Fraunhofer IME

Fraunhofer Institute for Molecular Biology and Applied Ecology IME




Annual report 2022/23

AgriN'omics – for a resilient agriculture and a sustainable food production

Preface

Despite the challenges issued by the energy crisis and the ERP system cutover, which led to higher costs and administrative efforts, the Fraunhofer Institute for Molecular Biology and Applied Ecology IME could achieve numerous scientific and strategic successes in 2022.
At the Schmallenberg location, additional factors – such as the reorganization of departments, delayed completion of construction work and the financing of initial equipment – temporarily led to exceptional charges. With the implementation of a worldwide unique aquaculture test facility and modern chemical-analytical, microbiological and molecular biological laboratories, we are able to offer our customers a comprehensive evaluation concept for aquaculture. The test facility is part of the new IME platform "AgirN'omics" (p. 24), which deploys the broad spectrum of molecular biological methods ("omics") of all four Fraunhofer IME locations to develop and provide sustainable solutions for agriculture and the food industry.

In November 2022, Prof. Dr. Stefan Schillberg was appointed director of Fraunhofer IME. Concurrently, he is now also the head of the Institute for Molecular Biotechnology at RWTH Aachen University, which further expands the collaboration of both institutions. Under his appointment, two junior groups have been established at Fraunhofer IME – "Cultured Meat" and "Single Cell Protein". Both groups will support the department "New Agricultural Systems" to establish procedures for the provision of alternative protein sources in human food. As recombinant proteins are also in increasingly high demand within the agricultural and food industry, the Aachen location could produce several protein candidates at a large scale in different expression systems for industrial use. Additionally, the biotechnological production of energy sources like C1 compounds is gaining more importance, e. g. by using microorganisms or biohybrid systems.

At the Münster location with the "Functional and Applied Genomics" department, there was a strong focus on the knowledge-based development and application of biotechnological processes in agriculture. Together with academic and industrial partners, researchers successfully advanced the establishment of alternative crops such as various medicinal plants along the entire value chains. In the optimization of established crops such as potatoes, the emphasis was on the utilization of biogenic side streams generated in the course of production and further processing. Our newcomer topic in 2022 is multipurpose seed coating. Together with the Fraunhofer Institutes IMM and ICT, we are developing a coating of ecologically safe formulations designed to safeguard and increase crop yields by protecting and nourishing the seedling. Researchers at the Schmallenberg location are developing a new strategy and methodology for the assessment of sustainability and safety of such coatings.

In order to perspectively establish a separate department dedicated to the exploitation of animal venoms at the Branch for Bioresources in Giessen, the Hessian Ministry of Science and the Arts supports the project "Animal Venomics" via the LOEWE Centre for Translational Biodiversity Genomics. This project deploys modern and innovative systems biology methods, such as genomics, transcriptomics, proteomics, and bioinformatics, to systematically examine animal venoms. One major focus of the venom research in Giessen is the identification of new biotherapeutics, particularly to treat infectious diseases and tumors.

The Animal Venomics project supports the junior group of Dr. Tim Lüddecke, which, among other things, researches the venom of spiders and snakes, focusing on native species. In October 2022, Dr. Lüddecke was invited to present his group's research activities on Central European venomous animals and their role in biomedicine at the World Congress of the International Society on Toxinology in Abu Dhabi. The successful Animal Venomics project has contributed to the approval of a second funding phase of the LOEWE Centre for Translational Biodiversity Genomics from 2022 to 2014, with a sum of 15.6 million euros. The Branch for Bioresources has also hosted the annual meeting of the LOEWE Centre at its new building in Giessen.

Important topics such as resource technologies and bioeconomy will remain a focus of our various research activities. Our aim is to put the results of these activities to the most efficient use in industry.

Prof. Dr. Stefan Schillberg

Prof. Dr. Christoph Schäfers

Content

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. In 2022, Prof. Dr. Stefan Schillberg became the director of Fraunhofer IME. Prof. Dr. Christoph Schäfers is Head of the Applied Ecology Division.

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, small and medium enterprises and on the public sector. In 2022, Fraunhofer IME collaborated with more than 110 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 2022, the institute employed about 422 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 Applied Entomology at the Justus-Liebig University Giessen, and the world's first Institute for Insect Biotechnology, founded in Giessen in 2016. We cooperate with many international research partners and remain in close contact with universities and other research organizations. Our aim is to recognize trends and developments as they emerge, and to develop and implement novel research strategies and technologies.

Molecular Biotechnology

Molecular Biotechnology is the basis of a modern bioeconomy and contributes sustainably to the knowledge-based production and industrial use of renewable raw materials. On behalf of our customers, the Molecular Biotechnology Division develops tailored plants, animal cells and microbes for applications such as the production of food and 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.

Symbol used in the annual report MB

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.

Symbol used in the annual report BR

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.

Symbol used in the annual report AE

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 30,000 employees are qualified scientists and engineers, who work with an annual research budget of 2.9 billion euros. Of this sum, 2.5 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

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

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

Prof. Dr. Annika Jahnke (guest)
Hemholtz Centre for Environmental Research, Leipzig

Prof. Dr. Joybrato Mukherjee
President of the University of Giessen, Giessen

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

Prof. Dr. Dr h.c. mult. Ulrich Rüdiger (guest)
Rector of RWTH Aachen University, Aachen

Dr. Karin Schlesier
Federal Institute for Risk Assessment, Berlin

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

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

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

Business fields

Molecular Biotechnology

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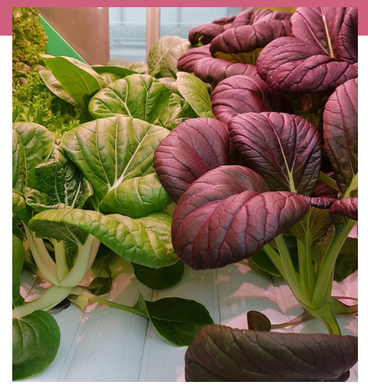
Bioproduction and Industrial Biotechnology

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.

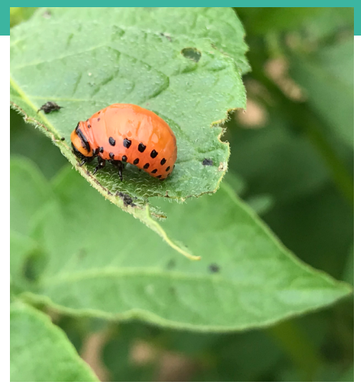
The departments and project groups involved in this business field focus on precision breeding techniques and the development and testing of GM crops. The department "New Agricultural Systems" establishes technologies such as vertical farming to provide alternative protein sources for human food. Based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

Production of Recombinant Proteins

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

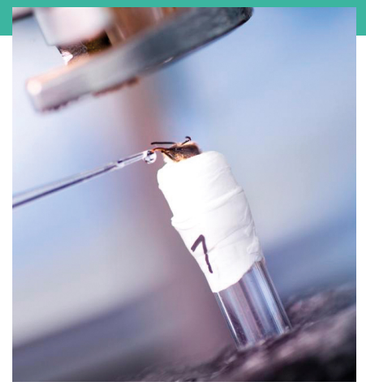
Business fields

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

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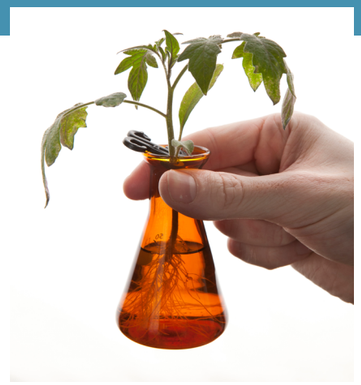

Environmental Risk Assessment of Substances

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

Food Safety and Quality

The safety and quality of food depend on the production method and on the primary and further processing of agricultural raw materials. We focus on the qualitative properties of raw materials and foods, and the damage caused by harmful substances. For example, we take existing methods used to analyze the metabolism of plant protection products in crops and farm animals and adapt them to study the metabolism of veterinary pharmaceuticals and feed supplements, and we develop cell-based alternatives to animal testing. We track breakdown and conversion products by radioactive labeling throughout the food production cycle. Within the Fraunhofer Agriculture and Food Industry Alliance, the focus is on issues along the entire food chain, with emphasis on food analysis/processing, microsystems technology and logistics. The research is being expanded to include R&D activities on the upstream and downstream areas such as agriculture or utilization networks.

Sustainable Agricultural Production of Substances

We develop across divisions concepts for the sustainable agricultural production of substances for a diversified bioeconomy: To achieve this, amongst other things, we use Fraunhofer technologies of the lead project „Cognitive Agriculture“ to meet socio-economic and ecological requirements (Community claims) with new crops, improved seeds and exposure models adapted to the new technologies. We take into account differentiated soil and microclimate properties, the use and optimization of plants for the production of valuable and active substances (Aachen and Münster), and waste and insects for obtaining protein (Gießen). Regulatory requirements arising from digital agriculture in the application of plant protection products, veterinary medicines and fertilizers, and other agricultural adjuvants, are also taken into account (Schmallenberg).

Institute management and locations

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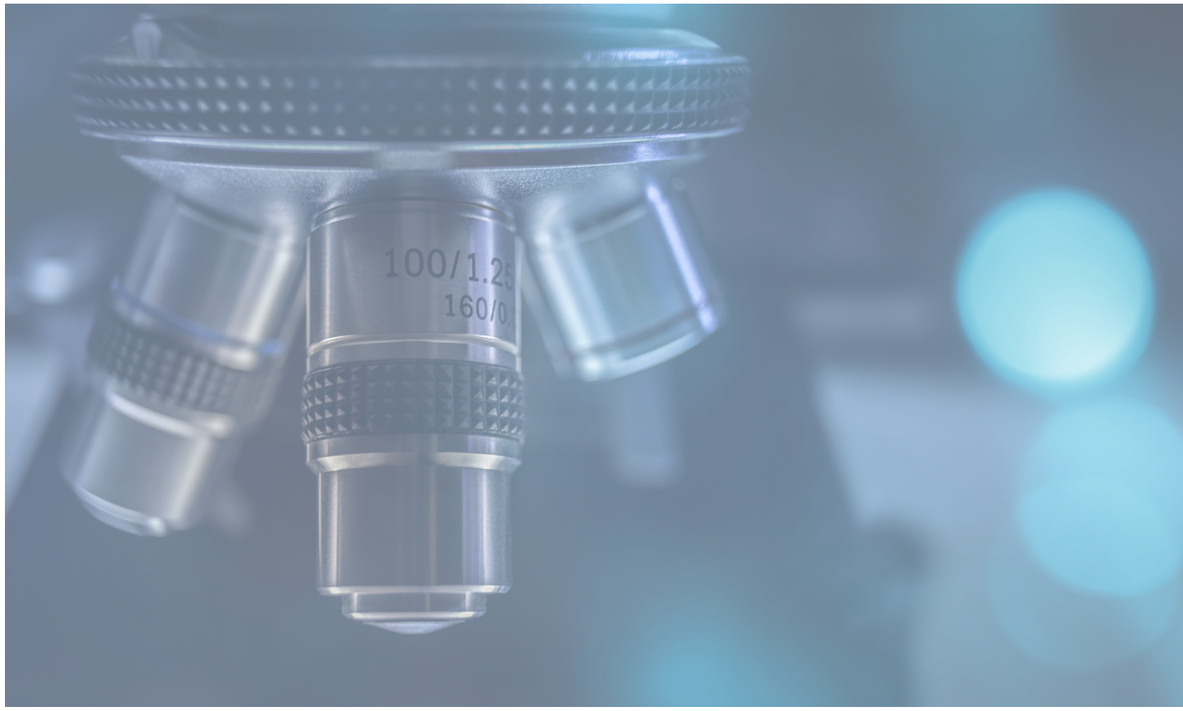
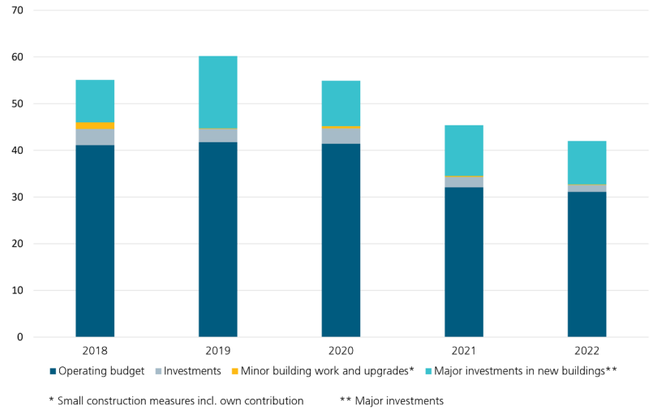


Institute data

As of January 1, 2021, Fraunhofer IME comprises the four locations Aachen, Münster, Giessen and Schmallenberg. At the turn of the year, the former Fraunhofer IME locations Frankufrt a.M., Hamburg and Göttingen became the the newly established Fraunhofer Institute for Translational Medicine and Pharmacology ITMP. Consequently, as of 2021, the budget and financial numbers are lower in comparison with previous years.

Budget

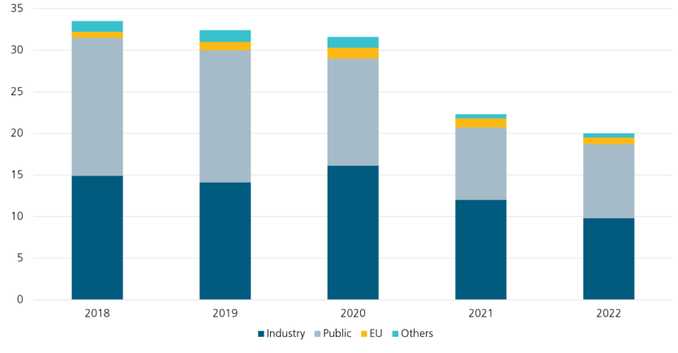
In 2022, Fraunhofer IME had an operating budget of 31.1 million euros. In addition, about 1.5 million euros were invested in equipment. Fraunhofer IME recorded an expense of 9.4 million euros for construction activities, primarily the new institute buildings in Giessen and Schmallenberg. 64.2 percent of the budget was financed by external income. Economic earnings of roughly 10 million euros remain at a constantly high level. This corresponds to an economic revenue share (Rho Wi) of 31.5 percent.



32.6 million euros

External financing

Compared to the previous year, Fraunhofer IME recorded less external financing, which particularly impacted the economic revenue share. For this, the delayed accounting due to the implementation of the Fraunhofer-Gesellschaft's enterprise resource planning (ERP) system was primarily responsible.



20 million euros

422 people
were employed at Fraunhofer IME by the end of 2022

56.2 percent
of the employees are female

Employees include:

115
Scientific staff

108
Staff in administration and infrastructure

94
Technical staff

45
Students

32
Postgraduates

28
PhD candidates

Highlight

AgriN'omics: Unique technology platform for evaluating functional substances in agriculture/aquaculture.

by Prof. Dr. Christian Schlechtriem

Aquaculture of rainbow trout..

Sustainable agriculture requires an ecological approach to production processes in order to conserve land, water and genetic resources. Numerous functional substances are used in agriculture. AgriN'omics is concerned with the holistic evaluation of these substances, their interaction and effect on metabolic processes in the organisms involved in the agricultural production process. For this purpose, Fraunhofer IME offers a broad spectrum of molecular biological methods at its four locations, which will also be used in the field of aquaculture research in the future with the establishment of a globally unique aquaculture recirculation unit in Schmallenberg in 2022.

AgriN'omics

A large number of functional substances are used in agriculture. These substances interact and influence the metabolic processes of the organisms involved in the production process. A unique method platform is available at the Fraunhofer IME for the holistic observation and evaluation of these processes: AgriN'omics. This involves the application of molecular biological methods ('omics') in agricultural research with the aim of ensuring sustainable agricultural production, producing high-quality food and raw materials, ensuring animal welfare and preserving biodiversity. In 2022, a globally unique aquaculture facility was commissioned at the Schmallenberg site, which in the future will also enable the comprehensive study of metabolic processes in aquaculture cycle systems.

