therapeutic compounds.

Our research group investigates the venom composition, their mode of action and the application potential of their biomolecules. The Milos Viper (*Macrovipera schweizeri*) is one of Europe's largest venomous snakes and a sister species to the Levant Viper (*M. lebetinus*), the most dangerous snake in Europe. However, the composition of the Milos Viper's venom cocktail has not been elucidated so far. Utilizing mass spectrometry, we decoded its composition and compared it with the venom cocktail of the Levant Viper. Furthermore, we compared the activity of both species in bioassays. The comparison revealed a great similarity in venom composition and activity. In particular, the effects on mammalian cells and the similiar protease activity between Milos and Levant Viper suggest that the bite of a Milos Viper can also cause severe damage as reported for the Levant Viper. Additionally, we detected the presence of antibacterial components in Milos Viper venom, leading us to test the venom's antibacterial properties on various bacteria. It exhibited growth-inhibiting effects against some pathogens (*Escherichia coli*, *Staphylococcus aureus* and *S. epidermidis*). However, if and how Milos Viper toxins could be translated into antibiotics in the future is uncertain and requires further investigation.

Schulte, L., Damm, M., Avella, I., Uhrig, L., Erkoc, P., Schiffmann, S., Fürst, R., Timm, T., Lochnit, G., Vilcinskas, A. and Lüddecke, T.
Venomics of the milos viper (*Macrovipera schweizeri*) unveils patterns of venom composition and exochemistry across blunt-nosed viper venoms. (2023) Frontiers in Molecular Bioscience, 10. **DOI**

Selected doctoral thesis

Dr. René Lämmer

Did they come to stay? On the behavior of PFAS in arable soils

Per- and polyfluorinated alkyl substances, or "PFAS" for short, are known as "forever chemicals" and have recently been intensely reported in the media. In his doctoral thesis, Dr. René Lämmer from the Fraunhofer Institute for Molecular Biology and Applied Ecology IME in Schmallenberg investigated the behavior of these harmful substances in the environment.

PFAS are a group of purely man-made substances that are used in many consumer products due to their grease-, dirt- and water-repellent properties, for example in food packaging or coatings for kitchen cookware such as a frying pan and outdoor clothing. Despite their many applications, the use of PFAS is controversial. The molecules are hardly degraded in the natural environment, which is why many PFAS are considered environmentally persistent. In combination with proven toxic and bioaccumulative properties for some compounds, adverse health effects might occur in humans and animals.

For this reason, the discovery that more than 1,000 hectares of agricultural land in Baden-Württemberg were contaminated with PFAS, attracted a lot of attention. Consequently, it was important to investigate the current contamination and to assess the future development of this occurrence. In his doctoral thesis, Dr. Lämmer studied the environmental behavior of selected representatives of the PFAS substance class. He was able to prove that certain PFAS degrade incompletely in soil, while more stable representatives remain unchanged even after several years. Some PFAS migrate through the soil and can consequently end up in the groundwater. Experiments using plants have shown that certain PFAS can be taken up by maize plants and accumulate primarily in the leaves. This means that via contaminated feed for livestock, PFAS may indirectly end up in the food chain. As the consumption of contaminated water, plants and animal products constitutes a health risk to humans and animals, future environmental contamination with PFAS must be prevented by regulatory measures.

The doctorate was part of the BWPLUS program and was supervised by Prof. Dr. Mark Bücking (Fraunhofer IME) and Prof. Dr. Hans-Willi Kling (University of Wuppertal).

> "Over 1,000 hectares of arable land are contaminated with environmentally harmful PFAS in a German hotspot. Knowledge of the processes in the soil helps to protect nature and humans."

Lämmer, R.
Untersuchungen zum Sorptions- und Transferverhalten von Perfluoralkylsäuren und ausgewählten Polyflouralkylphosphatdiestern in den Wirkungspfaden Boden - Nutzpflanze und Boden - Grundwasser vor dem Hintergrund bestehender Schadensfälle (2023) **DOI**

In conversation with

**with Dr. Che Julius Ngwa &
Dr. Monika Konarzycka-Bessler**

Dr. Che Julius Ngwa was born in Cameroon where he earned his bachelor and master degree in Biochemistry from the University of Buea, Cameroon. In 2010, he was awarded the German Excellent Initiative PhD Fellowship at the Graduate School of Life Sciences, University of Wuerzburg and in 2013 he obtained his PhD in Molecular Cell Biology. Subsequently he moved to the RWTH Aachen University as postdoc at the Institute of Molecular Biotechnology. From 2016, he became group leader at the Section of Cellular and Applied Infection Biology at the RWTH Aachen University. During this period, he acquired several third party fundings and published over 30 publications in peer reviewed journals. Dr. Ngwa joined Fraunhofer IME in May 2023 and is currently leading the Cultured Meat research group in the New Agricultural Systems department.

Dr. Monika Konarzycka-Bessler was born in Poland and studied technical chemistry at the Warsaw University of Technology. In 2000, she came to Germany and worked in the area of biocatalysis at the University of Greifaswald, where she did her PhD on the topic "High-throughput screening and application of hydrolases for chemo- and enantioselective reactions" and obtained her doctorate in 2004. Subsequently, Dr. Konarzycka-Bessler worked as a postdoc at the Institute for Molecular Enzyme Technology at Forschungszentrum Jülich. In 2009, she and her family relocated to the U.S. where she developed cosmetic formulars for the Henkel company. Upon her return to Germany, she resumed her scientific work, first at the Institute for Biochemistry II at the University of Düsseldorf. In 2016, she and her family moved to Aachen where she worked in the quality management department and then the regulatory deparmtnet at the Dalli Group. In 2019, she fulfilled her long-time dream of founding her own cosmetics company, which had to be put on hold due to the COVID-19 pandemic. Since April 2023, Dr. Konarzycka-Bessler is the leader of the work group "Single Cell Protein" in the New Agricultural Systems department at Fraunhofer IME in Aachen.

What exactly is "cultured meat" and "Single Cell Protein"?

