Fraunhofer ITEM

Annual Report 2023

Fraunhofer ITEM – pioneers for sustainable health

Annual Report 2023

Fraunhofer ITEM – pioneers for sustainable health

To our readers

Being “Pioneers for sustainable health” – this is our vision! In this annual report, you can read just how successfully we are translating this vision into reality through our research.

Director
Prof. Dr. Norbert Krug

The institute enjoys an outstanding reputation worldwide as a result of its long-standing expertise in conventional toxicology and its development of novel assessment models such as next generation risk assessment. Fraunhofer ITEM's clinical and preclinical lung research is held in the same high renown and focuses on the safety of drugs and chemical substances.

A vital part of the institute's work centers around the development of human-relevant models with the aim of achieving research results that are appropriate and meaningful for people. These range from precision-cut slices of various types of human tissue right through to in-vitro and in-silico models. As a natural consequence, our work is accelerating improvements in animal welfare and reduction of animal testing. To ensure that our research – and the research conducted by our partners and customers – produces effective results, we focus within our mission on regulatory acceptance of our methods and findings.

The future Chair of Toxicology at the Hannover Medical School (MHH) will hold a shared role as head of Fraunhofer ITEM, strengthening our expertise in the area of toxicology. The appointment process, being led by a joint nomination committee involving both MHH and the Fraunhofer-Gesellschaft, is already underway with the aim of filling this important position soon. This future appointment will reinforce the links between the academic research at MHH and Fraunhofer's own applied research. Additionally, we are intensifying our work in infection research through our collaboration with the Helmholtz Centre for Infection Research (HZI). Through the work we are doing with our partners from MHH, the University of Veterinary Medicine Hannover, the HZI and Leibniz University Hannover, we are advancing the transfer of basic research into application here at Fraunhofer ITEM.

I would like to thank the institute colleagues at the Hannover, Braunschweig and Regensburg sites, whose dedication, expertise and creativity have helped us achieve success. Over the coming year, we intend to keep pursuing our vision of being pioneers for sustainable health.

I would also like to thank our customers and partners for the fruitful cooperation we have enjoyed with them, and for trusting us to work with them on finding solutions and promoting innovations. All of us at Fraunhofer ITEM are looking forward to further collaborations and exciting projects.

Norbert Krug
Institute Director

Contents


hofer
ITEM

Profile

Human health in the focus of research

Mission statement

Our vision – what we stand for

We are living in an increasingly dynamic world. Technological cycles are getting ever shorter, demography and lifestyles are changing rapidly. These developments entail questions and challenges – challenges in particular that affect people's sustainable health. We do not want to "alleviate symptoms in the short term" – we want to contribute to a healthy future in the long term. For us, this does not just mean helping people who are ill to gain better health, but also protecting people from health risks in their everyday lives and working environments. Creatively and with a view to practical application, we develop solutions to address these needs. We are pioneers for sustainable health.

Our mission – what drives us

- We do research to improve health, to protect against hazards, and to generate safety.
- We assess and develop tomorrow's materials, medicines, and medical devices.
- We combine basic research and industrial application in the regulatory environment.

Our values – how we collaborate

- We act responsibly for the organization, its employees, our colleagues and ourselves.
- We cultivate open, respectful and result-driven communication.
- We practice multi-disciplinary teamwork.
- We support and develop our employees.
- We make decisions by involving the competence of our employees.
- We acknowledge good performance, of both individuals and teams.
- We are a reliable partner for clients.
- We establish a learning culture and deal with errors openly and constructively.

Fraunhofer ITEM
Pioneers for sustainable health

The Fraunhofer ITEM headquarters in Hannover (Germany).

To be "pioneers for sustainable health" is the vision of the Fraunhofer ITEM researchers. Research at Fraunhofer ITEM is thus focused on human health – and this has been so for more than four decades. Numerous ideas and innovations emerge at the interface between medical science, natural science, computer science, and engineering, and this interdisciplinarity is the strength of the institute. By transferring insights and know-how into values, services, and products for society and humankind, the researchers are pursuing their vision.

The institute's main emphasis is on airway research, focusing on two aspects: firstly, on protecting health from potentially harmful, in particular airborne substances, be they gases, aerosols, particles, fibers or nanomaterials, and secondly, on investigating and developing diagnostic and therapeutic approaches, both at the preclinical and clinical levels.

At three institute locations – in Hanover (headquarters), Braunschweig, and Regensburg – scientists apply their research and development expertise in the fields of pulmonary research, toxicology, RNA technologies, immunology and infection research, malignant disease research, medical and pharmaceutical engineering, and bioinformatics and AI. These are geared towards translation into commercial applications and provide the basis for the three business areas Drug Development, Chemical Safety and Assessment, and Translational Biomedical Engineering.

www.item.fraunhofer.de/network

Fraunhofer Group for Health Research

Health research at Fraunhofer addresses the four major areas of medical science: drugs, diagnostics, devices, and data. Numerous innovations emerge at the interface between medical science, natural science, computer science and engineering. With its emphasis on transdisciplinary research, the Fraunhofer-Gesellschaft offers the perfect environment for close collaboration in health research – and for cost-intelligent precision medicine for the benefit of patients.

Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD

Fraunhofer ITEM is one of the three core institutes of the Fraunhofer CIMD, next to the Fraunhofer institutes ITMP and IZI. In this cluster, the collaborating institutes are pooling their expertise to generate a substantial gain of knowledge in the pathophysiology of immune-mediated diseases, identify novel targets, and eventually translate innovative ideas into individualized therapies for immune-mediated diseases. Fraunhofer ITEM is leading the competence platform "Alternative methods to animal testing" as well as the sub-platform "RNA therapeutics" that is part of the competence platform "New drug classes".

Fraunhofer Chemistry Alliance

The Fraunhofer Chemistry Alliance is a collaboration of 15 Fraunhofer institutes aimed at leveraging complementary competencies and interdisciplinary synergies to support industrial customers in technology development and scale-up to develop sustainable, innovative products and processes. With bundled Fraunhofer know-how, inventiveness and a unique infrastructure, the Fraunhofer Chemistry Alliance is a strong partner to the chemical industry on its ambitious path to defossilized and circular production processes.

"Production for Intelligent Medicine" innovation cluster

The "Production for Intelligent Medicine" innovation cluster pools the know-how of 23 Fraunhofer institutions to work on novel development and production technologies for cell and gene therapeutics, as well as vaccines. Fraunhofer ITEM is involved in designing the production and quality control of ATMPs (Advanced Therapy Medicinal Products) and vaccines.

High-Performance Center Medical and Pharmaceutical Engineering

Easing the translation of ideas into successful applications, with a consistent focus on user safety, is the aim of the Fraunhofer institutes ITEM, IST in Braunschweig and IMTE in Lübeck. They combine their expertise in the key research areas of implant and inhalation technologies and pharmaceutical process engineering, and act as innovation pilots to create the ideal conditions for faster translation of research results into patient applications.

Fraunhofer Nanotechnology FNT

Fraunhofer Nanotechnology FNT is a cooperation of several Fraunhofer units that work together in the field of nanotechnology. They cover the entire value chain from application-oriented research to industrial implementation and also deal with questions of toxicity and the safe handling of nanoparticles.

The Understanding Animal Testing Initiative

Fraunhofer actively participates in the Understanding Animal Testing Initiative, a public information and education initiative of the scientific organizations in Germany that provides comprehensive, up-to-date, and fact-based information on animal experimentation and ethics.

Quality management according to international standards

Fraunhofer ITEM is committed to meeting high quality standards for the services and products offered and to ensuring maximum safety for study participants in clinical trials performed at the institute.

In order to ensure compliance with internationally accepted quality standards, the institute has implemented the GXP quality assurance systems. These include Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), and Good Clinical Practice (GCP). Furthermore, the institute is certified to DIN EN ISO 13485:2016 for the testing of medical devices as well as to DIN ISO 9001:2015. With their respective scopes of application, these quality assurance systems enable the translation and regulatory use of research results, also in authorization processes for drugs, chemicals, and medical devices.

Drug Development

From drug candidate to proof of concept

We are committed to translating innovative drug research into therapeutic applications – safely, reliably and efficiently. Based on our scientific expertise, we offer appropriate methods and approaches to this end: with custom-tailored strategies for process development and manufacturing of active biopharmaceutical ingredients and sterile investigational medicinal products, for preclinical testing – both pharmacology and toxicology – and for early-phase clinical trials – from first-in-human to the clinical proof of concept.

Our state-of-the-art equipment and innovative research approaches allow us to develop new methods and techniques – also in cooperation with our clients. Already in the early phase of drug development, we provide assistance as independent consultants and negotiators in the dialog between applicant and regulatory authority. We work in compliance with regulatory and legal requirements for drug development and according to the quality assurance systems GLP, GMP, and GCP.

With the services offered by Fraunhofer ITEM, we can cover either the complete drug development chain or individual phases on the way from the drug candidate to clinical trials:

- Development and manufacturing of active biopharmaceutical ingredients
- Regulatory research and risk assessment in drug development
- Preclinical testing
- Clinical trials

www.item.fraunhofer.de/drug-development

Chemical Safety and Assessment

From risk analysis towards safe products

Our commitment is to assess the potential risk from chemical substances and their use in specific products. We use a tiered approach for this, referred to as integrated testing strategy.

We offer the studies and services required to assess the potential risks from chemicals to human health and the environment and to register these substances for the intended use. Our portfolio includes industrial chemicals, biocides, food additives, and both human and veterinary medicinal products. In close collaboration with our clients, we gather the data required for substance registration to comply with legal requirements, and we take care of regulatory issues.

With self-initiated research projects, we contribute to the development of novel assessment strategies to help improve and refine existing risk assessment methods and ultimately to minimize the need for experimental studies, in particular animal studies – in the spirit of next generation risk assessment. Examples of such projects are elucidation of structure-activity relationships ((Q)SAR), category approaches such as read across, the setting up of databases and further development of the TTC concept.

We offer the services that can assist you on the way from risk analysis towards safe products:

- Bio- and environmental analytics
- Toxicology testing of chemical substances
- Exposure characterization
- Regulatory issues, risk assessment and authorization
- Regulatory research in the field of chemical safety

www.item.fraunhofer.de/
chemical-safety

Translational Biomedical Engineering

From idea to safe medical device

Development of medical devices is a complex process. Besides specific technical expertise in this area, compliance with the relevant regulatory requirements is of pivotal importance. In this environment, which has been subject to stringent regulation since the European Medical Device Regulation (MDR) became effective in 2017, we conduct research and development projects as well as device testing to prepare for clinical investigation.

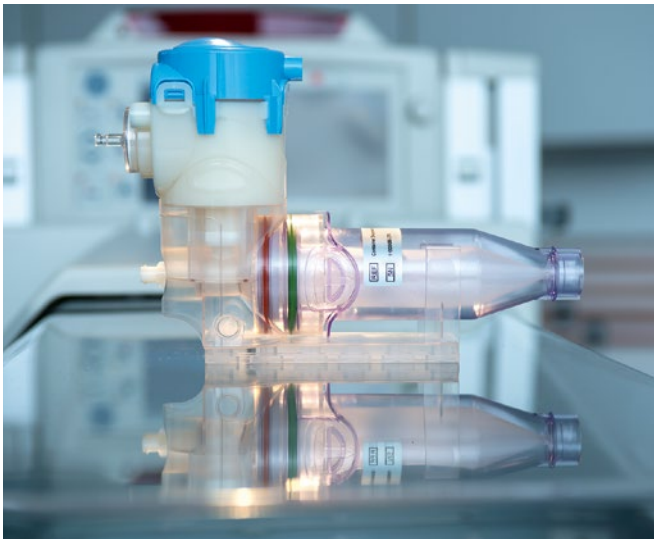
In the field of device development, our focus is on neural implants and on conducting and assisting the development of novel technologies for administration of therapeutic aerosols towards smart drug/device combination products.

Numerous collaborations with both internal and external development partners from industry and academia enable flexible responses to project-specific requirements. We can thus comprehensively assist our clients in the medical device development process, including biocompatibility testing according to ISO 10993. In the field of quality management and risk management (ISO 13485 and ISO 14971), we provide regulatory support in the qualification of external technology processes and the assessment of medical device safety right up to preparation of the registration dossier.

We offer the services that can assist you on the way from idea to safe medical device:

- Device development and manufacturing processes
- Testing and test methods
- Regulatory support

www.item.fraunhofer.de/biomedical-engineering



Personalized Tumor Therapy

From molecular analysis to personalized therapy

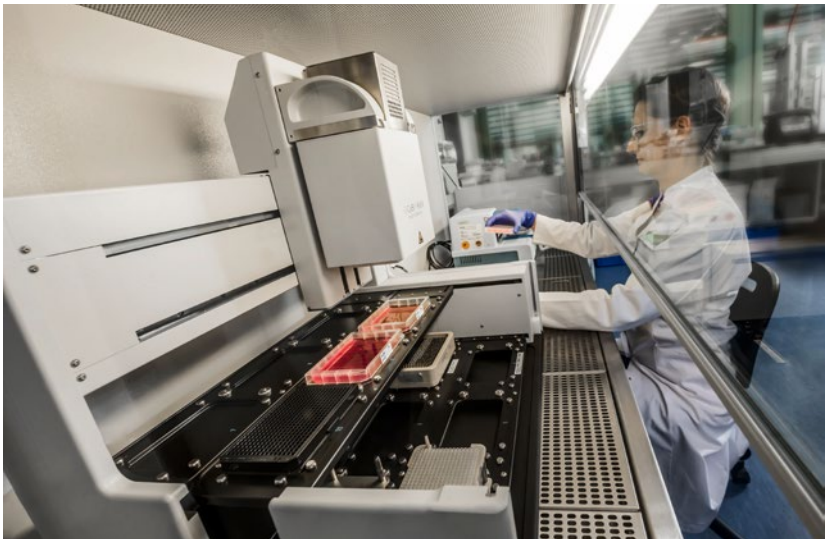
The scientists in the Division of Personalized Tumor Therapy at the Fraunhofer ITEM Regensburg site have extensive expertise in detecting, isolating, and analyzing rare cell populations and small quantities of nucleic acids. The Division of Personalized Tumor Therapy has been certified according to DIN ISO 9001:2015 by TÜV Süd and thus complies with international standards.

The scientists' goal is to advance targeted diagnostics for prevention and therapy for patients with systemic cancers and to improve the preclinical development of new pharmaceutical ingredients. For example, they use multiomic analysis of single cells and innovative preclinical cell models from patient samples acquired from specific projects to generate molecular and functional data. In addition, the in-house, GDPR-compliant data management and robust bioinformatics enable tailored data analysis for developing applications and products for our customers.

We offer the services that can assist you on the way from molecular analysis to personalized tumor therapy:

- Method development
- Preclinical application
- Clinical translation

www.item.fraunhofer.de/
personalized-tumor-therapy



Organizational structure

Headed by the institute director, Fraunhofer ITEM is organized in seven divisions and six additional units (as at May 2024)*. Furthermore, Fraunhofer ITEM hosts two Fraunhofer Attract groups – one dedicated to bioinformatics "IDA – Intelligent Data Analysis for better health and chemical safety" and one focusing on "IMMUNITY – designer cells: novel immune cell platforms for health research". The grant program "Fraunhofer Attract" offers outstanding external scientists the opportunity to develop their ideas towards actual applications close to the market within an optimally equipped Fraunhofer Institute.

The Fraunhofer ITEM headquarters are in Hannover (Germany). The institute's Division of Pharmaceutical Biotechnology has its facilities in Braunschweig on the "Science Campus Braunschweig-Süd", the Division of Personalized Tumor Therapy is based in Regensburg's BioPark.

* Until December 31, 2023, Prof. Dr. Dr. Thomas Thum co-directed the institute with Prof. Dr. Norbert Krug (executive director). Until that date, Prof. Dr. Dr. Thomas Thum had been leading the Division of Cardiovascular Research. On January 1, 2024, Prof. Dr. Norbert Krug has taken over as acting division director. The Division of Pharmaceutical Biotechnology was led by Prof. Dr. Holger Ziehr until March 31, 2024. As of April 1, 2024, a management team has assumed responsibility for this division. The members of this team are Dr. Stefanie Hebecker, Katrin Rimkus, Dr. Claudius Seitz und Dr. Sarah Wienecke.

Staff and institute budget performance

At the end of 2023, Fraunhofer ITEM staff at all three sites – Hannover, Braunschweig and Regensburg – altogether amounted to 478 persons, with a female proportion of approximately 63 percent. People from 18 countries work and do research together at Fraunhofer ITEM.

The institute's staff in 2023 included:

- 383 scientific, technical and administrative staff
- 25 Ph.D. students
- 54 students (bachelor's and master's programs)
- 13 apprentices
- 3 interns

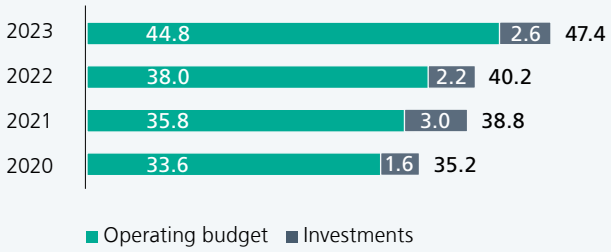
In 2023, the institute's budget reached a level of approximately 44,8 million euros. Financing by acquired funding amounted to 63 percent. The share of industrial income in the institute's budget was 42 percent. Investments of Fraunhofer ITEM amounted to approximately 2.6 million euros.

Fraunhofer ITEM staff

Number of employees

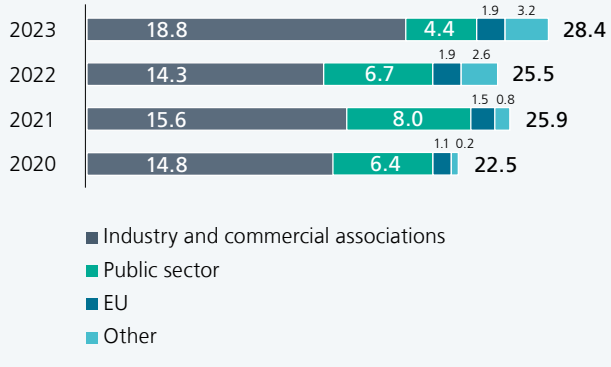
Fraunhofer ITEM total budget

In million euros



Fraunhofer ITEM sponsors and external income

In million euros



Board of trustees

The board of trustees as an external expert committee assists the institute management by providing advice on strategic issues. Its members include representatives from academia, industry and public institutions. The members are appointed by the Executive Board of the Fraunhofer-Gesellschaft in consultation with the institute management. The board of trustees meets once a year to discuss the performance of the institute and to make recommendations for the institute's strategic development from an external perspective.

