Fraunhofer ITEM

Annual Report 2022

Fraunhofer ITEM – pioneers for sustainable health

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To our readers

Executive Director Prof. Dr. Norbert Krug

Director Prof. Dr. Dr. Thomas Thum

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.

We are very grateful to have played a role in the fight against the SARS-CoV-2 pandemic in recent years by contributing our expertise from lung, infection and aerosol research as well as developing innovative and interdisciplinary health solutions in close cooperation with our partners. Fraunhofer ITEM initiated or participated in a total of 21 projects with a total volume of 9.1 million euros from 2020 to 2022. These projects have been financed or contracted by industry, public or Fraunhofer internal funds.

After focusing on pandemic-related research topics, we were again able to advance our strategic research fields in 2022. Three fields are of particular interest to us:

Next generation risk assessment to set the stage for the future

Toxicology testing of chemicals, active pharmaceutical ingredients and drugs is a research expertise at Fraunhofer ITEM that we have been continuously enhancing for more than 40 years. During this period, we have developed numerous new methods and assessment approaches — not least with the aims of improving animal welfare, obtaining research results that are more relevant to humans and providing predictive models for risk and safety assessments.

Development of RNA-based active substances ready for clinical use

The further development of RNA technologies is a very important field of research at our institute. RNA-based strategies have huge potential for health research, both as a drug class and as biomarkers — and scientists have barely scratched the surface of their possible use. Our research and development work ranges from target identification via lead optimization, efficacy testing, RNA-based analytical methods, toxicology testing, manufacturing and targeted delivery to phase-I and phase-II clinical trials.

Getting the most out of bioinformatics and artificial intelligence for biomedicine

The availability of large amounts of data and the use of artificial intelligence have revolutionized research in the life sciences in the past few years, offering a wide range of opportunities for biomedical translation. We continue to expand our research expertise in bioinformatics, partly in individual research projects, partly in an accompanying and supporting capacity.

We would like to take this opportunity to express our sincere thanks to our nearly 450 employees in Hanover, Braunschweig and Regensburg for their impressive commitment to health research, as well as to our partners and customers for their close and fruitful cooperation.

Prof. Dr. Norbert Krug

Prof. Dr. Dr. Thomas Thum

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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 focus of research is 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. The focuses at Fraunhofer ITEM are on airway research and cardiovascular research, and linking these offers enormous potential for translational research. The institute's extensive experience in the development of RNA-based diagnostics and therapeutic approaches is being strategically expanded in line with the current trends in health research.

At three institute locations – in Hannover (headquarters), Braunschweig, and Regensburg –, scientists work in different fields of research and development expertise: cardiopulmonary 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 institutes Fraunhofer ITEM, Fraunhofer IST, and the Fraunhofer research institution IMTE. Their combined expertise offers an ideal basis for accelerating scientific developments in medical and pharmaceutical engineering to provide state-of-the-art applications for patients.

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.

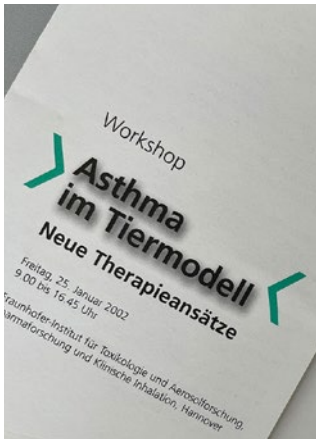
In order to ensure compliance with internationally accepted quality standards, the institute has implemented the GXP quality assurance systems. These include Good Laboratory Practice (GLP), Good Manufacturing Practice (GMP), and Good Clinical Practice (GCP). Furthermore, the institute is certified to 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.

20th Fraunhofer Seminar "Models of Lung Disease" paves the way for lung research

"When we launched the Fraunhofer Seminar 'Models of Lung Disease' over 20 years ago, we never dreamed that it would become one of the most important forums for translational lung research and an ideal platform for exchange between industry and academia. Personally, I am delighted every time I return to this relaxed atmosphere, where I can discuss science with old and new friends and colleagues."

Prof. Dr. Armin Braun
Division Director of Preclinical Pharmacology and Toxicology
and pioneer of the seminar series

The international Fraunhofer Seminar "Models of Lung Disease" has brought together specialists from around the world at Fraunhofer ITEM in Hannover each year since it began in 2002, when it was named "Asthma im Tiermodell".



First Invitation in 2002

At the event, experts from academia and industry from all over the world gather to discuss new pharmaceutical developments and recent findings in experimental lung research. Together, they pave the way on the journey from laboratory to application.

The poster exhibition is a key part of the seminar and provides creators with the opportunity to discuss their research directly with other participants.

The Fraunhofer seminar has an excellent program on offer. With the focus on COVID-19 research in 2022, we were particularly pleased to host a lecture by virologist Prof. Christian Drosten of Charité in Berlin.

In years past, Models of Lung Disease took place at the start of the year. To limit the risk of infection, in 2022, we decided to delay the event for the first time, holding it in the summer season instead. The terrace and barbecue were so much enjoyed that the 2023 event will also take place in the summer.

Models of Lung Disease

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.

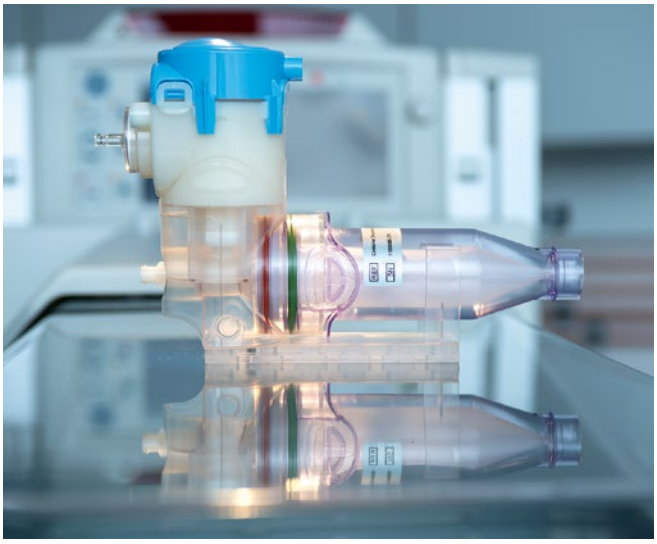
In the field of device development, our focus is on neural implants and on conducting and assisting the development of novel technologies for administration of therapeutic aerosols towards smart drug/device combination products.

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 institute's Regensburg-based Division of Personalized Tumor Therapy is committed to doing research on metastatic disease, to understanding a patient's individual condition, to establishing appropriate diagnostics and to advancing prevention and therapy optimization.

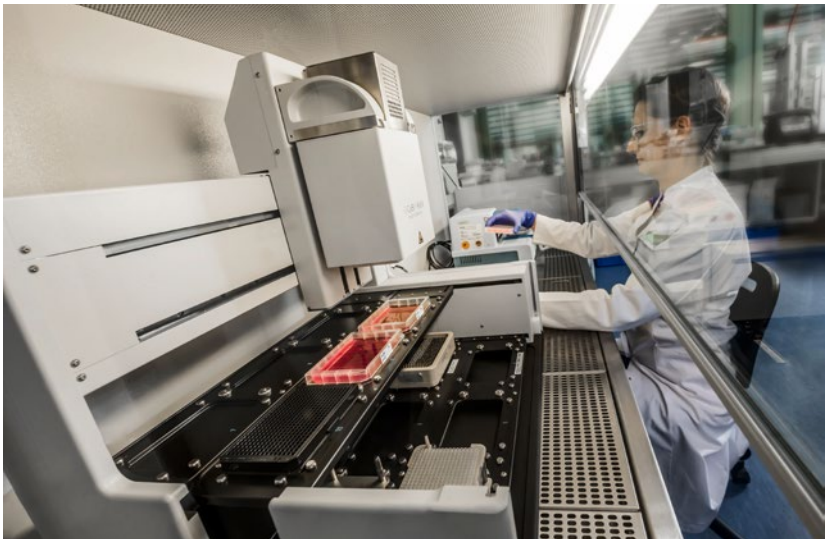
We have special expertise in the comprehensive characterization of circulating or disseminated cancer cells. These can be collected as circulating tumor cells by taking ordinary blood samples (also referred to as "liquid biopsy") from patients or they can be isolated from lymph node tissue or bone marrow as disseminated cancer cells. Our expertise also includes the analysis of cell-free, tumor-derived blood components (circulating tumor DNA, microvesicles) and innovative tissue-based analytical methods, also referred to as tissue biopsy. A tissue bank with corresponding logistics for sample storage is being set up.

With our expert knowledge in the fields of cellular and molecular diagnostics, biomarker discovery, preclinical therapy models, disease modeling and high-throughput screening technologies, we work on a broad variety of topics in the context of liquid biopsy and rare cell populations. Our in-house data management and comprehensive bioinformatics enable custom-fit analysis of the generated data. The Division of Personalized Tumor Therapy has been certified to DIN ISO 9001:2015 by TÜV Süd and thus complies with international standards.