Che Julius Ngwa: "Cultured meat" is simply meat produced by in vitro cultivation of animal cells. It's basically mimicking the process of muscle cell building in animals. In order to produce cultured meat, you have to take a biopsy from an animal without necessarily killing it. Then you isolate stem cells from the biopsy, which you can subsequently cultivate and put them on a scaffold, a 3D construct to mimic the extracellular matrix allowing the cells to attach and differentiate into muscle fibre inside a bioreactor. At this point, it can be processed into your desired meat.

Monika Konarzycka-Bessler: "Single Cell Proteins" comprises the production of edible proteins that are obtained through microorganisms in the environment such as bacteria or yeast, for example. In our case, these organisms produce proteins for cell growth by using oxygen as the main carbon source. In doing so, their microbes produce such high amounts of proteins that they can be used and processed as a sustainable protein alternative in the food sector – for human or animal food. Of course, our activities target the human food sector.

How did you get interested in your research fields?

Che Julius Ngwa: I come from an area where you eat meat and I personally eat a lot of meat. However, due to the fact that traditional meat production is not sustainable as it destroys our environment, uses most of our water and comes with a lot of ethical and public health issues, it's natural for me to say, "Since I want to keep eating meat, I should move to a more sustainable alternative". And that is how my interested in cultured meat started and why I chose to take this position here at Fraunhofer IME.

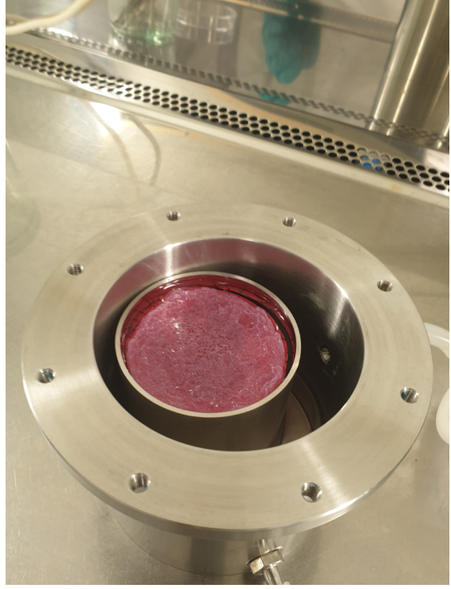
Monika Konarzycka-Bessler: I have always had an interested in science and research activities that you can apply in daily life. Initially, I wanted to be a medical doctor, but it didn't work out like that. Another subject that I really liked in school was chemistry, especially organic chemistry. So, I decided to study chemistry and later went into the direction of biotechnology, because it was very interesting for me to be able to work with enzymes. Biocatalysis was the first step into this area as well as cosmetic chemistry. They were both slightly different things, but still it was organic chemistry. When I discovered enzymes for biocatalysis, it was something really cool for me and so, step by step, I went more into using microorganisms for different purposes. One of these purposes is to produce edible proteins from microorganisms, of course, which is what I am doing as the leader of the "Single Cell Protein" work group at Fraunhofer IME now. It's a very interesting job for me, because biocatalytic processes of bacteria to produce food or refine their flavour have been used in the food sector for centuries; however, using bacteria as a protein-containing end product for food processing opens up completely new perspective.

Mr. Ngwa, what are the challenges of Cultured Meat production?

Che Julius Ngwa: In order for cultured meat to compete with conventional meat, we need to have a comparable price parity, which is not the case at the moment. That's because there are challenges throughout the complete production chain of cultured meat. For the cell line development, the source that we use now are mainly satellite cells, which eventually stop replicating. But we need immortalized cells that will continue to divide and multiply to scale up the production. On top of that, we also need efficient bioreactors for this process, which are expensive. Moreover, the growth factors, which in some cases are obtained from animals, are also expensive and not always ethically acceptable. So, the main challenge that were facing is to reduce the production costs of cultured meat.

Left:
Bioreactor in which cultured meat are produced.

Right:
Scaffold with muscle cells inside the biorectors from which meat is cultivated.



Can you replicate any type of meat and different consistencies using cultured meat?

Che Julius Ngwa: Yes, we can mimic the meat of any animal as long as we have the respective cells. We can also replicate the taste of the individual meat so that it tastes exactly like natural meat. We are not only using the muscle cells but also fat cells so that we are able to provide the required taste. Moreover, we can add other substances and supplements to obtain the nutritional value that the cultured meat product should have. Naturally, we also want to mimic the consistency of a steak, which is where our scaffold or processes like bioprinting come into play that allow us to form such a steak or whatever form of meat you want. The easiest product to achieve is minced meat, of course.

What about seafood?

Che Julius Ngwa: That is also possible and quite interesting. There are many groups working on cultured fish, which follows the same principle as cultured meat. In fact, there is a company in Germany that is very advanced in this particular area. They have obtained the fish cells and from what I have heard, they are actually better because they are continuously replicating instead of going into early replicative senescence where the cells stop dividing and replicating.

Ms. Konarzycka-Bessler, are there bacteria that are particularly well-suited for Single Cell Protein?

Monika Konarzycka-Bessler: Yes, there are. The research on Single Cell Protein goes back quite a bit, as the first experiments were carried out in the 1950s and 60s. Back then, the question was the same – how to feed people with alternative food sources? Research on the topic was discontinued due to high costs and technical limitations at the time, but the first results could give some indications of how we can sustainably produce Single Cell Protein today, not just in my group but all over the world. So, what we know at the moment is that the group of bacteria called "Knallgas bacteria" are particularly well-suited, because they produce proteins with profiles that are very similar to animal protein. This means that most of the essential amino acids, which humans cannot produce themselves and need to absorb through nutrition, are already there in high quantities. To work with Knallgas bacteria requires special equipment, since we need to have higher amounts of CO_2 and hydrogen – that's why it is called "Knallgas", because it can explode and demands adequate safety measures.

Knallgas bacteria have been approved as being safe to eat and some global companies already use them for food applications – predominantly for animal feed, though. A Finnish company

is already far advanced and has established a targeted process optimization of bacterial protein powder, which uses the protein-rich ingredients for the production of human food such as noodles and, most recently, ice cream as well as chocolate bars. In spring 2023, the first human food products could already be tasted in Singapore.