Innovative research facility

The importance of aquaculture is growing steadily. In 2014, human consumption of aquaculture products exceeded that of wild fish for the first time. In order to be able to implement the 2030 Sustainable Development Goals of the Food and Agriculture Organization of the United Nations (FAO), capacities in aquaculture production must be significantly increased while conserving the required resources as much as possible. Against this background, the development of sustainable production processes is of particular importance. In recirculating aquaculture systems (RAS), the aquaculture of fish, algae or crustaceans takes place in tanks. The holding water is purified in an integrated water treatment system and then returned to the holding tanks (recirculation). The use of recirculation technology allows a significant reduction in water requirements compared to conventional flow-through systems. However, the low water exchange rates also lead to a potential enrichment of the water with organic substances such as feed and related additives, which are continuously added to the recirculation system. This requires efficient water treatment to ensure optimal husbandry conditions for the fish. Biological filter systems contribute the degradation of dissolved organic compounds from feed residues and fish excreta with the help of bacteria, which are offered the largest possible colonization area in special filters. Effective disinfection processes (e.g. UV irradiation or ozone treatment) are also available to reduce germ pressure and the pollutant load in the holding water.

Since recirculation systems have individual cleaning dynamics, the comparison of several units is necessary in the context of recirculation management studies. The test units commissioned in Schmallenberg consist of 7 identical individual circuits, which allow the comparison of treatment and control groups, each with several replicates. To minimize the effort required to conduct the studies, the size of the individual circuits (production tank size of 250 l per circuit) was kept to a minimum. The individual circuits are made of stainless steel, which allows the use of ^{14}C-labeled substances. This allows valuable information to be obtained on the fate of feed-related and biogenic substances in the production chain. The new RAS system can be operated in both freshwater and saltwater modes. Different fish species such as rainbow trout (*Oncorhynchus mykiss*), Nile tilapia (*Oreochromis niloticus*) or European sea bass (*Dicentrarchus labrax*) can be used for the feeding experiments.

Recirculating Aquaculture Systems (RAS) at Fraunhofer IME in Schmallenberg.

> **"The extensive expertise available at Fraunhofer IME in the fields of molecular biology, substance analysis and assessment, ecotoxicology and process development is unique in the world and enables develpment holistic solution concepts for the current and future challenges in agriculture."**
>
> **Stefan Schillberg**

The totality of all non-genetic, endogenous as well as exogenous environmental influences in the aquaculture system represents the "exposome" of the facility to which the animals are exposed during the production process. Modern analytical instruments available at the site can be used to quantify organic matter in water and fish tissue samples collected during the studies. The combination of highly specific analytics and isotope-labeled compounds enables the identification of metabolites of organic substances.

AgriN'omics in aquaculture research

Microbiomics: The performance of biofilters in aquaculture recirculation systems depends significantly on the composition of the microbial community and its metabolism. Substances continuously applied via the feed can influence the biofilter microbiome and thus the water purification performance of the biofilter. It can be assumed that the application of different substances (e.g. feed additives) in the recirculation system promotes the development of specific metabolizing bacteria, which leads to the degradation of the applied substances. Methods for the analysis of genetic signatures by means of high-throughput sequencing are available at Fraunhofer IME, which allow the investigation of microbial community structures (microbiome) in the filter system and offer already the possibility of performing a comprehensive examination of feed-RAS system interactions during product development.

Ecotoxicogenomics: Enrichment of recirculating water with organic substances can lead to specific (sublethal) changes in farmed fish. Ecotoxicologically relevant mechanisms of action of substances dissolved in the holding water can be detected by transcriptome studies in the context of a modified fish embryo test according to OECD TG 236 developed at Fraunhofer IME. In this way, substances that have an endocrine or immunotoxic effect, for example, can be identified. To investigate the extent to which any acute toxic changes in the fish can be attributed to the substances used in the production system, comparative studies can be carried out using water samples from the fish tank and aqueous solutions of the pure substance. The performance of water treatment processes to reduce the contaminant load in the holding water can also be evaluated by the transcriptome study. The ecotoxicogenomic evaluation method supports the development of functional substances that contribute to animal welfare and environmental protection.

Nutrigenomics: Feeds and their components can have a significant impact on animal gene expression. Functional components (immunostimulants, antioxidants, pre- and probiotics) are used in fish nutrition to improve fish growth and/or feed efficiency, stress tolerance and disease resistance. At Fraunhofer IME, transcriptomic methods are available to study the expression of specific performance-related genes as part of the development of functional feed components.

Proteomics: Fish meal has so far been considered the best source of feed protein. However, due to overfishing of the world's oceans, it is essential to reduce the amount of fishmeal in fish feed. Up to now, legumes and oilseeds in particular have been used for this reduction due to their high protein and fat content in so-called compound feeds (feed pellets). However, leaf material and other plant components can also be rich in protein. This often requires pretreatment of the plant raw materials to reduce the content of antinutritive substances. Technical solutions for obtaining high-quality plant proteins that are free of contaminants and antinutritive substances have been developed at Fraunhofer IME in Aachen. In addition, insects are being investigated as an alternative source of protein for animal feed as part of biotechnological research at the site in Giessen. The protein extracts obtained from plant and animal matrices can be analyzed by mass spectrometry with subsequent peptide-protein mapping in Schmallenberg.

With the innovative aquaculture test facility and the modern chemical-analytical, microbiological and molecular biological laboratories at the Schmallenberg site, Fraunhofer IME has the possibility to offer its customers a comprehensive evaluation concept for aquaculture in the field of AgriN'omics. Furthermore, the studies can all be carried out under GLP.

AE

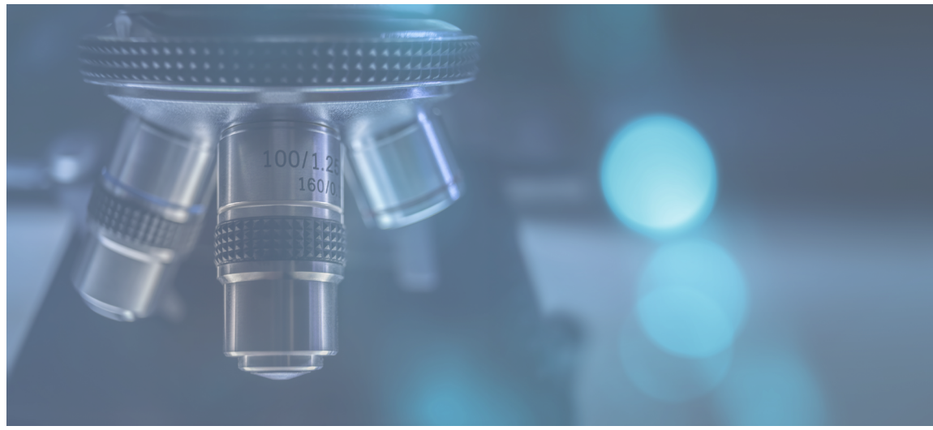
With the innovative aquaculture recirculation system, we offer our customers a comprehensive concept for the evaluation of functional substances for use in aquaculture."

Christian Schlechtriem

Fish fillet.

Use of feed pellets in commercial aquaculture.

Insights into our research



Pharmaceuticals are becoming more effective – does this also apply to unwanted environmental side effects?

Determination of the anaerobic degradation of chemicals in liquid manure

New approaches to environmental hazard prediction in aquatic model organisms

Reviewing OECD Test Guidelines relevant to environmental assessment with regard to the state of the art in science and technology

Regional added value with medicinal plants in the Rhenish mining area

We explore new ways - crowdfunding campaign "2detect"

Active and passive targeting to combat cancer

Microorganisms to control phytopathogenic fungi

Investigations into the translational potential of wolf spider venom

Environment-friendly insecticide

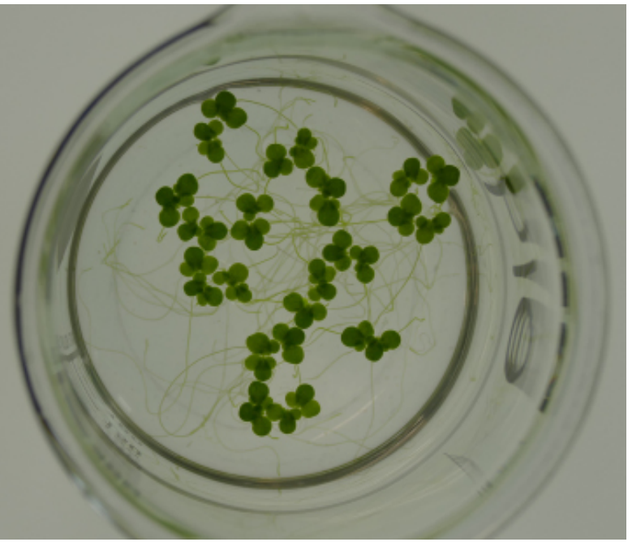
Pharmaceuticals are becoming more effective – does this also apply to unwanted environmental side effects?

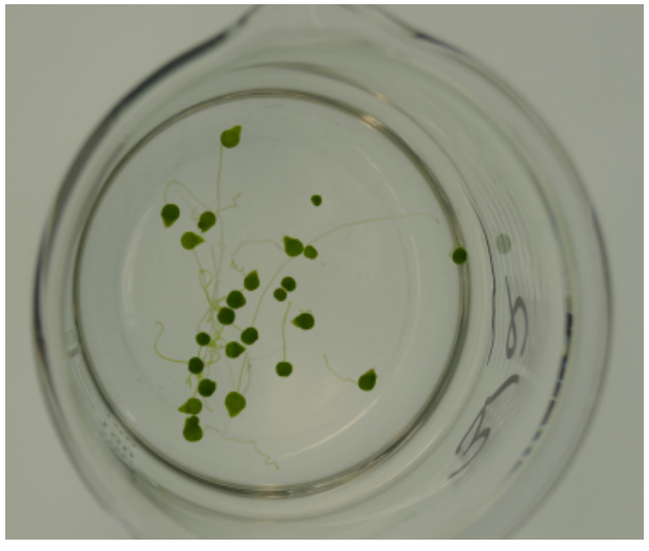
by Dr. Elke Eilebrecht

In 2006, the European Medicines Agency adopted guidance on the environmental risk assessment of medicinal products for human use. Since then, numerous active pharmaceutical ingredients with specific modes of action (MoAs) have been approved, which can cause adverse effects on organisms in the aquatic environment even at very low concentrations. This raises the question: Does the environmental risk assessment based on studies requested by the authorities still provide sufficient protection?

Like other chemicals, medicinal products for human use must be evaluated for their side effects on the environment. The guidance developed for this purpose by the European Medicines Agency (EMA) requires an assessment of the hazards and risks of the active substances. The guidance has been in force since 2006, and since then medicinal products must be tested for their effect on algae, water fleas and fish before they are approved and marketed. This is performed according to standardised guidelines on the chronic toxicity of active substances such as the Algae growth inhibition test according to OECD TG 201, the *Daphnia sp.* reproduction test according to OECD TG 211 and the Fish early life stage study according to OECD TG 210. Before the guidance was approved, these three test systems provided sufficient informative value for most substance classes. Only for a few substance classes such as endocrine disruptors or antibiotics were adapted strategies required.

A literature study conducted by our staff and colleagues at the Fraunhofer ITMP in Hamburg (at that time still IME Screening Port) as part of a project supported by the Federal Environment Agency (UBA), identified 448 active substances that have been approved since 2006. Most of these active substances were developed with the aim of being more specific and effective so that they could be administered to humans in the lowest possible doses. This raises some questions: Does this increased effectiveness also apply to their side effects on environmental organisms? Perhaps there are new substance classes or MoAs that were not even considered in 2006? And: Is the test strategy of the guidance developed in 2006 still sufficient to adequately assess the hazards and risks of the new generation of active substances? These questions were investigated in this project.





Lemna gibba *(humped duckweed) in the control (left) and in the highest test concentration (right) in a test with the cholesterol-lowering drug rosuvastatin.*

Does the current EMA guideline still offer sufficient safety?

First, in a literature study we identified the substance categories in which most substances have been newly approved and which have not yet been considered for an adapted assessment strategy. These include, among others, the oncologics and the cardiologics. Furthermore, test systems that are particularly sensitive to the specific MoAs should be identified in order to check whether the risk of these substances can also be better assessed with an adapted assessment strategy.

The growth inhibition test with the duckweed *Lemna minor* and *Lemna gibba* according to OECD TG 221, and the Fish embryo toxicity (FET) test according to OECD TG 236 with additional sublethal endpoints, were identified as potentially sensitive test systems. Furthermore, we wanted to check whether the comet assay, which is routinely performed with mammalian cells according to OECD TG 489, can be adapted to environmentally relevant cell types to predict potential effects of oncological drugs on environmental organisms. Accordingly, this test was performed with freshly extracted cells of *Daphnia magna* and with a liver cell line of the zebrafish *Danio rerio.* In cooperation with ECT Oekotoxikologie GmbH in Flörsheim, these test systems were applied to selected pharmaceuticals and compared with existing data collected in accordance to the EMA guideline. The aim was to determine whether the strategy described in the guideline still provides enough certainty in the safety assessment of active substances of the new generation or whether an adapted assessment strategy is necessary based on the results obtained for those substance classes.

The study with the duckweed offers the potential to be integrated into an assessment strategy.

The test with Lemna sp. according to OECD TG 221 demonstrated that it was particularly sensitive to a specific class of active substances. It was particularly striking that a high sensitivity was shown in the growth of duckweed when the test was carried out with cholesterol-lowering agents from the statin class. In humans, the specific MoA causes the regulation of lipid metabolism by inhibiting an enzyme that catalyses the cholesterol synthesis. In duckweed, this enzyme is also involved in lipid and sterol metabolism, thus influencing development and growth. This hypothesis was confirmed in the guideline studies with the statins pitavastatin, atorvastatin and rosuvastatin. In comparison with data required in the risk assessment for algae, water flea and fish, the study with duckweed proved to be very sensitive to rosuvastatin. However, since the other two statins were approved before 2006, no comparison could be conducted for these substances. We would like to fill these data gaps in cooperation with the UBA in order to strengthen our hypothesis.

Lemna sp. also proved to be sensitive to other substance classes. The oncological agents of the folic acid antagonist class also showed a strong effect on *Lemna minor* and *Lemna gibba*. This is probably due to the effect of the substances on fast-growing organisms, which include duckweed.

With the other test systems (fish embryo test and comet assay), studies were also carried out with potentially specifically acting drugs. However, no effects were shown here that necessitate an expansion of the test strategy for pharmaceuticals to include these test systems. However, with our study we found that for the hazard and risk assessment of medicinal products, an extension of the required studies by including the duckweed test is useful in specific cases to ensure comprehensive protection of the aquatic environment. However, there are still some data gaps that need to be filled in the future. We see this as our mission!

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Determination of the anaerobic degradation of chemicals in liquid manure

by Dr. Dieter Hennecke

Chemicals are used in a wide variety of areas in agricultural livestock farming. Manure represents the main sink for most of these substances. However, in order to enable manure to be used as a fertilizer in agricultural soils, it is necessary to investigate the fate of the substances in manure. After more than 10 years of research and development, the OECD Guideline 320 has now been introduced, which describes a standardized method for determining the fate of substances in manure and enables the generation of reliable data for regulation purposes.

Liquid Manure is a Problematic Matrix

One of the greatest challenges in developing a guideline for such a problematic matrix was the manure itself. In addition to the animal species (e.g. pig or cattle), the type of husbandry (e.g. milk production, breeding, fattening, feeding) has an influence on the composition of the manure. There are also different storage conditions and seasonal variations (e.g. outdoor breeding vs. stabling). To solve the problem, Kreuzig et al., 2010, presented methods for producing a reference liquid manure. At the same time, investigations were carried out at Fraunhofer IME to examine the actual variability of liquid manure in agricultural practice (Weinfurtner, 2011).