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

- Single-cell analysis
- Innovative tumor models
- Mathematical modeling and bioinformatics

www.item.fraunhofer.de/tumor-therapy



Organizational structure

The two institute directors Prof. Norbert Krug (executive director) and Prof. Thomas Thum are managing Fraunhofer ITEM in tandem. The institute is organized in seven divisions and three additional units. 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.

INSTITUTE MANAGEMENT

Prof. Dr. Norbert Krug (Executive Director)
Prof. Dr. Dr. Thomas Thum

Central services
Marlene Rauschenbach

STAFF OFFICES

Information Management
Petra Wiedemeier

Institute Strategy and Communication
Dr. Henning Weigt

Project Management
Dr. Sabine Kafert-Kasting

Quality Assurance
Dr. Jens Gerdelmann

Chemical Safety and Toxicology Dr. Annette Bitsch	**Airway Research** Prof. Dr. Jens Hohlfeld	**Translational Biomedical Engineering** Dr. Gerhard Pohlmann	**Personalized Tumor Therapy** Prof. Dr. Christoph Klein
Pharmaceutical Biotechnology Prof. Dr. Holger Ziehr	**Preclinical Pharmacology and Toxicology** Prof. Dr. Armin Braun	**Cardiovascular Research** Prof. Dr. Dr. Thomas Thum	
Attract Group Bioinformatics Prof. Dr. Lena Wiese	**Attract Group IMMUNITY** Prof. Dr. Nico Lachmann		

As at June 2023

Staff and institute budget performance

At the end of 2022, Fraunhofer ITEM staff at all three sites – Hannover, Braunschweig and Regensburg – altogether amounted to 463 persons, with a female proportion of approximately 62 percent. People from 18 countries work and do research together at Fraunhofer ITEM.

The institute's staff in 2022 included:

- 381 scientific, technical and administrative staff
- 21 Ph.D. students
- 49 students (bachelor's and master's programs)
- 9 apprentices
- 3 interns

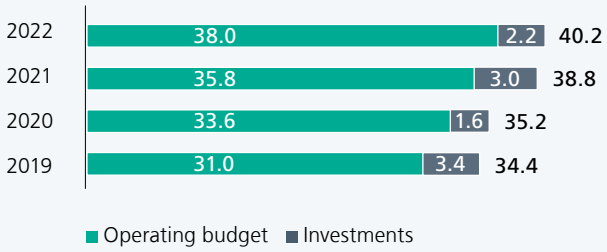
In 2022, the institute's budget reached a level of approximately 38 million euros. Financing by acquired funding amounted to 67 percent. The share of industrial income in the institute's budget was 38 percent. Investments of Fraunhofer ITEM amounted to approximately 2.2 million euros.

Fraunhofer ITEM staff

Number of employees

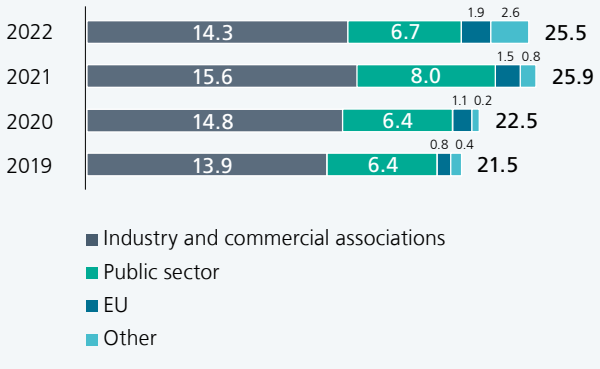
Fraunhofer ITEM total budget

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 2022:

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. 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

Dr. Sylvia Jacobi
Corporate Toxicology Director, Albemarle Europe (Belgium)

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
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 (UKGM)

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

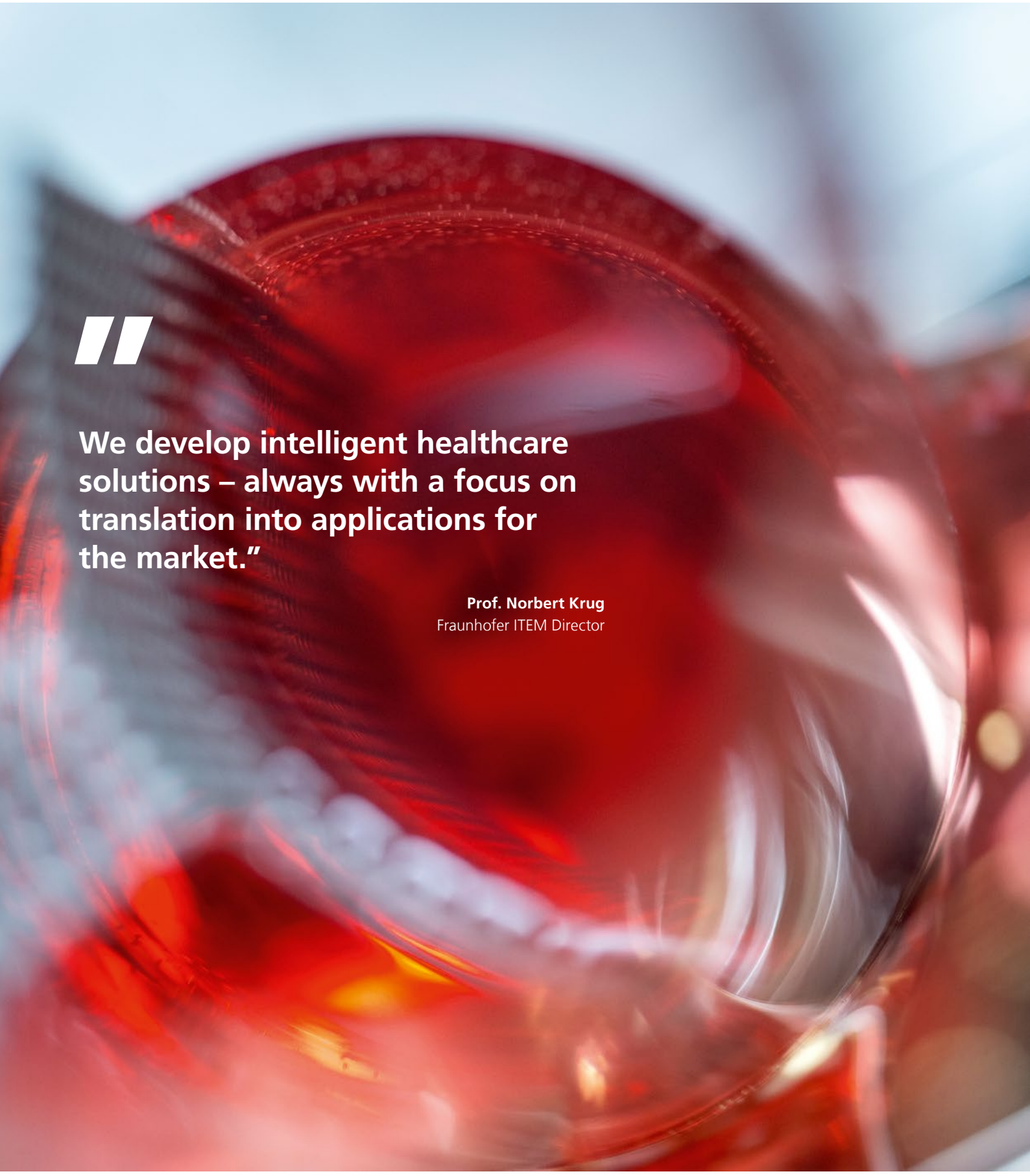
Dr. Torsten Wagner
Senior Vice President, Corporate Technical Operations, Merz Pharma GmbH & Co. KGaA

The Fraunhofer-Gesellschaft

The Fraunhofer-Gesellschaft based in Germany is the world's leading applied research organization. Prioritizing key future-relevant technologies and commercializing its findings in business and industry, it plays a major role in the innovation process. A trailblazer and trendsetter in innovative developments and research excellence, it is helping shape our society and our future.

Founded in 1949, the Fraunhofer-Gesellschaft currently operates 76 institutes and research units throughout Germany. Over 30,000 employees, predominantly scientists and engineers, work with an annual research budget of 2.9 billion euros. Fraunhofer generates 2.5 billion euros of this from contract research.

www.fraunhofer.de/en



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

Cardiopulmonary research

Research for healthy hearts and lungs

The heart and lungs interact in a complex interplay. Both systems are affected by partly similar risk factors and there is an overlap of pathogenic molecular mechanisms such as organ fibrosis. Due to high morbidity and mortality, diseases of the heart and lungs play a major role in terms of health economics.

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 approaches, both at the preclinical 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 such as the P.R.I.T.® in-vitro exposure system, for example for the characterization of materials such as nanocarriers that may be used as drug delivery systems in the long term.