Besides Knallgas bacteria, we also want to look into Single Cell Protein processes using anaerobic bacteria, which only grow with the exclusion of oxygen. There organisms are also able to utilize carbon dioxide from the environment and generate biomass –however, they do grow much slower, but research has shown that they are also well-suited production organisms for food protein. But we need to look deeper into that.

What products can be provided for the food industry using Single Cell Protein?

Monika Konarzycka-Bessler: The use is very versatile, from meat substitutes to dairy products like milk or proteins for breads as well as egg substitute – basically anything that requires proteins.

What are the benefits of cultured meat and Single Cell Protein with regard to sustainability?

Che Julius Ngwa: It has quite a lot of benefits. First of all, it reduces greenhouse gas emissions. You have to use less land and water for animals as well as less energy. And then, of course, there's the ethical aspect. Animals used for meat production are often kept in very unhygienic conditions, very overcrowded, and there is the influx of antibiotics given to these animals, which will eventually increase antibiotic resistance. It is also possible for animals to transmit diseases to humans. So, cultured meat could minimize and, to some degree, eliminate some of these negative factors altogether.

In Single Cell Protein, CO_2 serves as the primary carbon source to produce proteins.

In the food sector, Single Cell Protein can be used in various forms: as a powder that you can mix into your food at home or as a component of ready-to-eat products such as pasta or ice cream.

Monika Konarzycka-Bessler: A benefit of Single Cell Protein is that bacteria can grow indefinitely, since they are always available in the environment and after a few hours you can already harvest them again for proteins. If we compare this to agriculture where food is grown in the field, we have limited amounts of crops – sometimes once a year, depending on the type of food, whereas lettuce is harvested more frequently, of course, but has a significantly lower nutrient content. We are dealing with bacterial proteins here, which also require several steps to produce – beginning with biomass production in a gas fermentation plant, a possibly necessary extraction of the proteins, followed by a concluding purification and drying of the protein-containing biomass. A great advantage of bacterial biomass accumulation is that it can be done all year round in particular space or plant, allowing for a failsafe production of proteins without underlying any limitations from nature such as weather or climate conditions. Another benefit is that besides plant-based meat alternative, we can provide another alternative protein source, meaning that people have a bigger range to choose from. With a view to sustainability, the CO2 we use, either from the environment or from companies that produce CO2 in their processes, can be re-used for the production of Single Cell Protein and thus create an economic cycle.

How do cultured meat and Single Cell Protein products differ from other non-animal products like soy or wheat protein alternatives that are already available on the market?

Che Julius Ngwa: The biggest difference between cultured meat and soy- or wheat-based protein alternatives, which have been on the market for a while now, is that they are obtained from plants. Cultured meat, on the other hand, is produced from animal cells and is not yet approved for commercial use. But technically speaking, cultured meat products would ideally be an exact replica of the natural meat without killing the animal to get the meat, whereas plant-based meat alternatives are still quite different, both in terms of taste as well as consistency.

Monika Konarzycka-Bessler: The biggest difference of Single Cell Protein, same as in cultured meat, is that it's not plant-based. Bacteria are not plants, but living microorganisms found in our environment. Also, the amino acid components in bacterial proteins are different from those found in plants. Thus, bacterial proteins extend the range of edible proteins. Single Cell Protein products could also be used in different forms, such as powder to mix into your food at home or as an ingredient in ready-made products like noodles or dairy.

Are there any technical novelties required for CM and SCP that the Fraunhofer IME is working on?

Che Julius Ngwa: At Fraunhofer IME, we have developed a novel patented bioreactor. Our idea is to use a bioreactor as a vessel that contains a porous scaffold to which the cells can attach and then multiply. Inside this vessel is also a membrane that will be used to close it and then we have a mechanism that will alternatingly compress and relax the scaffold containing our cells from above. In doing so, we are mimicking muscle cell activity and while this is happening, we mix a medium into it and thereby stimulate the cell to develop into muscle. And at the end of the day, we are able to get our piece of meat. Another of our objectives is to scale up this process.

Monika Konarzycka-Bessler: It's difficult to talk about technical novelties at the moment, since we are still at the beginning of our activities. We are working to find bacteria strains in the environment that are suitable for this process. But what we at Fraunhofer IME definitely need at the moment is a special bioreactor, like a fermentor, that is explosion-proof. It's not a novelty, but rather a requirement. There are some groups already working on processes using lower amounts of hydrogen, which means that they want to create a very safe environment without the high risk of explosions, so it would be a good thing to look into this process further. But as for now, we are still waiting for results of experiments that will give us indications of what technical process control will be required in the future.

Do you think that alternative protein products will dominate the food industry in the future?

Che Julius Ngwa: Yes, I think alternative proteins will become more and more important. They are much more sustainable with a view to the environment and also animal-friendly. However, it is important to keep in mind that these alternatives may not have the same nutritional value as actual meat. So, it's always necessary to check if these products have the necessary nutrients for our diet and refine them in that respect before making them available on the market. At the same time, it's also a cultural thing because the consumption of meat is an integral part of some cultures around the world. Therefore, cultured meat or any other protein alternative may not be popular in some parts of the world. Another important aspect is also social acceptance. People need to be educated.

Monika Konarzycka-Bessler: I do not think that protein alternatives will dominate the food industry. Of course, there is a change in people's eating habits. When I was a student studying and I was going for lunch at the canteen, people were usually getting meals with meat. Today, when I go for lunch at the canteen, I see a large cue for the vegetarian meals. It's a big difference now. But we can't forget that what comes from the nature is the best that we can get and that includes meat, too. I don't believe killing animals for our food will be completely gone, because this is how we were conditioned and have been eating for ages. It is good to have alternatives, as it gives you a personal choice – either you are fine with animals suffering because you want a piece of meat or you are not and want to consume proteins from different sources that don't come from animals. It's always an individual question.

Cultured meat is a promising method to ensure sustainable and ethically acceptable meat production in the future.