As a result, experiments were carried out with manure from 10 different locations, 2 animal species (pigs, cattle) and 2 reference substances (Junker et al. 2020, Hennecke et al. 2015, Herrchen et al. 2016). It was shown that manure from different animal species produced significant differences in the test results. For other parameters, such as seasonal influences or different animal husbandry, results did not exceed the general range of variation of the test. Therefore, the OECD Guideline 320 stipulates testing in only one manure per animal species, but manure from all animal species relevant to the test substance must be examined separately. The only specification for the test manure is a specific content of solids, which must be confirmed in the laboratory.

Test procedure

The test procedure itself is incubation of the test substance in the manure under semi-static or flow-through conditions. Basically, the test setup is similar to that of the OECD test guideline 307 for anaerobic degradation in soil.

Incubation takes place under strictly anaerobic conditions at a standard temperature of 20°C. Before the test substance can be applied, a 3-week pre-incubation is required so that the anaerobic conditions can be established. The test itself runs for up to 90 days, or longer in specific justified cases. Due to the anaerobic test procedure, methane (CH_4) must also be determined in addition to carbon dioxide (CO_2). In order to distinguish the CO_2 and CH_4 formed by the degradation of the test substance from that naturally formed by the liquid manure, ^{14}C radiolabelled test substances must be used.

Compared to soil, some adjustments had to be made when handling liquid manure. A special procedure had to be developed for the production of sterile samples using an autoclave. In addition, liquid manure binds relevant amounts of CO_2. Consequently, for an accurate mass balance after sampling, the CO_2 produced must be released using mineral acid. If the test substance is sensitive to hydrolysis under acidic conditions, additional samples should be prepared to determine mineralisation and metabolism in separate samples. Specific parameters were also defined for the characterization of the liquid manure, which differ from those of the test with soil.

The reproducibility of the method was finally checked and confirmed in an international ring test (Juncker et al. 2016). This paved the way for the new OECD 320 "Anaerobic Transformation of chemicals in Liquid Manure", which was adopted on June 30, 2022.

In the period between the publication of the ring test results and the adoption of the guideline, another aspect was included which addressed the issue of the characterization of non-extractable residues (NER) formed in the test, which eventually found its way into the guideline. In the latter, Fraunhofer IME is also actively researching and, with the results of a research project funded by the Federal Ministry of the Environment, is currently setting the standard for regulation (UBA FKZ 3718 65 407 0, Consideration of non-extractable residues (NER) in PBT-assessment, 2019 - 2022, report to be finalized). Since this method has so far only been evaluated for soils, the need for further research is already implied.

AE

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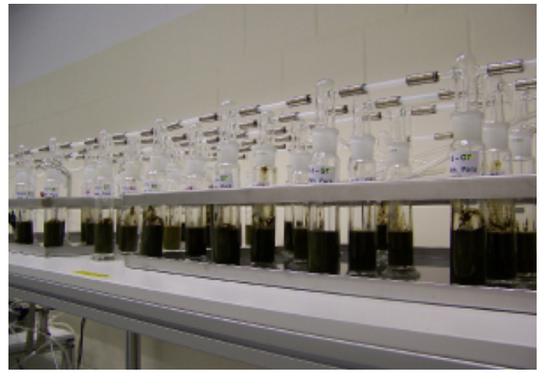

System of incubation vessels at Fraunhofer IME in Schmallenberg.

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New approaches to environmental hazard prediction in aquatic model organisms

by Dr. Sebastian Eilebrecht

For the marketing authorization of chemical substances, the data sets required by regulation usually include information on acute and chronic toxicity in aquatic model organisms at all levels of the food chain. In particular, tests for chronic toxicity are time-consuming and costly, but rarely provide evidence of a substance's harmful mechanism of action. The Fraunhofer Attract group Eco'n'OMICs at the Schmallenberg site of Fraunhofer IME has developed approaches for the detection of mechanisms of action in model organisms of all trophic levels. For this purpose, OMICs methods are also applied to reduced guideline tests for organisms that have so far been rarely investigated genomically, in order to predict harmful mechanisms of action on the basis of gene expression changes.

Identification of molecular endpoints at all levels of the food chain

A major goal of regulatory environmental risk assessment of substances is to minimize adverse effects on the living environment. Especially chronic effects, which can already be triggered by relatively low substance concentrations over a long exposure period, often lead to an impairment of the ecosystem. Such effects can only be detected in ecotoxicological tests with significant expenditure of time and effort. Due to the limited number of endpoints in such tests for chronic toxicity, no – or only few – conclusions can be drawn about the toxic mechanism of action of a substance, depending on the test. However, knowledge of the molecular mechanism that causes adverse effects in organisms in the environment would be of great benefit both in pre-regulatory substance development and in environmental hazard assessment.

Specific mechanisms of action cause a characteristic molecular response in the organism that can be measured as a change in gene expression. If a mechanism of action is unknown, the addressed target genes are also unknown initially. Therefore, measurement of the molecular response should not focus on a few candidate genes, as is the case with conventional methods, but should be based on untargeted methods to measure all genes. These requirements are met by OMICs methods, which are concerned with analyzing the entirety of a particular biomolecule class in a sample: transcriptomics measure changes at the level of RNA and proteomics measure changes at the level of proteins. In genomically well-studied model organisms, gene functions are known, so that from the change in gene expression considered as a whole, impaired biological processes and thus the mechanism of action can be inferred.

Attract's Eco'n'OMICs group is focused on integrating OMICs methods into regulatory guideline assays to capture molecular mechanisms of action and derive biomarkers for testing and prediction. To maximize time savings and throughput, guideline tests are shortened and miniaturized to measure compound-induced effects via transcriptomics and proteomics. In this context, tests in ecotoxicologically relevant aquatic model organisms of all trophic levels, such as the duckweed *Lemna minor*[1], the water flea *Daphnia magna*[2] or the embryo of the zebrafish *Danio rerio*[3] are established and further developed.

Assignment of gene functions in non-standard organisms

In model organisms that have been rarely studied genomically to date, such as duckweed *L. minor*, the function of specific genes and gene products is usually not yet known, i.e. the genome has not yet been functionally annotated. Thus, it is not possible here to infer from the gene expression response to the impaired biological processes and thus the toxic mechanism of action, using conventional evaluation methods.

In the Attract group Eco'n'OMICs, the seven-day OECD 221 guideline test for the investigation of toxicity in *L. minor* was shortened to three days and combined with transcriptomics and proteomics as part of a master's thesis. It was shown using reference compounds that the low effect concentrations of the original test setup in this shortened test were sufficient to obtain significant, concentration-dependent and specific responses at the gene expression level. To now deduce mechanisms of action from these responses, a bioinformatics pipeline was developed for functional annotation of the genome. This pipeline is based on the homology principle, i.e. the assumption that genes or gene products with a similar sequence also perform a similar function. Thus, for all the genes of duckweed *L. minor*, genes with a very similar sequence were identified in genomically well-studied plants and their biological function was assigned to them. With this assignment, associated impaired biological functions could be identified in *L. minor* for reference compounds with known mechanism of action, thus validating the functionality of the pipeline.

Duckweed (Lemna minor) as a model organism for aquatic plants.

The developed pipeline is applicable to all – including non-standard organisms – given a known genome sequence, thus opening up the use of functional OMICs methods to study a wide range of ecotoxicologically relevant species. The results of such studies contribute significantly to the integration of molecular endpoints in guideline tests and thus to improved quality in substance-based environmental hazard assessment.

AE

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Reviewing OECD Test Guidelines relevant to environmental assessment with regard to the state of the art in science and technology

by Prof. Dr. Christian Schlechtriem

OECD Test Guidelines represent an important tool to evaluate the impacts of chemicals on the environment. The update of the Test Guidelines is organised by the Working Party of National Coordinators for the OECD Test Guidelines Programme (WNT) and the OECD Secretariat. The procedure relies on proposals from OECD member countries and does not contain a regular update check. The German Environment Agency contracted Fraunhofer IME, Fraunhofer ITEM and Ramboll to identify and prioritise any potential updates needed and to come up with a list for potential actions.

Reviewing OECD Test Guidelines relevant to environmental assessment

The OECD Test Guidelines (TG) for Chemicals are a specific tool for assessing the potential effects of chemicals on human health and the environment. These internationally standardised and accepted TGs for the testing of chemicals are used by industry, academia and authorities in the testing and evaluation of chemicals (industrial chemicals, pesticides, biocides, pharmaceuticals, etc.). As part of the OECD Test Guidelines Programme (TGP), the OECD TGs are developed and updated by the OECD Working Group of National Coordinators for the OECD Test Guidelines Programme (WNT). To ensure that the OECD TGs reflect the state of the art in science and technology and meet the regulatory requirements of member countries, the OECD TGs are to be continuously expanded and updated. As a regular review of the OECD TGs is not a standard requirement, it is the responsibility of OECD member countries to identify, propose and implement the projects necessary to update the TGs. Therefore, the focus is often on guidelines in which member countries have a particular interest and for which sufficient resources are available to initiate a revision process. Test guidelines that are used less frequently or are of low interest tend to be neglected in this approach, although a revision may be necessary. The aim of this project was to identify OECD TGs that are not state of the art. Only OECD TGs were considered that refer to the effects of chemicals on biotic systems, to the behaviour and fate of chemicals in the environment or to their physicochemical properties when used for environmental risk assessment.

Identification of OECD Test guidelines that are not state of the art

An online survey had been conducted during the course of May - July 2021 to collect potential update needs and suggestions. Based on a detailed questionnaire the needs for TG revisions were identified. The joint efforts led to a total number of over 500 individual suggestions. In order to work towards a prioritization of the update needs, the reported suggestions were shared with the stakeholders for a pre-evaluation of the general significance of an update need. Both surveys were open to all interested parties including industry, science, contract labs, NGOs and authorities. After completion of the surveys, the results were discussed in three thematic workshops covering one of the three different blocks ("fate", "terrestrial" and "aquatic") each and recommendations for the revision of the OECD TGs were developed and prioritised. Following the workshops, two presentations were given to the National Coordinators involved in the OECD Test Guidelines Programme (WNT) to summarize the outcome of the project, and to lead an open discussion on the use of the results obtained for the future TG revision process.

Conclusions

A high number of suggestions to further improve OECD TGs were received (max. 55 per TG) which were further evaluated regarding their relevance for the future TG revision process. A high number of respondents contributed per TG (5-35). The pre-evaluation of the suggestions resulted in many comments expressing agreement/disagreement with the update suggestions and these provide a comprehensive basis for further discussion. The survey respondents expressed a high interest in OECD Expert Group participation.

There was agreement that there is a high demand for updating certain TGs and efforts should be undertaken to establish a regular process to check update needs and to support the required revision process.

The research project was funded by the German Environment Agency under contract number FKZ 372 064 4080. Further information on the project are presented on the related website. The final report of the project, including a comprehensive overview of the results obtained, will be published by the German Environment Agency in the near future.

AE

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Regional added value with medicinal plants in the Rhenish mining area

by Dr. Lena Grundmann

Herbs and medicinal plants offer an almost infinite source of pharmaceutically useful substances for phytopharmaceuticals and have a high value-added potential in the agricultural, cosmetics and food industries. We intend to use this potential as one element to establish a model region for the bioeconomy in the Rhenish mining area and thus help to manage structural change.

Of the approximately 50,000 plant species used for medicinal purposes worldwide, only 900 species are cultivated and currently about 90 percent of the medicinal plants needed in Germany are imported. In addition, most of the raw material required for phytopharmaceuticals derives from wild collections. This approach is neither sustainable nor ecologically sound and therefore wild collections have been severely restricted as a result of the Nagoya Protocol coming into force. Furthermore, the active ingredient content in wild plants varies considerably, often leading to unacceptable quality losses.

In the department "Functional and Applied Genomics", to-gether with other partners Fraunhofer UMSICHT and Forschungszentrum Jülich, we therefore dedicated ourselves to the sustainable production of sufficient quantities of high-quality medicinal plants in the BMBF-funded project "Circular PhytoREVIER". We focus our activities on the establishment and consolidation of a highly efficient and economically viable process chain: from the breeding of yield-optimized plants and the development of new and effective cultivation and harvesting technologies to the efficient extraction and supply of the active ingredients from the raw material. The focus of our R&D activities is on transforming valuable medicinal plants into crops adapted to agricultural conditions by means of selection and modern plant breeding (including proof-of-concept studies using genome editing). Together with our partners, we want to develop innovative processes for the targeted control and increase of the active ingredient content through biological, chemical and physical stress.

Focus plant arnica

One of the focus plants is the medicinal plant *Arnica montana* L. Its bright yellow and aromatic flower heads are used in a variety of phytopharmaceutical preparations. For skin application, they are processed into tinctures as well as ointments, creams or gels. The main field of application is in all non-bleeding, i.e. blunt injuries such as bruises, swellings, sprains and bruises. The pharmacological properties of the flower heads are primarily attributed to the sesquiterpene lactones helenalin and dihydrohelenalin and their derivatives. In nature, these serve the arnica plants as antifeedants against herbivores and defense against microorganisms.

It is known that both the composition and content of sesquiterpene lactones (SLs) depend on a variety of different abiotic and biotic factors that control their biosynthesis and accumulation. In flowers, SL content varies from 0.3 to 1 g per 100 g dry weight. The European Pharmacopoeia (Ph. Eur. 11.0 Arnica flowers No. 1386) requires a minimum content of sesquiterpene lactones of 0.4 g per 100 g in the dried drug Arnicae flos (arnica flowers). Depending on the origin, two different chemotypes are distinguished, which are clearly differentiated in their SL composition: *Arnica montana* subsp. *montana* of Central European origin has mainly helenalin/esters and *A. montana* subsp. *atlantica* of Spanish origin has dihydrohelenanin/esters as main sesquiterpene lactones (Fig.1A).

Sesquiterpene lactone biosynthesis in arnica: first steps elucidated

Knowledge of the biosynthesis of desired products is an essential prerequisite for innovative breeding of yield-optimized plants. For *Arnica montana*, the biosynthesis of sesquiterpene lactones (SLs) has not yet been elucidated. Based on studies in closely related species, scientists assume that the initial steps of biosynthesis are conserved in the Asteraceae family, they proceed identically up to the intermediate product germacrene A acid (GAA). For arnica, the genes responsible for this process have not yet been described and characterized, and no genomic sequences of Arnica are available in public databases. Therefore, we used sequence data from closely related species such as sunflower (*Helianthus annus*) to derive the corresponding genes from arnica. In this way, we started by generating and sequencing fragments of the corresponding genes. With the help of various PCR techniques, we succeeded in completing the gene sequences in the next step. Thus, in both chemotypes we identified seven genes coding for key enzymes of terpene biosynthesis and ten candidate genes possibly coding for enzymes of helenalin biosynthesis.

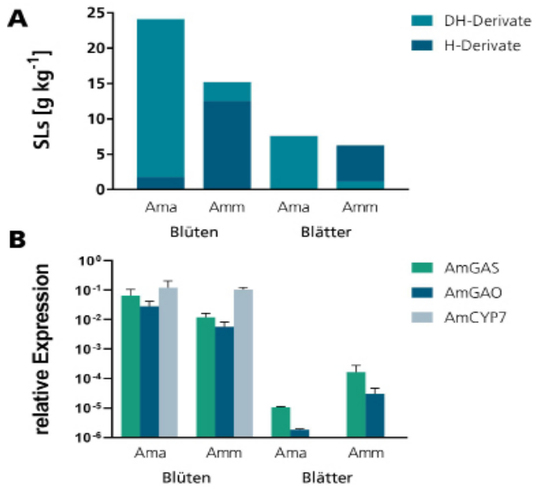

Fig. 1: SL content in flowers and leaves of two Arnica chemotypes A. montana subsp. montana (Amm) mainly helenalin derivatives, A. montanta subsp atlantica (Ama) mainly dihydrohelenaliv derivatives (A). Comparative expression analysis of potential SL biosynthetic genes AmGAS, AmGAO, AmCYP7 *in flowers and leaves (B).*

We can detect SLs in both flowers and leaves of arnica plants, with higher content in flowers (Fig.1A). These results can be explained by biosynthesis in both organs and/or interorgan transport. To verify this, we performed expression analyses: *AmGAS*, *AmGAO*, and *AmCYP7* genes are expressed more than 100-fold higher in flowers than in leaves (Fig.1B). The conclusion: SLs biosynthesis is enhanced in the flower; however, it also occurs in the leaf; in addition, SLs could also be transported from the leaf to the flower.