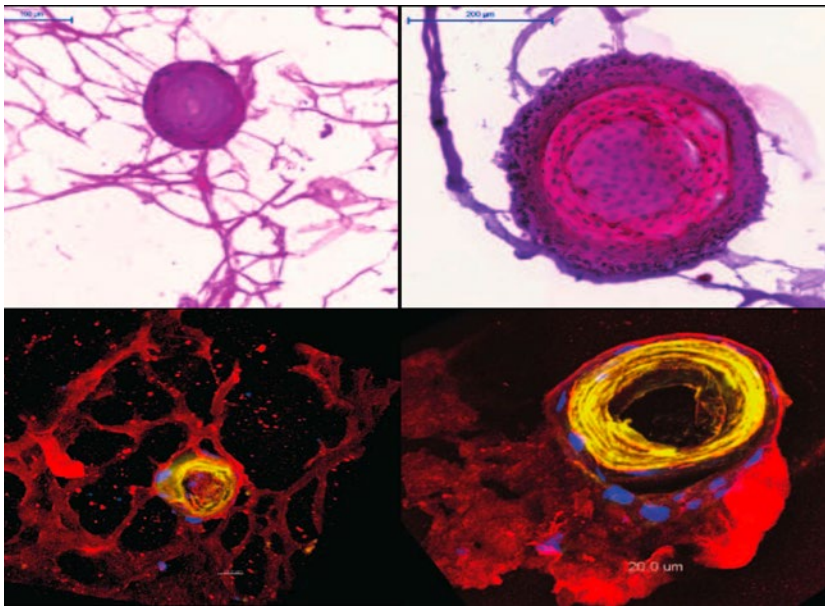
The establishment of a university-affiliated Division of Cardiovascular Research has generated new methodological and scientific overlaps at Fraunhofer ITEM. As a result, the long-standing expertise in lung research has experienced a synergetic further development of high clinical relevance. RNA molecules in particular are being investigated very successfully as diagnostic biomarkers and therapeutic targets for the benefit of patients with cardiac and pulmonary diseases.

Computer-assisted translational bioinformatics, used to predict molecular mechanisms based on RNA molecules, is of particular importance in this context. Fraunhofer ITEM researchers are currently exploring the potential of RNA molecules for toxicology and efficacy testing of drugs.

To efficiently translate ideas from bench to bedside, the scientists use appropriate exposure systems, some of which have been developed specifically for this purpose, 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.

At Fraunhofer ITEM, drug candidates can be tested for efficacy and side effects to provide the proof of concept in humans, i.e. the necessary evidence of the drug's mode of action. Through their clinical research, Fraunhofer ITEM scientists enable a direct transfer of findings to humans, for example, by using chip cytometry and exhaled breath analysis.

Our highlights



Airway basal cells from patients with idiopathic pulmonary fibrosis form large spheres which become hollow tube-like structures after 21 days of 3D culture. In the co-culture system of basal cells with lung fibroblasts, fibroblasts surround bronchospheres and form a mesh-like structure.

Airway basal cells as key cells in the pathogenesis of pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a fatal disease with limited treatment options. Fraunhofer ITEM researchers have gained groundbreaking insights into IPF, more precisely into the role of basal cells in the airways (1 Jaeger et al., 2022: DOI 10.1038/s41467-022-33193-0). They showed that airway basal cells from IPF patients promote fibrosis as a result of their atypical gene expression and altered differentiation. In a 3D organoid model, airway basal cells from IPF patients generated more bronchospheres and de-novo bronchial structures resembling lung developmental processes, compared to airway basal cells from healthy donors. In addition, they induced fibroblast proliferation and extracellular matrix deposition in co-culture. Furthermore, the researchers developed a completely new mouse model of IPF that is based on airway basal cells derived from IPF patients and therefore mimics the disease much better than any previously used model. By applying bioinformatic analyses to transcriptome data sets of patient-derived cells, they were able to create models enabling prediction of the response to therapy. As a result of these in-silico analyses, the SRC signaling pathway, among others, was identified as a driving factor.

The researchers were able to show in their newly developed in-vitro and in-vivo models that the SRC inhibitor saracatinib therapeutically downregulates developing fibrosis. These findings have demonstrated basal cells to be key players in the pathogenesis of human IPF and thus an important target for the development of novel therapeutic measures.

Contact

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Clinical and Translational Research on Pulmonary Fibrosis
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Focus on ambrosia pollen: finding the threshold dose in allergic rhinitis patients

Even small amounts of ragweed pollen can trigger severe allergic reactions in humans. Ragweed is native to North America, but is also spreading more and more in Germany, which is why the number of allergic individuals is increasing here as well.

Common ragweed (*Ambrosia artemisiifolia*), a plant that has been classified as posing a health risk, is native to North America and, due to climate change, is spreading increasingly in northern and central Europe. Ambrosia pollen is considered to have a high allergenic potency, especially compared to allergenic plants native to Germany such as sweet grasses and broadleaf trees (e.g. birch). The aim of an exploratory clinical study funded by the German Federal Environment Agency is to determine the respective threshold doses that trigger allergic symptoms in people allergic to ragweed or birch pollen. With a newly developed experimental setup in the Fraunhofer Allergen Challenge Chamber (Fraunhofer ACC), the Fraunhofer scientists have managed to dose the pollen supply into the allergen chamber so finely that spatially and temporally stable, very low room concentrations can be achieved, for example 10 pollen/m³. The study participants are tested in a screening challenge with 1000 pollen/m³ to see if they react mildly to moderately to the respective pollen, with the aim to select a group of individuals showing average reactions. Thereafter, the study design follows an adaptive scheme: In addition to a sham exposure to clean air, up to four further exposure sessions in the Fraunhofer ACC are performed with either higher or lower pollen concentrations, depending on the previous outcome. The experimental part of this study with birch pollen was completed in fall 2022. The part with ambrosia pollen is planned to be performed in the fall of 2023.

Contact

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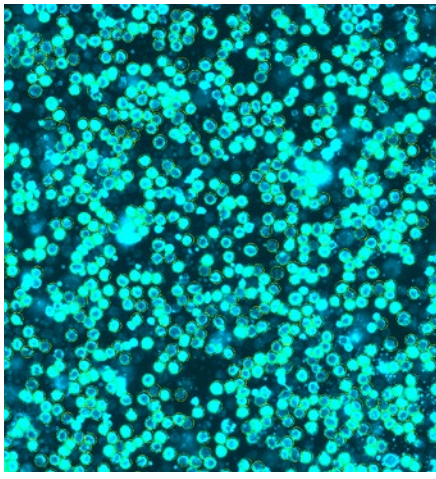
Neutrophil subset as potential therapeutic target for secondary lung tissue injury

The acute respiratory distress syndrome (ARDS) can result from a state of acute hyperinflammation caused by direct or indirect lung injury. Among the players causing this massive immunological overreaction are neutrophils, which in a pathological setting can induce significant secondary tissue injury. While not all neutrophils seem to be involved in this overreaction, experimental findings point to a neutrophil subset expressing the dual endothelin-1/signal peptide receptor (DEspR). These so-called "rogue" neutrophils are characterized by delayed apoptosis, so that the cells stay active for a longer period than usual.

In collaboration with scientists of the Boston University School of Medicine, Fraunhofer ITEM researchers demonstrated increased pulmonary and systemic DEspR-positive neutrophil counts in rats, Rhesus macaques and humans as a result of endotoxin-induced inflammation or acute tissue injury. Prophylactic treatment with an anti-DEspR antibody reduced endotoxin-induced hypoxemia in macaques and increased the median survival in rats. The results have been published (Carstensen et al., 2022: DOI 10.3389/fimmu.2022.1008390) and suggest a new therapeutic target for neutrophil-mediated secondary tissue injury, such as that seen in ARDS.

Light blue-colored neutrophils in cells from a bronchoalveolar lavage after endotoxin-induced inflammation. The fluorescence image was taken with the chip cytometer.



Contact

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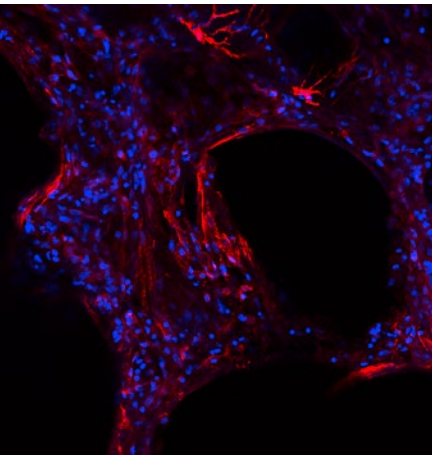

Human precision-cut lung slice, prepared from a lung graft of a patient with pulmonary fibrosis. Due to immunofluorescence staining, muscle actin proteins glow red and cell nuclei appear in blue.