Members of the Fraunhofer ITEM board of trustees in 2023:

Chairman
Prof. Dr. Paul-Georg Germann
Global Head of Chemical and Preclinical Safety (CPS), Biopharma, R&D, Discovery and Development Technologies, Merck Healthcare KGaA

Dr. Karin Conde-Knape
Corporate Vice President Diabetes, Cardio-Renal and Translational Research, Novo Nordisk A/S (Denmark)

Prof. Dr. Susanne Herold
Director of the Clinic for Infectiology and Hospital Hygiene, University Hospital Giessen and Marburg

Prof. Dr. Wolfgang Herr
Full professor and Head of the Department of Internal Medicine III, University Hospital Regensburg

Prof. Dr. Edith M. Hessel
Chief Scientific Officer, Eligo Bioscience (UK)

Prof. Dr. Michael Hildebrand
Managing Director, Hildebrand Pharma Consulting

Prof. Dr. Dieter Jahn
Head of the Institute of Microbiology, Technische Universität Braunschweig, Spokesman of the Braunschweig Integrated Centre of Systems Biology – BRICS

Dr. Frank Kalkbrenner
Managing Director, Boehringer Ingelheim Corporate Venture Fund

Prof. Prof. h. c. Dr. Thomas Lenarz
(Member of the board of trustees until June 2023)
Director of the Department of Otorhinolaryngology and Director of Deutsches HörZentrum, Hannover Medical School

Prof. Dr. Michael P. Manns
President and Member of the Presidium responsible for the Division of Research and Teaching, Hannover Medical School

Ministerialrätin Dr. Evelyn Obele
Head of the Division of Health Research, Medical Technology, German Federal Ministry of Education and Research

Prof. Clive Page, OBE, Ph.D.
Head of Sackler Institute of Pulmonary Pharmacology, School of Cancer and Pharmaceutical Science, King's College London (UK)

Prof. Dr. Werner Seeger
Director of the Department of Pulmonology, Internal Intensive Care, Infectiology, Gastroenterology, Nephrology, University Hospital Giessen and Marburg (UKGM)

Anna Teschner
Head of the Division of Life Sciences, Humanities, Social Sciences and Academic Libraries, Lower Saxony Ministry of Science and Culture

Dr. Torsten Wagner
Senior Vice President, Corporate Technical Operations, Merz Pharma GmbH & Co. KGaA

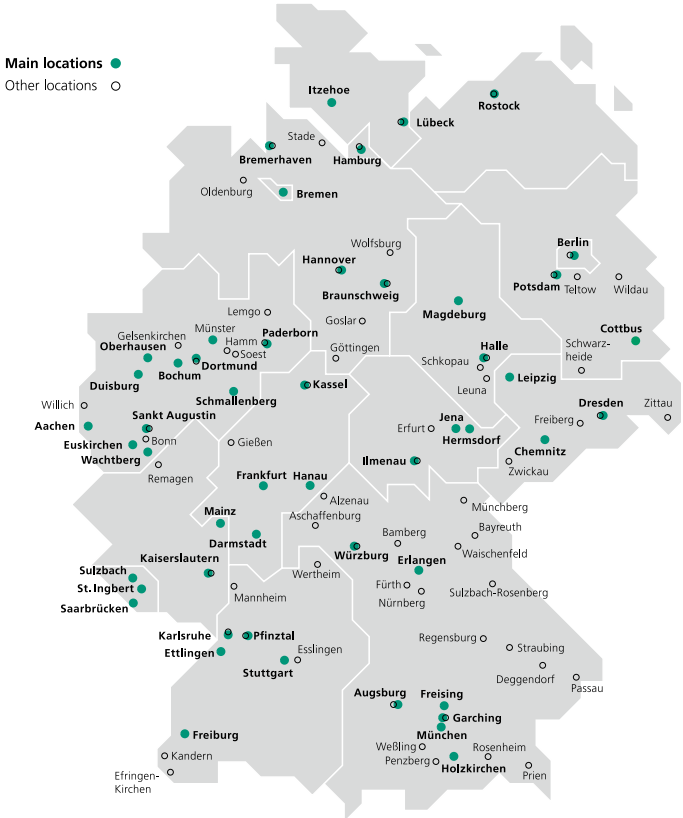
Prof. Dr. Tobias Welte (died March 2024)
Director of the Clinic for Pneumology and Infectiology, Hannover Medical School

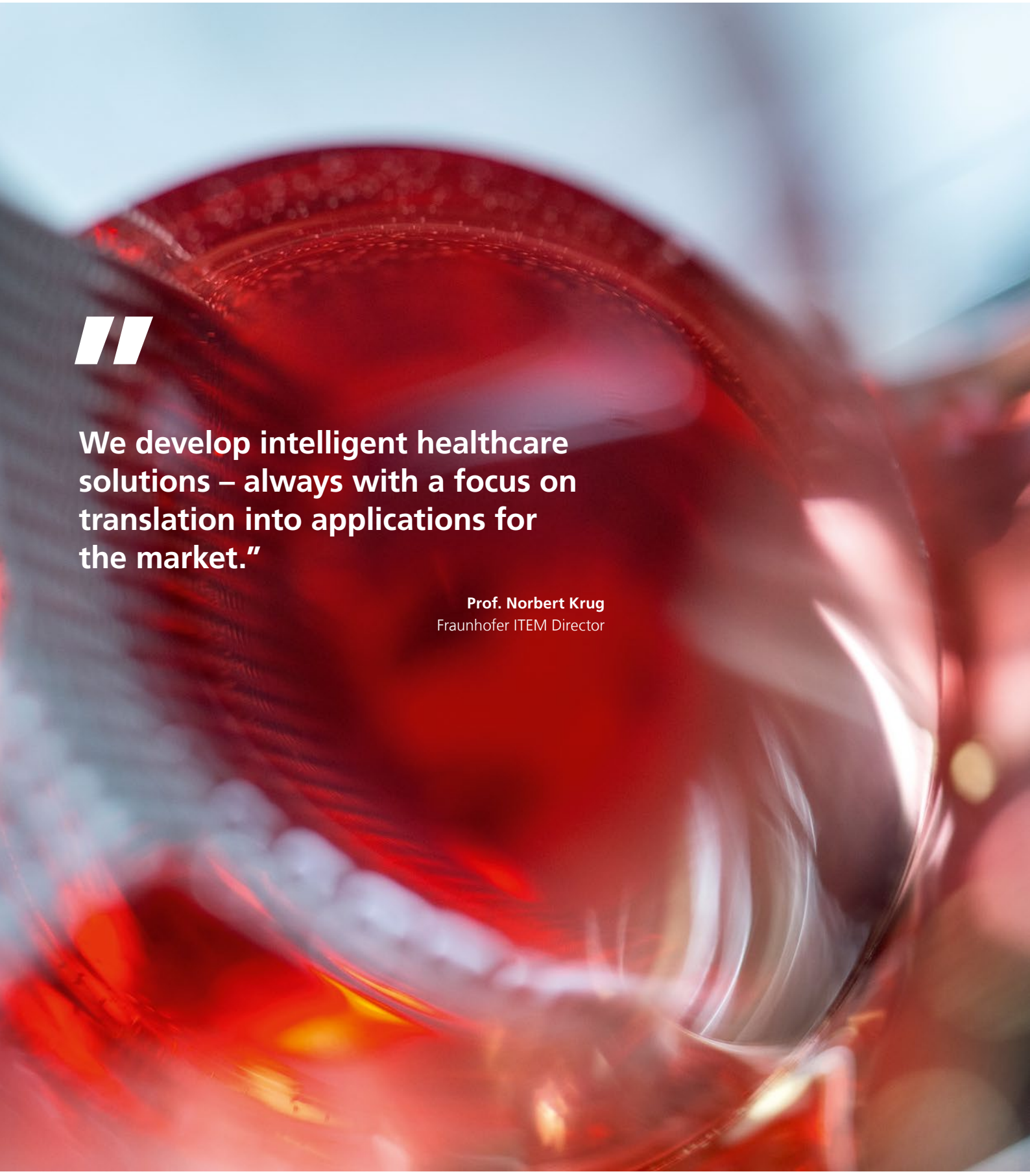
The Fraunhofer-Gesellschaft

The Fraunhofer-Gesellschaft, based in Germany, is one of the world's leading applied research organizations. It plays a crucial role in the innovation process by prioritizing research in key future technologies and transferring its research findings to industry in order to strengthen Germany as a hub of industrial activity as well as for the benefit of society.

Founded in 1949, the Fraunhofer-Gesellschaft currently operates 76 institutes and research units throughout Germany. Its nearly 32,000 employees, predominantly scientists and engineers, work with an annual business volume of 3.4 billion euros; 3.0 billion euros of this stems from contract research, which is divided into three funding pillars. Fraunhofer generates a share of this from industry and license-fee revenue, totaling 836 million euros. This high proportion of industrial revenue is Fraunhofer's unique selling point in the German research landscape. Another share of contract research revenue comes from publicly funded research projects. The final share is base funding supplied by the German federal and state governments and enables our institutes to develop solutions now that will become relevant to the private sector and society in a few years.

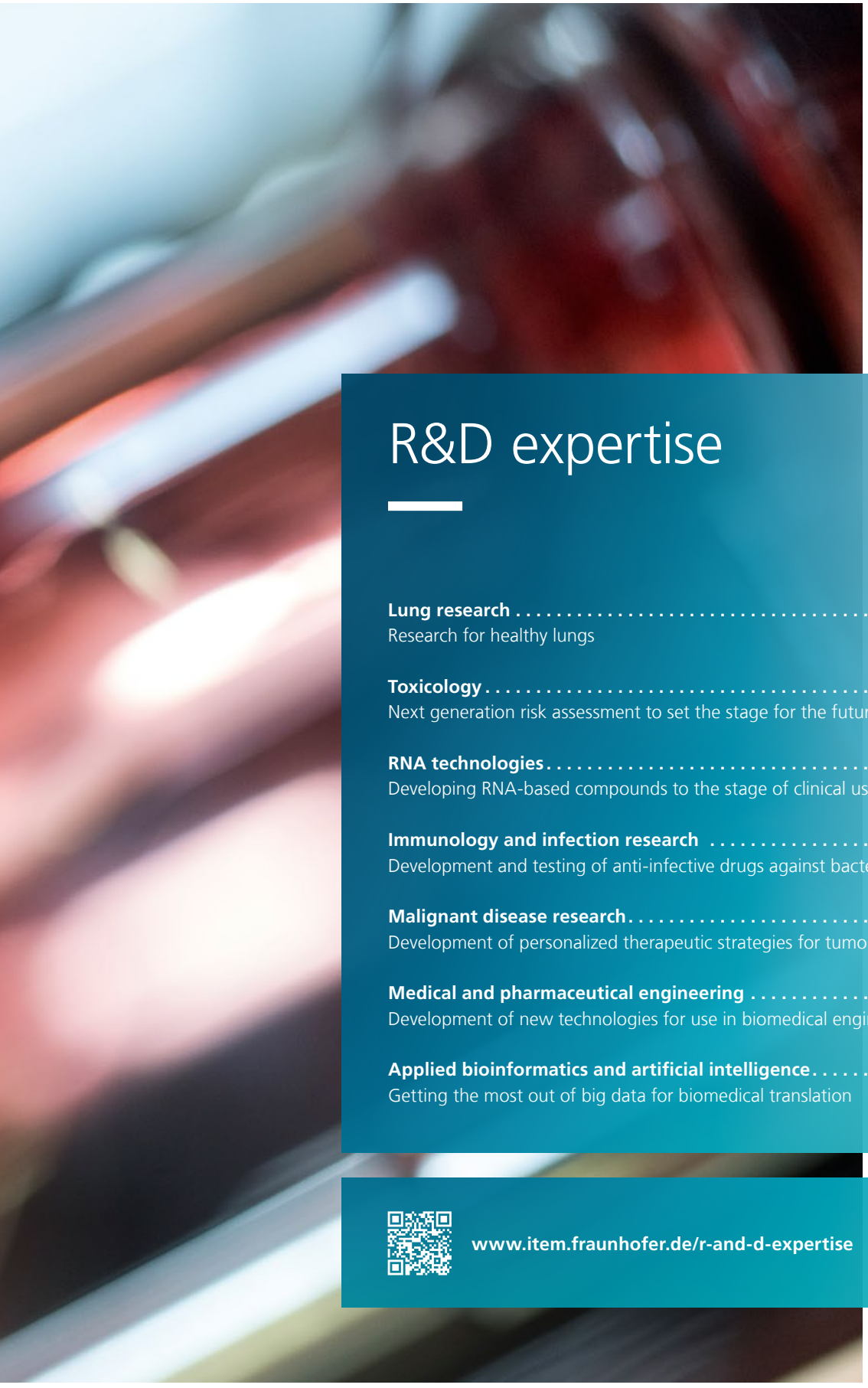
www.fraunhofer.de/en.html





We develop intelligent healthcare solutions – always with a focus on translation into applications for the market.“

Prof. Norbert Krug
Fraunhofer ITEM Director



R&D expertise

www.item.fraunhofer.de/r-and-d-expertise

Lung research

Research for healthy lungs

Airway research has been a focus at Fraunhofer ITEM ever since the institute was founded. One emphasis has been on protecting health from potentially harmful, in particular airborne substances – be they gases, aerosols, particles, fibers, or nanomaterials – and another one on investigating and developing diagnostic and therapeutic concepts, both at the pre-clinical and clinical levels. To characterize the exposure to airborne substances, Fraunhofer ITEM researchers implement novel nebulizers and test beds and further develop already established technologies, for example for the characterization of materials such as nanocarriers that may be used as drug delivery systems in the long term.

To efficiently translate ideas from bench to bedside, the scientists use appropriate exposure systems, some of which have been developed specifically for this purpose, such as the P.R.I.T.® ExpoCube®, and innovative model systems that closely mimic the situation in patients. They use the generated data to further develop and refine their modeling approaches, so as to allow in-vitro results or findings to be extrapolated both qualitatively and quantitatively for the prediction of the expected in-vivo effect in humans.

Based on their comprehensive experience and expertise in clinical airway research, the scientists also work on patients with respiratory diseases such as asthma, COPD and allergic rhinitis, as well as interstitial lung diseases, in particular idiopathic pulmonary fibrosis (IPF), and inflammatory diseases. Through their clinical research, Fraunhofer ITEM scientists enable a direct transfer of findings to humans, for example, by using chip cytometry, ultra-sensitive biomarker measurements and exhaled breath analysis.

Our Highlights

Cases of severe asthma are treated using biologics injected under the skin with a syringe. Fraunhofer researchers are now testing an inhalable formulation.

Demonstrating proof of concept for an inhaled asthma biologic

Until now, biologics for treating severe bronchial asthma have been injected under the skin. The company Novartis has produced a new inhalable formulation of an antibody to target an alarmin (anti-TSLP antibodies) that is now being clinically tested by Fraunhofer ITEM scientists together with a network of German and Canadian test sites to determine its safety, tolerability and effectiveness. In the early development stage of this formulation, rather than measuring the direct effect to protect against exacerbations in patients with severe asthma, the inhaled allergen challenge model was used with patients with mild asthma as a proof of concept. Overall, 28 test subjects at 10 test sites received treatment once daily with a dry powder inhaler for a period of 12 weeks. Three inhaled allergen challenges were administered before the start of the treatment and again six and twelve weeks afterward to measure the effectiveness of drug treatment in protecting against allergen-induced lung function decline. It was found that the treatment with the inhaled biologic is safe and well tolerated and effectively prevents lung function decline. The results were published in the European Respiratory Journal (Gauvreau, G. M. et al., 2023: DOI 10.1183/13993003.01193-2022).

Contact

Prof. Dr. Jens Hohlfeld
Airway Research
jens.hohlfeld@item.fraunhofer.de

Using segmental LPS challenge to demonstrate the effectiveness of a B1R antagonist

Drugs that specifically target signaling pathways in inflammatory diseases could help to treat patients with chronic obstructive pulmonary disease (COPD). Bradykinin receptor-1 (B1R) is activated during inflammation and increases the migration of pro-inflammatory cells to the lungs. The company Boehringer Ingelheim has developed an antagonist that can block B1R and thus has the potential to reduce inflammation of the lungs. At Fraunhofer ITEM, the segmental lipopolysaccharide (LPS) challenge model was used to test the safety, tolerability and effectiveness of the B1R antagonist. Segmental challenge involves instilling LPS, a component of the bacterial cell wall, into the lungs, where it causes a local inflammatory reaction. Over a period of four weeks, the B1R antagonist was administered to 29 healthy subjects, and placebo was given to 28 healthy subjects. Both treatments were administered orally twice daily.

By determining the number of neutrophils in the bronchoalveolar lavage following LPS challenge, researchers examined whether the inflammatory response was reduced in the B1R antagonist treated group compared to the placebo group. Treatment with the B1R antagonist was found to be safe and well tolerated. However, it did not lead to a reduction in the number of neutrophils in the LPS challenge model. The results were published in the Pulmonary Pharmacology & Therapeutics journal (Gress, C. et al., 2023: DOI 10.1016/j.pupt.2023.102246).

Contact

Christina Gress
Airway Research
christina.gress@item.fraunhofer.de

A bronchoscope is used to apply LPS segmentally in the lungs, where it causes a temporary local inflammation. The researchers used this challenge model to investigate the effectiveness of the bradykinin receptor-1 antagonist.

Developing methods in the Fraunhofer Allergen Challenge Chamber

In the Allergen Challenge Chamber at Fraunhofer ITEM, a patented process is used to mix a commercially available allergen solution with a lactose solution, which is then spray-dried. Allergen-lactose particles of a set size are then spread throughout the allergen chamber. In the past, this process has been used to carry out clinical trials with house dust particles. However, a lactose solution with the required level of concentration is not commercially available – it must be specially produced for the clinical trials. Numerous regulatory provisions must be fulfilled in order to carry out this manufacturing task, and quality assurance steps must be completed. This results in a very time-consuming, expensive process.

The aim of this method development study was to examine whether the lactose solution could be replaced with sodium chloride solution (NaCl), as it is easy to obtain this solution commercially. In a controlled study, patients with a dust mite allergy and allergic rhinitis were exposed five times to five different atmospheres in the Allergen Challenge Chamber, for four hours each time. One atmosphere was clean air; one had lactose particles; one had only NaCl particles; one had lactose house dust particles; and one had NaCl house dust particles.

The results showed there was no difference between the performance of lactose and NaCl particles as allergen carriers. This means that the researchers have made significant advancements in their allergen challenge model using allergen solutions. In the future, it will be possible to carry out these allergen chamber studies more quickly and for a lower cost.

Contact

Dr. Philipp Badorrek
Clinical Airway Research
philipp.badorrek@item.fraunhofer.de

The allergen particles are spread evenly throughout the Allergen Challenge Chamber using a device that resembles a green palm tree.

Hay fever patients had their allergies triggered with grass pollen in the Fraunhofer Allergen Challenge Chamber. Nasal secretions were measured based on the weight of paper tissues that the patients had used.

Clinical trials of a medical product in the Fraunhofer Allergen Challenge Chamber

Although there is a wide range of very effective hay fever drugs available, some sufferers would rather not rely on pharmacological substances. In terms of non-pharmacological treatment options, there are nasal gels and sprays that create a barrier, thus protecting the nasal mucosa from contact with allergens and reducing allergic symptoms in the nose.