For the candidate genes, we also used expression studies to clarify the exact nature of the involvement of the gene or gene product in the biosynthetic pathway. Scientists usually use heterologous expression systems such as the yeast *Saccharomyces cerevisiae* for these analyses. Fraunhofer IME in Münster has a yeast production strain specifically designed for the biosynthesis of selected secondary metabolites. We stably integrated the coding sequences of the candidate genes, either individually or in combination, into the yeast genome. A few days after induction, we harvested the cultures, extracted potential biosynthetic products and performed GC/MS analysis. Thus, AmGAS1 was identified as a functional germacrene synthase and, based on this, AmGAO1 was also characterized as a functional germacrene A oxidase (Fig. 2).

The first steps of SL biosynthesis towards GAA in arnica could be successfully elucidated and serve as a basis for the characterization of additional identified candidate genes (*AmCYPs*) for the subsequent steps towards the synthesis of active helenalin and dihydrohelenalin derivatives and for the establishment of a cell culture-based drug production platform.

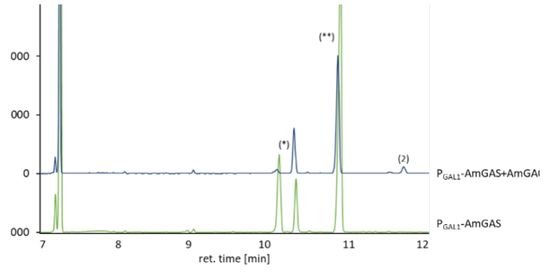

Fig. 2: By GC/MS analysis, a first precursor (germacrene A, peak (1)) of SL biosynthesis was identified in AmGAS and AmGAS-AmGAO expressing yeast cultures. According to the additional AmGAO gene present in AmGAS-AmGAO expressing yeast cultures, another peak (2) was detected here, which is characteristic of Germacrene A acid (GAA).

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We explore new ways - crowdfunding campaign "2detect"

by Lena Julie Freund

With the crowdfunding competition 2022 "Science-ForGood", the Fraunhofer Future Foundation involved general public in its decision on the funding allocation for the first time ever. With their donation, a large number of individuals (the crowd) decided whether a project was convincing and should be carried out. Crowdfunding is often seen as an early market indicator. Together with five other Fraunhofer institutes the "2detect" team from Fraunhofer IME joined the competition. With the project idea: "Covid or flu? With a 2in1 test reliable and fast to the right treatment" the team was successful.

Fever, cough or cold – flu or corona, which is it? In autumn and winter, when both waves coincide, it is difficult to make a diagnosis based on the symptoms. However, this is important for the rapid and proper treatment especially for at-risk groups including older people, people with health conditions and young children under 5 years of age. PCRs are used for differential diagnosis in such cases, but this method is laborious, expensive and time-consuming. A correct and fast result is important to choose the right treatment. High infection rates quickly lead to overloads of medical staff, in test centers and laboratories. The result: valuable time is lost. We are therefore developing a 2in1 test that will enable us to distinguish between COVID and influenza simultaneously, reliably and quickly.

Simple procedure

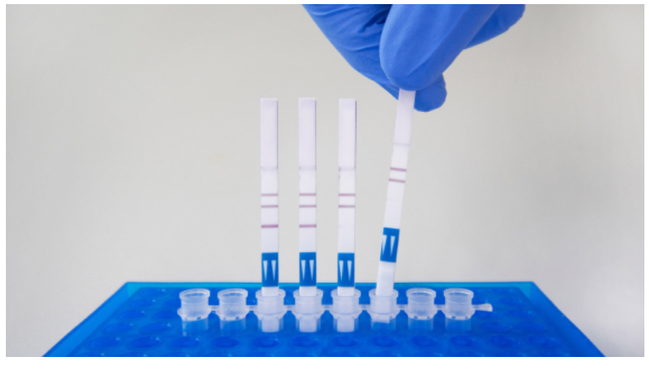
The test method we chose is called LAMP (loop-mediated isothermal amplification). It is more sensitive and reliable than antigen rapid tests as known from the test centers, but simpler and faster than the gold standard PCR. We have already developed the LAMP test for the different SARS-CoV-2 variants. The idea for the crowdfunding campaign was the 2in1 combination with the detection of influenza. As with the other test methods, a simple swab from the nasal or pharyngeal cavity is transferred into a special buffer and used for our LAMP. In contrast to PCR, however, the sample does not have to be prepared in a complex manner. It is sufficient to heat it briefly in a simple heating block. The viral genetic material is released. In the next step, as in PCR, the viral genetic material is amplified. For a reliable result, two independent, conserved regions of the viral genome are amplified simultaneously so that, even if viral variants occur, the test remains reliable. In our LAMP reaction, we use Bst DNA Polymerase I to amplify the viral genome. It originates from the thermophilic bacterium *Geobacillus stearothermophilus*. The functionally optimized variant of the large subunit used operates in a temperature range of around 65 °C and has a superior specificity. To further improve specificity, the Bst DNA polymerase possesses an additional "warm start" modification: this polymerase does not operate at room temperature, thus preventing the non-specific incorporation of deoxynucleoside triphosphates. In LAMP, the amplification of the nucleic acid segments takes place in a constant reaction known as isothermal amplification rather then in cycles as in PCR. The isothermal amplification also can be carried out in a simple heating block.

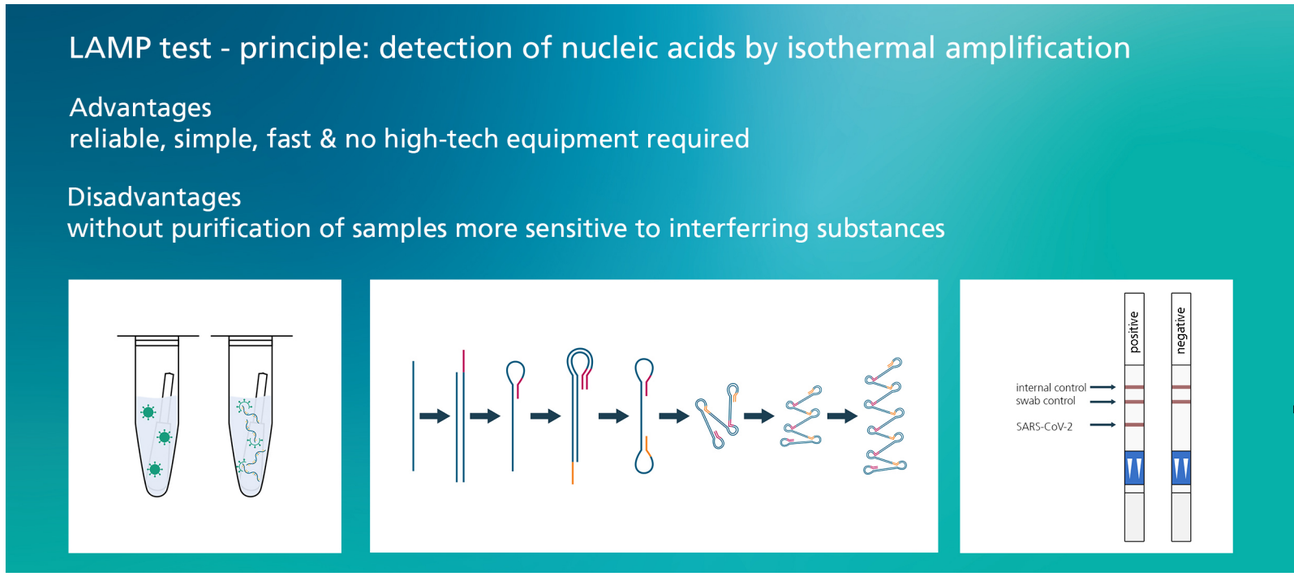
We have already developed the LAMP for the Corona virus variants. The successful crowdfunding campaign now helps us to combine it 2in1 with influenza.

Rapid visualization

The product could be detected, analogous to PCR, using special thermal cyclers, by measuring fluorescent markers. However, we have chosen a simple method of visualization that does not require any expensive equipment: the lateral flow test. It combines thin-layer chromatography with immunostaining, and "only" the human eye is used for evaluation.

The sample is applied to the test stripe and migrates in the buffer to the conjugate area due to capillary forces. Here, gold particles to which a specific antibody (AK) has been coupled are placed. Once the sample fluid hits this area, the gold-AK conjugate gets resuspended, allowing interaction between labeled viral material and the antibody. The mixture continues to migrate to the reaction area, a small section on which a capture protein has been immobilized. Here, the gold-AK viral material is bound and enriched, resulting in a stain, the familiar red line: the sample is positive.





A major advantage of the LAMP: high-tech equipment is not required, a simple heating block and pipettes are sufficient.

Reliable results

In addition, two further lines become colored. One is the internal control line, which indicates the correct use of the test strip. Second, another control line that documents the presence of the human actin gene from mucosal cells in the swab. This serves as proof of correct sampling and test functionality and makes our LAMP test particularly reliable. In numerous laboratory tests, we have been able to reliably detect samples with very low SARS-CoV-2 loads using our LAMP. The detection limit is approximately 10^4 viral copies per milliliter of sample, which is a factor of one hundred to one thousand below the threshold value described by the Robert Koch Institute (RKI) as just infectious. Clinical patient samples were also analyzed - the test proved to be sensitive and specific and showed very good agreement with reference results from PCR. Different virus variants were very well detectable.

Outlook 2in1: The Covid and Influenza LAMP test

We have already developed the LAMP for the Corona virus and its variants. The successful crowdfunding campaign now helps us to combine our test with the simultaneous detection of influenza. Influenza has different subtypes, two of which, influenza A and B, cause most severe infections. Therefore, we chose A+B for our 2in1 test. For the 2in1 combination we need a new test strip that additionally shows the presence of influenza viruses on a separate line. This is being developed together with a cooperation partner. Once the strip is ready, it must of course be extensively tested in the laboratory. Here, we focus the analyses on the following questions: How sensitive is the new flu test? Sensitivity indicates the percentage of infected persons in whom a test actually detects the infection. Can our combination test reliably distinguish between covid and influenza in one and the same sample? If both viruses – influenza and SARS-CoV-2 – are present in the sample, do both lines appear on the test strip?

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Active and passive targeting to combat cancer

by Dr.Matthias Knödler and Dr. Henrik Nausch

For the longest time, the therapy of numerous types of cancer was almost exclusively based on the use of unspecific drugs that can damage both the tumor as well as healthy tissue, which is accompanied by severe side-effects and can lead to a lower life expectancy of the patients. Therefore, new therapeutic concepts rely on the targeted delivery of the drugs to the tumor by means of two strategies: active and passive targeting. Both strategies are being studied as part of the Research Training Group "Tumor-targeted drug delivery" at the Institute for Experimental Molecular Imaging at RWTH Aachen University. Fraunhofer IME as part of the Research Training Group focuses on the production of the aforementioned drugs in plant-based expression systems.

Active tumor targeting using plant-made, recombinant immunotoxins

Active tumor targeting is based on the coupling of a toxic drug as payload to an antibody, which selectively binds to surface structures – also known as antigens – of cancer cells. These are only present on the cancer cells but not on normal cells. Such antibody-drug conjugates (ADCs) have already been approved for therapeutic treatment in humans. However, the clinical application is currently limited because of the high manufacturing costs that arise from the very complex production method. The antibodies are produced in mammalian cells which are not capable of expressing drug payloads that are toxic for them. Hence, the payloads are synthetically manufactured and then coupled in vitro with the isolated antibodies produced in mammalian cells – a very expensive process.

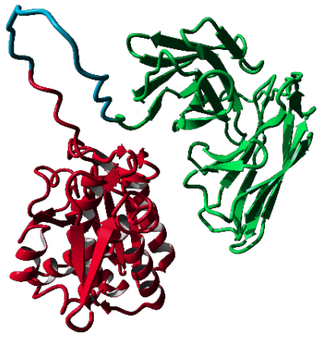
At Fraunhofer IME, we focus on developing so called recombinant immunotoxins (RITs) as alternatives for ADCs. Here, we leverage the property of plant cells to produce proteins that are toxic towards mammalian cells by storing them in vacuoles. This allows us to jointly produce the antibody and the toxic payload as a fusion, thus omitting the very complex coupling process. For the production of novel RITs, we employ a highly flexible framework that enables an easy substitution and combination of antibody and toxin components. Using this strategy we were able to identify an active RIT against acute monocytic leukemia by generating and examining more than 120 individual RIT constructs. In doing so, the anti-CD64 antibody H22 in combination with the mistletoe lectin viscumin as active toxin was identified as RIT candidate that can be produced as a fusion protein in plants in high quantities. The anti-CD64 antibody viscumin RIT will now be used in animal studies for the treatment of AML.

Passive tumor targeting using plant-made ferritin nanoparticles

Passive targeting of tumors can be enabled by means of the "enhanced permeability and retention" (EPR) effect. This effect arises from an increased vascularization of tumor tissue in comparison to normal tissue, which leads to an enhanced accumulation of certain substances. Ferritin nanoparticles, which are result from the assembly of individual ferritin protein subunits and natively serve as iron carriers, are such a substance that accumulates in the tumor tissue via the EPR effect. The targeted accumulation of the ferritin nanoparticles is additionally amplified by receptors for ferritin which are enriched on their surface of tumor cells and which facilitate the absorption of ferritin nanoparticles into the tumor cell. For cancer therapy, the iron atoms are substituted with a toxic agent, thus mediating the targeted transport to the cancer cell. Currently, ferritin is produced in bacteria and yeasts, but due to high costs it is currently not yet used in clinical applications.

We have therefore established a simple method for the production of human ferritin (FTH1) in plants. We were able to express and accumulate high amounts of FTH1 nanoparticles in the apoplast of plant cells. Moreover, we have developed a simplified process that allows to isolate the nanoparticles from plant extracts based on the size of the FTH1 nanoparticles, which substantially reduced the production costs to less than a tenth compared to current sales prices of commercially available recombinant ferritin. In addition, we were able to load the FTH1 nanoparticles produced in plants with doxorubicin for the treatment of hepatocellular carcinoma. The plant-derived FTH1 nanoparticles will now be loaded with other pharmaceutical agents for further studies.

Plant cell packs for the screening of the accumulation of recombinant ferritin in plants.



3D structure of a recombinant immunotoxin.

Tobacco plants inside a phytotron for the expression of recombinant ferritin.

Further literature

Knödler, M.; Buyel, J. F.
Plant-made immunotoxin building blocks: A roadmap for producing therapeutic antibody-toxin fusions (2021) Biotechnol Advances, 47, 107683. DOI: 10.1016/j.biotechadv.2020.107683.

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Microorganisms to control phytopathogenic fungi

by Joana Bauer

Due to the climatic changes of our time, extreme weather events increase. This leads to multidimensional plant stress. Under the influence of hot spells and droughts as well as extreme rainfalls, indigenous and foreign crop pests gain ground. These include fungal pathogens, which impair crop yields in conventional agriculture and organic farming. The agricultural sector is facing increasing problems due to resistance developments of these pests. Therefore, alternative fungicides are needed.

Chances and Challenges of Agriculture

Approximately 35 percent of the area of Germany are used for the cultivation of agricultural commodities. Thereby, conventional farming systems achieve high crop yields, particularly by using chemical-synthetically produced pesticides and agrochemicals. Due to that, the conventional agriculture is responsible for almost the entire environmental pollution, based on plant protection products. This results in a serious loss of biodiversity, the destruction of habitats and the manifestation of pesticides in food chains. The constant and unilateral application of these agents cause a misguided selection pressure and finally the resistances of harmful organisms. To counteract these current developments, a realignment of the agricultural systems towards bio-economically compatible, sustainable food production is indispensable. In the "strategy for the future of organic farming" the German federal government aims to double the area of organic farming from 2019 until 2030. However, this form of cultivation reaches 20 percent less yield than the conventional agriculture. Moreover, the yield stability is subject to substantial fluctuations.