People and events

Grand opening of large laboratory building in Schmallenberg with Prime Minister of North Rhine-Westphalia

On June 1st, 2023, Fraunhofer IIME in Schmallenberg celebrated the opening of its new laboratory building with numerous guests. The new building with a laboratory area of over 3,300 m², two thirds of which is in the radioactive monitoring area, was financed by the federal and state governments to the tune of 32 million euros and, after 10 years of planning and construction, was ready for occupation. The celebrations were accompanied by greetings from Hendrik Wüst, Prime Minister of the Federal State of North Rhine-Westphalia, Prof. Dr. Axel Müller-Groeling (Executive Board of the Fraunhofer-Gesellschaft), Prof. Dr. Tanja Schwerdtle (Vice President of the German Federal Institute for Risk Assessment) and Tatjana Sikuljak (Vice President Regulatory Science Crop Protection, BASF SE) as well as a video message by Prof. Dr. Ulrich Rüdiger, Rector of RWTH Aachen University, accompanied the celebrations. Over the course of the year, Institute Director Prof. Dr. Christoph Schäfers welcomed Prof. Dr. Rüdiger and further guests who could not join the opening ceremony, such as representatives of the Federal Environment Agency in Berlin to enable an in-depth insight into our new infrastructure.

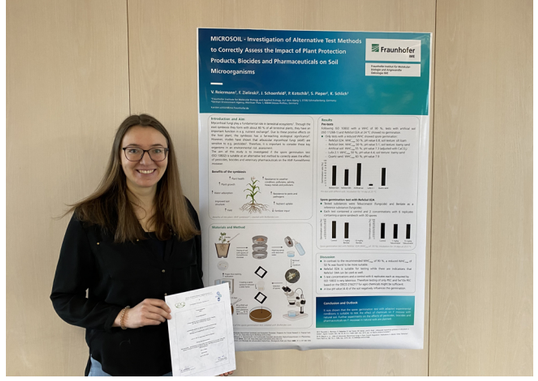
Introducing the Team4You

The Team4you is a group of employees in Schmallenberg, who put the focus on occupational health management since the beginning of 2023. Psychological, physical and social health of every single employee and the accessibility to information on these topics are most important to the team. Their projects range from installing water dispensers in the institute, arranging health days and offering various sports courses, which are currently being planned. Thanks to the Fraunhofer Diversity funding programme, setting up Room4you was made possible and allows room for peace, meditation and prayer for colleagues from all cultural backgrounds.

The trained group is supported by professional counsellors for psycho-sociological guidance from the TeamPrevent (BAD group). Furthermore, the team is in close contact to their colleagues from the works council, the representative for disabled personnel and the representative for equality as a part of the whole occupational health management.

Ecology between Fraunhofer IME Schmallenberg and RWTH Aachen University

Applied Ecology at Fraunhofer IME has a long history with the Chair of Ecotoxicology at RWTH Aachen University. Since the 1990s, there has been a collaboration with the working group of Prof. Toni Ratte in the field of mesocosm studies and modelling, which continues to this day with the RWTH Institute gaiac. GLP multisite studies are carried out under the direction of IME employee Dr. Udo Hommen, who holds a doctorate from RWTH Aachen University. From 2001 to 2007, the holder of the Chair of Ecotoxicology at RWTH Aachen University, Prof Andreas Schäffer, was also Head of the Applied Ecology Division at Fraunhofer IME. Even then, the further development of Fraunhofer IME was already apparent through the expansion of staff and the research profile. After his retirement from the management of the division, both sides agreed to continue their co-operation, which led to joint projects. On the institutional side, there were ongoing conversations between RWTH Aachen University and Fraunhofer IME, which were initiated after Prof. Schäffer's retirement at the end of 2023 with his successor, Prof. Thomas Backhaus, for the purpose of structurally reconnecting Applied Ecology. These attempts are supported by the rector of RWTH Aachen University, Prof. Ulrich Rüdiger.

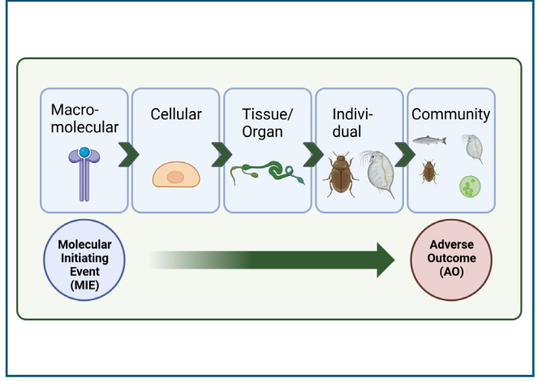


Vivian Reiermann wins poster prize at the SETAC-GLB conference in Basel

Vivian Reiermann, a Master's student at the Schmallenberg site, was delighted to successfully participate in the SETAC German Language Branch (GLB) in Basel in September 2023. She was not only able to present the interim results of her Master's thesis, but also impressed the jury, so that she was awarded the poster prize.

Vivian Reiermann has been working on her Master's thesis as part of the UBA MICROSOIL project in the "Aquatic Primary Producers and Microbial Diversity" working group since March 2023. This group is currently looking for alternative test systems to more accurately assess the impact of pesticides, veterinary medicines and biocides on soil microorganisms. One of the test systems identified as part of the project is the spore germination test according to ISO 10832 (2011).

The aim of Vivian's master thesis is to find out whether the spore germination test with the arbuscular mycorrhizal fungus *Funneliformis mosseae* is a suitable, sensitive test system for environmental risk assessment compared to the standard test (OECD guideline 216; N-transformation test).



Workshop on endocrine disruption in invertebrates

On June 6th, 2023, the Department of Ecotoxicology hosted a virtual workshop entitled "Endocrine disruption in invertebrates - current status and research needs". The workshop was an international event with contributions from Fraunhofer IME Schmallenberg, Bayer AG, BASF, Syngenta and Unilever.