The aim of this medicinal product study was to fulfill the American approval requirements for the barrier-forming nasal spray Bentrio® (which is approved for use in Europe) by comparing it with a barrier-forming nasal spray that has already been approved in the USA. To this end, 36 patients with hay fever and grass pollen allergies had their allergies triggered with grass pollen on two separate occasions seven days apart in the Fraunhofer Allergen Challenge Chamber. They did not receive any treatment prior to the first challenge.

However, before the second challenge, half the participants were administered Bentrio®, while the other half were administered the reference product. During the challenge, the patients' clinical symptoms were assessed every 20 minutes using the Total Nasal Symptom Score (TNSS), a self-reported symptom scale. Nasal secretions were measured hourly by weighing tissues, which the patients were instructed to use as needed.

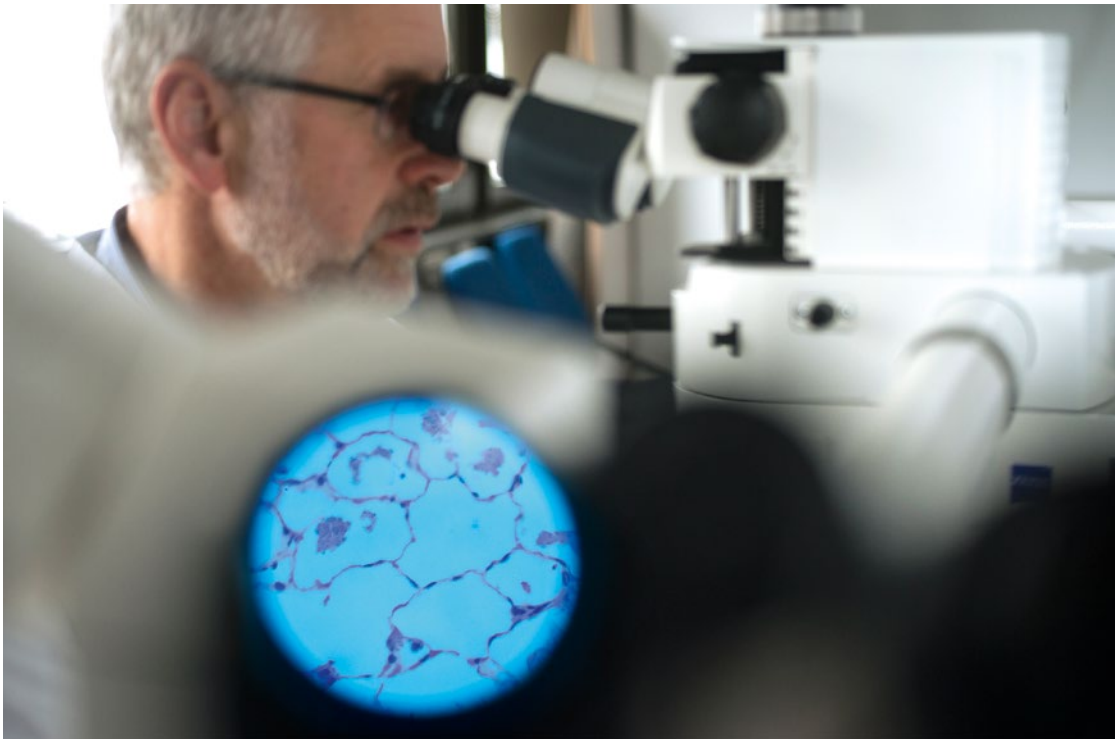
The study showed that based on the TNSS and the amount of nasal secretions, there was no significant difference between the effectiveness of the two compounds. In a subjective overall evaluation, Bentrio® was rated higher than the reference product. As such, the product has fulfilled the requirements for approval in the USA.

Contact

Dr. Philipp Badorrek
Clinical Airway Research
philipp.badorrek@item.fraunhofer.de

Toxicology

Next generation risk assessment to set the stage for the future



Fraunhofer ITEM stands for toxicology testing and risk assessment of chemicals, drugs, and medical devices – from exposure characterization, collection of toxicological data, and the implementation of testing strategies to accompanying and providing consultancy to companies in product registration and authorization. A special focus is on inhalation toxicology and on characterizing inhalable substances. Continued development of the corresponding exposure methods enables very small amounts of test substances to be used with high efficiency in toxicological studies.

Toxicological research at Fraunhofer ITEM is geared to the ethical principle of the 3Rs: to reduce the number of laboratory animals, to consistently improve research methods, and to replace animal experiments by alternative methods whenever possible. The development of human-derived test systems furthermore makes it possible to obtain research results that are more relevant to humans.

While conventional toxicology testing is still the required regulatory standard, our researchers are contributing to new assessment strategies through their own research projects based on the next generation risk assessment concept, aiming to provide predictive models for assessing the safety of compounds. Examples include the elucidation of structure-activity relationships ((Q)SAR), category approaches such as read across, in-vitro to in-vivo extrapolation (IVIVE), including the use of PBPK models (physiologically based pharmacokinetic modeling), human in-vitro and ex-vivo systems as well as organ-on-a-chip models. Based on the precision-cut lung slices (PCLS) technology that is well established at the institute, more human or humanized ex-vivo organ models, for example of the heart and liver, are in the process of further development. These models can also be used to test biopharmaceuticals and advanced therapy medicinal products (ATMPs). To analyze the results, the researchers combine the traditional endpoints among others with omics technologies, in particular metabolomics and functional genomics, and complex advanced bioinformatics analyses.

Assessment methods based on databases, such as the TTC (threshold of toxicological concern) concept, are being further developed, for example to identify nongenotoxic tumorigenic substances or to allow these methods to be used in the development of medical devices.

Our Highlights

The number of metabolites in each organism is vast. A single model is not enough for a complete analysis. One important analytical tool is NMR spectroscopy.

Standardized, high-throughput targeted metabolomics

What are known as the four omics – genomics, transcriptomics, proteomics and metabolomics – are in a state of constant multidimensional flow in biological systems. Significant deviations in metabolite levels can indicate changes in the other three omics, whether they are benign or malignant in nature or an adaptation to external factors. Every organism contains an enormous number of metabolites that cannot be measured using a single analytical method. In 2016, a kit-based LC-MS/MS workflow (Biocrates®) was introduced at Fraunhofer ITEM, which allows the quantification of 1,019 metabolites in one sample. When used in combination with other targeted methods (e.g. NMR IVDr by Bruker BioSpin), metabolomics has become an integral, standardized high-throughput tool that generates comprehensive data sets for numerous metabolic pathways. Bioinformaticians at Fraunhofer ITEM are developing customized methods for data analysis to aid data interpretation.

Scientists at Fraunhofer ITEM have brought their targeted metabolomics approaches to numerous projects in the areas of clinical and veterinary medical research, both within Germany and internationally. One use case for their approaches included targeted metabolic profiling to identify severe clinical cases of COVID-19 in a study led by the German Heart Centre Munich and the German Centre for Cardiovascular Research. They also recently made a further scientific contribution in this field as part of the NuEva study led by Friedrich Schiller University Jena.

Contact

Dr. Sven Schuchardt
Bio- and Environmental Analytics
sven.schuchardt@item.fraunhofer.de

REMADYL – processing old PVC as an example of the circular economy model

Fraunhofer is one of 15 multidisciplinary European partners investigating the possibility of integrating "old" PVC into the circular economy as part of the EU-funded REMADYL project. The term "old" refers to PVC that contains hazardous legacy substances such as short-chain phthalates and lead-based stabilizers that exceed the limit values now permitted. The use of short-chain phthalates is restricted as per Annex XVII to Commission Regulation No. 552/2009, and the EU enacted Regulation 2023/293 in May 2023 to revise the restrictions on the use of lead and lead compounds. Processing "old" PVC involves removing the hazardous legacy substances and then mixing the recovered PVC with new PVC. The resulting product is in line with the current legal provisions and fulfills the growing customer demand for safe, sustainable recycled materials.

Fraunhofer ITEM was responsible for carrying out risk and exposure assessments on four processes for removing hazardous legacy substances. These processes, which were developed and optimized by several project partners, include methods of removing phthalates using $scCO_2$ (Fraunhofer Institute for Chemical Technology ICT), removing lead using solid-liquid extraction (Centexbel) and MoS_4-LDH (AIMPLAS) and for recovering high-purity metallic lead (Azor). The final risk assessment results were summarized on safety cards for each process as part of safety guidelines. After 4.5 years of collaborative work, the project is complete, and the final results will be published in 2024.

Contact

Ariane Zwintscher
Regulatory Affairs
ariane.zwintscher@item.fraunhofer.de

Katharina Blümlein Ph.D.
Bio- and Environmental Analytics
katharina.bluemlein@item.fraunhofer.de

Draft of an EU register for health-based limit values

As part of its "one substance, one assessment" approach, the European Commission is planning a centralized, structured database for health-based limit values (HBLVs). This database will make it easy to access all relevant HBLVs in one place.

In collaboration with Novamechanics Ltd., a team of scientists from Fraunhofer ITEM worked on designing, developing and planning the implementation of this register. The Fraunhofer researchers mapped all the available human, animal and environmental HBLVs from EUCLEF, OpenFoodTox, the EU Pesticides Database and an online survey of the register's future users. Overall, they identified 128 HBLVs and provided background information and associated metadata for each of these, so that they could then identify the relevant limit values.

In the online survey, future users of the register were asked about usage patterns and their needs and requirements, and their responses were then analyzed. The results of the mapping step were combined with the findings from the survey to create an initial list of the limit values and metadata that must be included in the future register. Novamechanis Ltd. drafted the register's structure, functionalities and metadata framework. This included ensuring data reusability and quality assessment. In addition, processes were established for maintaining and updating the database and for involving the most important EU authorities.

On this basis, the team developed an initial version of the HBLV register (https://op.europa.eu/en/publication-detail/-/publication/a64ae83c-8cda-11ee-8aa6-01aa75ed71a1/language-en).

Contact

Bianca Pieczyk
Regulatory Affairs
bianca.pieczyk@item.fraunhofer.de

Fraunhofer ITEM and its partners are investigating whether and how "old" PVC can be integrated into the circular economy as part of the EU project REMADYL.

The European Commission is planning a centralized, structured database for health-based limit values (HBLVs).

The EU project MUTAMIND includes ITEM researchers working on gaining a better understanding of the processes leading to mutagenicity of nitrosamines – particularly those derived from active substances – and to develop custom-fit in-vitro detection methods for sensitive genotoxicity screening.

Active substances can form nitrosamines inside the body. Clustering methods based on molecular properties help ITEM researchers to identify which active substances are more reactive.

MUTAMIND: optimized in-vitro test systems for investigating the genotoxicity of Nnitrosamines

In recent years, some drugs have been recalled from the market due to slight impurities consisting of carcinogenic N-nitrosamines (NAs). These "NA drug substance-related impurities" (NDSRIs) are giving rise to increasing concern in the pharmaceutical industry, because their mutagenic and carcinogenic potential is often unknown. As a result, regulatory activities have been initiated to improve risk assessment, including the EMA-financed MUTAMIND project. Led by Fraunhofer ITEM, eight partners are working to obtain a better understanding of the mechanisms that contribute to the mutagenicity of NAs and of NDSRIs in particular, and to develop custom-fit, sensitive in-vitro genotoxicity screening. The SC02 in-vitro subproject was aimed at optimizing the Ames test (mutagenicity in bacteria) to detect mutagenic NAs, and at evaluating the predictivity of the Ames fluctuation test and the in-vitro alkaline comet assay (to detect DNA strand breaks) with respect to the carcinogenicity of NAs using five liver models.

The subproject, spearheaded by Fraunhofer ITEM and involving six partners from Germany, the United Kingdom, Italy and the USA, covered the selection of substances, literature reviews, the corresponding experimental work and a final "Benchmark Dose Modeling" (BMD). The substances that were ultimately selected included more than 40 structurally different carcinogenic and non-carcinogenic NAs for validation purposes and NDSRIs of unknown mutagenicity. First of all, the metabolic competence of the selected liver cell models and exogenous metabolic activation systems (S9 mix) was characterized, as metabolic conversion is essential for the mutagenicity of NAs. Following this, the Ames test was optimized, and the comet assay was evaluated using a small group of NAs. For the Ames test, the pre-incubation method with three bacterial strains, water or a low concentration of DMSO as a solvent and 30 percent hamster S9 mix as exogenous metabolic system was found to be optimal for testing the mutagenicity of NAs. This design was then used to investigate the remaining, structurally diverse NAs, including many NDSRIs.

With the help of BMD analyses, the project demonstrated that the in-vitro comet assay with normal human liver cells, HepG2 cells plus hamster S9 mix or human liver slices is a promising tool for identifying mutagenic and non-mutagenic NAs. Subject to further validation, this test could usefully supplement the Ames test in assessing NA-related risks. The data obtained in the SC02 project will help to improve the accuracy of the potency categories determined using the Carcinogenic Potency Categorization Approach (CPCA) and make an important contribution to the ongoing regulatory activities regarding the risk assessment of NAs, including NDSRIs.

Contact

Dr. Christina Ziemann
Genetic Toxicology
christina.ziemann@item.fraunhofer.de

Endogenous formation of nitrosamines – are they a risk to humans?

Nitrosamines (NAs) are chemical compounds that usually have carcinogenic and genotoxic effects. They often occur in foods, such as grilled meat, and as contaminants in medicines. As part of the GITox project funded by the European Medicines Agency (EMA), 14 drugs were examined to see if they might form NAs under realistic conditions – for example, in the stomach or the human microbiome – in the presence of physiological amounts of nitrite.

Scientists at the German Federal Institute for Drugs and Medical Devices (BfArM) showed that under acidic conditions typical to the stomach, drugs containing secondary aromatic amines exhibit a higher conversion rate to NAs than aliphatic amines. Overall, four out of twelve of the active substances were prone to forming NAs under acidic conditions, although most of them only produced very small quantities. Scientists at the University of Bonn found that some bacteria from the large and small intestine exhibit very high levels of nitrite reductase activity, which converts the nitrite to ammonium, detoxifying it in the process. In addition, no NA was formed during

experiments under anaerobic conditions using 16 different bacteria from the large and small intestine and the stomach and a combination thereof. From these two findings, the conclusion can be drawn that the gut microbiome has a detoxifying effect and does not significantly influence NA formation.

A structure-activity analysis by Fraunhofer ITEM scientists showed that the protonation status of the secondary amines is the main factor determining their ability to form the corresponding NAs under acidic conditions. Clustering the drugs according to molecular properties showed that these tools can be used to distinguish reactive drugs from those that are less reactive.

Contact

Dr. Sylvia Escher
In-silico Toxicology
sylvia.escher@item.fraunhofer.de

Cell culture plate with inserts on which human lung cells are exposed to airborne substances, such as room sprays, using in-vitro inhalation methods.

In-vitro inhalation methods help with safe product development of cosmetic sprays

The ban on animal testing and increased characterization requirements for inhalation exposure pose challenges for the development and safety evaluation of spray products. In spite of this, major progress is still being made with in-vitro inhalation applications. Quantitative in-vitro to in-vivo extrapolations (QIVIVE) enable relevant in-vitro test environments, aerosol characterization and the estimation of inhalation exposure to be integrated into a single concept that can generate data to support the development and safety evaluation of cosmetic products.

Fraunhofer researchers have been investigating a spray product for room conditioning in hairdressing salons. They have carried out in-vitro inhalation experiments to investigate acute effects on the respiratory tract with a battery of tests using cells from human lungs and the P.R.I.T.® ExpoCube® exposure system patented at Fraunhofer ITEM. They have obtained dose-response relationships for the atomized product that consider real human exposure conditions. A QIVIVE approach was used to compare NOAELs (No Observed Adverse Effect Levels) obtained in vitro to results from exposure estimates based on a hairdresser's eight-hour working day.

With this process, it was possible to calculate safety factors between the onset of a (potentially adverse) biological effect determined in vitro and actual human exposure as a function of exposure conditions, forming a basis for an initial safety evaluation. Furthermore, these effects could be attributed to a particular component of the spray product, allowing an alternative product formulation to further reduce the – already minimal – biological effects.

This case study therefore shows the potential of integrating in-vitro inhalation and exposure estimation methods into a QIVIVE concept. The approach enables a quantitative assessment of potential biological effects and an identification of potentially harmful substances, and could thus make a crucial contribution to the development of safe products.

Contact

Dr. Detlef Ritter
In-vitro Test Systems
detlef.ritter@item.fraunhofer.de

Modeling approaches for estimating inhalation exposure from spray applications

Although sprays offer numerous advantages, such as even and highly efficient distribution of substances over surfaces, they are associated with high levels of substance inhalation. Protecting both human health and the environment requires a reliable method for quantifying exposure to the substances distributed via sprays – such as measurement by experimental means or, if no suitable data is available, through model-based predictions. However, exposure models with varying complexity levels that can be used for spray applications are still underrepresented in the relevant guidelines. ITEM scientists published an overview of the available models and the current status of and further need for modeling of spray applications in 2021 (Hahn, S. et al., 2021: DOI 10.3390/ijerph18157737). The study indicated a need for improvements to existing spray models, including more user-friendly software.

For the BAuA project "Modular Exposure Models for OSH Risk Assessment in Chemical Safety" (MEMORA), Fraunhofer researchers created a complete model for estimating inhalation exposure from spray applications.

The German Federal Institute for Occupational Safety and Health (BAuA) has initiated various projects for (further) developing exposure models and evaluating the models' validity, all under the header of "Modular Exposure Models for OSH Risk Assessment in Chemical Safety" (MEMORA). As part of this initiative, Fraunhofer ITEM researchers created an overall tool for estimating inhalation exposure from spray applications. To do this, the ITEM team analyzed and refined three existing models and combined them into a two-step approach. The individual models included a generic 2-box spray model with two refinement options based on the use of correction factors or airborne release factors determined by experimental means (Hahn, S. et al., 2024: DOI 10.3389/fpubh.2024.1329096). The other two models used were SprayExpo and SprayEva. The model approaches were translated into the programming language R and combined into one overall tool. The tool's performance was then tested using existing measurement data from workplaces and example scenarios.

The theoretical and practical results obtained in this project in relation to the modeling of inhalation exposure from sprays will be used to support the industry sector and government authorities in assessing risks to human health in the context of regulatory processes.

Contact

Dr. Stefan Hahn
Chemical Safety and Toxicology
stefan.hahn@item.fraunhofer.de

EVape helps to improve safety for e-cigarette consumers

Fraunhofer researchers and engineers have developed the EVape prototype for controlled vaporization of e-liquids, allowing them to analyze the resulting emissions and subsequently perform precise toxicological evaluations. Although e-cigarettes are considered to be less harmful than conventional cigarettes, the vaporization of e-liquids can result in the formation of compounds that cause health problems. The risk is particularly strong when the e-cigarettes contain substances that do not pose problems when consumed orally or inhaled, but that break down into other dangerously toxic substances when they are heated.