Consequently, throughout the transformation to environmentally compatible agricultural systems, the organic cultivation needs to maintain or increase its productivity and its resilience towards factors associated with the climate change. An essential factor for yield loss are fungal diseases. However, especially for organic farming systems, there is a lack of eradication tools. Consequently, the specific need for suitable, bio-based antifungal products really exists. Their development must be based on scientifically secured foundations that comply with the ecological and sanitary application standards of the EU.

Biocontrol agents based on natural products as solution

One possible solution is the usage of biocontrol agents, which are approved as a future oriented technology in ecological agriculture. These agents are plant protection products that are not of chemical-synthetic origin. Instead, they are applied in form of isolated natural products or strain-preparations of microorganisms, for plant stimulation and pathogen defense.

Biocontrol agents with an antifungal activity already available are based on bacterial or fungal strains. These products contain inter alia Bacilli and Actinobacteria as active components and function based on their bacterial natural mechanisms. The bacterial groups are united by a complex lifecycle that leads to the formulation of spores to survive rough environmental conditions. Microorganisms that produce heat- and dehydration-resistant spores provide a natural solution for the product formulation. This facilitates an important step during the development from the living organism towards an applicable product.

Both soil living groups of microorganisms produce a broad range of bioactive natural products. These include substances, which promote plant health. Yet, strains of these two bacterial groups are also known producers of medicine-associated agents as antibiotics, or toxic compounds. The application of medicinally relevant substances contradicts the common scientific understandings and has to be avoided with regard to resistance developments. Moreover, toxic substances as insecticides or herbicides can have devastating effects on the sensitive ecosystems of the agricultural landscape.

Therefore, potential producer strains have a wide-ranging feature profile that has to be determined in case of an agricultural application.

The published knowledge on metabolic potentials of such strains, already available on the market, is poor. Additionally, the range of strains used is not satisfactory.

For a safe application of this type of products, it is decisive to identify the specific mode of actions that are responsible for their functionality. This way the risk for the environment and us humans can be assessed on a scientific fundament. In addition, the potential for resistance development can be determined.

The collection at Fraunhofer IME comprises 120,000 microorganisms.

Strain collection of Fraunhofer IME: a valuable resource for the development of antifungal natural products

In a three-phased project, Actinobacteria and bacteria of the genus Bacillus, from the 120,000 microorganisms counting strain collection of Fraunhofer IME, are tested for a potential antifungal activity, against *Septoria tritici* in wheat and *Colletitrichum coccodes* in potatoes. Guided by antifungal bioactivity data, the overall metabolite profile of every active strain is assessed due to metabolomic technologies. Moreover, the antifungally active substance is identified. Along with the genomic-driven analysis of the biosynthetic potentials, the production of plant growth promoting agents as phytohormones, complexing agents or organic acids, as well as undesired metabolites can be examined.

This way, strains with low-risk feature profiles can be identified. They are tested as strain preparations or isolated natural products on their toxicity towards mammalian cells, insects and plants.In final plant experiments, the potential for the application as a bio control agent is assessed. Due to this process, a global risk-assessment of potential bio control strains can be performed before their further application as bio control agents in the organic farming research.

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Investigations into the translational potential of wolf spider venom

by Ludwig Dersch

Antibiotic-resistant germs combined with the lack of new antibiotics are an increasing problem. Linear peptides from animal venoms often show antimicrobial properties and have potential as novel antibiotics. In previous works only single peptides from spider venoms were characterized. Within my master thesis in the "Animal Venomics" Group at Fraunhofer IME, I succeeded in analyzing a whole family consisting of 16 peptides. The project was carried out in close cooperation with the LOEWE Center for Translational Biodiversity Genomics TBG.

Antimicrobial peptides (AMPs) have the potential for new antibiotics

AMPs are known components of the innate immune system of many organisms. They often exist in the form of short linear peptides with an amphipathic character. This means they have both polar and non-polar regions. These are responsible for membrane interactions on different cell types, bacteria, or viruses. Charge differences trigger a conformational change in the vicinity of membranes and amphipathic α-helices are formed. Through interactions with the negatively charged hydrophilic head groups of membranes, AMPs penetrate and damage the membrane, which can lead to cell inhibition or death. AMPs may be specific to bacterial membranes and in this case, do not harm mammalian cells. They, therefore, have the potential to serve as template material for new antibiotics. Many animal toxins, especially those of amphibians and arachnids, also contain AMP-like toxins. The vast majority of these toxins, especially from spiders are completely unexplored so far.

The peptide repertoire of *Lycosa shansia*

A particularly rewarding species to search for new AMP-like toxins is the Chinese wolf spider *Lycosa shansia*. It belongs to the wolf spider family and thus to a young and highly diverse clade of spiders characterized by a retro lateral tibial apophysis (the so-called RTA clade). Spiders of this clade are the only ones in whose venoms AMP-like toxins have been discovered so far. They are actively hunting spiders, which do not use webs to catch prey and are completely dependent on their venom. Therefore, the venoms of these animals are particularly interesting and have been studied in detail. A total of 52 AMP-like toxins in eight families have been identified in *L. shansia* venom, but have not yet been functionally studied. The so-called A-family is the oldest and chemically most diverse family of these peptides. The goal of my work was to gain a fundamental understanding of the activity and potential of these compounds. For this purpose, we produced all members of this family by solid phase synthesis and tested different bioactivities.

Spider of the genus Lycosa (Lycosa hispanica) *with prey. Closely related species of the studied* Lycosa shansia.

Procedure and findings

The synthetically produced A-family peptides from the spider *L. shansia* were investigated in a multi-pronged analysis pipeline. Consisting of a bioinformatic study of physicochemical properties, injection experiments in larvae of the great wax moth (*Galleria mellonella*), cytotoxicity screens on mammalian cells, antiviral activity screens against different types of influenza viruses, and antimicrobial activity against bacterial pathogens or significant environmental pathogens. Bioinformatic analysis revealed highly conserved regions within the A-family and similarities to AMPs found in various skin toxins of frogs of the genus *Litoria*. The peptides are largely capable of forming complete α-helices and exhibit both a nonpolar hydrophobic region and an anionic region, consistent with the basic structure of AMPs. The injections into larvae of the wax moth *Galleria mellonella* did not show lethality, but mostly caused a strong melanization of the animals, which could be indicative of a tissue-damaging effect or at least an immune response of the larvae to the peptides. However, cytotoxicity assays in MDCKII cells showed no activity. Also, no protective effect against various influenza virus strains was observed. However, a broad spectrum of activity was documented against various relevant bacterial pathogens or significant environmental pathogens that tend to develop antibiotic resistance. In particular, inhibitory effects against the frequently antibiotic-resistant germs and triggers of various infections *Staphylococcus aureus* and *Staphylococcus epidermidis* and the trigger of listeriosis *Listeria monocytogenes*. However, these effects occur only at high concentrations, and translation into novel anti-infectives seems unrealistic for the time being. Furthermore, the data obtained here mainly support the hypothesis that A-family peptides serve mainly to protect the venom gland against microbial colonization and probably play no role in predator-prey interactions. Further work is needed to test this hypothesis. It should also be noted that individual AMPs of the 52 present in *L. shansia* venom were examined here. Further investigation of multiple AMPs in combination with each other would also be interesting, as potential interactions among them could enhance their effects. Another step is to create artificial derivatives of the peptides to manipulate their biochemical properties. Higher charges or enhanced hydrophobicity of the peptides could be used here to produce stronger effects. In principle, the linear peptides of the A-family from the venom of the spider L. shansia are not uninteresting, since they can be biochemically classified as AMPs, show no cytotoxic effect in mammalian cells, and exhibit inhibition of various bacteria.

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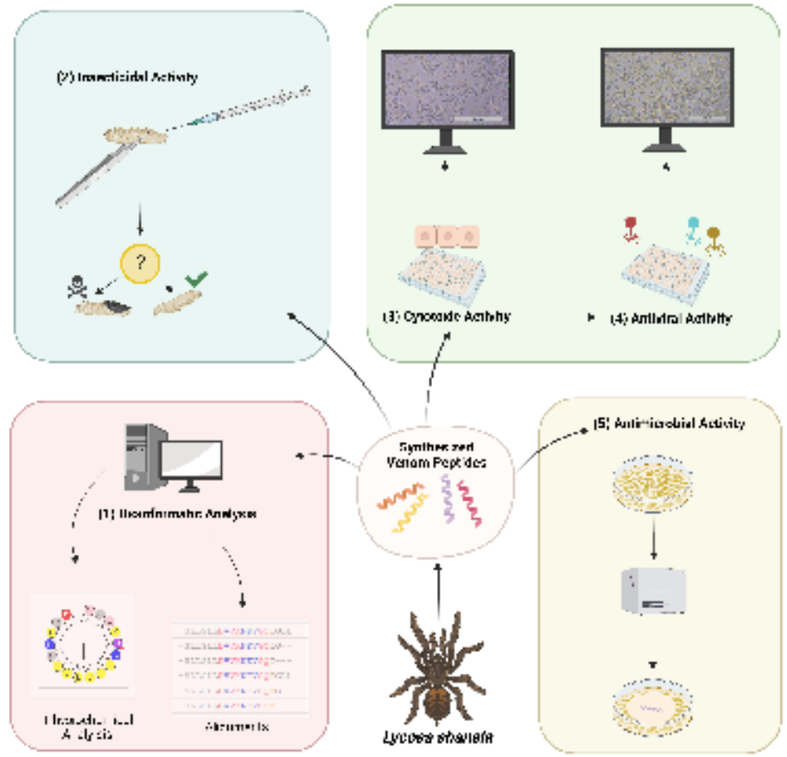

The different steps and screening methods used in the master project.

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Environment-friendly insecticide

by Maurice Pierry

Beautiful wildflower meadows buzzing with life during summers are just a reminiscence of the past for most people. Potent, chemical insecticides used in agriculture are mere one of the causes for this occurrence, participating in the fade away of insect wildlife.

Combating this urgent global issue, the EU did not renew the permission for systemic neonicotinoids, a major player in pest control and a potent unspecific insecticide, in 2019. This sparked novel problems for agricultural businesses. The green peach aphid (*Myzus persicae*) is amongst the insects with the most resistances against chemical components and is thus a sturdy pest. Sugar beet is severely affected since the aphid is a vector for several sugar beet yellowing virus, reducing the harvest and sugar yield drastically.

Breakthrough: RNA Interference

Fraunhofer IME takes on a new approach to surpass the aphids' resistances. Our aim is to produce a RNA-based spray, which will be applicable similar to current pesticides by agriculturists. Being a natural immune response against exogenous viral genetic material available as double stranded RNA (dsRNA), RNA interference (RNAi) offers a biological, species-specific pest control method.

During RNAi, dsRNA is taken up by the cell and cleaved by the enzyme Dicer into small interfering RNA (siRNA). Afterwards, the enzyme complex RNA-induced Silencing Complex (RISC) incorporates the siRNA. RISC then degrades the passenger strand of the siRNA and uses the remaining strand to cleave, to the guide strand homologue, messenger RNA (mRNA) to hinder the exogenous genetic material from further spreading.

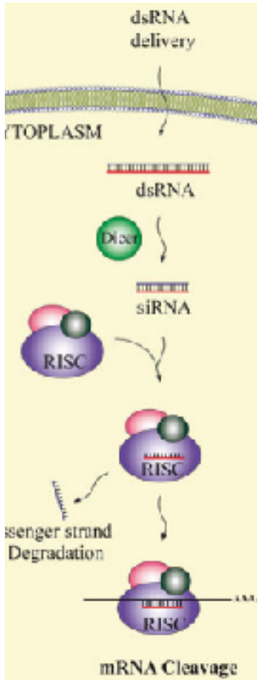
Inserting produced dsRNA designed to be genetically identical to essential genes into the insect can disrupt the corresponding mRNA and thus effecting the survivability or reproduction.

At the beginning of this process potential essential gene and their sequences must be identified. This is followed by the molecular biological synthesis of suitable dsRNA.

From Lab to field

The first step following the successful dsRNA synthesis on the road towards usable RNA-Sprays is the research on caused effects within the aphid. Injections are conducted to exclude all possible environmental factors, like predators, salivary enzymes, RNases and weather. Thus, the pure effect of the dsRNA can be observed.

Feeding trials follow to study the effects during oral uptake, including the factor of salivary enzymes and RNases. If promising results are observed, the first spraying trials directly on the host plant are conducted. This trial is the closest to a field trial and only excludes weather and predators. The last step are the aforementioned field trials, now including the so far excluded environmental factors.



Mechanism of the RNA interference.

Fraunhofer IME also develops formulations, enhancing the effect and reducing the cost of the dsRNA, to cut the overall needed output by agriculturists on the field.

The formulation would bind around the dsRNA molecule to stabilize and guard it against degradation as well as improving the transport into the organism and thus increasing the molecules potency.

Safe for other organism

Specifically adapted synthesized dsRNA has an effect on the target organism, in this case *Myzus persicae*, yet are not affecting other organisms like humans or beneficials. This is possible due to the choice of the right target genes and the produced species-specific dsRNA. Nonetheless, following successful observation of effects within the target organism, risk assessments need to be conducted. These assessments evaluate the effects of a treatment on non-target organisms and, at best, do not detect a significant difference between the treated group and the control group.

This pest control method currently rises in popularity within research groups worldwide and displays major potential for the future. At this time, there is no commercially used RNA-Spray against pest insects.

Fraunhofer IME cooperates with the Julius Kühn-Institut (JKI) and the Institut für Zuckerrübenforschung (IFZ), thanks to funding by the Federal Ministry of Food and Agriculture, to develop one of the first functional and effective RNA-Sprays, within the joint research project ViVe_Beet.

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Aphids.

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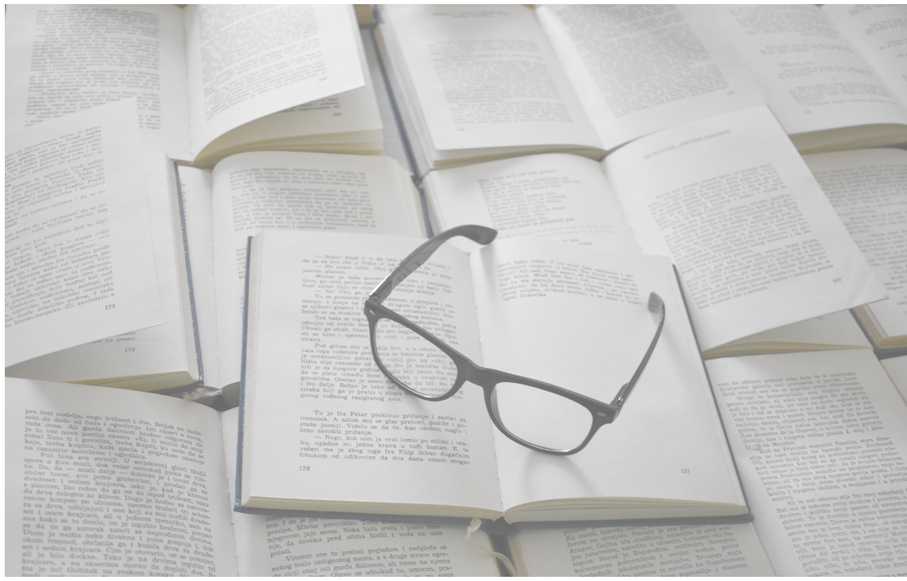
Selected publications



Investigation of immunotoxic mechanisms of action in the zebrafish embryo

Prioritising nano- and microparticles toxicity to algae

In vitro assay reveals species differences in biotransformation rates

The development of the bacteroidetes for natural product research

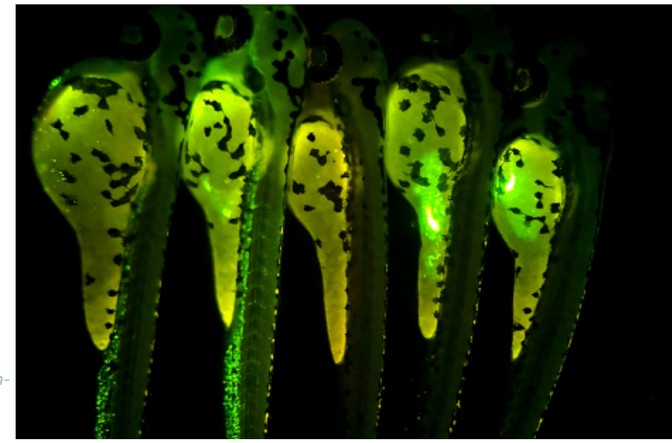
Caterpillars as a replacement for mammalian models in preclinical research

Lighting systems for the optimization of plant cell cultures

Eternal life and continuous plant growth - how do they fit together?