After Kirsten Germing, research associate at Fraunhofer IME, had introduced the participants to the topic with an overview presentation, the industry representatives shared their insights. The focus was on the question of how new guidelines for testing endocrine disruption in invertebrates should be developed. Furthermore, it was discussed whether the current methods are sufficient to determine these effects or if other methods and approaches are more promising to establish a causal link between molecular mode of action and adverse effect.

The participants agreed that there are still major gaps in research in this field and that these should be closed. Nevertheless, the question of whether this topic will find its way into regulatory issues remained open at the end. Fraunhofer IME in Schmallenberg will continue to pursue this topic.

Fraunhofer IME at Fi Europe 2023 in Frankfurt

From November 28th to 30th, 2023, Fraunhofer IME and Fraunhofer IVV were at the Food ingredients Europe in Frankfurt to jointly present our innovative research activities for the food sector.

Representatives of the food industry had the opportunity to network with our researchers and to inform themselves on how alternative protein sources for our food of tomorrow are produced. The Fraunhofer IME activities were primarily represented by the leaders of the new work groups "Single Cell Protein" and "Cultured Meat".

New Fraunhofer President Holger Hanselka visits Fraunhofer IME in Aachen

As part of his dialogue tour, the new Fraunhofer President, Prof. Holger Hanselka, visited Fraunhofer IME in Aachen on December 11th, 2023.

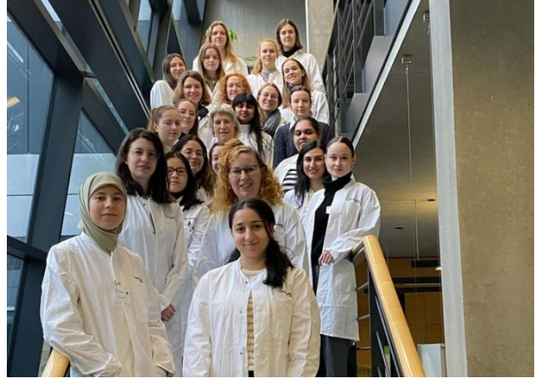
During a tour of the institute, the president had the chance to see some of our research highlights – including our vertical farming system as well as bicycle tires made from dandelion. As he absorbed the impressions, Prof. Hanselka constantly remained in dialogue with the researchers and his questions kept building a bridge between science and economy. Lastly, employees had the opportunity to converse with the president and ask him questions concerning research and organization at Fraunhofer.

Afterwards, the president also visited the neighbouring Aachen-based Fraunhofer institutes IPT and ILT.

Fraunhofer IME team workshop in in Giessen

On August 24th and 25th, 2023, the staff of administration and public relations of Fraunhofer IME participated in a team workshop at the institute branch Bioresources in Giessen – it was the first in-person meeting in three years following the COVID-19 pandemic.

During the two-day workshop, the team members of administration and PR had the opportunity to network, get to know each other personally and inform each other on the current developments in their different areas. Of course, it was also discussed how activities at the Fraunhofer IME can be optimized so that we can support our researchers to the best of our abilities and maintain our good team spirit.



Fraunhofer IME at Gamescom 2023

Fraunhofer IME was at the Gamescom 2023 in Cologne – not for gaming but for informative purposes. At the stand of IN FORM, an initiative of the Federal Office for Agriculture and Food dedicated to more exercise and healthy nutrition, we had the opportunity to present our project “Novel Sweets” to the attendees. The project explores sweet-tasting proteins that can be used as healthier alternatives to conventional sugar or sweeteners in beverages and desserts. These proteins are nearly calorie-free, while possessing high sweetness and a pleasant flavor profile.

The IN FORM initiative promotes the effective use of digital media for a successful communication of knowledge about nutrition, sport and activity and to motivate users.

Fraunhofer Research Campus 2023 in Aachen

From November 29th to 30th, 2023, Fraunhofer institutes IME, ILT and IPT jointly hosted the Fraunhofer Research Campus in Aachen. During the two-day event, female MINT students and graduates had the opportunity have a look behind the scenes of the three Aachen-based institutes and get insights into the daily work life of scientists. Apart from lab tours, there were presentations held by the Fraunhofer researchers and participants also had the chance to have one-on-one conversations for career-specific questions. During a panel discussion, the participants were able to ask the scientists individual questions about their personal career paths and receive valuable tips and inspiration for their professional future.

Fraunhofer IME at the Global Forum for Food and Agriculture (GFFA) 2024

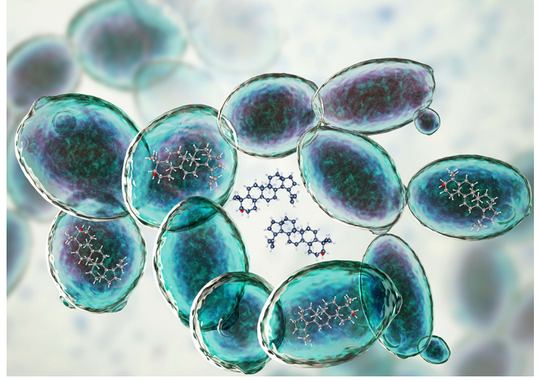
From January 17th to 20th, 2024, the 16th GFFA conference took place in Berlin under the title "Food, Climate and Security: Joining Forces for a Safer Tomorrow". Fraunhofer IME and Fraunhofer IVV were also there to jointly present the Fraunhofer Lighthouse project "FutureProteins".

The conference was opened by Claudia Müller, Parliamentary State Secretary in the Federal Ministry of Food and Agriculture, who also visited the Fraunhofer stand afterwards. During the four conference days, innovative ways for food security and seminal food systems were introduced. "FutureProteins" focuses on protein sources for the food industry that are obtained from plants, fungi, algae and insects. The closing highlight was the Minister of Agriculture Conference, which brought together ministers from more than 60 states.