When submitting the notification regarding their liquids, manufacturers need to provide the relevant toxicology and emission data; however, as this data is generated using different commercially available e-cigarettes that have diverse temperature profiles, the results are not universally valid or comparable. EVape solves this issue by conducting vaporization under controlled conditions across a wide range of temperatures, which means the results are independent of the e-cigarette used. This ensures greater safety for consumers and can support regulatory authorities with monitoring the e-cigarette liquids sold on the market. The prototype has been patented and will be available to laboratories, regulatory authorities and industry companies in the future.

Contact

Dr. Stefanie Scheffler
Regulatory Affairs
stefanie.scheffler@item.fraunhofer.de

The RITA pathology database: an indispensable resource in toxicological pathology for over 35 years

In 1988, the Fraunhofer institute in Hannover (then called Fraunhofer ITA) created a database for assessing spontaneously arising proliferative changes during long-term studies on rodents and launched the project in collaboration with pharmaceutical and chemical companies. From then until the present day, 345 studies comprising more than 125,000 individual findings from control animals have been reviewed by Fraunhofer pathologists and entered in the RITA database (Registry of Industrial Toxicology Animal-data).

A key foundational element of this database was the collective development of a standardized nomenclature for histopathological findings and the definition of unambiguous diagnostic criteria. These were published under the auspices of the International Agency for Research on Cancer (IARC) and the World Health Organization (WHO), and a digital version of them was made available to RITA members under the title of RENI (REgistry Nomenclature Information system). In 2007, this information system was made available in a more open format, namely goRENI (global open RENI), which enabled a global initiative to revise the findings, lasting until 2019, and led to the absorption of this standardized nomenclature into the FDA's SEND format (Standard for Exchange of Nonclinical Data).

Best practices have been maintained in data validation over the years by ensuring that only pathologists with many years of experience perform the initial review of the findings and then discuss them with a large group of other pathologists if necessary. Great advances have been made in terms of developing digital resources for supporting these processes. These resources cover all forms of data transfer, along with the digitization of tissue sections and voting tools that facilitate online discussions.

Contact

Dr. Rupert Kellner
Databases and Information Systems
rupert.kellner@item.fraunhofer.de

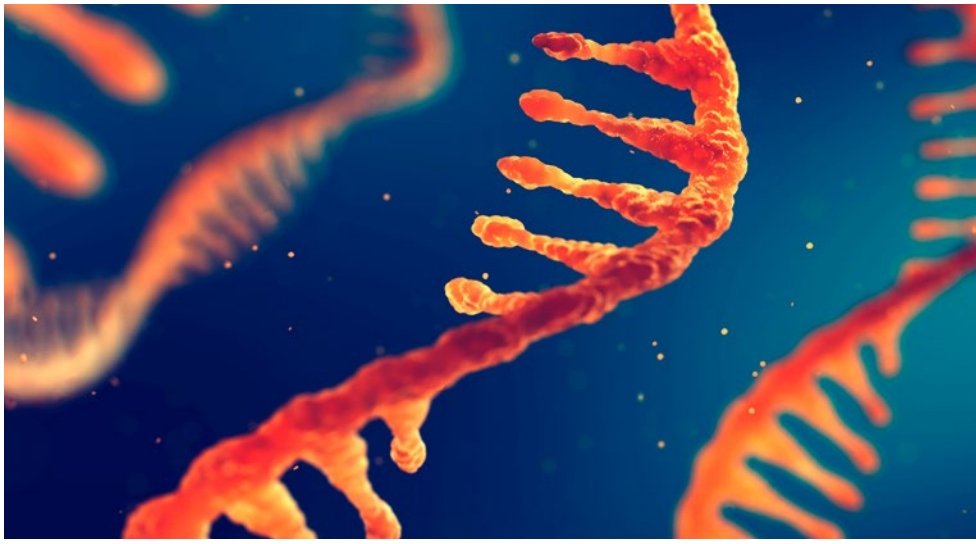
Dirk Schaudien Ph.D.
Pathology and Clinical Chemistry
dirk.schaudien@item.fraunhofer.de

Pathologists share information at regular meetings and discuss findings at the 21-head discussion microscope at Fraunhofer ITEM.

The patented EVape prototype allows e-liquids to be vaporized in a controlled manner so that the emissions they generate can be analyzed and subjected to a precise toxicological assessment.

RNA technologies

Developing RNA-based compounds to the stage of clinical use



RNA-based therapeutics are a drug class with huge potential for medicine – and scientists have barely scratched the surface of their possible use. Fraunhofer ITEM researchers develop novel drugs and methods for RNA-based therapeutic concepts.

The targeted use of RNA compounds based on coding or non-coding RNA sequences enables a tailored response of the respective target cells under certain pathological conditions. Fraunhofer researchers use a wide range of RNA-based compounds, such as small interfering RNA, nucleoside-modified messenger RNA or RNA blockers – from target discovery through to preclinical development programs. Bioinformatic models play a key role when it comes to selecting disease-associated RNAs, studying their interaction with other genes, and optimizing drug design.

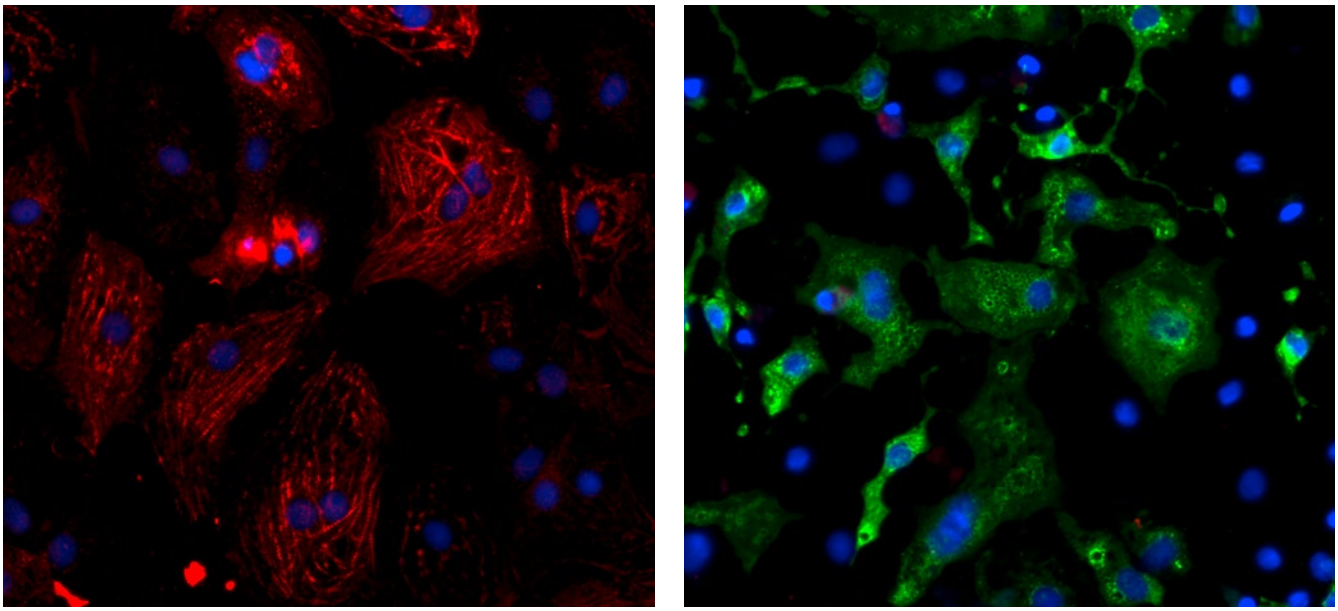
Special viral and non-viral administration technologies, both at the molecular and equipment level, are being developed for the targeted use of RNA compounds. Local delivery via the airways is a promising solution in particular for RNA therapeutics used to combat lung diseases.

For safety and efficacy testing of therapeutics, researchers use proven in-vitro and in-vivo animal models and are continuously developing new model systems that are based on human tissues as well as mini organs and cells derived from stem cells.

Researchers at Fraunhofer ITEM are developing bioprocessing methods and production technologies for the modular and automated manufacture of RNA molecules and RNA nanocarriers that can be scaled right up to industry level. Rapid, safe and reliable production technologies for the manufacture of RNA-based vaccines and drugs are a fundamental requirement for successful translation into marketable products. To support this, process development and GMP production of mRNA therapeutics for early-phase clinical trials take place at Fraunhofer ITEM, and the early-phase clinical trials can also be conducted in-house.

RNA molecules are attracting increasing interest for diagnostic purposes as well. The expression profiles of RNA molecules are altered in many pathologies, such as lung diseases and cancer. RNA can be obtained from various liquid biopsies, such as blood, urine or cerebrospinal fluid. Taking a liquid biopsy is much less invasive for patients than a tissue biopsy. Next generation sequencing technologies allow the RNA composition of a sample to be determined. RNA expression profiles can thus be used as biomarkers to characterize diseases, predict the response to a specific therapy, and monitor treatment success. Fraunhofer ITEM researchers have developed technologies that enable the analysis of even very small quantities of RNA as well as determination of the expression profiles of single cells or cell-free, circulating RNA.

Our Highlights



SARS-CoV-2 infects not only lung cells but also heart muscle cells.
The comparison of the two images – on the left, healthy heart muscle cells, and on the right, heart muscle cells infected with SARS-CoV-2 – shows that cardiomyocytes lose their sarcomeric organization (cardiac troponin T in red) after a SARS-CoV-2 infection (staining of the SARS-CoV-2 nucleocapsid in green) and the cells increasingly die.

Circular RNA: an innovative RNA therapy agent?

Since the COVID-19 pandemic, the idea of using mRNA in vaccines has garnered universal attention. Messenger RNA, also known as mRNA, can translate the genetic information stored in DNA into proteins. However, these protein-coding RNAs actually represent only a very small portion of the human transcriptome. The majority of RNAs are actually classified as noncoding RNAs (ncRNAs); these are functional RNA molecules that regulate a wide range of biological processes. Now, a new class of ncRNAs has come to join known forms such as microRNAs (miRNAs) and long noncoding RNAs (lncRNAs): closed, ring-shaped RNA molecules known as circular RNAs (circRNAs). Scientists identified these molecules by applying new bioinformatic high-throughput analysis methods in transcriptome sequencing.

Although every cell contains thousands of circular RNAs, we have yet to discover what their functions are for the most part. However, because of their ability to interact with other biomolecules such as miRNAs, mRNAs and proteins, more and more experts are coming to view circRNAs as important regulators of gene expression that play a fundamental role in the emergence of diseases. These molecules can be turned on or off using recombinant circRNAs or antisense oligonucleotides, which means that they could be an innovative starting point for the development of new therapeutic strategies.

Researchers participating in the RNA Therapeutics platform by the Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD are studying circRNAs in human cardiomyocytes from patients that have experienced a SARS-CoV-2 infection. The SARS-CoV-2 virus severely attacks cardiomyocytes as much as lung cells and research has shown that underlying cardiovascular conditions are associated with a sharply increased risk of serious or fatal

cases of COVID-19. The research team has already identified a number of circRNAs that seem to play an important role in SARS-CoV-2 infection of cardiomyocytes. Using inhibitory antisense oligonucleotides for targeted silencing of a specific circRNA, which the team has dubbed "circCOV-1," led to a significant reduction in viral load. At present, the scientists are conducting mechanistic studies to determine whether inhibiting circCOV-1 prevents SARS-CoV-2 from entering the cell or whether it disrupts the virus' replication within cardiomyocytes.

Contact

Prof. Dr. Christian Bär
Regenerative Cardiology
christian.baer@item.fraunhofer.de

RNAi therapy to treat viral respiratory diseases

There are still no effective drugs for most viral diseases. Antiviral therapies are therefore urgently and quickly needed. However, the development of therapeutics can take decades. In the iGUARD (integrated Guided Ultrafast Antiviral RNAi Drug Development) project, a team of researchers from Fraunhofer ITEM and Hannover Medical School (MHH) has set the goal of developing customized therapies as quickly as possible. The iGUARD project has already been funded twice by the German Federal Agency for Disruptive Innovation (SPRIND) as part of the SPRIND Challenge "Broad-Spectrum Antivirals" and, in the third and final round of the innovation competition in 2023, received follow-up funding of 2.5 million euros for the further development of new viral inhibitors.

The researchers are concentrating on RNA-based active substances that can be adapted to different viruses quickly so as to enable protection against emerging viral infectious diseases. To this end, they are initially focusing on the parainfluenza virus. The aim is to use what is known as RNA interference (RNAi) to prevent the virus from replicating and spreading in the body. RNAi is a natural mechanism in our cells for switching off genes in a targeted manner. The research team has developed suitable RNAi building blocks that specifically degrade different sections of the parainfluenza virus genome that the virus needs to replicate. The efficacy and safety of these RNAi candidates have been successfully tested on human lung tissue sections as well as in 3D cell cultures from human lung epithelium and in animal models. The RNAi candidates were able to suppress the parainfluenza virus by 95 percent in vitro and in vivo. The researchers have also developed an inhalable formulation to deliver the therapeutic RNA directly to the target cell infected by the virus in the lung. Studies on the ex-vivo model of the isolated perfused lung showed that the drug can be nebulized well and reaches the lung epithelium as desired.

In the third funding stage, the researchers now want to meet the regulatory requirements for a clinical trial. This means that the efficacy and safety of the approach will now be worked out even more clearly and important steps regarding clinical application will be developed. The long-term goal is to use the developed iGUARD platform to construct corresponding RNA therapeutics for other known viral diseases. Ultimately, the aim is to quickly adapt active substances to unknown, newly emerging virus types and thus be able to develop customized therapies very quickly.

The project is a collaboration between the MHH – specifically the Institute of Experimental Hematology (Prof. Axel Schambach, Philippe Vollmer Barbosa) and the Clinic for Hematology, Hemostaseology, Oncology and Stem Cell Transplantation (Prof. Adrian Schwarzer) – and the Fraunhofer ITEM Division of Preclinical Pharmacology and Toxicology (Prof. Armin Braun, Philippe Vollmer Barbosa).

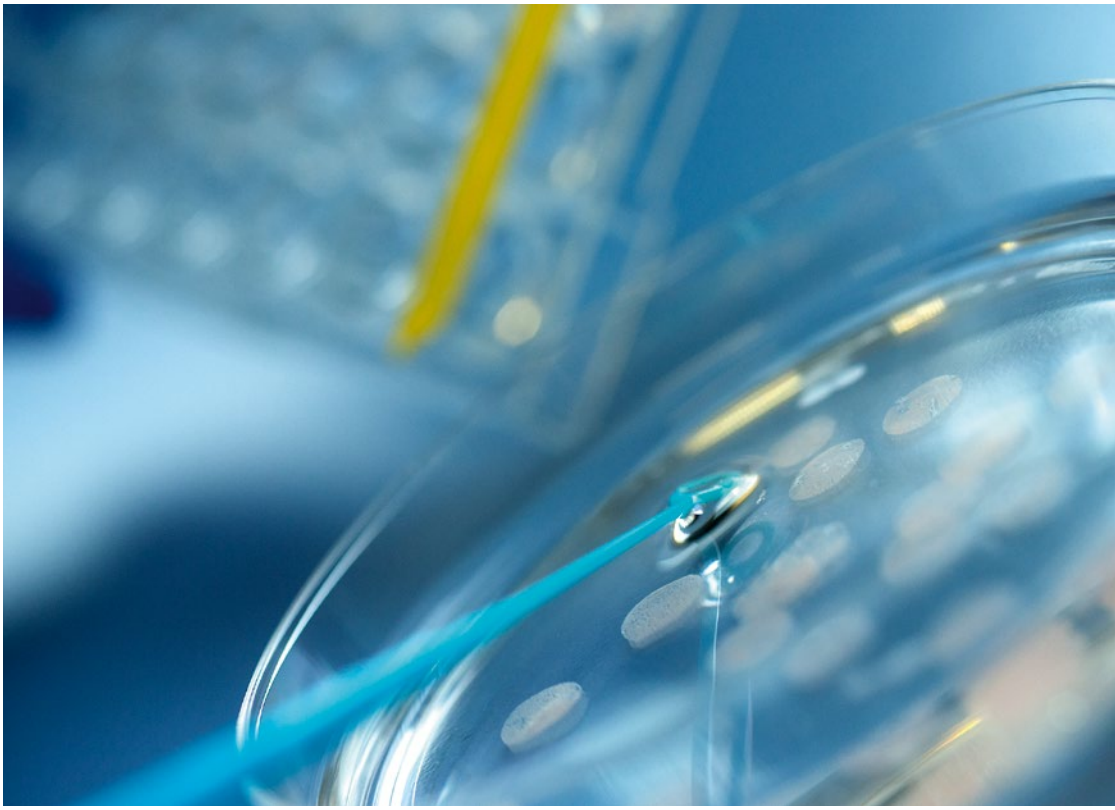
Contact

Dr. Philippe Vollmer Barbosa
Preclinical Pharmacology and Toxicology
philippe.vollmer.barbosa@item.fraunhofer.de

Initially, in-vitro studies on human lung tissue sections are carried out to determine whether the new RNAi active substances are effective. These studies are then followed by further tests on inhaled administration using in-vitro lung test systems.

Immunology and infection research

Development and testing of anti-infective drugs against bacteria and viruses

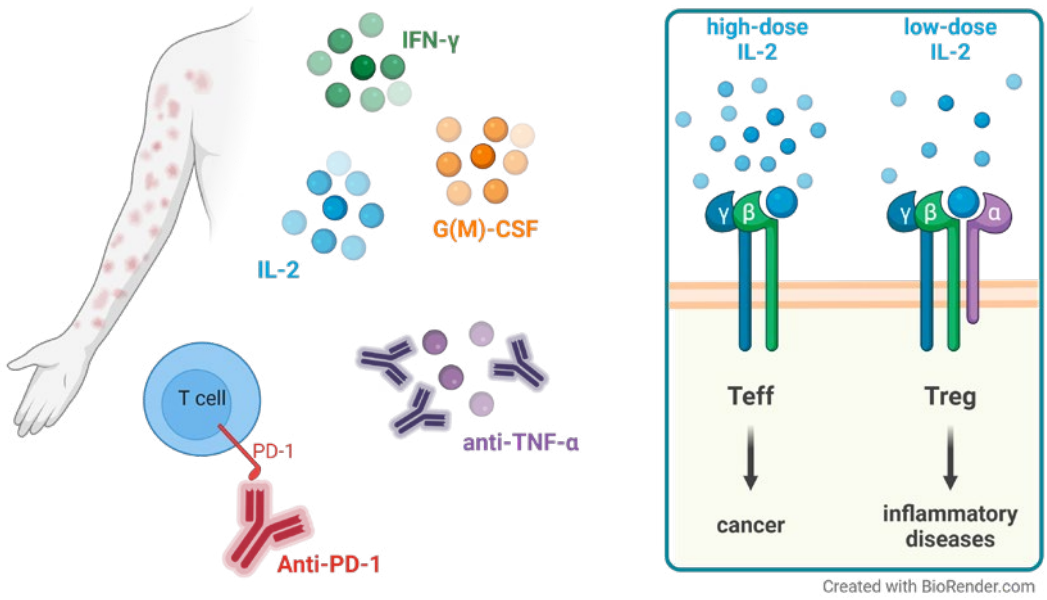


About eight percent of the population worldwide suffer from immune-mediated diseases. Almost any organ or tissue can be affected. In most cases, immune-mediated diseases are treated symptomatically with drugs that non-specifically suppress the patient's immune system. Therapies that eliminate the cause of the disease and, ideally, are individualized are hardly available at present. There is a great need for research, both on pathophysiological issues and on potential therapeutic targets, and Fraunhofer ITEM is addressing this need.