"Molecular signatures of immunotoxic effects contribute to the development of *Adverse Outcome Pathways* for predicting adverse environmental effects."

Fabian Essfeld, PhD candidate at Fraunhofer IME in Schmallenberg.



Fluorescent nanoparticles injected into zebrafish embryos confirm the optimal distribution of PAMPs (pathogen-associated molecular patterns) within the organism.

Investigation of immunotoxic mechanisms of action in the zebrafish embryo

Active ingredients, for example from plant protection products, biocides or for cosmetics, can be denied marketing authorization if they have mutagenic, reprotoxic or endocrine effects on organisms in the environment. The EU Commission has formulated the goal of extending this hazard-based approach to other harmful mechanisms of action, such as neurotoxicity, respiratory toxicity or immunotoxicity. However, due to the complexity of the immune system and the resulting lack of standardized methods, the study of immunotoxicity has been neglected in ecotoxicological hazard assessment of chemicals.

Several approaches exist to gain a deeper insight into the underlying molecular mechanisms of immunotoxicity, such as immunochallenge or infection models using zebrafish embryos incorporating transcriptomics. In this study, we present a new approach that combines the strengths of both approaches and identifies molecular biomarkers for the study of immunotoxic mechanisms of action in fish. This approach is based on global gene expression analysis during acute infection with and without chemical-induced immunosuppression. For this purpose, freshly fertilized zebrafish (*Danio rerio*) embryos were exposed to the immunosuppressive drug clobetasol propionate. After 48 hours, the immune system of the embryos was activated by microinjection of different pathogen-associated molecular patterns. Three hours later, changes in gene expression were examined by transcriptome analyses. In this way, we were able to identify molecular changes that could be attributed to activation or suppression of the immune system and, accordingly, provide early clues to immunotoxic mechanisms of action. Our approach is able to identify regulated processes and signalling pathways in a sublethal acute infection model in the zebrafish embryo, thus providing a powerful method to detect gene biomarkers for immunosuppressive modes of action. The results obtained contribute to the future consideration of immunotoxicity in the assessment of environmental hazards from chemicals.

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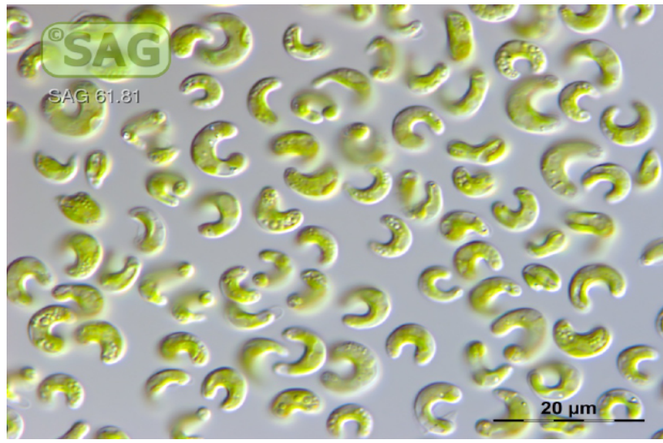
Transcriptomic profiling of clobetasol propionate-induced immunosuppression in challenged zebrafish embryos (2022) Ecotoxicology and Environmental Safety. DOI: 10.1016/j.ecoenv.2022.113346

"We have developed a simple classification scheme that can be used to obtain an indication of the expected algal toxicity of innovative nano- and micromaterials."

Dr. Kerstin Hund-Rinke, laboratory head of the ecotixicology department at Fraunhofer IME in Schmallenberg.



What are important drivers for the ecotoxicity of nano-/microparticles in the algae growth inhibition test?

Prioritising nano- and microparticles toxicity to algae

Advanced/innovative materials are an undefined group of nano- and microparticles encompassing diverse material compositions, structures and combinations. Due to their unique properties that enable specific functions during applications, there are concerns about unexpected hazards to the environment. By applying algae growth inhibition tests according to OECD 201 with *Raphidocelis subcapitata*, and extensive material characterisation, we aimed to identify indicators of concern. This allows a better prediction of the hazardous properties of these materials in the future. In total, 45 nano- and microparticles of various organic and inorganic species, morphologies and sizes were systematically investigated.

The chemical composition (toxic ion releasing materials vs. others) and agglomeration behaviour which is affected by size (nm vs. µm) and morphology (fibres vs. others), were obvious drivers of their ecotoxicity to algae. A high wrapping of algae by the particles resulted in high ecotoxicity.

Considering the identified effects and the material characteristics, we developed graphs to indicate the expected toxicity of advanced/innovative materials to algae. Due to the different toxicity mechanisms, materials releasing toxic ions are separated from the others. The results indicate that in the case of the former, their dependence on the manufacturing process and the substances used must be taken into account. This is not necessarily reflected by the solubility measurements carried out in the test medium. For the latter, morphology, size and agglomeration behaviour are considered. The approach can also support read-across and the justification of sets of nano-/microforms.

AE

Hund-Rinke, K., Broßell, D., Eilebrecht S., Schlich K., Schlinkert R., Steska T., Wolf C, Kühnel, K.
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Kühnel D., Schlich K., Steska T., Nickel C., Wohlleben W., **Hund-Rinke, K.**
Polymers of low concern? Assessment of microplastic particles regarding their toxicity on *Raphidocelis subcapitata* and *Daphnia magna* (2023); in preparation.

"For the first time, information on the ability of *in vitro* biotransformation rate assays to predict *in vivo* species differences of chemical bioaccumulation in fish were provided."

Dr. Ina Bischof, research associate at Fraunhofer IME in Schmallenberg.

Rainbow trout (left) and carp (right) as model fish species for biotransformation testing.

In vitro assay reveals species differences in biotransformation rates

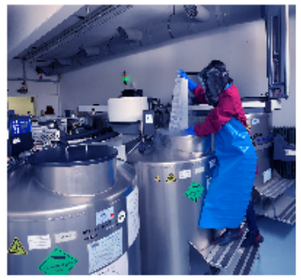
Bioaccumulation assessment according to OECD Test Guideline 305 (fish flow-through test) is part of the hazard assessment of industrial chemicals, pesticides, biocides, etc. in the registration and authorization process. The test guideline allows the use of a wide range of cold- and warm-water fish as test species, including rainbow trout (*Oncorhynchus mykiss*), common carp (*Cyprinus carpio*), fathead minnow (*Pimephales promelas*), medaka (*Oryzias latipes*) and stickleback (*Gasterosteus aculeatus*). In contrast, existing protocols for *in vitro* biotransformation testing to predict the bioaccumulation potential of chemicals are limited to a single fish species, the rainbow trout. In this study, we investigated whether *in vitro* assays for biotransformation assessment may be limited to a single fish species or whether extension to different fish species is necessary. To this end, our study compared biotransformation rates from *in vitro* assays using hepatocytes from a cold-water fish species, rainbow trout, and a warm-water fish species, carp. In a first step, the protocol for the trout hepatocyte assay was adapted to carp hepatocytes for this purpose. It was shown that the *in vitro* biotransformation assay with trout hepatocytes can be technically transferred to other fish species. In a second step, the biotransformation rates of two model xenobiotics, benzo[a]pyrene (BaP) and methoxychlor (MXC), were compared in trout and carp hepatocytes. The *in vitro* data were used to predict bioconcentration factors (BCFs) using *in vitro in vivo* extrapolation (IVIVE) models, which were then compared to BCF values measured in *in vivo* tests. The results of the study indicate that the challenge is not so much the transfer of the *in vitro* methods to other fish species, but the need for improved species-specific parameterization of the IVIVE models.

AE

Bischof, I., Arnot, J.A., Jürling, H., Knipschild, G., Schlechtriem, C., Schauerte, A., Segner, H.
In vitro biotransformation assays using fish liver cells: Comparing rainbow trout and carp hepatocytes (2022) Front. Toxicol. 4, 1021880. DOI: 10.3389/ftox.2022.1021880

"Utilizing OMICS-technologies for the systematic exploitation of underinvestigated bacterial Taxa shows high potential for discovery of novel natural products."

Dr. Marius Spohn, Deputy Head of Department "Natural Products" at Fraunhofer IME in Giessen.



The Fraunhofer strain collection is a unique bioresource to discover novel natural products.

The development of the bacteroidetes for natural product research

By 2020, the Fraunhofer-Gesellschaft received the industrial strain collection from Sanofi. This collection includes over 120,000 microbial isolates and has been generated within a period of 80 years. Specifically conceptualized for industrial natural product research, this collection is composed of 20 percent fungi and 80 percent bacteria. The latter again reflecting the historically most relevant taxa for natural product discovery as e.g. Actinomycetes, Myxobacteria, *Bacillus sp.* and *Pseudomonas sp.*

A dogma states that there is a positive correlation between the produced chemical diversity of natural products and the taxonomic diversity of investigated organisms. We thus targeted the exploitation of a further layer of microbial natural product diversity, guided by a genomics-workflow to rate bacterial taxa by their predicted biosynthetic potential.

The bioinformatic evaluation of 600 genome sequences of the phylum Bacteroidetes revealed the accumulation of the natural product biosynthetic potential in certain phylogenetic »hotspots«. Our analysis showed that the predicted potential is not only huge but also largely unexploited. Translating the predictions into the lab enabled the mapping of the synthetic potential of prioritized strains by using metabolomics and the isolation of novel natural products. This includes glycerophospho-lipids, lipo-amino acids, pentapeptide aldehydes and cyclic lipodepsipeptides.

This strategy to investigate and exploit the underexplored taxonomical space will be continued and expanded towards other bacterial phyla.

BR

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Genomic and chemical decryption of the bacteroidetes phylum for its potential to biosynthesize natural products (2022) Microbiology Spectrum, 10(3): e02479-21. DOI: 10.1128/spectrum.02479-21

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Bioactive natural products from bacteroidetes (2022) Natural Product Report, 39, 1045-1065. DOI: 10.1039/D1NP00072A

"Inflammation research is becoming more ethical and economical: caterpillars help to understand gut inflammation and enable the faster and more efficient development of new therapies."

Dr. Anton Windfelder, research associate at Fraunhofer IME in Gießen.

*Larvae of th tobacco hornworm (*Manduca sexta*).*

Caterpillars as a replacement for mammalian models in preclinical research

Insects such as the tobacco hornworm (*Manduca sexta*) - a moth species from America that is controlled as a pest - can suffer from the same or similar diseases as humans. About 75 percent of the genes that can cause disease in humans are also present in insects. The larvae of the tobacco hornworm can therefore be used as a model organism for human diseases. In this way, diseases can be better understood and new therapies and diagnostic methods can be developed. However, compared to traditional laboratory animals such as rats or mice, insects such as the tobacco hornworm offer several advantages: Their use in research is faster and more cost-efficient than animal experiments with mammals and involves less stress for the animals.

For this reason, together with a national and international network, we developed a high-throughput platform that can precisely characterize and non-invasively diagnose inflammatory changes in the intestines of tobacco hornworm larvae using imaging techniques from radiology and nuclear medicine.

In the paper published in Nature Communications, we show that *Manduca sexta* larvae can be used in a variety of ways for preclinical research using computed tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET).

These methods offer the advantage that many animals can be studied in a short time. In computed tomography, up to 100 animals can be examined in a few seconds. In contrast to traditional molecular biological or histological methods, the animals survive the anesthesia and imaging very well and continue to live unharmed afterwards.

The spectrum of potential applications is extremely broad: The high-throughput platform can be used for *in vivo* testing of new contrast agents and tracers in radiology and nuclear medicine for the detection of inflammation for the characterization of gastrointestinal pathogenicity of microorganisms and for the testing of new antimicrobial or anti-inflammatory drugs.

Moreover, our alternative in vivo platform can contribute to answer important questions about the etiology of inflammatory bowel diseases such as Crohn's disease or ulcerative colitis and to develop new therapies.

BR

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., Flocke, V., Merzendorfer, H., Krombach, G.A., Vilcinskas, A., Grimm, J., Trenczek, T.E., Flögel, U. High-throughput screening of caterpillars as a platform to study host-microbe interactions and enteric immunity (2022) Nature Communications. DOI: 10.1038/s41467-022-34865-7

"We aim to make plant cell cultures more economically attractive by using optimal lighting conditions to increase the secondary metabolite yield of the cultures."

Dr. Ann-Katrin Beuel, research associate at Fraunhofer IME in Aachen.

LEDitSHAKE lighting system to optimize plant cell cultures for secondary metabolite production.

Lighting systems for the optimization of plant cell cultures

Plant cell cultures (PCCs) consist of undifferentiated, propagable plant cells that can be cultivated on solid medium (callus cultures) or in liquid medium (suspension cultures) in bioreactors (up to m^3 scale). Depending on the tissue of origin, PCCs have the same metabolic properties as the parent plant and can thus produce secondary metabolites (e.g. active ingredients, colorants and flavors) for the cosmetics, chemical, food and pharmaceutical industries. PCCs represent a sustainable and resource-saving alternative to the cultivation of plants, as they are cultivated locally, independent of environmental influences, available acreage and without using pesticides. This guarantees high quality and a secured supply.

Important hurdles for a broader application of PCCs are especially the rather low product yields. Genetic engineering could be used here, but this lacks customer acceptance mainly in the cosmetics or food sector. Light is an attractive alternative to increase the yields in PCCs as the use of defined wavelength compositions can optimize metabolic processes of the cells.

Therefore, Ann-Katrin Beuel developed lighting systems for PCCs (LEDitREST for callus cultures, LEDitSHAKE for suspension cultures) in her PhD thesis to determine the optimal light recipes for the production of valuable plant ingredients. Both systems are equipped with six different LEDs (red, green, blue, white, farred, UV) that can be individually adjusted to study the effect of intensity, duration and spectrum of the light. Significant improvements in the production of ingredients have already been achieved: compared to standard light conditions 50-130 percent more 4-hydroxyisoleucine (active ingredient in clinical trial, diabetes treatment) was formed in a PCC from fenugreek and up to 130 percent more anthocyanins were accumulated in a PCC from grapes.

MB

Beuel, A.-K.
LEDitGROW – Lighting systems to optimize plant cell cultures for secondary metabolite production (2022) Doctoral thesis, RWTH Aachen University. DOI: 10.18154/RWTH-2022-09555

"Research on aging is always at the cutting edge, and an unconventional research approach opens new doors and provides new impulses."

Dr. Philip Känel, research associate at Fraunhofer IME in Münster.

The Drosphilia melanogaster *fly.*

Eternal life and continuous plant growth - how do they fit together?

The body and its cells are subject to a constant cycle of maintenance and renewal. Processes responsible for this are illuminated in research by selecting suitable models in individual cells or in the entire organism. Cellular control and repair mechanisms in particular, eminently important in cell and tissue regeneration, no longer run smoothly at some point in the course of aging. And in the molecular coordination of when cells or a tissue should be formed or renewed, interestingly enough, plants, humans and animals often use comparable networks.

The fly *Drosophila melanogaster* is one of the most important model organisms used in research to study biological aging because of its short life span and a variety of molecular and genetic tools. On the other hand, the tobacco plant is an important model crop from the nightshade family used to elucidate developmental processes such as flower regulation. By combining the two model organisms from different kingdoms, we were able to demonstrate the action of so-called PEBP proteins in the aging process of animals. In addition, we demonstrated that a plant protein does amazing things in the fly: with the help of a signal protein from tobacco, the life span of the fly was extended by several days, in our case by about one third of the total life span. The maintenance system of the proteome, the totality of all proteins of an organism, is a target that could be improved by the plant protein. Not only was life prolonged, but the flies also showed very high vitality in advanced aging, as measured by their activity and movement profile. Increased fitness in old age corresponds to an overarching goal of aging research – we eagerly await what conclusions can be drawn from this work for human aging.