Biomarkers of collagen formation or degradation in human PCLS

Pulmonary fibrosis (PF) comprises a spectrum of rapidly progressive lung diseases that are mainly characterized by aberrant wound healing processes leading to uncontrolled deposition of extracellular matrix (ECM) proteins and consequent destruction of lung architecture. The underlying mechanisms are not yet fully understood. In the context of the COVID-19 pandemic, it has been reported that a large number of patients who had recovered from their acute COVID-19 pneumonia develop advanced PF or post-COVID interstitial lung disease (PC-ILD), highlighting the importance of identifying new biomarkers for distinct PF diseases.

Together with several industry partners, Fraunhofer ITEM scientists published novel data on neoepitope biomarkers of type I, III and VI collagen formation or degradation in precision-cut lung slices (PCLS) from patients with PF (Hesse et al., 2022: DOI 10.1186/s12931-022-02116-4), with a focus on the treatment effects of antifibrotic drugs. They found that PRO-C3 and C3M were modulated by nintedanib, suggesting that nintedanib exerts antifibrotic effects via type III collagen remodeling.

Linking the study to clinical data showed C3M to be a promising biomarker of response to treatment with nintedanib. This study has once again highlighted the use of PCLS as a highly translational model to study the underlying mechanisms of pulmonary fibrosis and to advance preclinical drug development and clinical decision-making.

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With each breath people take, they exhale particles. By collecting these, scientists non-invasively obtain material from deep within the lungs to study diseases.

Non-invasive examination of the lungs by means of exhaled particles

With each breath we take, we exhale particles that are formed in the tiny airways of the lungs. The particles are made from the fluid film lining these airways, which contains lipids as well as proteins. Such particles can be collected by means of an impactor, directing the exhaled air via small nozzles onto a surface, where size-dependent inertia causes the particles to be deposited. This method allows material from deep within the lungs to be sampled non-invasively to study diseases. The challenge is the small quantity of particles, whose weight is determined based on their number and size distribution. Usually, less than one quarter of a millionth gram is available for this purpose. Highly sensitive detection methods are thus required for further analyses.

To evaluate whether this new method is suitable for use in clinical settings, volunteers inhaled bacterial endotoxin in a clinical study. This inhalation exposure causes a short-term inflammatory response in the lungs, as has been demonstrated by standard methods such as sputum analysis. In the present study, the Fraunhofer researchers for the first time successfully demonstrated the increase in inflammatory cytokines in exhaled particles as well. They have published the data (Holz et al., 2022: DOI 10.1038/s41598-022-09399-z) and have already used the method of exhaled particle measurement in several clinical studies.

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Safety and efficacy of inhaled booster vaccination with the vector vaccine MVA-SARS-2-ST

The approved COVID-19 vaccines elicit the temporary formation of antibodies and a systemic T-cell response that provide protection against a severe course of the disease, but not against infection. Most importantly, intramuscular injection of the available vaccines does not induce mucosal immunity in the respiratory tract.

In cooperation with the Hannover Medical School, which is also the sponsor of this investigator-initiated clinical trial, Fraunhofer ITEM

scientists are investigating the safety and efficacy of inhaled booster vaccination with the vector vaccine MVA-SARS-2-ST in a phase-I trial. This vaccine contains an attenuated strain of the vaccinia virus (Modified Vaccinia Ankara), which is related to the smallpox virus but unable to replicate. For decades already, it has been used as a platform for vaccine production and has now been developed to target the S protein of SARS-CoV-2.

After successful non-clinical development and evidence of a mucosal immune response in the respiratory tract in animal models, the first study in humans involving inhaled administration of the vaccine is now being performed. In addition to assessing local and systemic safety, a focus will be on efficacy, which will be evaluated by bronchoscopy with comprehensive characterization of the humoral and cellular immune response before and after administration of the vaccine. The study is expected to be completed in mid-2023.

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Fraunhofer project FibroPaths®: facilitating rapid and safe development of antifibrotic drugs

There is a huge need to facilitate rapid and safe development of antifibrotic drugs. More than 100 million individuals worldwide suffer from organ fibrosis, a pathological proliferation of connective tissue in an organ, such as the lung, heart, and liver; however, hardly any causal treatments are available to date.

The unmet medical need is partly due to the fact that the existing disease models for fibrosis research are insufficient and little predictive. This challenge has now been addressed by the Fraunhofer institutes MEVIS, IMW, IWS, and ITEM in the FibroPaths® project, receiving Fraunhofer-internal funding. Under the lead of Fraunhofer ITEM, the institutes have joined forces to facilitate rapid and safe development of antifibrotic drugs.

The aim of FibroPaths® is to develop a novel system for preclinical testing of antifibrotic drug candidates. It will be based on a standardized and automated biochip that includes human tissue and is thus closer to the clinical situation. In addition, it will help avoid animal experiments, in the sense of the 3Rs principle. The aim is that the innovative biochip will allow extensive structural, molecular, and functional characterization of fibrotic processes. Furthermore, the project will include comprehensive functional and molecular data analyses using AI-assisted methods, and the establishment of a corresponding database.

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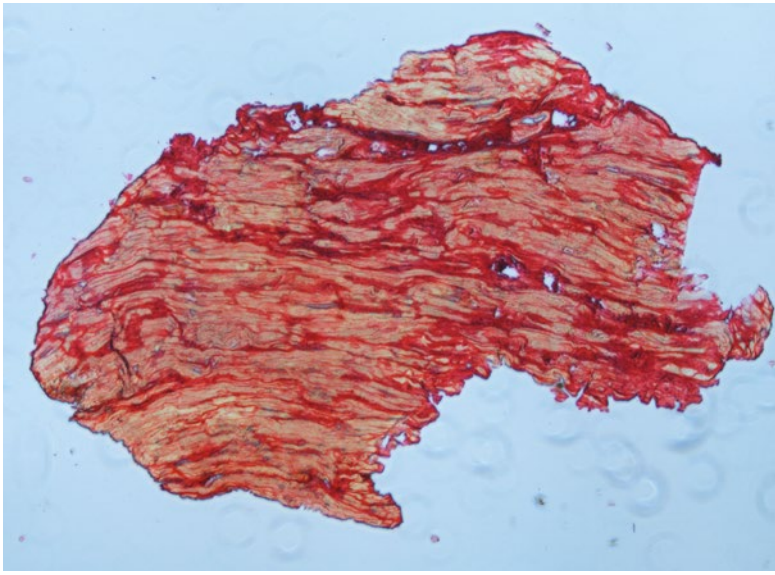
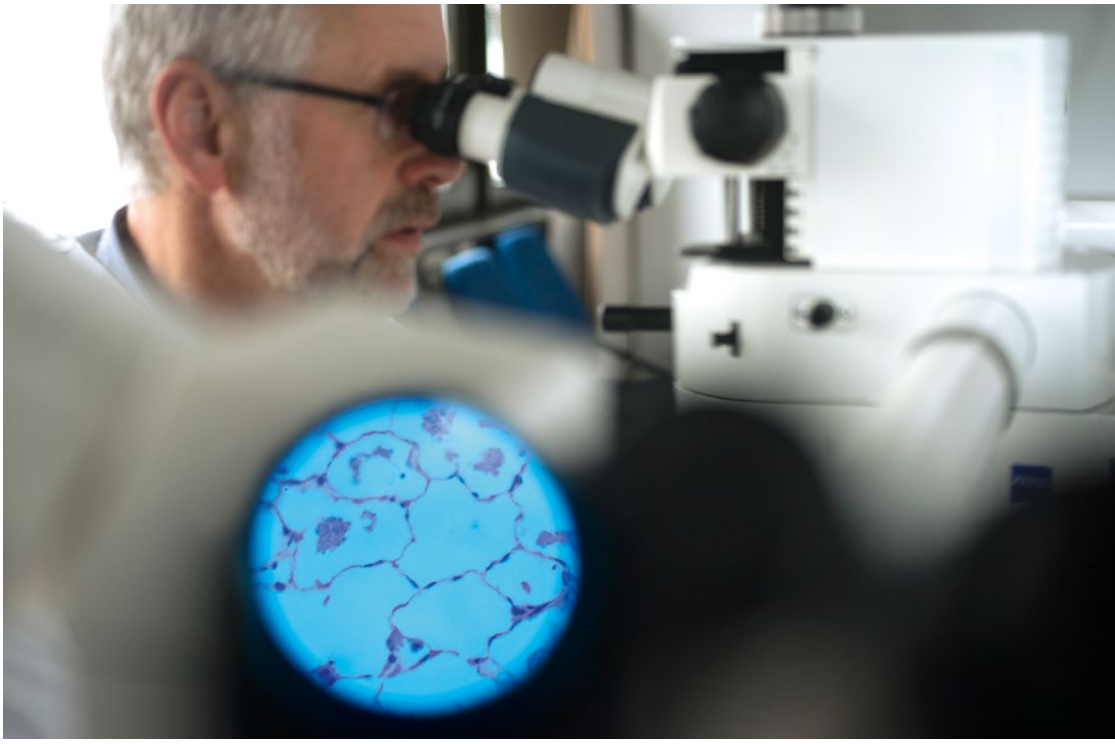
Broncoscopy is one method used to evaluate the efficacy of inhaled booster vaccination with the vector vaccine MVA-SARS-2-ST. In addition, the scientists analyze the humoral and cellular immune response before and after administration of the vaccine.