The development, formulation, and mode of delivery of anti-infective substances are current research topics at the institute. The expertise in formulation development is being further expanded and the development and production of anti-infectives for inhaled administration as drug aerosols is being pushed. As far as bacterial infections are concerned, Fraunhofer ITEM has a special focus on the development of manufacturing processes for bacteriophages – in this field the institute is at the cutting edge. Fraunhofer ITEM researchers produce phages as investigational medicinal products and establish models for safety and efficacy testing.

Fraunhofer ITEM has many years of expertise in immunotoxicology and immunopharmacology, centered on the development of biopharmaceuticals and advanced therapy medicinal products (ATMPs) in addition to mechanistic research. The focus here is on diseases of the lungs and airways – especially asthma, chronic obstructive pulmonary disease (COPD), fibrotic lung diseases, allergies, and infections. For the investigation of immunomodulatory substances and ATMPs, the institute is further developing in-vitro and ex-vivo models (e.g. precision-cut tissue slices), innovative testing strategies, and endpoints in toxicity studies. Human organ models and materials from patients play a pivotal role in this context to enable an even better pharmacological and toxicological understanding of the immune mechanisms relevant to humans.

Our Highlights



Interleukin-2 is used in different doses for cancer therapy or to treat inflammatory diseases, with skin rashes as a common side effect.

Mechanism of skin inflammation triggered by interleukin-2

Under the EU project "imSAVAR" financed by the Innovative Medicines Initiative (IMI), experts from a number of countries and disciplines are working together to improve the prediction of undesirable effects of medicines. A particular focus is on treatments that affect the immune system, such as CAR-T cells, antibodies and interleukins.

Researchers at Fraunhofer ITEM have taken a closer look at treatment with interleukin-2 (IL-2) and the side effects that have occurred. IL-2 is used for treating inflammatory diseases and cancer. However, this treatment is often associated with skin rashes. To ascertain the causes of these side effects, the researchers investigated how IL-2 triggers immune responses in the skin and what role the IL-2 receptor plays in this.

After carrying out subcutaneous IL-2 injections in mice, the researchers observed that various immune cells were accumulating in the skin, including innate lymphoid cells (ILC2), which produce IL-4 and IL-13, and dermal γδ T cells, which produce IL-17. This caused a shift leading to type 2 and type 17 immune responses. While examining the significance of the IL-2 receptor, they found that its reduction on regulatory T cells in the skin aggravated the skin inflammation.

In summary, the results show that immune cells in the innate immune system are the main cause of the side effects of IL-2 treatment and underscore the significance of the receptor in this process.

Contact

Dr. Katherina Sewald
Preclinical Pharmacology and In-vitro Toxicology
katherina.sewald@item.fraunhofer.de

The isolated perfused lung is a model for the investigation of airborne substances. It provides an alternative to animal models in the spirit of the 3Rs.

Innovative use of drug candidates for respiratory tract infections

The SARS-CoV-2 pandemic made it clear to all of us how seriously respiratory infections can affect people's health. The Fraunhofer "Infection and Immunology" research group conducts various projects to investigate the efficacy of unique drug candidates for viral and bacterial respiratory infections. In the past year, it has succeeded in developing and testing new viral inhibitor candidates.

Researchers at Fraunhofer ITEM and the Hannover Medical School have jointly pursued an innovative approach: Together, they have developed an RNA-based active substance to treat human parainfluenza virus (HPIV3) and have also tested it successfully in a preclinical setting. First, they identified potentially effective RNA candidates in cell culture models. Using an in-vitro approach, the researchers demonstrated a significant reduction in viral load in HPIV3-infected LLC-MK2 cells with some of these candidates. The most promising candidate also demonstrated efficacy in a more complex, human tissue system: human precision-cut lung slices (PCLS). To increase efficacy at the infection site, an RNA formulation was developed specially for administration by inhalation. The RNA was packaged in lipid nanoparticles (LNPs) and various LNP formulations were tested after administration by inhalation in isolated perfused rat lungs. The German Federal Agency for Disruptive Innovation (SPRIND) funded the project through a national research competition.

Since efficacy testing for clinical development of a medicinal product has to be done in an animal model, the researchers at Fraunhofer ITEM developed an infection model in cotton rats. In line with the 3R principles (reduction, refinement, replacement of animal testing), PCLS were first generated from cotton rats and treated similarly to human PCLS. A successful reduction in viral load was observed, which meant that cotton rats could be treated with inhaled LNP-packaged RNA for the first time. The next development steps include toxicological tests.

Another project also involves an inhaled treatment for viral infections. Together with OM Pharma, researchers at Fraunhofer ITEM are investigating the immunological response of virus-infected and non-infected murine PCLS or human cells following ex-vivo and in-vitro treatment with the active substance OM-85. The active substance was also tested in isolated perfused lungs following administration by inhalation. This made it possible to plan the next steps toward developing a treatment with inhaled OM-85.

Contact

Dr. Franziska Dahlmann
Infection and Immunology
franziska.dahlmann@item.fraunhofer.de

The iCAIR® team introduce themselves at the Swiss Biotech Days in a round table discussion.

iCAIR® established as an internationally visible antiviral drug research brand

Infectious diseases continue to be one of the biggest global threats to human health – partly because of evolving drug resistance and partly due to the emergence of new diseases. The International Consortium for Anti-Infective Research, iCAIR®, comprising the Institute for Glycomics at Griffith University in Australia, the Hannover Medical School, the Helmholtz Centre for Infection Research and Fraunhofer ITEM, has set itself the objective of closing the gap between the discovery of new active substances and developing them into usable therapeutics. To this end, iCAIR® is focusing on the scientific development and testing of novel viral inhibitors and on business development to strengthen the iCAIR® brand.

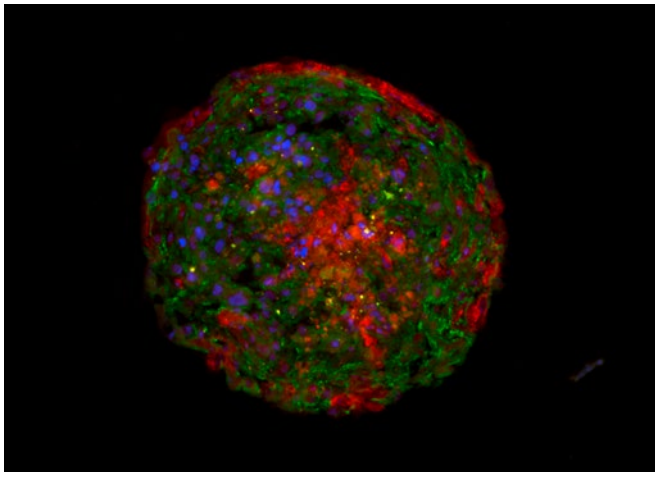
To develop iCAIR®'s own drug candidates as well as to conduct research on behalf of industry, Fraunhofer researchers have been working closely with the researchers from the iGUARD project to establish state-of-the-art in-vivo infection models. These models augment the preclinical portfolio to help ensure the safety and efficacy of new medicines and enable subsequent clinical trials.

Based on their preclinical expertise and their collaboration, iCAIR® partners Griffith University and Fraunhofer ITEM were selected by the Australian government to showcase the iCAIR® consortium in a round table discussion at the Swiss Biotech Days 2023. At BIO-Europe 2023, international networks were formed with industry and institutions such as the Australian QIMR Berghofer Medical Research Institute in order to establish iCAIR® as a recognized platform for drug development.

Contact

Dr. Sebastian Konzok
Preclinical Pharmacology,
Chemical Safety and Toxicology
sebastian.konzok@item.fraunhofer.de

Heart organoids are functional miniature heart structures that can beat spontaneously or be controlled through electrical stimulation, similarly to a pacemaker.



Miniature hearts: Heart organoids with their own immune systems

In recent years, there have been some major advances in cancer treatments, largely due to the development of new immunotherapies. In particular, this includes treatments using monoclonal antibodies and cell therapies such as CAR-T cells, which directly target tumor cells. However, it has been shown that these treatments – much like "conventional" cancer treatments that use anthracylines or receptor tyrosine kinases – can often have cardiotoxic properties and lead to heart failure. On the one hand, the new treatments are a blessing, as they are allowing more and more patients to overcome cancer; on the other hand, the cardiotoxicity of the treatments, which sometimes only becomes apparent years later, is posing an increasingly serious clinical problem.

The potential cardiotoxicity of a new immunotherapy or cell therapy agents cannot be sufficiently predicted or simulated in conventional cell cultures due to the necessary complexity. In order to solve this issue, scientists at the Hannover Medical School and Fraunhofer ITEM have established a new complex heart organoid model that more effectively mimics the properties of the natural human heart during its (patho-)physiological development. The research team has already produced the first functioning organoids. They consist of cardiomyocytes, cardiac fibroblasts, endothelial cells derived from induced pluripotent stem cells (hiPSC), and stem cells obtained from adipose tissue. These create functional miniature heart structures that can beat spontaneously or be controlled through

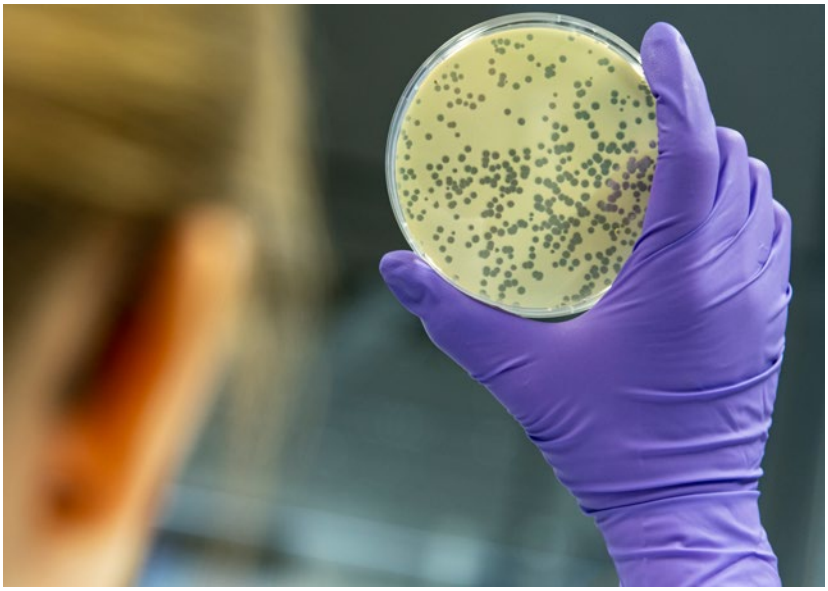
electrical stimulation, similarly to a pacemaker. Disease modeling approaches have shown that the heart organoids' contractility can be influenced medicinally and that administering conventional chemotherapeutics leads to a cardiotoxic contractile imbalance.

The next step will be to supplement these organoids with another cell type – designer immune cells derived from stem cells. These cells will provide the miniature hearts with an immune system, making it possible for scientists to model and test the cardiotoxicity of new immunotherapies and cell therapies in the future.

Contact

Prof. Christian Bär
Regenerative Cardiology
christian.baer@item.fraunhofer.de

Prof. Nico Lachmann
Attract Group "IMMUNITY"
nico.lachmann@item.fraunhofer.de



Certain phages cause lysis in bacteria – this creates holes in the bacterial lawn, as shown here on this agar plate.

First manufacturing authorization granted for phage drugs in Germany

In the Phage4Cure project, three bacteriophages (or phages for short) are being used as anti-infectives to combat bacterial infections caused by Pseudomonas aeruginosa. This bacterium is a major cause of comorbid disease in patients with cystic fibrosis (mucoviscidosis), as it can further impair lung function.

The pharmaceutical biotechnologists at Fraunhofer ITEM have developed processes for manufacturing phages to serve as active pharmaceutical ingredients for investigational medicinal products (IMPs). They have designed a technological platform that enables the production of all three phages by adjusting some parameters. The individual steps in this manufacturing platform include cultivating the production strain, propagating the phages in the cells, initial separation and filtration, multiple chromatographic purification processes, and formulation and aseptic filling of the IMPs. At the start of 2023, Fraunhofer ITEM's Division of Pharmaceutical Biotechnology became the first institution in Germany to receive manufacturing authorization to carry out this pharmaceutical-technological process for producing phages. With this authorization in place, three phage IMPs were produced in accordance with GMP conditions and handed over to the project partner Charité Research Organisation. Since the clinical trial was authorized by the German Federal Institute for Drugs and Medical Devices (BfArM) in August 2023, Charité Research Organisation has been using IMPs produced at Fraunhofer ITEM to conduct the first clinical trial with phages in Germany.

Contact

Dr. Sarah Wienecke
Microbial Cultivation
sarah.wienecke@item.fraunhofer.de

Malignant disease research

Development of personalized therapeutic strategies for tumor diseases

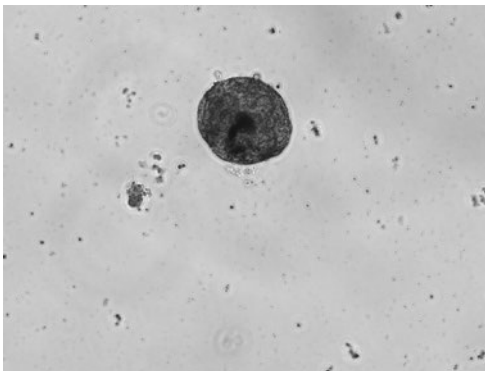
Research into metastatic disease and the development of diagnostics and pharmaceuticals are at the focus of Fraunhofer ITEM in Regensburg. The aims are to understand a patient's individual condition, establish appropriate diagnostics, advance prevention, and optimize therapies.

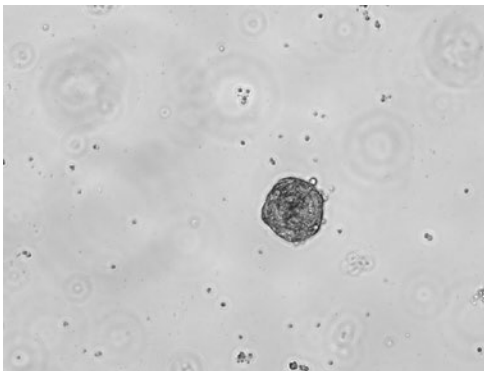
An area of special expertise of the researchers is the molecular biological characterization of single cancer cells, which can be collected as circulating tumor cells by liquid biopsy or isolated from lymph node tissue or bone marrow as disseminated cancer cells. In order to define new treatment monitoring strategies, the liquid biopsy concept and the technology for single-cell analysis have been further developed, so that cancer cells from the cerebrospinal fluid (CSF) can now also be isolated and analyzed.

For the development of patient-specific therapies, for example with monoclonal antibodies as checkpoint inhibitors and advanced therapy medicinal products (ATMPs), the researchers are establishing integrated testing strategies based on ex-vivo models derived from human tumor samples. In addition, they continue to enhance the high-throughput drug screening technology based on patient-specific models. The data management established at the institute and comprehensive bioinformatics enable custom-fit analyses of the generated data.

Tumorigenesis is also an issue in the risk assessment of active pharmaceutical ingredients and chemicals. Fraunhofer ITEM is developing examples of risk assessment of nongentoxic substances by means of QSAR and in-vitro models on behalf of European regulatory authorities, including EMA, ECHA, and EFSA. This will further add to the researchers' existing wealth of experience in exploring and applying integrated assessment and testing strategies (IATA) – risk assessment that is in line with the principle of the 3Rs.

Our Highlights





Cell suspensions were taken from the lymph nodes of lung cancer patients, and so-called spheres were formed from them in culture. The sphere formation in the lymph node samples correlates with the detection of disseminated tumor cells and significantly poorer prognoses for patient survival.

Ex-vivo expansion of disseminated cancer cells is associated with progression of the disease in patients

Lung cancer is one of the most common tumor diseases in Europe and the most common cause of cancer-related deaths worldwide. There appears to be a correlation between the occurrence of disseminated cancer cells (DCCs) in the lymph nodes or bone marrow, the functional and molecular properties of these cells, and later incidences of metastasis. The presence of these epithelial cells can be detected primarily by means of the markers cytokeratin or EpCAM (epithelial cell adhesion molecule). Ex-vivo expansion of these cells has yet to be adequately investigated and so far, it has not been studied in the context of increased metastasis. To detect the cells that metastasis originates from and to gain a better understanding of the cellular basis of metastasis, researchers in a recent study used a cultivation method that does not rely on markers, focusing instead on sphere formation and characterization (Treitschke, S. et al., 2023: DOI 10.1002/ijc.34658).

A total of 131 lung cancer patients were recruited for this study, in collaboration with the University Hospital Regensburg and the hospital Krankenhaus Barmherzige Brüder Regensburg. The scientists took 199 lymph node biopsies and used them to generate cell suspensions, which were then analyzed using different methods in parallel. In one of these methods, immunocytological quantification was used to test the cell suspensions for the presence of EpCAM-positive DCCs, while in another, the specimens were cultivated in non-adherent, serum-free sphere cell culture conditions for a period of weeks. Sphere formation was observed in 35 percent of all the cultures in the study (69/199). The spheres formed in ex-vivo conditions and their cellular composition were then characterized using a wide range of analysis methods from molecular biology, such as gene expression signatures, the detection of typical lung cancer mutations and the identification of genome aberrations. Interestingly, a correlation was shown between sphere formation and the detection of DCCs, along with significantly poorer prognoses for patient survival. In addition, the researchers showed that the prognostic impact of sphere formation was strongly associated with high numbers of EpCAM-positive DCCs and aberrant genotypes in the expanded spheres. While there were some individual cases where sphere formation was observed in patients that showed no signs of cell dissemination in their lymph nodes, these spheres only showed infrequent expression of signature genes and did not exhibit typical lung cancer mutations or copy

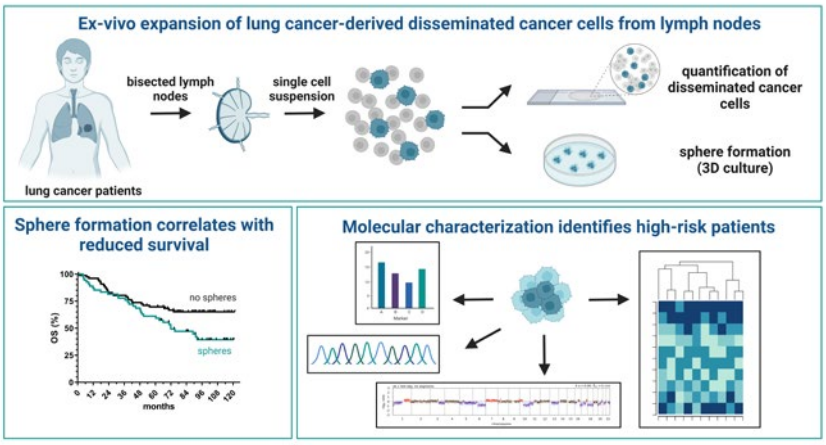
number variations. However, they may be linked to disease progression more than five years after curative surgery.