MB

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The tobacco phosphatidylethanolamine-binding protein NtFT4 increases the lifespan of *Drosophila melanogaster* by interacting with the proteostasis network (2022) Aging, 14, 2989-3029. DOI 10.18632/aging.204005

In conversation

with Fabiola Neitzel

"I am particularly pleased that I can work with many people at Fraunhofer whom I already know from my time as a student assistant."

Fabiola Neitzel graduated with a B.Sc. in "Food Management" from the Weihenstephan-Triesdorf University of Applied Sciences. Inspired by the need for more sustainable protein sources, she completed internships in the fields of plant proteins and insect breeding before enrolling in the newly introduced master's program "Insect Biotechnology and Bioresources" at the Justus Liebig University Giessen (JLU). At neighboring Fraunhofer IME, she worked as a student assistant during her studies and was able to use her practical experience to establish a soldier fly breeding program. As part of her master's thesis, she investigated how the interaction of edible fungi and insects can convert lignin into protein. After graduation, she founded a start-up for silkworm protein. She also started a doctorate on novel edible insects at the institute's "Bioresources" department in Giessen.

Foods with the label "High in Protein" are in trend. This is surprising, since people in Germany are generally already well supplied with protein. A "too much" of protein, especially if it comes from milk or meat, is not only harmful to health, but also to the environment. How can we counteract this negligent hunger for protein? Fabiola Neitzel has devoted herself to this question. She would like to provide answers especially in the field of insect proteins.

Ms. Neitzel, your path at Fraunhofer IME started as a student assistant during your studies. What experiences did you have during this time?

Many students know them - part-time jobs. Me too juggled shifts at the discount store checkout, babysitting and lecture hours during my bachelor's studies. In the first weeks of my master studies, I was offered a position as a student assistant at Fraunhofer IME in Giessen. An ideal opportunity to gain relevant practical experience on campus while supplementing my student budget with a good salary and reliable working conditions.

From the very beginning, the insights behind the scenes of current research projects and into the everyday work of those we otherwise encounter as lecturers were exciting. The topics of the then newly introduced international master's program "Insect Biotechnology and Bioresources" at the JLU Giessen are closely linked to the research fields of Fraunhofer IME. I particularly appreciated the fact that at Fraunhofer, science always comes first and that the work schedule is always flexible to accommodate exam times, etc. I was very happy with this.

I have always experienced that if you want to get involved, you get the opportunities. I was therefore very pleased to be able to contribute my practical experience with soldier fly breeding to the establishment of a research breeding program at the site.

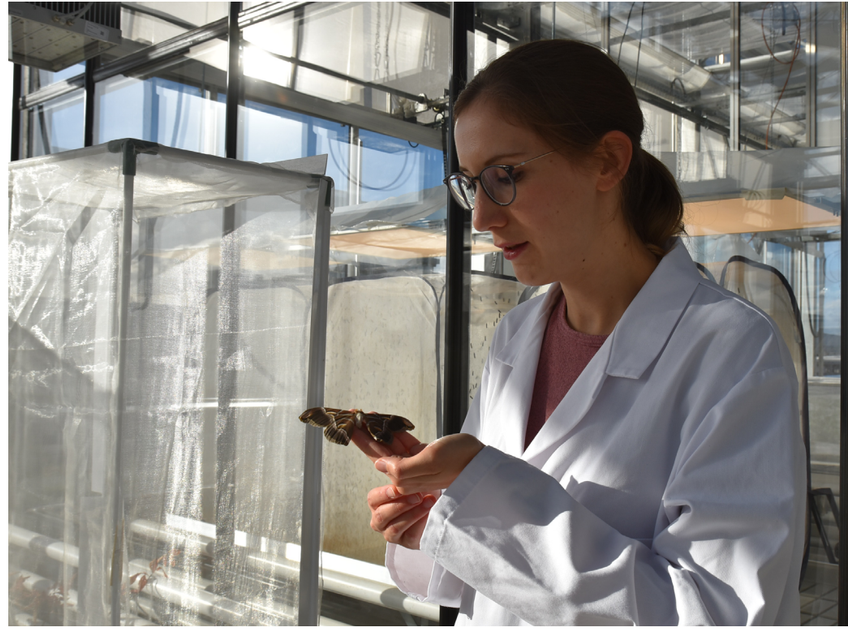
A particular highlight was my participation in the Fraunhofer Scientific Assistant Days. During a multi-day event in Stuttgart, I was able to visit the institutes there, meet Fraunhofer Scientific Assistants from all over Germany and find out about career paths at Fraunhofer.

After graduating, you first dedicated yourself to founding a start-up. How did that come about?

This journey started during my master studies with the participation in an international student competition about the protein supply of the future. What started with a vague idea about "Something with insect protein" evolved over an intense six months and several selection rounds into a concept and first prototype for using silkworm pupae as a protein source. I learned what "Pitching" means in a business context and how such short presentations to introduce a business idea differ from scientific presentations.

After my team finally won first place and 5,000 euros in prize money, and invitations to congresses and investor events followed, the question arose: Was this just a nice experience or should this path be pursued further? After graduation, a Hessen Ideas Scholarship provided the necessary freedom for further considerations and start-up preparations. It quickly became clear that there is much more behind a real start-up than in beautifully elaborated theoretical concepts from the competition.

At the beginning of 2021, I took the step of founding a GmbH (limited liability company) and have since been experiencing what self-employment means on a daily basis. The original business plan had already been thrown overboard three months after the founding due to the ongoing



Fabiola Neitzel breeds the Samia ricini *moths in net cages in the greenhouse.*

international Covid pandemic. Despite many sleepless nights, I would not want to miss this experience and hope that I can contribute to a better use of the available resources.

Start-up and PhD thesis - how can this be reconciled?

In spring 2022, a PhD position was advertised at Fraunhofer IME that fit my profile well. My curiosity was piqued and so I contacted Prof. Martin Rühl to learn more about the topic. He had already supervised my master thesis on the use of harvested edible fungal substrates as food for soldier fly larvae and gave me the opportunity to participate in the student competition on protein supply in parallel. Even now, he encouraged me to apply for the job in parallel with starting my own business. After another phone call with my thesis advisor Prof. Holger Zorn, I submitted my application documents.

I am particularly pleased that I can work with many people at Fraunhofer whom I already know from my studies and my time as a student assistant. I appreciate that I am offered a framework in which I can fully concentrate on research. At the same time, I am given enough flexibility to meet the deadlines for my start-up.

My experience with silkworm protein of the species *Bombyx mori* is benefiting me in my PhD thesis, in which I am currently breeding the less commercially used silkworm species *Samia ricini* and investigating its suitability as a future protein source for food. Together with colleagues from Fraunhofer IVV and partners from the "Indonesian Coffee and Cocoa Research Institute", we would like to pave the way for other insect species as a food source. Insects are the most diverse class of animals. We are only at the beginning of exploiting their potential as diverse suppliers of raw materials.

What makes an insect species that is good for breeding as a protein source?

One of the main aspects is certainly the feeding. As with other animal species, insects range from "omnivores" to absolute food specialists. For commercial breeding, it should ideally be possible to feed the insects with by-products that are available year-round, inexpensive and in large quantities.

Another essential characteristic is, of course, the nutritional value of the insect. Here, there are sometimes significant differences from species to species. While it is clear to the consumer that

beef has different properties than pork, "insect protein" is often still lumped together across the board. For the future, a more differentiated approach and an adapted selection according to the desired properties would be desirable.

For commercial breeding to succeed, the insect species used should be as harmless as possible to humans and the environment. Poisonous, stinging or biting insects require extensive protective measures (e.g., the beekeeper's protective suit). Less mobile, "tame" insects are easier to keep. Just as cattle and pigs evolved over long periods of domestication from their wild form to their current farmed form, for example, the silkworm *Bombyx mori* was bred from a wild moth to its current flightless form. To minimize the environmental impact of accidental release of farmed insects, insect species should at best be non-viable in the wild.

Biomass growth per unit time is also important for economic viability. There is an enormous range here, often related to generation time. This can vary from a few days to years.

Are there other aspects of insect breeding that are being worked on at Fraunhofer IME?

The metabolism of insects and thus their growth rate depends to a large extent on the ambient temperature. In times of high energy prices, the focus is therefore also shifting to the ambient temperature required for insect breeding. On the one hand, it is important to make use of favorable heat sources such as waste heat from other industries. On the other hand, insect species can be selected or adapted to grow well at lower ambient temperatures.

The field of diseases and their treatment is still in its infancy, which can endanger insect breeding on a large scale. Fraunhofer IME is also conducting research in this area.

Silkworm Samia ricini.

Cocoon, worm and moth of the Samia ricini.

The Samia ricini *worm can be fed with cherry laurel leaves.*

Will it soon be normal for us to have insects on our menu?

Our diet is strongly influenced by our culture. The acceptance of edible insects and products made from them, such as burgers, pasta, pastries and sausage spreads, is unfortunately not very high in our latitudes. In addition, the prices for insect-containing foods are still high compared to »conventional« products. This has led to many insect foods disappearing from the market again in recent years.

Indirectly, however, it could certainly work: Insects as protein feed for farm animals such as chickens, pigs and fish are much better accepted by consumers. For example, soy from South America can be replaced by insects from side streams.

People and events

Angela Bauer - Chairperson of the works council for 12 years

Angela Bauer has been employed at Fraunhofer IME in Schmallenberg for 35 years and works as a chemical engineer in the Ecological Chemistry Department. She is especially responsible for the investigation of difficult substances and for mass spectrometry in the "Exposure of Organisms" Laboratory.

Through her professional competence and her responsible, prudent actions across all employee levels, Angela Bauer has gained respect and authority that earmarked her for the works council (Betriebsrat, BR) in Schmallenberg, of which she has been a member for more than 30 years. As chairperson, she had a significant impact on its work. She has a great deal of commitment and heart and soul for all employees. She has also been a constructive discussion and negotiation partner on an equal footing with the divisional management. She has made a significant contribution to the development of an increasingly participative corporate culture from confrontational beginnings, which has a model character within the Fraunhofer-Gesellschaft. Angela Bauer's qualities include a sense of proportion for the social and economic concerns at the Schmallenberg site, which has contributed to the success story of the last 15 years. As a representative on the Fraunhofer General Works Council (Gesamtbetriebsrat GBR), she has a view beyond the IME. She has repeatedly addressed important issues for Fraunhofer IME and due to very good networking with the GBR chairmanship, leading to the advancement of the IME.

In 2022, she resigned from the BR chairmanship at her own request, but will remain with the council until the end of the term. We thank her for her tireless and successful work.

AE

"Maus Türöffner-Tag 2022" at Fraunhofer IME

On October 3, the Gießen site of the Branch for Bioresources opened its doors for the first time for the "Maus Türöffner-Tag 2022" (Mouse Door opener Day), (WDR, Die Sendung mit der Maus), and allowed over 150 young visitors and their families to take a look behind the scenes of a research institute.

Following the motto "Exciting Connections", the interested Maus fans were able to carry out small experiments themselves at 10 different stations together with our scientists. In a quiz about everyday foods, their production and side streams that arise, the knowledge they had learned was put to the test. Courageous guests were given the opportunity to get up close and personal with the insects and spiders, to hold them in their hands or to look at them under the microscope.

Throughout the day, Prof. Zorn and Prof. Rühl guided the families in small groups through the laboratories, answered all the small and big questions about insects, fungi, food and sustainability, and explained how they are connected. At the end, the children and newly trained "research professionals" were given a certificate and a small gift. The day was a great success and not only the families but also our staff enjoyed it very much.

BR

Booth at the German Rubber Conference in Nuremberg

Synthetic rubber has been produced and constantly optimized since the beginning of the 20th century. Nevertheless, its mechanical properties cannot compete with those of natural rubber. Natural rubber, for example, is characterized by an unprecedented strain-induced crystallization. In the research project "BISYKA", a team of Fraunhofer researchers succeeded in the identification of relevant causes and successfully transferred them into a synthetic rubber preparation. At the German Rubber Conference in Nuremberg from June 27 to 30, the team presented how they managed to reduce abrasion without losing tire grip or low rolling resistance.

The German Rubber Conference and International Rubber Conference, the meeting place of the global rubber and elastomer industry, was held in Nuremberg from June 27 to 30, 2022. At the Science Campus, the Fraunhofer Institutes for Molecular Biology and Applied Ecology IME, Microstructure of Materials and Systems IMWS and, Applied Polymer Research IAP presented a tire made of biomimetic synthetic rubber. Visitors learned how the researchers succeeded in reducing abrasion without the tires losing traction or low rolling resistance. Fraunhofer IME researchers Boje Müller and Christian Schulze Gronover were available as experts on site for a lively exchange.

MB

Dr. Elke Eilebrecht appointed to the board of the German Centre for Micropollutants

It is the case that more and more pollutants contaminate our waters. However, it is not only those pollutants that enter the waters in large quantities that pose a hazard, but also the so-called micropollutants. These substances are of particular concern if they have a negative effect on the aquatic environment even at low concentrations. In order to protect our aquatic environment in a comprehensive and precautionary manner, the German Centre for Micropollutants was founded at the German Environment Agency in 2021.

In assessing trace substances, the German Centre for Micropollutants relies on the knowledge of 15 experts from authorities, science, industry, environmental and water associations. Dr. Elke Eilebrecht, head of the Department Ecotoxicology in Schmallenberg, has been appointed to the committee by the Federal Ministry for the Environment, Nature Conservation, Nuclear Safety and Consumer Protection (BMUV). In 4 to 6 meetings per year, the expert group assesses the relevance of the micropollutants on the basis of information available on specific properties such as application, occurrence in water bodies or ecotoxicity.

The aim of the German Centre for Micropollutants is to define measures applicable for trace substances that have been classified as relevant in order to ensure the protection of our water bodies and drinking water.

AE

INSECTA Conference 2022 in Giessen

The 7th INSECTA® International Conference took place in Giessen from September 14 to 16. This year, the Leibniz Institute of Agricultural Engineering and Bioeconomy (ATB) in Potsdam hosted the conference in cooperation with the Branch for Bioresources of the Fraunhofer IME. The international conference provides an annual overview of the latest state of insect biotechnology in a wide range of application areas.

Dr. Oliver Schlüter from Leibniz ATB welcomed the approximately 230 participants from over 30 countries together with Prof. Andreas Vilcinskas, Head of the Institute Branch for Bioressources at Fraunhofer IME, at the kick-off event in the main building of the Justus Liebig University in Giessen. In the following two days, the participants discussed this year's focal points of the conference in around 60 lectures and 40 posters. The topics covered the entire value chain of insect biotechnology from research, breeding and processing to safety and waste utilisation. The experts exchanged views on technological, but also ethical and ecological aspects. With over 60 representatives from industry, the conference has established itself in recent years as one of the most important platforms for the use of insects and the meaningful exchange between science and industry. The conference ended with a visit to the new building, which was opened two years ago, combined with guided tours of the laboratories.

BR

1st Bioeconomy Field Day in the Rhineland

On August 18, 2022, the motto of the BioeconomyREVIER initiative in the Rhineland was "Join us in the field! – Let us introduce you to the agriculture of the future." In its function as a supplier of food and raw materials, as well as in shaping the landscape, agriculture is one of the most relevant bioeconomy sectors in the Rhenish mining area, both economically and in terms of landscape. Here, a sustainable, bio-based circular economy is a living tradition. In addition to the structural change caused by the lignite phase-out the industry is affected by further upheavals and constantly changing framework conditions. Many are therefore concerned with the question of what the agriculture of the future will look like: What methods and crops will provide added value? And are these sustainable for the environment and climate? For the innovation lab "Circular PhytoREVIER", Dr. Lena Grundmann, scientist at Fraunhofer IME, presented the alternative plants nasturtium and arnica as raw materials with potential new value creation for agriculture in the Rhineland area. The extracts of both plants are highly demanded natural products for cosmetics and health industry.