Fraunhofer IME at the 9th Conference on Medicinal and Aromatic Plant Research

The 9th conference on medicinal and aromatic plants of the German Technical Committee for Medicinal, Aromatic and Spice Plants took place from September 11th to 14th, 2023, under the motto "Safety from cultivation to the consumer - top class or taken to the extreme?". It was hosted by the Bavarian State Research Center for Agriculture (LfL) and the Weihenstephan-Triesdorf University of Applied Sciences (HSWT) in Freising. The conference offered an attractive program with scientific lectures, posters, workshops and excursions on the topics of quality management and law, cultivation methods in the field and in cultivation rooms, breeding, plant protection, biodiversity effects and processing technology.
In the topic area "Cultivation and breeding", Dr. Lena Grundmann from Fraunhofer IME in Münster was speaking about the establishment of cell and tissue cultures for medicinal plants using the example of *Arnica montana* as part of the "Circular PhytoREVIER" project - integrated value creation with cultivation and utilization of medicinal plants in the Rhineland region.

The BMBF-funded project focuses on optimizing the performance of medicinal plants by using precision breeding. Cell and tissue cultures play a major role in the development and application of modern plant breeding and genome editing technologies. In her talk, Lena Grundmann presented the establishment of callus and hairy root cultures of arnica. The cultures are now being used to further advance the identification and characterization of active ingredient biosynthesis. The cell and tissue cultures open up further possibilities: on the one hand, they could be suitable as alternative production platforms for the valuable active ingredients; on the other hand, they allow the use of modern genome editing technologies such as CRISPR/Cas to accelerate breeding, among other things.



"Aspirant" is followed by "Perspective"

The follow-up project to "Aspirant" - "Perspective" - started at the beginning of February. The research and development proposal made it through the second phase of the initiative "Tailor-made biobased ingredients for a competitive bioeconomy" of the German Federal Ministry of Education and Research (BMBF). Based on the success of the first phase "Aspirant", in "Perspective" the network is intensifying its focus on the production and application of triterpenes.

The research team, coordinated by Fraunhofer IME, combines expertise from chemistry, biology, process engineering and pharmacy. Scientists from the Technical University of Munich (TUM), the Fraunhofer IME and the SMEs VivaCell Biotechnology GmbH and Phytowelt GreenTechnologies GmbH are once again pooling their expertise for "Perspective" to jointly further expand the steps of the value chain and exploit triterpenoids as the basis of innovative pharmaceutical products. The researchers opted for heterologous production of the triterpenoids in yeasts. Compared to the natural biosynthetic organism, the yield of the desired substances is drastically increased in our proprietary yeast strain. In addition, the purified triterpenoids exhibit a high purity of more than 98 percent and consistent quality. Based on the results from "Aspirant", the researchers drew up a priority list to meet the specific requirements of pharmaceutical or cosmetic applications through targeted diversification of the triterpenoids. In addition, "Perspective" is accompanied by experts from industry to enable seamless commercial exploitation of the results.

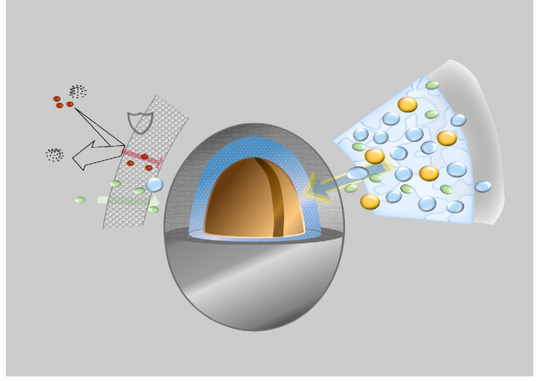
"InVaKaS" Brazilian - German Workshop

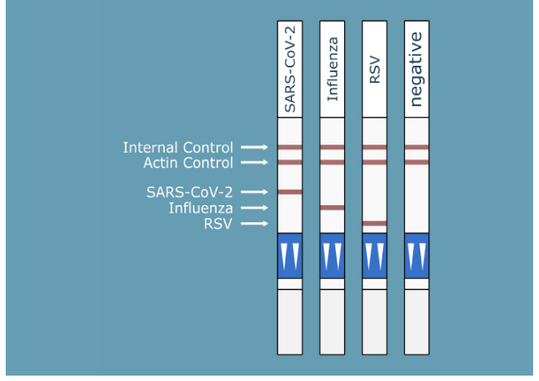
The trio of Natalie Laibach (CRAG, Barcelona), Débora Monteiro Moretti (Ruhr University Bochum) and Boje Müller (Fraunhofer IME) convinced with their workshop idea at the BMBF competition as part of the Brazil State Day. The "InVaKaS" workshop now took place from March 20 to March 26, 2023 in the state of Bahia in northeastern Brazil.

The workshop "Innovation potential for valorized cascade use of by-products of juice production InVaKaS" with experts from Brazil and Germany aimed to map the value chain and develop new research ideas for valorization and cascade use. Fruit production is resource-intensive and more sustainable practices are urgently needed - for example, the circular use of residual biomass. Almost 50 percent of all fruit produced is processed into juice. Citrus juice production alone generates 25 million tons of waste every year. This can make up between 20 and 80 percent of the entire fruit. The residual biomass of the fruit has a wide range of potential for further use and valorization, e.g., as animal feed, for the extraction of antioxidants, as a substrate for enzyme or biogas production or as a source of dietary fiber and specialty chemicals.

The interdisciplinary group of participants represented the various competencies along the value chain. The agenda offered a varied program of keynote speeches from different interest groups such as start-ups or research organizations, excursions, discussion and project planning sessions. One workshop day was organized as a hybrid event and allowed all those interested in this topic to participate.

The visit to the Coopaita pineapple producers' cooperative was the deciding factor in focusing on the pineapple value chain in future networking activities and projects.





The editors of Pflanzenforschung.de interviewed doctoral student Kai-Uwe Roelfs

The internet portal Pflanzenforschung.de is funded by the German Federal Ministry of Education and Research (BMBF). Its declared aim is to communicate the importance and fascination of plant research to an interested public. In April 2023, the editorial team interviewed plant researcher and bioinformatician Kai-Uwe Roelfs. He is working on his doctoral project at Fraunhofer IME in Münster. Together with partners from science and industry, he is involved in developing the wild form of the Russian dandelion *Taraxacum koksaghyz* as a useful crop for rubber production. Among other things, Kai-Uwe Roelfs explained why his work focuses on the flowering behavior of the dandelion, in particular the induction of flowering by a cold stimulus. It is of interest which genes play a role in this and how the cold stimulus affects them on an epigenetic level. With the help of these results, the researchers hope to be able to breed variants that are stably cold-stimulus-dependent or -independent. In the case of cold stimulus-independence, this made it possible to harvest seeds several times a year due to the shorter generation time, which significantly increased seed production.