In conclusion, the study showed that ex-vivo expansion of DCCs from the lymph nodes of lung cancer patients could be used to identify cells that are associated with the progression of metastasis.

Contact

Dr. Steffi Treitschke
Preclinical Therapy Models
steffi.treitschke@item.fraunhofer.de

Dr. Kathrin Weidele
Preclinical Therapy Models
kathrin.weidele@item.fraunhofer.de



Disseminated cancer cells from the lymph nodes of lung cancer patients are expanded and cultured ex vivo. The forming spheres are then analyzed using molecular biology techniques.

Complex biomarker studies help optimize treatment for rare or hard-to-treat cancers

Every day, hospitals face huge challenges in treating rare or very advanced cancers, because in general, the guidelines for managing treatment are inadequate or do not exist at all. For patients in these circumstances, personalized therapy models based on molecular testing are a very promising option for providing them with well-tolerated, modern, effective treatment that can extend their lives and ensure good quality of life.

Researchers at the Fraunhofer ITEM site in Regensburg played a vital role in designing and executing a complex biomarker study as part of the Omics/Genomics/Liquid Biopsy lighthouse project by the Bavarian Cancer Research Center (BZKF). The goal of the project is for a network of Bavaria's six university hospitals and their affiliated analysis laboratories to conduct an extensive analysis of specimens from primary FFPE tumors, particularly liquid biopsies of blood and saliva, using "omics" technologies and functional tests and to integrate the results into treatment models. The results will be made directly available to the molecular tumor board for the purposes of personalized treatment management, within a time frame that allows the treatment to be carried out. Beginning in 2024, the concept will be tested in a clinical setting as part of a prospective feasibility study with patients that have salivary gland tumors. As part of this project, in addition to participating in the coordination of the study, Fraunhofer ITEM will conduct functional, in-vitro tests for drug sensitivity on organoids generated from liquid biopsies. Then, the Fraunhofer team and their research partners from the BZKF will work together to study the results further for signs of primary and secondary resistance to treatment.

Contact

Dr. Florian Lüke
Clinical Oncology
florian.lueke@item.fraunhofer.de

Medical and pharmaceutical engineering

Development of new technologies for use in biomedical engineering

The development of production technologies for innovative drugs – ATMPs and biologics – is a research field that has increasingly become a focus at Fraunhofer ITEM. Certain therapeutics, such as CAR-T cells, require personalized manufacturing processes. Development of the necessary production technologies, however, so far has not kept pace with the rapid biomedical progress. Fraunhofer ITEM researchers are seeking to establish scalable and robust technology platforms for the development and manufacturing of biologics. In the future, automated and digitally supported production technologies are to enable rapid, safe, and reliable development of such drugs as well as their production to the high standards of pharmaceutical manufacturing.

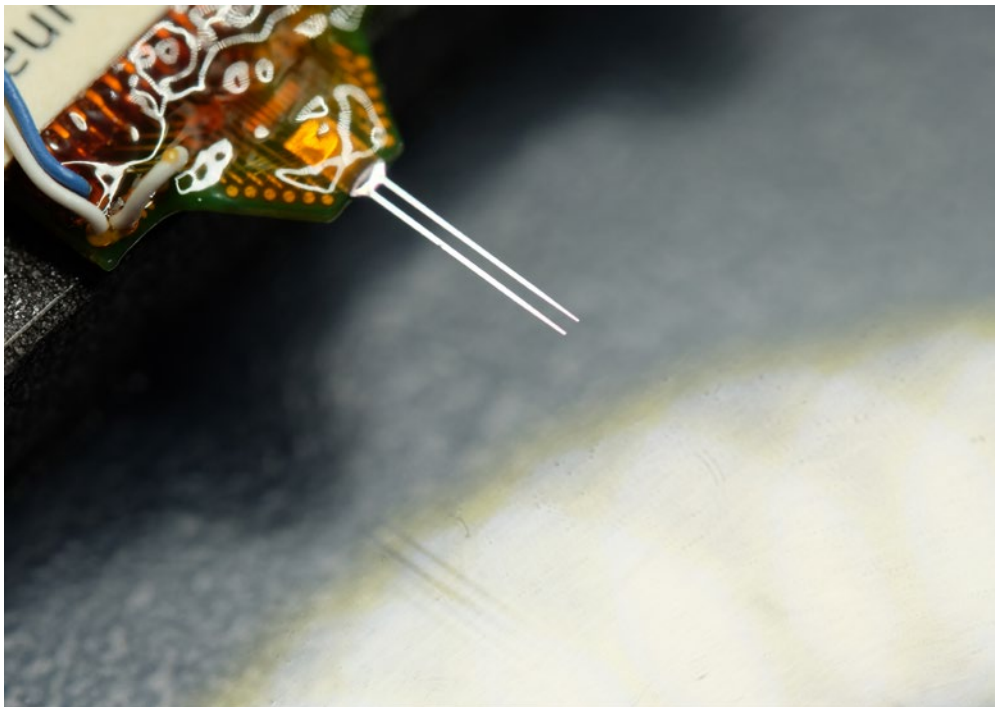
For in-vitro diagnostics, Fraunhofer ITEM is further expanding its existing expertise in the fields of single-cell analysis and liquid biopsy. By analyzing RNA and DNA from single cells, the researchers aim to gain additional information from the valuable clinical samples and to derive new therapeutic strategies from this information. The combination of multi-omics and functional data creates novel tailored analysis platforms for this purpose.

The High-Performance Center Medical and Pharmaceutical Engineering combines the expertise of the Fraunhofer institutes in Hanover, Braunschweig and Lübeck and intensifies their collaboration to turn innovative ideas into successful applications. One field of research is the development of innovative inhalation technologies. The current focus is on the development of novel technologies for administration of therapeutic aerosols towards smart drug/device combination products.

Another field of research establishes test methods that can be used to evaluate the long-term durability of implants. Key topics are the testing of active implants, such as evaluation of the long-term performance of neural implants, and test systems for functional implants, including ones with anti-infective or anti-fibrotic effects. The aim is to foster biomimetic approaches and reduce implant testing in animals. In view of the regulatory requirements for medical devices, it is particularly important to have a regulatory strategy in place as early as possible. The necessary conformity assessment can then be performed smoothly, accelerating time to market for new products. A comprehensive database of requirements and materials for optimized (re)certification of medical devices is being set up.

For the assessment of medical device safety, the researchers apply, among other methods, the new concept of next generation risk assessment. With this approach, they use modeling parameters that allow them to avoid laboratory experiments and animal testing in particular. They employ methods that are used primarily for risk assessment of industrial chemicals, such as TTC, read-across and QSAR.

Our Highlights



Fraunhofer researchers are developing solutions to ensure the quality and durability of neural implants while accelerating their development and market entry.

Long-term testing of neural implants

With an increasingly aging society, people wish to remain active for extended periods. Consequently, implants should be durable and stress-resistant. This also applies to neural implants, which are used, for instance, in patients with tetraplegia to significantly restore autonomy and quality of life. Extensive testing, particularly for the longevity of the implants, is thus essential; however, obtaining market approval for modern neural implants often takes decades.

Researchers at Fraunhofer ITEM focus on developing solutions that ensure the quality and durability of neural implants while accelerating their development and market entry. A well-structured methodology for developing such implants, considering the full product development cycle - covering raw materials, production, packaging, sterilization, and the surgical procedures - will enable a reduction of the average development time from 11 years and increase safety. This will help to avoid patient trauma, enhance societal acceptance, and make it more attractive for companies to engage in the field of neurotechnology.

A first step is the long-term testing of intracortical neural implants in animal models to understand different failure modes in a multi-stage testing process, including surgical techniques, implantation duration, signal quality, analysis, and histology. The goal is to overcome these challenges by developing and applying suitable quality criteria.

Through the High-Performance Center Medical and Pharmaceutical Engineering and in collaboration with scientists, engineers, manufacturers, medical professionals, patients,

and regulatory experts, Fraunhofer ITEM aims to establish a dynamic platform that sets new standards in neural implant technology.

Contact

Dr. Ulrich Froriep
Translational Biomedical Engineering
ulrich.froriep@item.fraunhofer.de

Paradigm shift in neonatal inhalation therapy: Fraunhofer ITEM plans spin-off "Inhale+"

Neonatal care is facing one of the greatest challenges in modern medicine, particularly when it comes to treating diseases of the respiratory tract in premature babies. Every year, around 14.8 million babies are born prematurely, and around 34 percent of them suffer from respiratory problems. Infants with acute respiratory distress syndrome are at high risk of bronchopulmonary dysplasia (BPD), which increases the risk of delayed growth in the future, impaired lung function in surviving children or even neonatal death. BPD prevention is therefore of utmost importance. There are a number of indications that inflammatory processes play an important part in the development of BPD. Glucocorticoids suppress these and have been used for treatment or prevention for over a decade. Treatment with medication for very young patients is traditionally systemic and invasive. It places strain on the entire organism and, because of the high risk of side effects, it is only initiated at a late stage – by which time there is often already irreversible lung damage.

In response to this problem, inhalation therapy offers a non-invasive, targeted approach that directly addresses the lungs and minimizes the risk of side effects. However, this approach is often ineffective, because up to 96 percent of the drug is lost to dilution in the ventilation system. The technology patented by Fraunhofer ITEM can be used universally in ventilation systems and, for the first time, enables effective inhalation therapy for premature babies. Laboratory tests have already shown an improvement in drug delivery up to four times compared to the standard inhalation system. These preliminary results form the basis for a proof-of-concept study currently being planned, which is expected to further substantiate the efficacy of this technology. To bring this technology to the market and enable significant improvements in neonatal care, there are plans to found the spin-off "Inhale+". The technology allows for early, preventive treatment of respiratory diseases to mitigate lung and long-term damage and to reduce the mortality rate. Correspondingly, the early intervention could also shorten hospitalization times for premature babies. Since the technology is scalable, it offers the potential for the development of further applications. The transfer of the Inhale+ technology to actual application is supported by the High-Performance Center Medical and Pharmaceutical Engineering.

Contact

Dr. Gerhard Pohlmann
Translational Biomedical Engineering
gerhard.pohlmann@item.fraunhofer.de

Premature babies with acute respiratory distress syndrome require early and effective treatment. This is traditionally systemic and invasive and puts strain on very young patients. The "Inhale+" technology patented by Fraunhofer ITEM is expected to change this. The undiluted aerosol is transported via an innovative adapter circuit (on the right in the photo) to the newly developed patient interface.

Applied bioinformatics and artificial intelligence

Getting the most out of big data for biomedical translation

The availability of large amounts of data has revolutionized research in the life sciences in the past few years, offering a wide range of opportunities for knowledge gain and future applications. By combining the disciplines of mathematics, computer science, medicine, and life sciences, bioinformatics has made it possible to store, categorize, analyze, evaluate, and visualize biological data and to simulate biochemical processes. In the future, the integration of multiparametric data and their complex analysis with the systemic medical and systemic toxicological approaches will be an important catalyst for subsequent experimental validations in appropriate model systems that closely mimic the situation in patients.

For regulatory purposes, both with regard to drugs and chemicals, as well as for personalized medicine, there is an increasing need to process large amounts of data. Furthermore, the continued development of novel methods, such as high-throughput technologies and omics analyses, is closely linked to the availability of efficient bioinformatics methods. Bioinformatics is a highly interdisciplinary field and a fundamental research expertise at Fraunhofer ITEM, which our researchers use to develop customized bioinformatics solutions for safety assessment and in medical contexts.

At Fraunhofer ITEM, researchers develop methods and possibilities for the preparation, analysis, and visualization of biomedical data, as well as data models and data analysis pipelines. The focus of our research is on the mapping of cellular and regulatory processes and their translation into applications for humans. Bioinformatics methods are used, for example, for personalized tumor therapy to develop optimized testing strategies and for research on RNA molecules as diagnostic biomarkers and therapeutic targets. For personalized therapies or for patient stratification, the knowledge gained from big data is key to identifying adequate treatment strategies. Stratification also plays a major role for hazard and risk assessment of chemicals, nanomaterials, and environmental exposure, as the sensitivity to noxious agents differs between subpopulations.

In addition, the Fraunhofer researchers are using bioinformatics and artificial intelligence to advance towards intelligent image data analysis and are further developing this technology, so as to optimize the analysis of histological images and support clinical processes.

Our Highlights

The overarching goal of the DigitaLung project is to develop and validate a machine-learning-based digital auscultation system that will improve patient care in the long term.

DigitaLung: Web app analyzes lung sounds

Chronic respiratory diseases have become a major health issue and, according to a publication by the Institute for Health Metrics and Evaluation (IHME) in April 2023, are now the third most common cause of death worldwide. In 2019, respiratory diseases affected one in twenty people globally and caused approximately four million deaths. Auscultation, i.e., listening to the sounds of the lungs and heart using a stethoscope, is the most commonly used diagnostic method worldwide and gives medical personnel invaluable insights into the structure and functioning of both organ systems. However, studies have shown that the reliability of this method is often dependent on doctors' experience and hearing ability, which can result in subjective, error-prone interpretations of the sounds. It is therefore crucial that we pursue innovative approaches that can improve our understanding of respiratory sounds and facilitate the development of new, more reliable diagnostic tools.

Fraunhofer ITEM is participating in DigitaLung, a project that aims to develop a digital auscultation system for the differential diagnosis of lung diseases using machine learning. Funded by the medical technology program of the German Federal Ministry of Education and Research (BMBF), DigitaLung is a collaborative project involving the partners ERKA Kallmeyer Medizintechnik GmbH & Co. KG, the Hannover Medical School and Leibniz University Hannover.

The ultimate goal of the project is to develop and validate a machine-learning-based digital auscultation system that will improve patient care in the long term. The project approach includes digitizing lung sounds, categorizing patients, conducting diagnostic training and integrating the resulting algorithm into a stethoscope, which is supported by a special app. These days, physiological signals are digitally recorded, which allows them to be viewed as a series of numerical values in chronological order, forming a medical time series. Obtaining insights from this data – primarily from the shape of the time series – is known as data mining. A number of existing techniques are being used to simplify this

process, including resampling, denoising, scaling and segmentation.

As part of DigitaLung, Fraunhofer ITEM scientists have honed and developed a custom web application that makes it easier for experts to analyze respiratory sounds. This web app serves as an independent tool that handles two key tasks during patient exams: visualization in multiple areas and the use of unsupervised machine learning algorithms in the app.

Contact

Prof. Dr. Lena Wiese
Attract Group Bioinformatics
lena.wiese@item.fraunhofer.de

PrivacyUmbrella: Anonymizing medical data

Health data is becoming more detailed all the time and is accessible to many parties. However, this means it is also vulnerable to attacks that breach the privacy of individual patients. Anonymization processes can protect patient privacy by ensuring it is no longer possible to identify individuals in data sets. However, protecting data is not the only challenge here; it is also important to ensure that the data being shared is sufficiently informative for data analysis processes in the context of personalized medicine – and to enable machine learning on a large scale.

In the PrivacyUmbrella project, Fraunhofer ITEM scientists are collaborating with the university hospitals in Frankfurt and Mainz and MCS Data Labs GmbH with the goal of achieving more reliable anonymization using a combination of different established techniques, while also maximizing usability for data analysis at the same time. The project is being financed by the German Federal Ministry of Education and Research (BMBF) and through NextGenerationEU funding.

PrivacyUmbrella covers the following concepts:

1) Mobile health: The concept of smart healthcare – and thus the idea of continuously monitoring the health of individuals – has become an important part of modern life for many people. The new anonymization processes ensure that medical data is usable for analyses and give patients the option of willingly sharing their data via mobile devices for the purposes of medical research.

2) Standardized formats for medical data: The researchers are also addressing the lack of standardization for anonymization applications by establishing connections with data integration initiatives that cover data formats such as Fast Healthcare Interoperability Resources (FHIR), which is supported by Health Level Seven International (HL7) with an open CC0 license.

3) Data usability: When determining the level of generalization for identifiable information, it is important to find a balance between data protection and data usability. However, the search for a suitable level of generalization for identifying information in the data is an inherently difficult task. This complexity is due to the development of hierarchical generalization trees, which results in a large search space that needs to cover the optimal combinations of generalized identifiers across different trees with different degrees of generalization.

4) Federated learning and data protection metrics: Formal data protection metrics play a major role in assessing and evaluating how effective technologies are in reducing data protection risks. Differential privacy is a mathematical framework that makes it possible to guarantee the protection of privacy in a system and also to quantify its level of privacy. The researchers are using the federated learning framework Flower (Das, P. P. et al., 2023: DOI 10.1007/978-3-031-49187-0_2) to run the system on the device, which reduces bandwidth, energy use and costs.

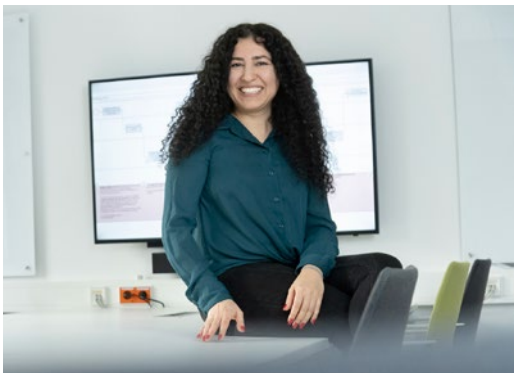
Contact

Prof. Dr. Lena Wiese
Attract Group Bioinformatics
lena.wiese@item.fraunhofer.de

For data analysis in the context of personalized medicine, it is important to protect the patient data while also ensuring that the data being shared is sufficiently informative.

People in research

It is people who are the centerpiece of research. It is their skills and expertise that enable the implementation of scientific findings in practice. In the following, four ITEM employees serve as representatives of the many others who work at Fraunhofer ITEM with enthusiasm and great commitment.



From top:
Dr. Stefanie Scheffler,
Sibel Can, Stefan Bol,
Dr. Gustav Bruer

"We've got a fantastic team here in the Department of Regulatory Affairs. Our doors are always open and we are in constant communication. This helps us get through even the tough times."

Dr. Stefanie Scheffler

Scientist in the Department of Regulatory Affairs

What excites you about your work at Fraunhofer ITEM?

The team! We've got a fantastic team here in in the Department of Regulatory Affairs. Our doors are always open and we are in constant communication. This helps us get through even the tough times. Another aspect of the institute's work that appeals to me is its interdisciplinary nature – the collaboration with different working groups constantly opens up new possibilities.

Which project at Fraunhofer ITEM do you think of with particular fondness?

Our internal research project EVape, which has developed a device for the controlled vaporization of e-cigarette liquids. Four different departments at the institute came together to work on this, with each individual contributing their own ideas. That was a fantastic experience, seeing how we can bring ideas to life by working together.

Which person or experience has been particularly helpful to the progress of your career?