MB

Secondments in OECD working groups

Dr. Sebastian Eilebrecht, head of the Fraunhofer Attract group "Eco'n'OMICs", has been seconded by the national coordinator of the OECD Test Guidelines Programs from the German Federal Environment Agency as a national expert to the OECD Extended Advisory Group on Molecular Screening and Toxicogenomics (EAGMST). The EAGMST addresses issues related to the integration of OMICs approaches into guidelines for the investigation of toxicological and ecotoxicological issues. In addition, the group coordinates the OECD's Adverse Outcome Pathway (AOP) program, develops related guidelines, and develops and operates the aopwiki.org platform.

AE

Strategy Meeting on Diversity in the Workplace

Staff from the Aachen, Schmallenberg, Münster and Giessen sites from the HR and PR departments as well as members of the respective works councils and equal opportunities representatives exchanged ideas at a strategy meeting in Giessen on September 7. The focus of the meeting was on standardizing and, in particular, improving the recruiting process at the various parts of the IME with the aim of achieving greater equality of opportunity in the recruitment of academic staff.

Within the team, which has already been working on examining and adapting the recruiting processes since the beginning of 2022, smaller working groups were set up, which will now deal with the points of "strategy development", "search and approach" and "selection and offer" in the long term. For each of these points, a roadmap in the form of checklists and handouts must be developed to accompany the process from the formulation of the need for a new hire to the new hire itself. The total of 14 team members are supported by Simone Schönfeld from CrossConsult as an external consultant in the field of recruiting. The documents that will be developed in the future are considered a pilot project and are to be made available to other Fraunhofer institutes if required.

BR

"Das Wissenschaftssofa" at Fraunhofer IME in Münster

"Das Wissenschaftssofa" (Science Sofa) is an event format of the Fraunhofer Future Foundation in which participants get in touch via livestream with researchers. In fall, "Das Wissenschaftssofa" went on tour again and visited Fraunhofer IME in Münster on October 26, 2022. Lena Freund and Dirk Prüfer took their seats on the sofa. They answered questions from the audience as well as of moderator Norbert Robers, press officer of the WWU Münster. The questions focused on developments for the simple, rapid and reliable detection of viral infections. The "Applied and Functional Genomics" department uses the so-called LAMP test, which, like the PCR method, detects the genetic material of viruses. The participants wanted to know, among other things, whether the specificity of the LAMP test is high enough to distinguish between different virus variants. Lena Freund explained: "The Covid LAMP test that we had already developed showed the typical red line for all known variants without additional modifications."

MB

WildOMICs: Implementation of molecular biological methods into environmental monitoring

How do chemical substances affect ecosystems? Can harmful effects, such as changes in biodiversity or ecotoxic modes-of-action in fish, be detected using molecular biological methods? These and other exciting questions were raised by scientists of Fraunhofer IME in Schmallenberg on the 2nd and 3rd of November 2022 together with guests from other research institutions. The participants were coming from the German Environment Agency, the universities of Trier, Duisburg-Essen and Frankfurt as well as from Senckenberg Nature Research Society.

During the workshop entitled "WildOMICs", there was extensive discussion on how molecular biological methods can be introduced into the environmental monitoring of the German Environmental Specimen Bank to correlate changes in the chemical burden and in the biodiversity or even link them causally.

During the meeting, specific pre-studies were planned and opportunities for public funding were discussed in order to further promote the research and application of this topic in the future.

AE

Sparking young Women’s Interest in Science

At the end of last year, Laura Horn completed a three-month internship at the Institute’s Branch for Bioresources as part of her participation in the "Hessen Technikum". The program is a cooperation between Hessian universities and selected companies with the aim of attracting more young women with Abitur or technical college entrance qualifications to STEM degree courses.

The participants complete a paid internship in a company four days a week and receive an insight into the STEM departments of the respective university on another day each week. The combination of internship and trial study is intended to show the participants the great potential of STEM fields of work and support them in making a carefully considered choice of study. The companies benefit from the opportunity to get to know and retain suitable STEM young people, so that they can continue to recruit enough professionally qualified female employees for the company in the future. The project is funded by the European Social Fund and the Hessian Ministry of Science and Art.

At our site in Giessen, Laura supports the “Animal Venomics2 workgroup headed by Dr. Tim Lüddecke.

BR

Team "MonChassis" on the track to success at the iGEM competition 2022

For the first time, students from the Westfälische Wilhelms-Universität Münster joined the "international Genetically Engineered Machine" (iGEM) 2022 competition.
The interdisciplinary team - 23 students from various disciplines - worked for ten months on the project "MonChassis - Monoterpenoid production in yeast coupled with cell-free monooxygenase catalyzation". Monoterpenoids are versatile biomolecules with broad applications in medicine, agriculture and consumer products. The team focused on the microbial production of the monoterpenoids in yeast. Using a wide variety of technologies, the team was able to circumvent existing production challenges such as product toxicity. As a proof-of-concept, the team produced verbenone, used to fight bark beetle invasion in forests locally, and globally. Colleagues from Fraunhofer IME in Münster supported the team with their expertise in terpenoid synthesis and analytics. Jos Cox, a doctoral student at our Münster location, also accompanied the team as an advisor to the three-day "Grand Jamboree" competition finals in Paris. The team impressed the judging panel: it was honored with a gold medal, the special prize for the "Best Software Tool" and nominations in the categories "Best Biomanufacturing", "Best Education", "Best Wiki", "Best Presentation" and "Best Part Collection", and as the icing on the cake, the team achieved a TOP 10 placement of the "Overgrads". These accomplishments are great feedback for the time and effort the team has invested in "MonChassis".

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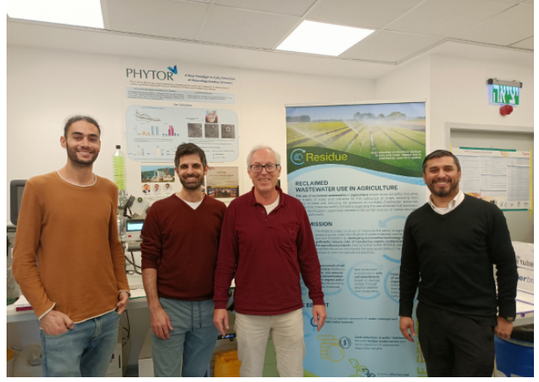

FIM enables visit in Israel and connects project partners

The Fraunhofer International Mobility Program (FIM) enabled Karlheinz Weinfurtner from Fraunhofer IME in Schmallenberg to spend three months at the Faculty of Agriculture of Hebrew University in Rehovot, Israel. There, the soil scientist worked together with Israeli scientists on the EU-funded project RESIDUE ("Risk reduction of chemical residues in soils and crops - impact due to wastewater used for irrigation"). The project investigates the fate of pharmaceuticals as contaminants in sewage sludge composts and treated wastewater used for soil improvement and irrigation in Mediterranean agriculture. The main purpose of the stay was to coordinate the parallel trials in Rehovot and Schmallenberg and to visit other partners involved in the project (Phytor, Compost Or). In addition, there was the opportunity to gain an insight into irrigation management, from seawater desalination to the use of economical irrigation techniques.

The picture shows (from left) Guy Rozner, Evyatar Mordechay (both University of Jerusalem), Karlheinz Weinfurtner and Yehoshua Maor (Phytor) during a visit to Phytor.

AE

Environment Minister Priska Hinz visits Fraunhofer IME

The Hessian Minister for the Environment, Climate Protection, Agriculture and Consumer Protection, Priska Hinz, was a guest in Giessen at the beginning of the year to find out about the latest developments in research in the field of bioresources.

The focus of the exchange was on various research approaches with which the scientists in Giessen are working on establishing biological plant protection. At present, classical pest control is based primarily on chemical insecticides, which have undesirable side effects on human health and the environment. Pests such as the invasive cherry vinegar fly, which is currently responsible for major agricultural damage in fruit growing, serve as model systems for current research projects in which, for example, insect-pathogenic microorganisms are to be used as natural counterparts of insect pests in modern plant protection. Research is also currently being conducted on the development of an RNA spray-based control option for virus-transmitting aphids in sugar beet.

"In future, however, research at the Branch for Bioresources will not be limited to insects," explains Prof. Vilcinskas, "There are already a large number of very different projects and research approaches being explored in Giessen." Minister Priska Hinz will remain in contact with Fraunhofer IME in the future.

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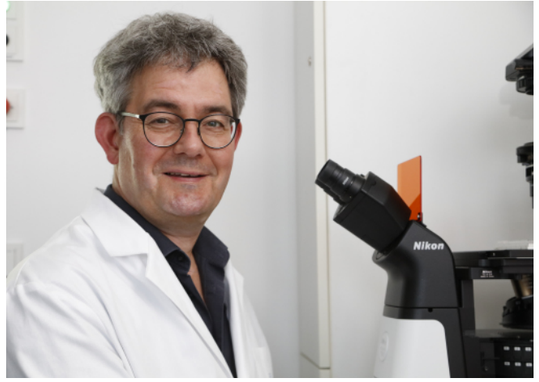

Henner Hollert - new department through affiliation with Goethe University Frankfurt

Prof. Dr. Dr. h.c. Henner Hollert has been head of the newly founded scientific department of "Environmental Media Related Ecotoxicology" in the Applied Ecology Division in Schmallenberg since August 2022. He is a W3 university professor at Goethe University Frankfurt am Main and head of the Department of Evolutionary Ecology and Environmental Toxicology. He is acting president of the *Society of Environmental Toxicology & Chemistry Europe - German language Branch*, (SETAC GLB) in 2022, and a member of the Working Group on Effect-based Methods of the European Commission's Working Group Chemicals. Furthermore, he is a member of the Working Group on Biological Methods for Water Quality Assessment/Genotoxicity, a member of the Wasserchemische Gesellschaft, and head of the Bioanalytical tools WG of the NORMAN Network, thus ideally complementing the portfolio of Applied Ecology. His Frankfurt research group develops methods for monitoring water, sediment and process quality and thus strengthens the acquisition of public research projects and non-GLP studies. Through his coordination of the activity in the thematic field of *Biodiversity Loss and Chemical Pollution* as well as spokesperson of the profile area "Sustainability & Biodiversity", he links the research of Goethe University with the transfer via non-university research institutions into the regulatory substance assessment (in the division of Applied Ecology), into the economy and also into public Interest.

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Excellent performance honoured by Fraunhofer Executive Board

Fraunhofer IME is pleased to announce that Prof. Dr. Christian Schlechtriem has been awarded an Excellence Award by the Fraunhofer-Gesellschaft. In the department "Bioaccumulation and Fish Metabolism". The department was founded in 2015, Prof. Schlechtriem was able to combine existing expertise with studies on ^{14}C-labelled test substances with his own knowledge from aquaculture and fish nutrition and further develop it to a globally unique profile in the transitional field between bioeconomy, food and environmental safety. In close coordination with industry and regulation, he fills some gaps in substance regulation with targeted development of suitable procedures. Examples are his contributions to bioaccumulation of chemicals in fish (OECD 305), the bioconcentration test with *Hyalella azteca* and a test concept for the testing of nanomaterials, as well as the EU guidelines on the characterization and quantification of pesticide residues in farmed fish. At the same time, he is developing in vitro tests with primary fish hepatocytes as animal test replacement methods. In 2022, he commissioned the world's first aquaculture recirculation facility for ^{14}C-labelled substances. Christian Schlechtriem's economic returns of 50 percent generated by his innovations and his role as chair of the *SETAC Global Bioaccumulation Science Interest Group* are an expression of his excellent networking in the international knowledge and economic space. An honorary professor at the University of Siegen, he is currently completing his habilitation in environmental sciences at RWTH Aachen University and contributes significantly to the IME's overall strategy as IME-AE strategy officer.

AE

Study Prize of the Olpe District for Dr. Sebastian Kühr

On May 9, 2022, the "Studienpreis des Kreises Olpe" (Study Prize of the Olpe District) was awarded to Dr Sebastian Kühr by district chief executive Theo Melcher as part of the University of Siegen's Young Scientists Day celebrations. The award for outstanding theses is endowed with a sum of 1,000 euros. After completing his teaching degree at the University of Siegen in biology and chemistry, Dr. Sebastian Kühr investigated in his doctoral studies at Fraunhofer IME in Schmallenberg how nanomaterials accumulate in aquatic organisms. Prof. Dr. Christian Schlechtriem, who supervised Dr. Sebastian Kühr's work over the course of the last three years, highlighted the exceptional quality of the work in his laudation. The results obtained have been published in high-ranking international journals. Dr. Sebastian Kühr is now continuing his research on the effects of nanomaterials in the environment as a postdoc at the renowned Norwegian Institute for Water Research (NIVA) in Oslo.

AE

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

Doctoral theses

Arne Baudach
The role of epigenetics in polyphenisms and transgenerational immune priming in Lepidoptera
University of Giessen

Ann-Katrin Beuel
LEDitGROW – Beleuchtungssysteme zur Optimierung von Pflanzenzellkulturen für die Sekundärmetabolit-Produktion
RWTH Aachen University

Stephan Brinkmann
Microfluidic-based miniaturization as well as genomics- and metabolomics-guided prioritization of bacterial producer strains leverages the numbers game to discover and characterize bioactive natural products
University of Giessen

Alexander Dorn
Application of a core sampling methodology and a mechanistic model to examine the spatial distribution of non-ionized organic compounds in sediment microcosms.
University of Frankfurt

Indra Hering
Nachweis einer Reduktion der Umweltbelastung mit Phamarzeutika durch die Anwendung nanobeschichteter Kolloidararzneiformen.
University of Frankfurt

David Kämpfer
Passive sampling for monitoring the removal of organic micropollutants by different wastewater treatment processes.
RWTH Aachen University

Kristina Klein
Ecotoxicological assessment of microplastics in limnic systems with emphasis on chemicals released by weathering.
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Regina Kölzsch
Approaches to generate herbicide resistant T*araxacum koksaghyz* by directed and undirected mutagenesis of the acetohydroxyacid synthase
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Characterization and optimization of 1-hexanol production in CO-utilizing clostridia
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Anne Kreutzer
Passive sampling and passive dosing: Novel approaches for the holistic assessment of marine sediment contamination by hydrophobic organic pollutants.
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Carina Lackmann
Impact of anthropogenic pollutants on earthworm *Eisenia andrei*: assessment strategy for pesticides and microplastics on multiple biological levels.
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Ira Lauer
Metabolic engineering of Clostridium ljungdahlii for the production of butanol and hexanol
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Untersuchungen zum Verbleib von ausgewählten 14C-markierten Lebensmittelinhaltsstoffen nach Lebensmittelverarbeitungsprozessen und der Verdauung.
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Methods for the investigation of fate of engineered nanoparticles in the environment / complex matrices.
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High-throughput approaches for bioprospection to leverage natural product discovery and for single-cell persister phenotyping
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Nanosonden-basierte Mykotoxin-Detektion in Agrarprodukten
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Hannes Reinwald
OMICs-basierte Erfassung Wirkstoffinduzierter Genexpressionsänderungen in aquatischen Nicht-Ziel-Organismen.
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Human Biomonitoring of Nonylphenol based on Oxidized Urinary Metabolites Method development, investigation of the human metabolism and application in exposure assessments.
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Synthetic approaches to new antimicrobial active natural products
University of Giessen

Aliaksandra Shuliakevich
Ecotoxicological profiling of sediments from the Wurm River (North Rhine-Westphalia, Germany) under different weather and wastewater treatment conditions.
University of Frankfurt

Christiaan Wijntjes
The effect of pesticide mixtures on the degradation of xenobiotics in soil and aquatic sediment systems.
RWTH Aachen University

Habilitation

Tonk Miray
Arthropod antimicrobial peptides: from immunity to medical applications
University of Giessen

Theses with the experimental part carried out at Fraunhofer IME

22 Bachelor's theses

50 Master's theses

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