Histology of a human heart slice with more than 40 percent fibrotic area; collagen accumulations as a sign of fibrosis have been stained red.



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 aim of the EASA-funded research project CAQ III is to assess cabin air quality with regard to the long-term effects of contaminants.

The CAQ III project: for a better understanding of cabin air quality

The quality of the air that passengers and aircrews are exposed to on board commercial transport aircraft has been at the core of a continuing debate for the past 60 years, both from the health and the safety points of view. Single cabin/cockpit air contamination events, also referred to as "fume events", caused by leakage of oil fumes from the engines into the cabin and/or cockpit via the bleed air system, are at the focus of the CAQ III project.

Supported by the European Commission, EASA launched the research project CAQ III "Cabin air quality assessment of long-term effects of contaminants" in 2022. Its aim is to collect additional scientific evidence regarding the potential hazards and frequency of oil-related fume events, enabling a more extensive assessment of health risks, and to support the evolution of aviation standards with regard to cabin/cockpit air quality. Through the collaboration of the European project partners, CAQ III is pooling first-class knowledge for the studies on systematic health effects of oil-related fume events that are being conducted in this project.

Complete characterization of chemical compounds involved in fume events and assessment of their exposure levels is attempted by running elaborate simulations as well as on-ground and in-flight aircraft experiments. After inhalation toxicity testing in mice and subsequent neurobehavioral studies, the project aspires to achieve comprehensive toxicological risk assessment of such fume events.

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Research aimed at predicting the carcinogenic potency of different nitrosamines

In recent years, drugs have been recalled from the market, due to detection of low levels of impurities consisting of N-nitrosamines (NAs). NAs are considered potent carcinogens with a mutagenic mode of action. The regulatory authorities, therefore, recently established a very low threshold of 18 ng/d for all NAs for which no specific carcinogenicity studies are available. But is this threshold justified for all types of NAs? This question has been addressed in the MutaMind project, funded by the European Medicines Agency (EMA) and led by Fraunhofer ITEM. In this project, eight partners – from academia, a regulatory authority, and a contract research organization – aim to better understand the processes contributing to the mutagenicity of NAs and to develop custom-tailored in-vitro tools for sensitive genotoxicity screening. A special focus is on NAs resulting from drugs.

To this end, the consortium is evaluating about 40 NAs and their capacity to form different types of DNA adducts (i.e., chemical modifications of DNA bases) upon metabolic activation. Differences in the corresponding DNA repair processes are investigated by using repair-proficient as well as repair-deficient human and mouse cell models.

To define NA-adapted, sensitive, and predictive genotoxicity screening tools, both DNA base mutations and DNA repair-dependent DNA strand breaks serve as endpoints. The standard Ames test is evaluated regarding the impact of the type and amount of solvent and the metabolic activation system (rat versus hamster) on the detection of mutagenic NAs. In addition, the researchers are evaluating the usefulness and feasibility of the Ames fluctuation assay for NA testing. As an alternative tool, they investigate the sensitivity and predictivity of the in-vitro alkaline comet assay with different liver cell models (HepG2 cells, primary rat and human hepatocytes). First promising results have already been obtained with primary hepatocytes. To complete the picture, the scientists are exploring the endogenous formation of NAs by bacteria from the human stomach and gut microbiome. To this end, they culture bacteria under anaerobic conditions and expose them individually or in combination to different drugs under physiological conditions. Fist result have already demonstrated differences in the kinetics of NA formation.

The obtained data will eventually be used to better distinguish groups of potent from less potent mutagenic NAs based on their structural properties and biological effects.

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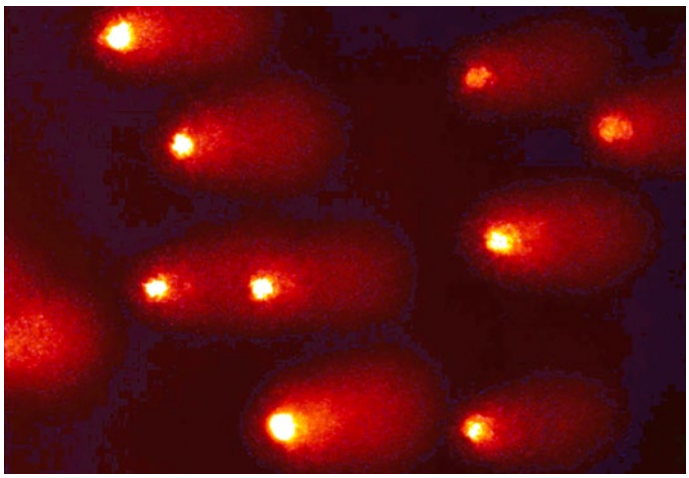
Comet assay, also known as single-cell gel electrophoresis, is a genotoxicity assay that indicates DNA damage at the single-cell level. The cells shown here were treated with ethyl methanesulfonate, a compound causing DNA strand breaks, prior to gel electrophoresis. After staining, comet-like entities can be seen: the brighter comet "heads" show undamaged DNA, while the "tails" represent DNA fragments that have migrated in the electric field depending on their size.



Assessing microplastic inhalation toxicity: towards a tiered strategy

Microplastic (MP) is an emerging contaminant that has generated intense public concern. A standardized approach for human risk assessment, both for inhaled and ingested MP, is not available to date. In addition to a lack of appropriate reference materials, there are analytical challenges in the detection and dose definition, and information about relevant physicochemical properties of MP materials that drive human toxicity is missing. Another challenge for scientists is the development of a tiered testing and assessment approach that is mainly based on mechanistic evidence from human in-vitro models. Fraunhofer ITEM scientists are addressing these topics in two projects: In the "Brigid" project recently launched by Plastics Europe, the oral route of exposure is under investigation, while the Cefic-LRI project aims to develop a tiered approach for the assessment of inhalable MP.

Based on solvent precipitation, the scientists initially developed appropriate methods for the generation of MP reference particles with an upper size fraction < 10 µm. At present, tools for visualization and quantification of MP particles in cells and biological matrices are under development. The aims of the next phase in the Cefic-LRI project are to identify MP descriptors that determine inhalation toxicity and to finally rank these descriptors by their relevance for the assessment of human health hazards from inhalation.

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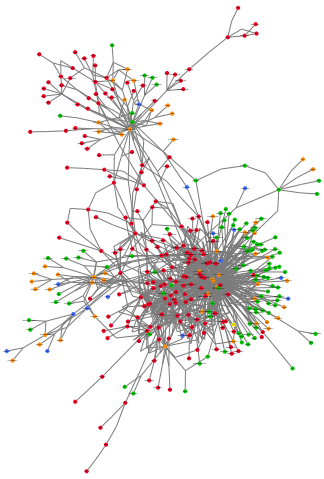
Transcriptome data as a possible basis for similarity assessment in read-across

Read-across (RAx) is a well-established method in the regulatory context to derive toxicological properties of a substance from similar compounds. It is usually difficult to assess the similarity of the substances, especially with regard to their mode of action, because in most cases only apical findings from in-vivo studies are available and these do not provide clear evidence of similar mechanisms of action. Novel technologies, such as transcriptome analyses, enable insights into the regulation of molecular processes and therefore have a high potential to reduce this uncertainty.

Less obvious than plastic waste in the environment is microplastic – very small fragments of plastic that are smaller than 5 mm in diameter. A standardized approach for human risk assessment of inhaled and ingested microplastic is lacking to date.

In the FibrOmics and EU-ToxRisk projects, an analysis strategy was developed based on an RAx case study. The aim was to demonstrate common mechanisms of action within the grouped substances by means of transcriptome data, while clearly differentiating dissimilar substances. Primary lung epithelial cells showed a largely common gene expression profile for the group of α-diketones after a single exposure, and this profile was clearly distinct from that of substances with a different mechanism of action. Further functional analyses have demonstrated that α-diketones regulate common signaling pathways and proteins associated with the known mechanism of action of pulmonary fibrosis. Consequently, transcriptome data can be used to elucidate the mechanism of action of substances or groups of substances and can be directly integrated into an RAx analysis. They thus help to substantiate the RAx hypothesis and to reduce the uncertainty of the RAx prediction.



Reconstructed networks, each based on genes associated with lung fibrosis, inflammation, and apoptosis, serve as a tool to visualize the mechanism of action.

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Inhalation toxicity of niobium

The chemical element niobium is marketed in large tonnage for industrial use. Niobium adds strength to materials and is used, among other things, as an alloying addition in a wide range of products. In addition, niobium is frequently employed in nuclear technology, in welding electrodes, capacitors, halogen lamps, catalysts, and for surface coating of implants.