I grew up in a scientific household. My parents are both chemists, and science was always part of everyday life at home. When I was at school, I often visited the chemistry lab where my mother taught and so got to see chemistry from a different perspective. And as far back as I can remember, we would visit natural history museums. My father had a very diverse range of scientific interests and liked to pass on his knowledge to us. This fostered a curiosity, a desire to understand things.

What's your most cherished illusion?

I like to dive into another world through circus and vaudeville.

How do you cope with hard times?

Keep looking ahead and push on. I make myself a plan that I follow step by step and think about the time afterward, about the liberating feeling that will come once I've got through this stretch.

What was the most recent thing that amazed you?

The stalactites in the Psychro cave on Crete.

What can always make you laugh?

My children.

What does a successful day look like to you?

That can vary a lot – I like to get out in nature, whether through sports or just taking a walk. Of course, if the sun is shining, that's even better. But an achievement at work, a family outing, a good book or a delicious dinner can also make for a successful day.

Sibel Can

Process manager in the Department of Central Services

Why did you choose to focus on this particular specialist field in your career?

I enjoy uncovering untapped potential and I want to encourage efforts to find new and better possibilities using the potential that already exists. I also really like breaking down "seemingly unsolvable" problems so that, in the end, all you can see is the solution. Every problem contains its own solution – if you approach it with discipline, focus and patience. My academic and professional experience has shown me that a lot of potential in companies is left unutilized. I've repeatedly found myself, on my own initiative, using process management tools and methods to create a better understanding of the potential available. Process management provides clarity. I identify very well with a process-based way of thinking and working, and I've incorporated systems and standards into my day-to-day life to make certain things easier for me.

What aspect of your work excites you?

Making process work solution-based and sustainable excites me. By analyzing and documenting the processes just once, you create a sustainable basis that you can continue to benefit from for decades. It's a lot of work at the start, but once the processes are documented in black and white, you can keep building on them. It's obviously easier to adapt things than to tackle them completely from scratch. As well as that, I also find it fascinating that process work converts implicit knowledge into explicit knowledge – making the knowledge available to everyone for the long term.

Which achievement at Fraunhofer ITEM do you think of with particular fondness?

I'm the first process manager for the commercial and HR sections of Fraunhofer ITEM, so I had a kind of blank slate when I arrived here. I had a very interesting start because SAP needed to be introduced across Fraunhofer, which was a major challenge. To avoid the potential process gaps that could arise with the introduction of a new system or develop possible workarounds with the individual teams, it was very important to be familiar with our own processes, underlying conditions and specifications. Together with the individual teams, we delved into the processes in depth to uncover potential and record the procedures in a transparent way. Even though the SAP launch was challenging and implementing it still is to some extent, as an SAP team at Fraunhofer ITEM we were able to avoid major mistakes thanks to the process work, and were functioning very quickly after SAP went live. I look back with fondness at how open my colleagues on the teams were and at the constructive cooperation at every level, particularly while SAP was being introduced, and I'm grateful that I was part of such an extensive project.

What have you discovered recently?

Recently, I discovered the "OPEN HAUS: Schauspielhaus foyer" project. The foyer of the theatrer "Hannover Schauspielhaus" opens its doors during the day and becomes a place for everybody to visit, be productive or just relax, whether alone or as a collective. It's a really comfortable set-up, with armchairs, small tables and a very good selection of books.

What's your most cherished illusion?

That pets understand us when we talk to them. I think they pick up more than we think.

How do you cope with hard times?

I'm usually well prepared and I remind myself that it's a phase. I stay positive and on the ball. There's always a way out. You just have to find it. Life has its highs and lows. Hard times are part of that.

What does a successful day look like to you?

Physical activity, ideally outdoors with the sun shining, and maybe music too – that's definitely part of a successful day.

"Making process work solution-based and sustainable excites me."

"A particular motivator for me is having the opportunity to work on projects that can directly impact people's health."

Stefan Bol

Biological laboratory technician in the Division of Translational Biomedical Engineering

Why did you choose to focus on this particular specialist field in your career?

From an early stage in my career, I had an intrinsic motivation toward working in the field of medical technology and making a direct contribution to the healthcare industry. What drives me is my desire to achieve something and bring about positive change. I'm especially fascinated by the unique combination of basic research, industrial application and clinical practice that plays a significant role at Fraunhofer ITEM. A key incentive for me is getting the opportunity to work in an environment that is intensively engaged in developing innovative inhalation therapy systems and advanced implant systems. The close collaboration between experts across various disciplines enables the development of pioneering solutions that have a direct impact on patients' medical care and quality of life.

What aspect of your work excites you?

A particular motivator for me is having the opportunity to work on projects that can directly impact people's health. The ever-present challenge of finding innovative solutions and the opportunity to collaborate with a highly qualified team make my work unique and fulfilling.

Which person or experience has been particularly helpful to the progress of your career?

Reading "The Power Of Now" by Eckhart Tolle was a game-changer for me in terms of supporting for my personal and professional development. This book's philosophy, which is based on mindfulness and conscious experience of the present moment, gave me some really valuable inspiration around continuous improvement and self-development. Over the course of my career, this inner sense of direction has not only helped me to strive for external success, but also to regard continuous personal development as an important part of my professional journey.

What's your most cherished illusion?

I love to believe that every setback represents a hidden opportunity for personal growth and new insights.

How do you cope with hard times?

During hard times, I rely on a healthy mix of reflection, sports and dialogue with colleagues. These strategies help me come away stronger after challenging periods.

What makes you laugh?

I laugh at myself. For me humor is not only a source of joy, but also a lesson in not taking yourself too seriously. A good joke that pokes fun at my quirks always makes me laugh. It reminds me that it's okay not to be perfect, that hearty laughter is often the best medicine, and that levity has become an important companion on my path through life.

What does a successful day look like to you?

To me, a successful day includes some productive work on projects, positive interpersonal interactions among the team, time for my personal interests and, at the end of the day, the feeling that I've come one step closer to my goals.

Dr. Gustav Bruer

Head of the Department of Inhalation Toxicology

What aspect of your work excites you? What is the best part of your job?

I like the variety. No two days are the same, and every project is different. There are always new questions and challenges to figure out. It never gets boring. As a department, we are financially independent. I have to think and act from both a scientific and commercial perspective, which complements the diversity of my role. In addition, many issues can only be dealt with and solved by working together. I am very thankful for the great team here at the Department of Inhalation Toxicology, which makes it particularly enjoyable. I often need to take business trips for customer meetings or to meet with project partners. This allows me to get to know many parts of the world. The exchange with new people is fun and has already led to friendships that go beyond my daily working life.

Which project or achievement at Fraunhofer ITEM do you think of with particular fondness?

I really appreciate our current nanoparticle project because it allows me to make a real difference through my everyday work. The results we're seeing in this study – although they only relate to very small details at first – could ultimately have a very significant impact, going as far as effecting the use or elimination of substances worldwide. Due to the current public awareness of the topic, it is also easy to explain my work in a way that people understand.

Which person or advice have you found to be especially helpful to your professional career?

My doctoral supervisor, Prof. Kietzmann, advised me that it's best to find a topic that really inspires and fully engages you scientifically. On the one hand, you are then in a position to achieve great things, but on the other hand, it doesn't feel like work because your daily tasks align with your own interests.

What's your most cherished illusion?

That time is a flexible resource which I can stretch and adapt at will to accommodate all my interests and passions. In my everyday life, I often schedule more activities and projects than are realistically achievable, hoping that I'll somehow find the time to manage everything. Unfortunately, that doesn't always work out.

What makes you laugh?

I always enjoy funny observations about daily life – the kind of things we all know and which are often expressed in stand-up comedy. There are also some pretty funny people in my circle of friends; there's never a boring moment when they're around.

What does a successful day look like to you?

To me, a successful day includes a balance between productivity and relaxation. It begins with a morning of concentrated work on my goals and tasks, following the slogan "Business before pleasure". Afterwards, I can enjoy the rest of the day, for example, by taking a drive in my car, which is my ultimate weakness. When the sound of six exploding cylinders combines with the whistle of the turbochargers and the roaring of the exhaust, I feel alive and can 100 percent switch off.

"To me, a successful day includes a balance between productivity and relaxation."

Names, dates and facts

Important information in brief – more details always up to date on our website

Being a research institution, our ambition is to find answers to questions and solutions for problems that are relevant to society and also to companies with regard to human health. In our research, we collaborate with national and international scientific organizations and actively participate in a broad range of panels. Unless precluded by the terms of the contract, we publish our results in renowned scientific journals and present them at congresses and meetings.

On the following pages, you will find details of our active participation in committees and a comprehensive list of contact persons for the different research topics. In addition, our website provides up-to date information throughout the year:

www.item.fraunhofer.de/annual-report

Active participation in committees

Prof. Dr. Christian Bär
MD/Ph.D. commission "Molecular Medicine" of the Hannover Biomedical Research School (HBRS) of the Hannover Medical School (MHH)

Ph.D. examination board for "Anatomy and Cell Biology" at the Hannover Medical School (MHH)

Working group on "Myocardial Function" (WG 4) of the European Society of Cardiology (ESC)

Working groups on myocardial function and energetics "AG 13 Myokardiale Funktion und Energetik" and on cardiovascular regeneration "AG 31 Kardiovaskuläre Regeneration" of the German Cardiac Society (DGK)

Program Committee "Medical Scientist Programme" of the Hannover Medical School (MHH)

Member of the editorial board of the international journal "Molecular Therapy Nucleic Acids"

Reviewer for numerous national and international organizations and foundations, incl. German Research Foundation (DFG), German Cardiac Society (DGK), Swiss National Science Foundation (SNF), Irish Research Council (IRC) and AFM-Telethon

Reviewer for international journals in cardiovascular diseases and therapies (incl. "Nature Medicine", "Nature Communications", "Nature Reviews Cardiology", "European Heart Journal", "Circulation Research", "Cardiovascular Research", "npj Regenerative Medicine", "Advanced Science", "ESC Heart Failure", "Basic Research in Cardiology", and "Molecular Therapy")

Dr. Annette Bitsch
Working committee on probabilistic exposure and risk assessment "Probabilistische Expositions- und Risikoabschätzung"

Board member of the German Toxicology Society (GT)

Expert panel 110 on cooling lubricants "Kühlschmierstoffe" of the Association of German Engineers (VDI) Technical Division 1 "Production Technology and Manufacturing Methods"

Interim Scientific Adisory Council (iSAC) for the reorganization of the Evidence-Based Toxicology Collaboration (EBTC) at Johns Hopkins Bloomberg School of Public Health

Mentor in the Fraunhofer career program for female scientists TALENTA

Reviewer in the peer-review process for the German Federal Health Bulletin "Bundesgesundheitsblatt"

Reviewer for international journals published by Elsevier (incl. "Regulatory Toxicology and Pharmacology")

Katharina Blümlein Ph.D.
Working group on analyses in biological materials "Analysen in biologischem Material" of the German Research Foundation (DFG)

Prof. Dr. Armin Braun
MD/Ph.D. commission "Molecular Medicine" of the Hannover Medical School (MHH)

Scientific advisory committee of the German Society for Allergology and Clinical Immunology (DGAKI)

German Center for Lung Research (DZL)

External assessor for international foundations

Reviewer for international journals in respiratory medicine and immunology (incl. "Journal of Allergy and Clinical Immunology")

Dr. Gustav Bruer
Working group "Respiratory Toxicology" of the German Toxicology Society (GT)

Reviewer for international journals in pharmacology and toxicology ("Nature Research – Scientific Reports")

Dr. Otto Creutzenberg
Reviewer for international journals in particle and fiber toxicology ("Particle and Fibre Toxicology", "Inhalation Toxicology")

Prof. Dr.-Ing. Theodor Doll
VDE/VDI Society Microelectronics, Microsystems and Precision Engineering GMM, chair of the expert panel on microsystems in medicine/functional surfaces "FA 4.6 Mikrosysteme in der Medizin/Funktionale Oberflächen"

German Society for Biomedical Engineering DGBMT, expert panel on sensor technology "Sensorik"

ASIIN reviewer for biomedical engineering careers

Guest editor of the journal "Physica Status Solidi (a)"

Uta Dörfel
Working group on GLP analytics "GLP-Analytik" of the German Quality Management Association (GQMA)

Dr. Sylvia Escher
DFG Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission): working group on carginogenic substances

Priv.-Doz. Dr. Jan Fiedler
Program committee for the Ph.D. program "Regenerative Sciences" at the Hannover Biomedical Research School (HBRS)

Reviewer for international journals in cardiovascular research

Dr. Ulrich Froriep
Member of the Focus Group Medical Technology of the IVAM Microtechnology Network

German Neuroscience Society

Society for Neuroscience (SfN)

Dr. Jens Gerdelmann
Working groups on GLP quality assurance/monitoring "GLP: Qualitätssicherung/Überwachung", GCP quality management "GCP-Qualitätsmanagement", and medical devices "Medizinprodukte" of the German Quality Management Association (GQMA)

Dr. Stefan Hahn
Chair of the German Chemical Society (GDCh) Division of Environmental Chemistry and Ecotoxicology

Working committee on chemical risk assessment of the German Chemical Society (GDCh) division of environmental chemistry and ecotoxicology "Umweltchemie und Ökotoxikologie"

Working group "Exposure models" of ISES Europe (Europe Regional Chapter of the International Society of Exposure Science)

Reviewer for international journals in environmental and exposure sciences (incl. "Environmental Science & Technology", "Annals of Work Exposures and Health", and "Journal of Exposure Science & Environmental Epidemiology")

Martina Heina
IT division of the International Association for Pharmaceutical Technology (APV)

Working groups on archiving "Archivierung" and information technology "IT" of the German Quality Management Association (GQMA)

Dr. Martin Hoffmann
Working group on bioinformatics at Comprehensive Cancer Center Ostbayern (CCCO)

Prof. Dr. Jens Hohlfeld
External assessor for the German Research Foundation (DFG)

Steering committee of the research network "Biomedical Research in Endstage And ObsTructive Lung Disease Hannover" (BREATH) within the German Center for Lung Research (DZL)

Board member of the interdisciplinary allergy center of the Hannover Medical School (MHH)

Reviewer for international journals (incl. "American Journal of Respiratory and Critical Care Medicine", "European Respiratory Journal", and "Journal of Allergy and Clinical Immunology")

Dr. Olaf Holz
Reviewer for international journals (incl. "American Journal of Respiratory and Critical Care Medicine", "Journal of Breath Research", "European Respiratory Journal", "PLOS ONE", "Respiratory Research", and "BMC Pulmonary Medicine")

Dr. Rupert Kellner
Councilor for electronic communication and member of the Executive Board of the European Society of Toxicologic Pathology (ESTP)

Global Editorial and Steering Committee (GESC) for the initiative "International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice" (INHAND)

Prof. Dr. Christoph Andreas Klein
External assessor for numerous national and international organizations and foundations: German Research Foundation, German Federal Ministry of Education and Research, Wilhelm Sander Foundation for Cancer Research, ERC, Deutsche Krebshilfe, Christian Doppler Research Association, Dutch Cancer Society, Association for International Cancer Research, EU-FP7, MRC, Cancer Research UK, Kegg-Foundation

Deputy chairman of the scientific committee of Comprehensive Cancer Center Ostbayern (CCCO)

Deputy spokesperson of the "Lighthouse Group – Omics, Genomics and Liquid Biopsy" of the Bavarian Center for Cancer Research (BKFZ)

Member of the advisory board of Bio^{M} Biotech Cluster Development GmbH

Reviewer for international journals in oncology (incl. "Nature", "Nature Biotechnology", "Nature Cell Biology", "Nature Medicine", "Cancer Cell", "Science", "PNAS", "American Journal of Pathology", "Cancer Research", "Clinical Cancer Research", "International Journal of Cancer", "Nucleic Acid Research", "European Journal of Immunology", "Lancet Oncology", "European Journal of Cancer", "PLOS ONE", and "Oncotarget")

Prof. Dr. Wolfgang Koch
Reviewer for international journals in aerosol physics and aerosol technology (incl. "Journal of Aerosol Science", "Aerosol Science and Technology", and "Annals of Work Exposures and Health")

Dr. Imke Korf
Reviewer for international journals on bacteriophages

Prof. Dr. Norbert Krug
Chair of the Clinical Trial Board of the German Center for Lung Research (DZL)

Steering committee of the research network "Biomedical Research in Endstage And ObsTructive Lung Disease Hannover" (BREATH) within the German Center for Lung Research (DZL)

External assessor for the German Research Foundation (DFG)

Steering committee of the Fraunhofer Research Cluster "Immune-Mediated Diseases" (Fraunhofer CIMD)

Scientific advisory committee of the German Society for Allergology and Clinical Immunology (DGAKI)

DEAL project group of the Alliance of Science Organisations in Germany

Working group "Fraunhofer-Gesellschaft and Deutsche Hochschulmedizin"

Reviewer for international journals in allergology, immunology, and respiratory diseases

Selection Committee of NIHR Research Professorships, UK

International evaluation panel of the Centers of Excellence Program (Severo Ochoa Centres of Excellence), Spanish State Research Agency

Prof. Dr. Nico Lachmann
Extended Board of the German Stem Cell Network (GSCN)

EU Deputy Representative of the Hannover Medical School (MHH)

Senate Section II of the Hannover Medical School (MHH)

Steering Committee REBIRTH – Research Center for Translational Regenerative Medicine at the Hannover Medical School (previously REBIRTH cluster of excellence "From REgenerative BIology to Recontructive THerapy")

External assessor for numerous national and international organizations incl. the European Research Council (ERC) and the German Research Foundation (DFG)

Reviewer for numerous international journals (incl. "Nature", "Nature Immunology", "Nature Reviews Immunology", "Nature Reviews Disease Primer", "Nature Communications", "Nature Communications Medicine", "Nature Biomedical Engineering", "Cell Stem Cell", "iScience", "Stem Cell Reports", "eBioMedicine", and "AJRCCM")

Dr. Oliver Licht
Working group on sustainable chemicals policy "Nachhaltige Chemikalienpolitik" of the 8th Lower Saxony Governmental Commission on sustainable environmental policy and digital change

Working committee on regulatory toxicology "Regulatorische Toxikologie" of the German Toxicology Society (GT)

Public relations delegate of the German Toxicology Society (GT)

Dr. Meike Müller
Network of ombudspersons in Lower Saxony

Dr. Gerhard Pohlmann
International Society for Aerosols in Medicine (ISAM)

PD Dr. Bernhard Michael Polzer
External assessor for the Wilhelm Sander Foundation for Cancer Research

External assessor for the Carl-Zeiss-Stiftung

Reviewer for international journals in pathology and oncology ("Cancers", "Chemical Science", "Cytometry A", "International Journal of Cancer", "Journal of Visualized Experiments", "Oncotarget", "Scientific Reports", "Expert Reviews of Molecular Diagnostics", and "Molecular Oncology")

Member of the clinical study groups on "Primary and Secondary Malignant Brain Tumors in Adults" and "Central Nervous System Tumors in Children and Adolescents" and member of the "Lighthouse Group – Omics, Genomics and Liquid Biopsy" of the Bavarian Center for Cancer Research (BKFZ)

Prof. Dr. Antje Prasse
External assessor for the German Research Foundation (DFG)

Board member of the Scientific Working Group for the Therapy of Lung Diseases (WATL)

Board member of Deutsche Atemwegsliga e. V.