In the interview, Kai-Uwe Roelfs also talked about his activities within the PLANT 2030 ACADEMY, such as his visit to a large plant breeding company: "This gave me an idea of how the different departments work together, both in quality assurance and in expanding the product range."

The SeedPlus project at the "Seed Symposium"

Dr. Philip Känel from Fraunhofer IME in Münster attended the "Seed Symposium" in Nossen in March 2023 on behalf of the SeedPlus project. The symposium was jointly organized by the Society for Plant Breeding (GPZ), the Society for Crop Sciences (GPW) and the Seed Section of the Association of German Agricultural Research Institutes (VDLUFA). The focus of this year's scientific seed symposium was on "Physical, biochemical and molecular methods for determining seed quality".

In his talk "Seed coating in times of climate change and sustainable agriculture: environmentally friendly and multi-functional seed coating to protect and nourish the seedling", Philip Känel presented the SeedPlus project, which is being carried out jointly with the Fraunhofer Institutes for Microtechnology and Microsystems IMM and for Chemical Technology ICT. Based on ecologically safe materials, the collaborative project SeedPlus aims to develop complex seed coatings that have inherent water and crop protection management to enable effective field emergence even under difficult environmental conditions. Fraunhofer IME contributes the expertise of two locations: In Münster, the focus is on the functional evaluation of the seed coatings and in Schmallenberg on the establishment of new testing and assessment strategies for the sustainability and safety of the developed product.

Support for our crowdfunding team!

In late 2022, we successfully completed the first phase of the Fraunhofer Future Foundation's "ScienceForGood" crowdfunding competition. During the second phase, we used the donations and our first-place prize money to combine our coronavirus test with the simultaneous detection of other viruses. A large number of different viruses are responsible for respiratory infections during the cold season. Diseases caused by the corona virus (SARS-CoV-2), influenza viruses or RS virus (respiratory syncytial virus; RSV) play a prominent role. We therefore decided to expand our LAMP corona test with the detection of influenza and RSV.

Last summer, Sai Aparna Nagarajan, a Master's student at Justus Liebig University in Giessen, joined our crowdfunding team. In her master's thesis, she is strengthening the research and development work. Our project partners developed a total of six lateral flow dipsticks (LFD) for visualization. Sai tested the various prototypes in the laboratory: prototype 6 with a modified sequence of test lines and optimized visibility of the colored lines won the race.

Sai established the LAMP reaction for both influenza and RSV. To simulate patient samples, she added positive controls to nasal swab matrix and was able to reliably detect them in duplex reactions together with the human actin control. She is currently testing the multiplex approaches.

Fraunhofer IME in Münster moves into additional space

Since the "Plant Biopolymers" branch of Frauenhofer IME opened on Schlossplatz at the University of Münster in 2010 in cooperation with the Chair of Plant Biotechnology, the team led by location manager Prof. Dirk Prüfer has grown considerably.

The premises were threatening to burst at the seams, but additional space in the Biotechnology Center (BioZ) at Johann-Krane-Weg 42 in Münster has now given the researchers more room. The BioZ is operated by Technologieförderung Münster GmbH; it is located in the Technology Park and is specially tailored to the needs of biotech R&D activities.

After an 8-minute bike ride - the typical way of getting around in Münster - the additional space can be reached from Schlossplatz. In mid-year, almost 20 employees moved into the laboratories and began their work there: they are carrying out research on plants, yeasts and microorganisms. In addition to molecular plant breeding research (e.g. marker development), synthetic biology for the optimization of terpenoid-producing yeasts is a central research topic at the new site in Münster. Parts of the department's extensive biochemical analysis are now also located at the BioZ.

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First all Fraunhofer IME PhD seminar

In Aachen, the PhD seminar is already part of the annual event repertoire since 2011. To provide our young researchers with a joint platform, the invitation to the 2023 seminar was extended to all doctoral students at the four Fraunhofer IME locations. The organization was in the hands of the students, who drew up an exciting program around our R&D topics. The seminar took place on November 16th and 17th, 2023, as a hybrid event in Aachen. 34 doctoral students accepted the invitation and presented their topics to the audience in 15-minute lectures or 3-minute poster pitches with poster presentation. Brief presentations of the R&D activities at our four locations and a guided tour to the highlights at the Aachen location completed the program.

Given the high quality of the contributions, the five-member jury faced the difficult task of selecting the four award winners. The jury was delighted to award a total of four prizes: In the Newcomer and Professional categories for the best talk and the best poster respectively. For poster and pitch, Sina Mäckelmann received the "Professional" and Tobias Poloczek the "Newcomer" award.

With his presentation, Pascal Geisler won in the group of "Professionals" and Josephine Dresler with hers in the "Newcomer"

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Venom scientist from Giessen meets Nobel Laureates

Since 1951, the Lindau Nobel Laureate Meetings have regularly brought together young researchers with the so-called "Laureates", scientists who have been honoured with the coveted Nobel Prize. The high-calibre meetings serve to promote intellectual exchange and rotate thematically between the disciplines of physics, chemistry, physiology and medicine. In a multi-stage, international and highly competitive selection process, Dr. Tim Lüddecke from Fraunhofer IME was chosen to participate. As a junior research group leader, Lüddecke heads the "Animal Venomics" working group at the Branch for Bioresources in Giessen. His research focusses on the biology, biochemistry and possible applications of animal venoms. The focus here is on the identification and functional characterisation of previously unknown natural substances using systems biology and biotechnology, as well as their translation into sustainable solutions for plant protection, industrial goods production and, in particular, biomedicine. "The discussions and scientific dialogue were extremely enriching and opened up completely new perspectives for me. I look forward to continuing to network with the Nobel Prize winners as well as with other young researchers in physiology and medicine as part of the Lindau Alumni Network," says Lüddecke.