The toxic potential of niobium pentoxide towards the respiratory tract was investigated in an in-vivo study conducted at Fraunhofer ITEM. In this 90-day inhalation study, a dose was identified that caused no effects. In the next step, a limit value will be derived, and this can then be used to define measures for the safe handling at workplaces and also for end users. In the study, niobium pentoxide proved to be what is known as an inert dust, i.e. a substance with no known harmful effect on the human body.

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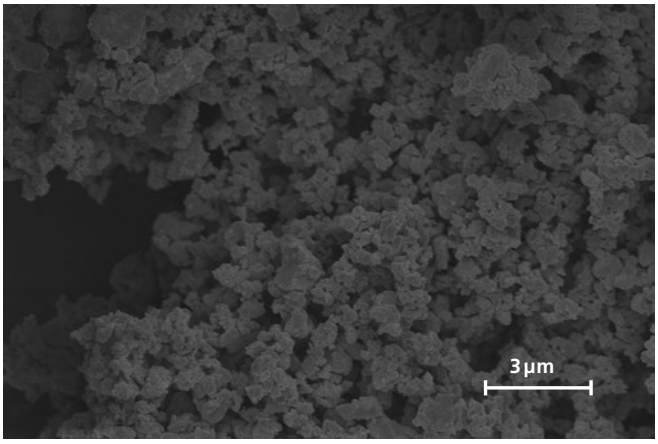
Fine and nanosized dusts occurring at industrial workplaces are highly relevant to occupational safety. They have therefore been subject to regulatory measures for a long time in order to protect employees from adverse lung conditions, such as fibrosis, silicosis or, in the worst case, lung tumors. The definition of limit values is aimed at ruling out health hazards to workers, especially from lung diseases, even for prolonged exposure.



The heavy metal niobium – the picture shows an electron micrograph of niobium pentoxide powder – adds strength to materials. Fraunhofer ITEM researchers have investigated the toxicity of niobium in the respiratory tract.

Foam spraying, for example for surface disinfection, in many cases results in lower aerosol release than droplet spraying under similar conditions.

Determination and prediction of inhalation and dermal exposure from foam spray applications

In recent years, application of biocides in the form of foam sprays has increased, for example, for large-surface disinfection in food processing areas or for biocidal pest control. Foaming is considered an alternative to droplet spraying, as it is assumed to result in lower aerosol emission. While for droplet spraying large data sets on inhalation and dermal exposure are available and established exposure assessment models are available, this information was lacking for foam spraying.

Fraunhofer ITEM and the Institute of Occupational, Social and Environmental Medicine of the University of Erlangen-Nuremberg collaborated in a project commissioned by the Federal Institute for Occupational Safety and Health (BAuA), aimed at generating a detailed data set on inhalation and dermal exposure during biocidal foaming activities. Using a methodology recently developed at Fraunhofer ITEM, the scientists determined the aerosol release for common foaming technologies applied according to their intended use. These data allowed the identification of the relevant process parameters as well as a classification of the foaming processes into different aerosol release categories with regard to practical application.

This provided the basis for the development of a modified two-box model to predict inhalation exposure during foam spray applications based on simple and well-known process and foam parameters, such as treated surface area, foaming method, and exposure duration. Comparison with measurements conducted at real workplaces has confirmed the high predictivity of the newly developed model. A second focus was on quantifying the exposure reduction during foam spraying compared with conventional droplet spraying processes, to assess whether foam spraying is an appropriate risk mitigation measure. In many cases, foam spraying results in lower aerosol release than droplet spraying under similar conditions; however, this cannot be generalized based on the data available to date. This is in contrast to the results for dermal exposure, where no difference between foaming and spraying was observed, because dermal exposure is dominated by direct contact and splashes rather than by aerosol deposition.

The theoretical and practical knowledge gained within this project on the inhalation and dermal exposure of workers during the application of biocidal foams is intended to support industry and authorities in the assessment of risks to human health within regulatory procedures. Recently, the model has been considered in the project "Advancement and connection of modeling approaches for estimating inhalation exposure during spray applications", commissioned by BAuA to Fraunhofer ITEM. This subproject is part of the larger BAuA project "Modular model approaches for occupational safety and health risk assessment in chemical safety."

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Cell painting – a promising tool for next generation risk assessment

Aiming to reduce, refine, and replace animal experiments (3Rs principle), Fraunhofer ITEM researchers are implementing new-approach methodologies (NAMs) to characterize potential toxic effects of chemical compounds and processes. A powerful tool referred to as "cell painting" (CP) allows them to detect an erosion of cellular health upon exposure to stressors, caused, for example, by variation of the cell metabolic state or by genetic perturbations, already at an early stage of exposure. CP is a high-content imaging-based method involving multiplexed fluorescent staining of different cellular compartments simultaneously. Using automated image analysis, CP can identify more than 5000 cellular features, forming a "cellular fingerprint" that reflects different biological responses induced by noxious compounds or processes.

Fraunhofer ITEM scientists have successfully established state-of-the-art CP assays including "wet-lab" workflows as well as challenging computational analyses. They are now able to determine the onset of morphological changes in terms of the minimal compound concentration that creates observable effects on the cells. The next steps will be to apply CP using different chemicals and detect their specific modes of action. With the CP technology, Fraunhofer ITEM has established a further strategic milestone towards the implementation of animal-free risk assessment.

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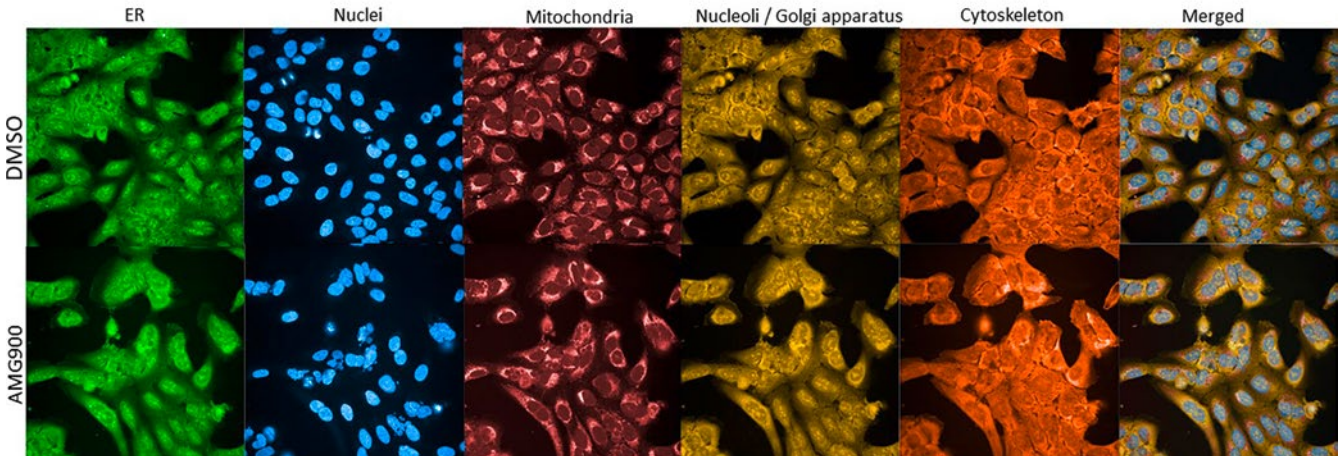
Cell painting with subsequent automated image analysis can identify more than 5000 cellular features, forming a "cellular fingerprint".



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.

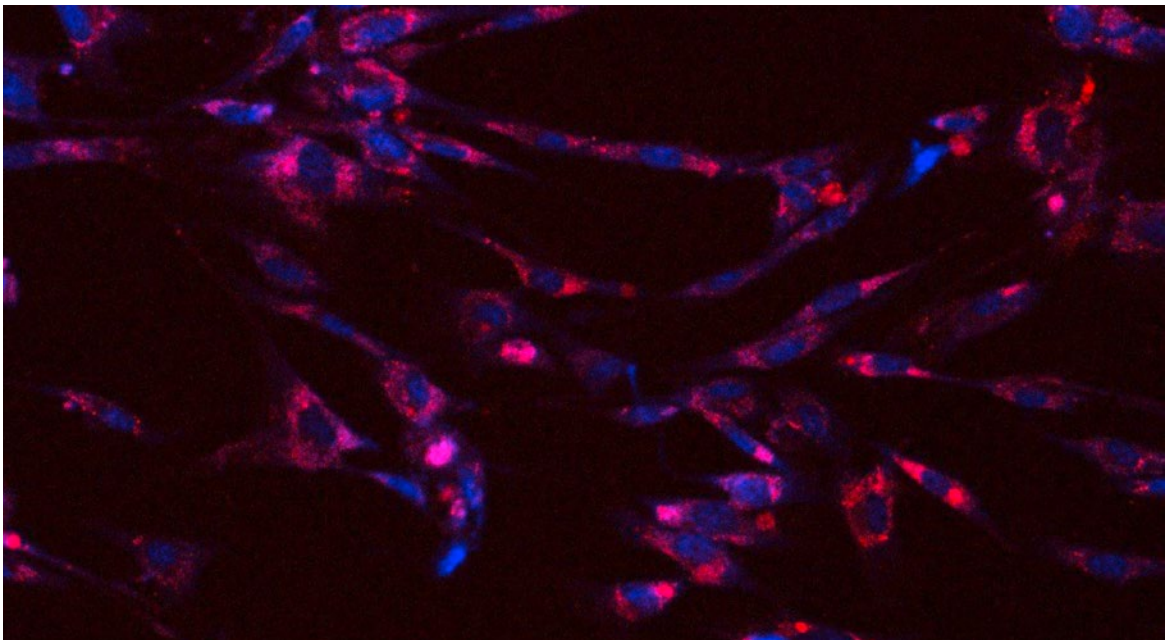
The targeted use of RNA compounds based on coding or non-coding RNA sequences enables a tailored response of the respective target cells under certain pathological conditions. Fraunhofer researchers use a wide range of RNA-based compounds, such as small interfering RNA, nucleoside-modified messenger RNA or RNA blockers – from target discovery through to clinical use. 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 existing and develop new model systems that are based on human cells and tissues.