Board member of the World Association of Sarcoidosis and other Granulomatous Disorders (WASOG)

Coordinator of the ILD group in the European Reference Network on Respiratory Diseases ERN-LUNG

Spokesperson for the disease area "DPLD" in the research network "Biomedical Research in Endstage And ObsTructive Lung Disease Hannover" (BREATH) within the German Center for Lung Research (DZL)

Deputy member of the Ph.D. admissions committee of the Hannover Medical School (MHH)

Reviewer for international journals (incl. "American Journal of Respiratory and Critical Care Medicine", "European Respiratory Journal", "Journal of Clinical Investigation", "JCI Insights", "Nature Communications", "American Journal of Respiratory and Cell Biology", and "Thorax")

Associate editor of "PLOS ONE"

Prof. Dr. Tobias Pukrop
Chairman of the working committee on malignant tumors of the CNS "ZNS Malignome" of the German Society of Hematology and Oncology

Board member/deputy speaker of CCC Alliance WERA

Steering board of the working panel on CNS/leptomeningeal spread "ZNS/Meningeosis" of the working group on internal oncology "Arbeitsgemeinschaft Internistische Onkologie (AIO)" of the German Cancer Society (DKG)

Steering board of the Collaborative Reserach Center/Transregio (SFB/TRR) 305: Striking a moving target: From mechanisms of metastatic colonization to novel systemic therapies

Steering board of the Molecular Tumor Board of the University of Regensburg

Steering board of the Brain Tumor Center (ZHT) of the University of Regensburg

Executive Board of the Bavarian Center for Cancer Research (BKFZ)

European Society for Medical Oncology (ESMO)

Priv.-Doz. Dr. Susanne Rittinghausen
"Guess What" committee of the European Society of Toxicologic Pathology (ESTP)

Global Editorial and Steering Committee (GESC) for the initiative "International Harmonization of Nomenclature and Diagnostic Criteria for Lesions in Rats and Mice" (INHAND)

INHAND (International Harmonization of Nomenclature and Diagnostic Criteria) organ working groups "Respiratory System", "Endocrine System" and "Soft Tissue"

DFG Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission)

Dirk Schaudien Ph.D.
INHAND (International Harmonization of Nomenclature and Diagnostic Criteria) working groups "Non-rodents: Minipig", "Respiratory System", and "Skeletal Tissues (Bones, Joints and Teeth)"

"Pathology 2.0" committee of the European Society of Toxicologic Pathology (ESTP)

"Guess What" committee of the European Society of Toxicologic Pathology (ESTP)

Examination board of the European College of Veterinary Pathology

Dr. Stefanie Scheffler
Working group on e-cigarettes and liquids for e-cigarettes of the DIN Standards Committee "Food and Agricultural Products"

Dr. Sven Schuchardt
Treasurer of the German Society for Metabolome Research

Working group on air analyses "Luftanalysen" of the German Research Foundation (DFG)

Leibniz-Institut für Analytische Wissenschaften – ISAS – e. V. (Leibniz Institute for Analytical Sciences)

SAE AC-9M Cabin Air Measurement Committee

Dr. Florian Schulz
DFG Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission): working group on the definition of threshold limit values for dusts

Committee on Hazardous Substances (AGS) under the German Federal Minister of Labor and Social Affairs: Subcommittee III for the evaluation of hazardous substances "Gefahrstoff-bewertung", working groups on metals and fibers/dust

Advisory Board of the European Certification Board for Mineral Wool Products (EUCEB)

External expert in the quality control committee of the mineral wool quality assurance association "RAL-Güteqemeinschaft Mineralwolle" (GGM)

Dr. Katherina Sewald
Steering group of the workshop "Respiratory Toxicity"

German Center for Lung Research (DZL): Young Scientists committee

Member of the official ATS Workshop „Guidelines for Precision-cut lung slices"

Co-chair of the expert group Human Tissue of the International Life Sciences Institute (ILSI), Europe

Executive committee on basic research in the research network "Biomedical Research in Endstage And ObsTructive Lung Disease Hannover" (BREATH) within the German Center for Lung Research (DZL)

Mentor in the Fraunhofer career program for female scientists TALENTA

External assessor for international research grants

Reviewer for the international journals "Toxicology Letters", "Toxicology in Vitro", "Nanotoxicology", "ATOX", and "PLOS ONE"

Prof. Dr. Dr. Thomas Thum
Scientific Advisory Board (SAB) or pool of experts of numerous national and international organizations: Interdisciplinary Center for Clinical Research (IZKF) at RWTH Aachen University; Independent Scientific Advisory Committee of the Ksilink association; International Scientific Advisory Board (ISAB) of the RECONNECT program (The Netherlands); National Committee for the Protection of Animals Used for Scientific Purposes of the German Federal Institute for Risk Assessment; Lower Saxony Life Science Startup Board

Board member of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC); HFA representative at the ESC Council on Cardiovascular Genomics; Board member of the HFA Specialist Group for "Cardio-Oncology; on Basic & Translational Research"; Chairman of the HFA Specialist Group for "Heart Failure in Hypertrophic Cardiomyopathy"

Coordinator of REBIRTH – Research Center for Translatio-nal Regenerative Medicine at the Hannover Medical School (previously REBIRTH cluster of excellence "From REgenerative BIology to Recontructive THerapy")

Chairman of the steering committee of the Hannover Unified Biobank (HUB)

External assessor for numerous national and international orga-nizations and foundations, incl. the European Research Council (ERC), German Research Foundation (DFG), German Cardiac Society (DGK), British Heart Foundation (BHF), French Research Association (ANR), Health Research Board Ireland, Austrian Science Fund (FWF) and Dutch Research Council (NWO)

Consulting editor or member of the editorial board of numerous international journals (incl. "Circulation Research", "Cardiovascular Research", "Arteriosclerosis, Thrombosis, and Vascular Biology", "Basic Research in Cardiology", "American Journal of Physiology – Heart and Circulatory Physiology", "PLOS ONE", "Physiological Genomics", and "Naunyn-Schmiedeberg's Archives of Pharmacology")

International associate editor of the "European Heart Journal"

Dr. Jens Warfsmann
Working group on bioinformatics at Comprehensive Cancer Center Ostbayern (CCCO)

Prof. Dr. Lena Wiese
Special interest group "Digital Health" and working group on "Data Science and Data Engineering" of the German Informatics Society

Dr. Dorothee Winterberg
Working group on respiratory toxicology "Respirations-toxikologie" of the German Toxicology Society (GT)

Association of Inhalation Toxicologists (AIT)

German Center for Lung Research (DZL)

Prof. Dr. Holger Ziehr
Association of German Engineers (VDI) committee "Technical Good Manufacturing Practice"

GMP discussion group "GMP-Gesprächskreis" of the Lower Saxony business inspectorate

Center of Pharmaceutical Engineering (PVZ) at Technische Universität Braunschweig

BioPharma-Translationsinstitut e. V.

Dr. Christina Ziemann
Chair of the working group on statistics of the German Society for Environmental Mutation Research (GUM)

Working group on "Genotoxicity" of the DIN Standards Committee "Water Practice"

Working groups on carcinogenesis "Kanzerogenese" and on respiratory toxicology "Respirationstoxikologie" of the German Toxicology Society (GT)

Member of the program committee for the annual Germa Pharm-Tox Summit (GPTS) of the German Society for Experi-mental and Clinical Pharmacology and Toxicology (DGPT) for contributions from the German Society for Toxicology (GT)

OECD pool of experts of the German Federal Institute for Risk Assessment

Reviewer for international journals in genetic toxicology, nanomaterials, and quartz

Panelist for the expert workshop of the Food and Drug Administration (FDA) and the Health and Environmental Sciences Institute (HESI) "Building A Research Roadmap for Hazard and Risk Assessment of Nitrosamine Impurities in Drugs"

Contact persons

The R&D services offered in the business areas Drug Development, Chemical Safety and Assessment, and Translational Biomedical Engineering are based on the expertise available in the institute's seven divisions and the two Attract groups Bioinformatics and IMMUNITY. The divisions are supported by business developers and various departments including Central Services, Information Management, Institute Strategy and Communication, Organizational Development and Collaboration, Project Management, and Quality Assurance. Below, please find our contacts for the different research topics and services offered. Please do not hesitate to contact these persons directly (as at Mai 2024).

Institute Director

Prof. Dr. Norbert Krug
Executive Director
Medical Director
norbert.krug@item.fraunhofer.de

Chemical Safety and Toxicology

Dr. Annette Bitsch
Division Director of Chemical Safety and Toxicology
annette.bitsch@item.fraunhofer.de

Dr. Gustav Bruer
Head of Department of Inhalation Toxicology
gustav.bruer@item.fraunhofer.de

Dr. Sylvia Escher
Head of Department of In-silico Toxicology
sylvia.escher@item.fraunhofer.de

Dr. Tanja Hansen
Head of Department of Mechanistic Toxicology
Manager of the Working Group on In-vitro Test Systems
tanja.hansen@item.fraunhofer.de

Dr. Rupert Kellner
Manager of the Working Group on Databases and Information Systems
rupert.kellner@item.fraunhofer.de

Dr. Sven Schuchardt
Head of Department of Bio- and Environmental Analytics
sven.schuchardt@item.fraunhofer.de

Dr.-Ing. Katharina Schwarz
Head of Department of Aerosol Technology and Biophysics
katharina.schwarz@item.fraunhofer.de

Prof. Dr. Lena Wiese
Manager of the Working Group on Bioinformatics
Manager of the Attract Group Bioinformatics "IDA – Intelligent Data Analysis for Health and Chemical Safety"
lena.wiese@item.fraunhofer.de

Dr. Christina Ziemann
Manager of the Working Group on Genetic Toxicology
christina.ziemann@item.fraunhofer.de

Ariane Zwintscher
Head of Department of Regulatory Affairs
Manager of the Working Group on Biocides / REACH
ariane.zwintscher@item.fraunhofer.de

Preclinical Pharmacology and Toxicology

Prof. Dr. Armin Braun
Division Director of Preclinical Pharmacology and Toxicology
armin.braun@item.fraunhofer.de

Dr. Annika Bach-Hagemann
Manager of the Working Group on Animal Laboratory
annika.bach-hagemann@item.fraunhofer.de

Dr. Franziska Dahlmann
Manager of the Working Group on Infection and Immunology
franziska.dahlmann@item.fraunhofer.de

Dr. Christina Hesse
Manager of the Working Group on Respiratory Pharmacology
christina.hesse@item.fraunhofer.de

Dirk Schaudien Ph.D.
Head of Department of Pathology and Clinical Chemistry
dirk.schaudien@item.fraunhofer.de

Dr. Katherina Sewald
Head of Department of Preclinical Pharmacology and In-vitro Toxicology
katherina.sewald@item.fraunhofer.de

Dr. Dorothee Winterberg
Head of Department of Preclinical Toxicology and Animal Laboratory
Manager of the Working Group on Preclinical Toxicology
dorothee.winterberg@item.fraunhofer.de

Pharmaceutical Biotechnology

Dr. Stefanie Hebecker
Management Team*
Manager of the Working Group on Downstream Processing
stefanie.hebecker@item.fraunhofer.de

Dr. Philipp Koch
Manager of the Working Group on Quality Control
philipp.koch@item.fraunhofer.de

Katrin Rimkus
Management Team*
Head of Quality Assurance at the Braunschweig site
Manager of the Working Group on Quality Assurance
katrin.rimkus@item.fraunhofer.de

Dr.-Ing. Claudius Seitz
Management Team*
Manager of the Working Group on Microbial Cultivation
claudius.seitz@item.fraunhofer.de

Dr. Sarah Wienecke
Management Team*
sarah.wienecke@item.fraunhofer.de

Airway Research

Prof. Dr. Jens Hohlfeld
Division Director of Airway Research
jens.hohlfeld@item.fraunhofer.de

Dr. Philipp Badorrek
Head of Department of Clinical Airway Research
philipp.badorrek@item.fraunhofer.de

Dr. Meike Müller
Head of Department of Biomarker Analysis and Development
meike.mueller@item.fraunhofer.de

Prof. Dr. Antje Prasse
Head of Department of Clinical and Translational Research on Pulmonary Fibrosis
antje.prasse@item.fraunhofer.de

Dr. Jonas Schupp
Manager of the Working Group on Translational Pulmonary Precision Medicine
jonas.schupp@item.fraunhofer.de

Cardiovascular Research

Prof. Dr. Norbert Krug
Division Director of Cardiovascular Research (acting)
Institute Director
norbert.krug@item.fraunhofer.de

Prof. Dr. Christian Bär
Manager of the Working Group on Regenerative Cardiology
christian.baer@item.fraunhofer.de

Priv.-Doz. Dr. Jan Fiedler
Manager of the Working Group on Cardiovascular Research
jan.fiedler@item.fraunhofer.de

Prof. Dr. Nico Lachmann
Manager of the Working Group on IMMUNITY
Manager of the Attract Group "IMMUNITY – designer cells: novel immune cell platforms for health research"
nico.lachmann@item.fraunhofer.de

Personalized Tumor Therapy

Prof. Dr. Christoph Andreas Klein
Division Director of Personalized Tumor Therapy
christoph.andreas.klein@item.fraunhofer.de

Dr. Martin Hoffmann
Manager of the Working Group on Mathematical Disease Modeling
martin.hoffmann@item.fraunhofer.de

Dr. Stefan Kirsch
Manager of the Working Group on Innovative Molecular Technologies and Biomarker Discovery
stefan.kirsch@item.fraunhofer.de

* The Division of Pharmaceutical Biotechnology was led by Prof. Dr. Holger Ziehr until March 31, 2024. As of April 1, 2024, a management team has assumed responsibility for the division.

Dr. Bernhard Michael Polzer
Manager of the Working Group on Cellular
and Molecular Diagnostics
bernhard.michael.polzer@item.fraunhofer.de

Prof. Dr. Tobias Pukrop
Manager of the Working Group on Clinical Oncology
tobias.pukrop@item.fraunhofer.de

Dr. Andrea Stutz
Manager of the Working Group on High-Throughput Drug
and Target Discovery
andrea.stutz@item.fraunhofer.de

Dr. Jens Warfsmann
Manager of the Working Group on Bioinformatics
and Data Management
jens.warfsmann@item.fraunhofer.de

Dr. Christian Werno
Manager of the Working Group on Preclinical Therapy Models
christian.werno@item.fraunhofer.de

Translational Biomedical Engineering

Dr. Gerhard Pohlmann
Division Director of Translational Biomedical Engineering
Head of Dept. of Inhalation Therapy / Medicinal Aerosols
gerhard.pohlmann@item.fraunhofer.de

Prof. Dr.-Ing. Theodor Doll
Head of Department of Implant Systems /
Regulatory Processes and Documentation (ISO 13485)
theodor.doll@item.fraunhofer.de

Mehmet Ramazanoglu
Manager of the Working Group on Inhalation Technology
mehmet.ramazanoglu@item.fraunhofer.de

Business Development

Karine Danielyan
Business Development for Airway Research
karine.danielyan@item.fraunhofer.de

Dr. Christopher Jakobs
Business Development for Personalized Tumor Therapy
christopher.jakobs@item.fraunhofer.de

Dr. Sebastian Konzok
Business Development for Preclinical Pharmacology,
Chemical Safety and Toxicology
sebastian.konzok@item.fraunhofer.de

Patricia Mattis
Business Development for Translational Biomedical Engineering
patricia.mattis@item.fraunhofer.de

Quality Assurance

Dr. Jens Gerdelmann
Head of Quality Assurance at the Hannover site
jens.gerdelmann@item.fraunhofer.de

Central Services

Marlene Rauschenbach
Director of Administration
Head of Central Services
marlene.rauschenbach@item.fraunhofer.de

Information Management

Petra Wiedemeier
Head of Information Management
petra.wiedemeier@item.fraunhofer.de

Project Management

Dr. Sabine Kafert-Kasting
Head of Project Management
sabine.kafert-kasting@item.fraunhofer.de

Organizational Development and Collaboration

Dr. Kathrin Bohle
Organizational Development and Collaboration
kathrin.bohle@item.fraunhofer.de

Institute Strategy and Communication

Dr. Henning Weigt
Head of Institute Strategy and Communication
henning.weigt@item.fraunhofer.de

Anna Juhrs
Marketing Communications Manager
anna.juhrs@item.fraunhofer.de

Dr. Cathrin Nastevska
Press and Public Relations Manager
cathrin.nastevska@item.fraunhofer.de

Publishing notes

Coordination and editorial work
Dr. Cathrin Nastevska

Translation
Transline Deutschland GmbH and Karin Schlemminger

Layout
Tine Linder, mcc Agentur für Kommunikation GmbH, Berlin (Germany)

Photo acknowledgements
P. 8: Henrik Abrahams
P. 10: Andreas Krukemeyer
P. 12: Nick Neufeld
P. 17: Patrick Reinig
P. 19: Fraunhofer
P. 23: Felix Schmitt Fotografie
P. 24: stock.adobe.com, ORG
P. 25: Felix Schmitt Fotografie
P. 31 (top): Fraunhofer ITEM, Ariane Zwintscher
P. 31 (bottom): stock.adobe.com, mewaji
P. 32 (top): Fraunhofer ITEM
P. 32 (bottom): stock.adobe.com, bukhta79
P. 35 (bottom): Fraunhofer ITEM, Paria Pajouhi Paad
P. 37: stock.adobe.com, nobeastsofierce
P. 38: MHH, Shambhabi Chatterjee; Christian Bär
P. 42: Fraunhofer ITEM, created with BioRender.com
P. 44 (top): Henriette Pook, Trade and Investment Queensland
P. 44 (bottom): MHH, Elisa Mohr; Christian Bär
P. 47: Patrick Reinig
P. 48: Fraunhofer ITEM, Kathrin Weidele
P. 49: Fraunhofer ITEM, created with BioRender.com
P. 52: Fraunhofer ITEM, Ulrich Froriep
P. 53: Fraunhofer ITEM, Felix Wiegandt
P. 55: stock.adobe.com, tippapatt
P. 56: stock.adobe.com, Who is Danny
P. 57: stock.adobe.com, Rumi X

Cover page, portrait photos and all other photographs:
Ralf Mohr Photographie, © Fraunhofer ITEM.

Fraunhofer ITEM
Headquarters
Nikolai-Fuchs-Strasse 1
(main entrance: Stadtfelddamm)
30625 Hannover
Germany
Phone +49 511 5350-0

Fraunhofer ITEM
Pharmaceutical Biotechnology
Inhoffenstrasse 7
38124 Braunschweig
Germany
Phone +49 531 6181-6001

Fraunhofer ITEM
Personalized Tumor Therapy
Biopark 1
Am Biopark 9
93053 Regensburg
Germany
Phone +49 941 298480-0

Further information: www.item.fraunhofer.de/en