Outstanding performance at the Fraunhofer IME in Giessen

Fraunhofer IME junior scientist Dr. Anton Windfelder received the prestigious Stolzenberg-Prize for outstanding achievements in the natural sciences.

The Dr.-Herbert-Stolzenberg-Prizes for outstanding performance in the natural sciences were awarded at the opening ceremony of the Giessen Graduate Centre for Natural Sciences and Psychology on July 3rd, 2023. The prizes, endowed with 3,000 euros, recognize young researchers at the beginning of their scientific careers who have distinguished themselves through exceptional achievements and special commitment to their scientific field. Anton Windfelder received the prize in the biology category for his outstanding work on the use of insects as alternative animal models in medical imaging and research.

His research findings have been recognized internationally as they contribute to making research more ethical and efficient. For example, by using insects in some areas of research, traditional laboratory animals with a complex social life such as rats or mice can be spared.

Encouraging more women to start a business

In view of the almost equal gender balance when it comes to taking up a study programme, an above-average number of women get ''lost'' on the way to the attractive and often lucrative career option of starting a business. Awakening women's interest in starting a business, preparing them adequately for this career option and organising start-up support services in a gender-appropriate way has not yet been sufficiently successful. At the same time, it can be assumed that better and more target group-orientated support for women as founders is one of the key factors for greater participation of women in innovative start-up activities overall. For this reason, the Bundesweite Gründerinnenagentur (BGA), funded by the Federal Ministry of Research and Education, has set itself the goal of giving women more visibility as founders. As part of the ''InnoGründerinnen'' campaign, 52 female founders with a university background were photographed for short films. One of them was Fraunhofer IME employee Fabiola Neitzel from the Branch of Bioresources in Giessen. She founded the company PROMBYX GmbH, which processes silkworm pupae from silk production into a high-quality source of protein for animal feed. In doing so, she also wants to make a contribution to better resource utilization in the area of protein.

More information:

https://innogruenderinnen-bga.de/

www.prombyx.com

Voluntary year in science, technology and sustainability

From September 2022, Fraunhofer IME in Schmallenberg offered a Voluntary Social Year in Science, Technology and Sustainability (FJN) in cooperation with the ijgd (Internationale Jugendgemeinschaftsdienste) for the first time. The FJN is aimed at young people between the ages of 18 and 26 who want to get involved in the environment, climate protection and nature. Volunteers spend a year working in research institutions, universities or local authorities and gain an insight into scientific work. At Fraunhofer IME, the volunteer worked in the soil sampling laboratory for a year as part of the FJN and supported the staff with nationwide sampling and the subsequent laboratory work. The summary from both sides was very positive: the FJN employee found the varied field and laboratory work very interesting and subsequently decided to study natural sciences. She provided active support in the laboratory and was a relief for our laboratory staff. Due to the positive experiences, three energetic "FJNlers" were hired for the year 2023/2024 (see photo: project manager Karlheinz Weinfurtner with his FJN team). Two FJN positions are also to be filled in the upcoming 2024/2025 FJN cycle.

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"Bring your Own BBQ" event

Before the summer came to an end, a "Bring your Own BBQ" event took place on September 7th, 2023, on the roof terrace of the Fraunhofer IME Branch for Bioresources. Employees from many different departments prepared food and drinks for the general public, resulting in a varied and delicious buffet. The employees used the event to socialise with each other and network across departments.

Before the BBQ event, our guest Professor Manjunatha Kini from the National University of Singapore gave an exciting presentation entitled: "ANP analogs for the treatment of acute decompensated heart failure patients". Professor Kini is one of the world's leading experts in the field of animal venoms, the biochemistry of venoms and, above all, the development of venom-based drugs. He has been working in this field since the 1980s and has led several ground-breaking projects that have identified new classes of proteins with therapeutic potential.

Dr. Thorsten Klawonn, scientist at Fraunhofer IME in Schmallenberg

Thorsten started as a chemist at Fraunhofer IME in Schmallenberg in 2009 and was subsequently responsible for the introduction and application of various OECD guidelines in the field of inorganic chemistry in his laboratory. He was particularly dedicated to the development of new methods for the speciation of metals in various matrices in the scientific team, where his chemical expertise was in great demand. He used this expertise for research contracts from industry as well as for scientific projects from public clients, such as the Federal Environment Agency. For Thorsten, it was always a particular pleasure to advise customers on specific chemical issues and to develop solutions together.

But it is not only in his day-to-day work that Thorsten has shown his dedication to science. At events such as "Schmallenberger Woche" and Girls' and Boys' Day, Thorsten was also enthusiastic about making scientific topics accessible to the public. In addition, working with young scientists was a matter close to his heart and he flourished when he was able to pass on his technical expertise to others, e.g. in the context of master's theses or doctoral dissertations, which he supervised in the laboratory. When it came to "his metals", he was always the first point of contact for employees from other departments and everyone who experienced him in discussions remembers his unique enthusiasm for science. Also, he occasionally came pretty close to the image of the "mad" scientist portrayed in many feature films – and this should not go unmentioned here. No matter what time of day, no matter whether he was a trainee or head of department, Thorsten always had time for his colleagues. He was there to help and advise everyone and was greatly appreciated at the institute for his great willingness to support others.

Thorsten died far too early on August 2nd, 2023, after a sudden and serious illness.

So long, Thorsten!

Ina, Burkhard and Dieter for the whole team at IME Schmallenberg

Facts

Scientific publications

For an overview of all scientific publications visit:

https://www.ime.fraunhofer.de/en/Media_Center/scientific_publications.html

Networks in science and industry

For an overview of all cooperations, activities, memberships and comittees visit in science and industry visit:

https://www.ime.fraunhofer.de/en/About_Us/networks.html

Fraunhofer IME in numbers

For an overview of institute data on budget, external financing and staff visit:

https://www.ime.fraunhofer.de/en/About_Us/institute_data.html

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