Fraunhofer ITEM researchers develop bioprocessing methods and production technologies for modular and automated manufacturing of RNA molecules and RNA nanocarriers, and these 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 cardiopulmonary 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



Nanoparticles help deliver fluorescence-labeled siRNA (red) into human lung fibroblasts (nuclei stained blue).

Interdisciplinary CIMD platform for RNA-based therapeutics

The Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD has been funding the development of novel RNA-based therapeutic concepts for two years now. The collaborating researchers used bioinformatics-based prediction of RNA targets in fibrosis to identify novel molecular effectors. In subsequent in-vitro and ex-vivo studies, they investigated their functional impact by means of what is known as siRNA molecules. Packaging of the siRNA-based agent in particular will be further explored in upcoming studies, also in cooperation with other Fraunhofer institutes. The researchers are making use of a variety of innovative technologies here, from lipid-based nanoparticles and liposomes to silica gel particles.

The same basic principles have been used for research on other topics within the platform, such as further development of an siRNA-based therapeutic approach targeting the inflammatory lung disease sarcoidosis or studies on COVID-19 treatment strategies based on circular RNA molecules. Results from the still-young CIMD platform RNA Therapeutics were also presented at the Day of Immune Research 2022, where Fraunhofer researchers and representatives from academia, university clinics, and industry got together to share and discuss their insights. The focus was on exchanging ideas with scientists working on other novel drug classes. The future development of joint treatment options – for example, using cell therapy approaches – has also been envisaged. The CIMD platforms thus provide an excellent single-entry point at all stages in the development of novel therapeutic concepts.

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RNAuto – automated production technologies for mRNA vaccines and therapeutics

There is huge potential for new mRNA-based pharmaceutical active compounds – following the Comirnaty and Spikevax vaccines, a large number of drug candidates for a wide range of applications have moved into the focus of attention. But the Corona pandemic has also shown that GMP-compliant mRNA manufacturing on an industrial scale is still in an early phase and a limiting factor.

The Fraunhofer lighthouse project RNAuto unites the expertise of seven institutes in medicine, biology and engineering around the common goal of automating the manufacturing processes for mRNA drugs. The Fraunhofer approach covers the entire process chain from target sequence design to biological functionality testing of the manufactured nanopackaged mRNA. Fraunhofer ITEM´s role is in process development at laboratory scale as well as in scale-up and implementation in pharmaceutical quality standards. The information and knowledge thus gained will serve experts to develop scalable and robust platform processes. The aim is to cover complete manufacturing process sequences – starting from the DNA template, via linearization, transcription to RNA and subsequent purification, to packaging in stable lipid nanoparticles. Guided by the release analytics of already approved mRNA drugs, a suitable method spectrum for quality control of mRNA lipid nanoparticles will be developed in parallel.

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ZET-O-MAP – development of an analysis pipeline to identify biomarkers for developmental toxicity

The zebrafish embryo toxicity assay (ZET) was originally developed for environmental biomonitoring (von Hellfeld et al., 2020: https://doi.org/10.1186/s12302-020-00398-3). The possibility it provides to observe numerous morphological changes occurring during zebrafish embryo development in the first five days furthermore makes it a suitable model for studying developmental toxicity (Beker van Woudenberg et al., 2013: https://doi.org/10.1016/j.reprotox.2013.06.067).

With the aim of identifying specific biomarkers for teratogenic effects at developmental stages, Fraunhofer ITEM researchers have developed an analysis pipeline in the CEFIC-LRI project ZET-O-MAP that links morphological changes with alterations in gene expression. For this purpose, they set up a database that pools and harmonizes data on morphological changes from published ZETs. In addition, they compiled transcriptome data from public sources such as GeneExpression-Omnibus (GEO) and reprocessed these using a uniform analysis approach. To supplement the data found, three test substances were additionally tested in concentration series in the ZET over five days and samples for RNA sequencing were taken at four different developmental stages of the embryos. For these substances, as well as for those with comparable data quality, it is possible to determine time-resolved biomarkers in addition to morphological changes.

This analytical approach is in line with the overall requirements for regulatory use (Verheijen et al., 2022: https://doi.org/10.1016/j.yrtph.2022.105143), enabling robust and comparable results. The combination of morphological data and transcriptome data allows the identification of biomarkers for particular morphological changes. In the next step, the data will be used to either substantiate or refute the read-across hypothesis for already established substance groups.

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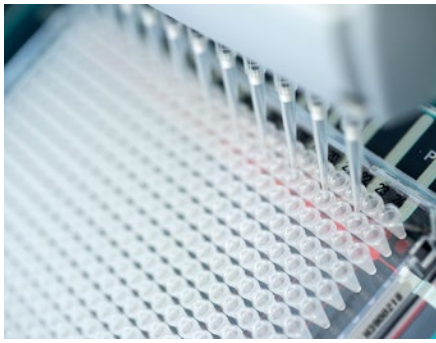
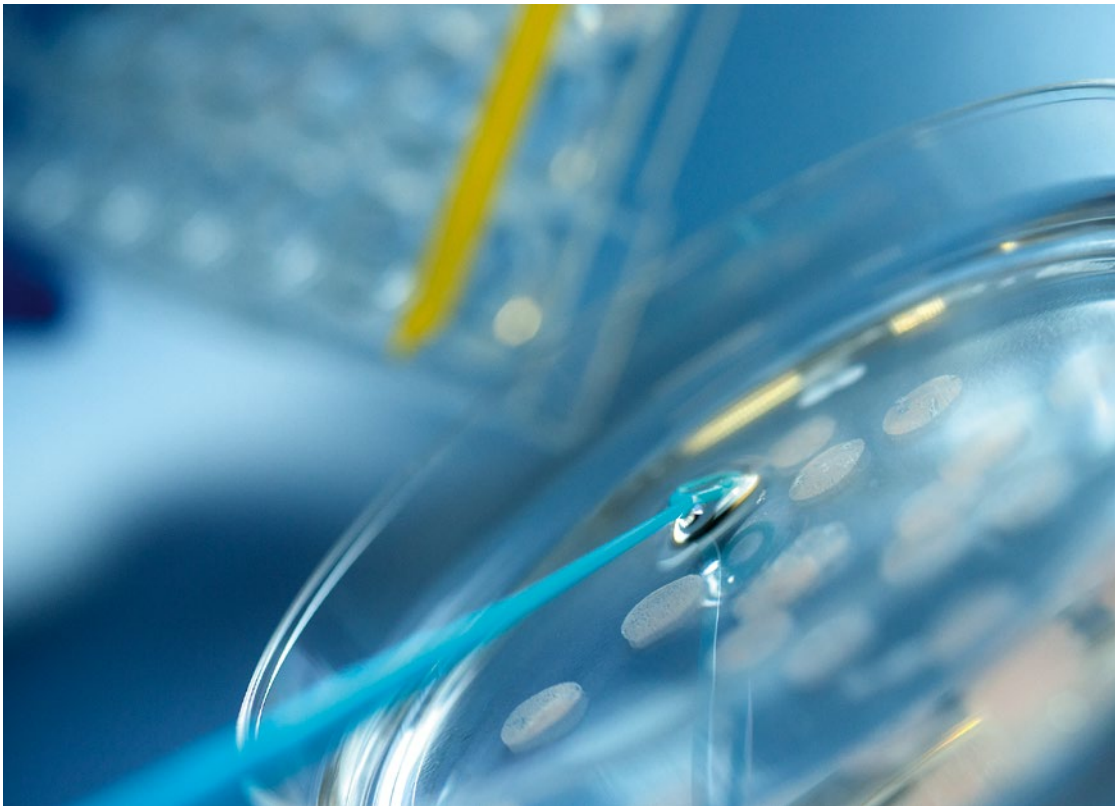
In the RNAuto project, seven Fraunhofer institutes are collaborating to develop automated manufacturing technologies for mRNA-based therapeutics.

By combining morphological data with transcriptome data, researchers are seeking to identify biomarkers for particular morphological changes.



Immunology and infection research

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

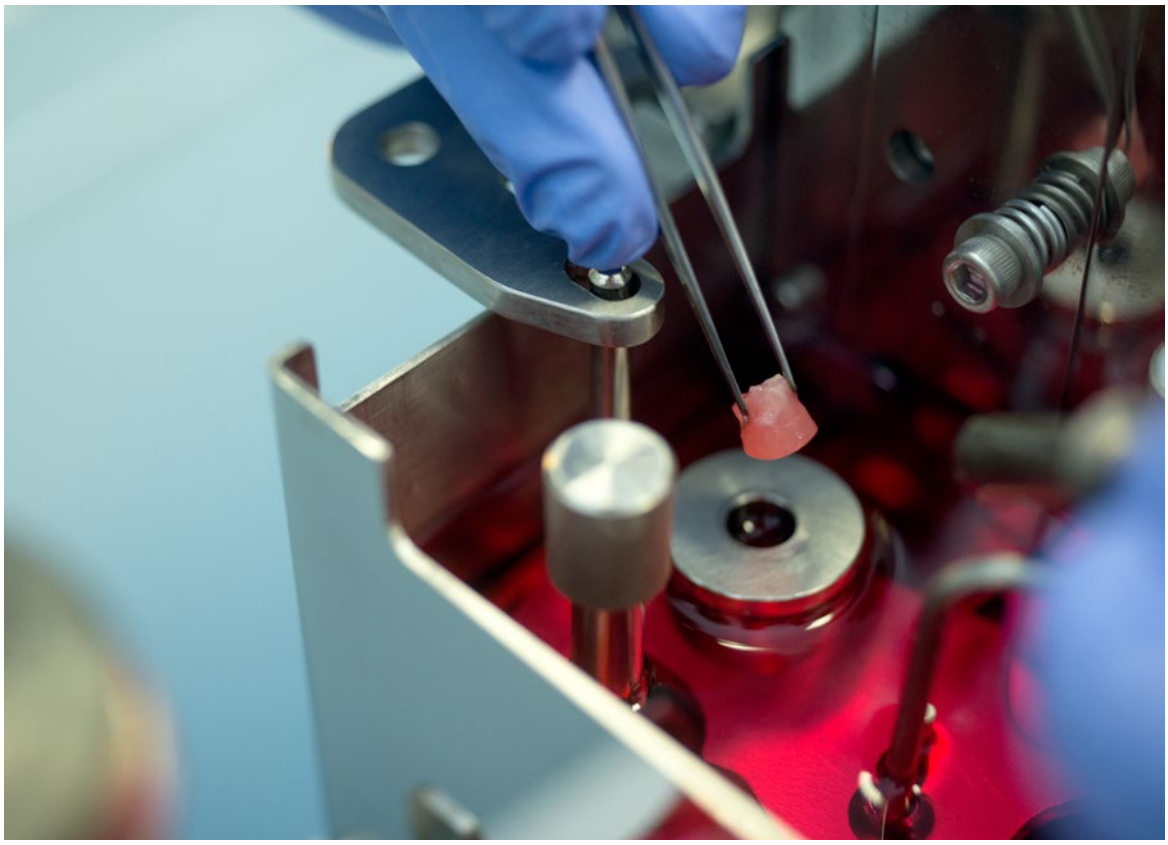


About eight percent of the population worldwide suffer from immune-mediated diseases. Almost any organ or tissue can be affected. In most cases, immune-mediated diseases are treated symptomatically with drugs that non-specifically suppress the patient's immune system. Therapies that eliminate the cause 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 models, 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



Preparation of human precision-cut lung slices (PCLS). SARS-CoV-2 has been proven to replicate in human PCLS. The antiviral and anti-inflammatory efficacy of cyclosporin A – a cyclic peptide found in the Norwegian microfungus Tolypocladium inflatum – can thus be investigated in PCLS.

Cyclosporin A: potent antiviral effects in preclinical models of SARS-CoV-2 infection

Despite successful vaccination programs, effective and readily available drugs for treating COVID-19 are still needed. Currently, both anti-inflammatory and antiviral treatment options are used, but with only limited success.

The immunophilin inhibitor cyclosporin A (CsA) combines antiviral and immunomodulatory effects and is a promising candidate for COVID-19 treatment. CsA is an immunosuppressive drug that is used, among other applications, to prevent graft-versus-host disease after organ transplantation. In addition, CsA was found to block replication of different viruses in vitro, including SARS-CoV-2.

In a German Center of Lung Research (DZL) collaboration with the group of Prof. Herold (University of Gießen), Fraunhofer researchers demonstrated strong antiviral potency of CsA against different SARS-CoV-2 isolates in translational in-vitro, ex-vivo and in-vivo models (Sauerhering et al., 2022: DOI 10.1164/rccm.202108-1830LE). The researchers investigated the antiviral and anti-inflammatory efficacy of this drug in human precision-cut lung slices (PCLSs) – evidence of efficient SARS-CoV-2 replication in PCLS had previously been provided. Treatment with CsA significantly reduced virus titers in the medium and E gene RNA, restored vitality of PCLS, and decreased

proinflammatory cytokine concentrations in supernatant of infected PCLS. These results may open the path for inhalation treatment of COVID-19 patients using adjusted CsA formulations – with high local efficacy but low systemic side effects.

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New development pipeline for RNA-based antiviral therapeutics

In the iGUARD project (integrated Guided Ultrafast Antiviral RNAi Drug development), a team of researchers at Fraunhofer ITEM led by Prof. Armin Braun and at the Hannover Medical School led by Prof. Axel Schambach is developing RNA-based therapeutics for treating viral diseases. The idea is that the drugs should be adaptable to different viruses particularly quickly so as to enable protection against emerging viral infectious diseases.

The iGUARD team of researchers is focusing on the parainfluenza virus, which can cause severe respiratory infections, especially in individuals with a compromised immune system. The aim is to use what is known as RNA interference (RNAi) to prevent the virus from replicating and spreading in the body. Patients with a viral infection could be treated with small RNA fragments (siRNAs) that specifically find and degrade the viral mRNAs, thereby preventing virus replication. Tests with RNAi compounds in human tissue slices and cell cultures have already demonstrated high efficacy. The next step will be to test the RNAi candidates for safety and efficacy in animal models. Furthermore, the RNA therapeutic is intended to be delivered directly to the lower respiratory tract by inhaled administration. Suitable inhalation systems are already being developed. The project has been funded by the German Federal Agency for Disruptive Innovation (SPRIND) since 2021 and is now receiving an additional 1.5 million euros of follow-on funding for another year.

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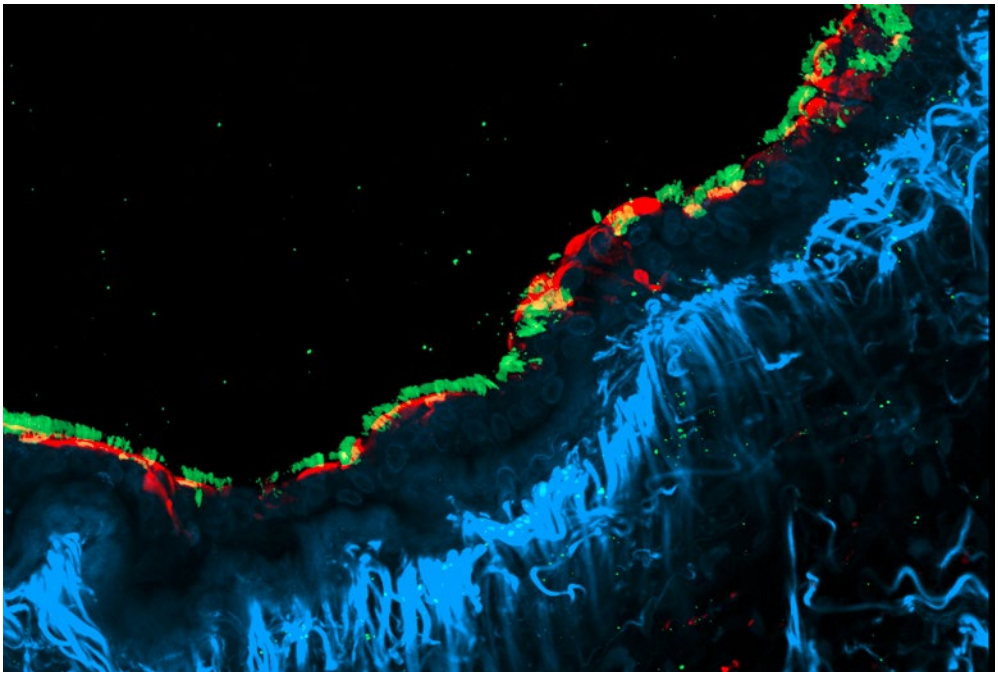
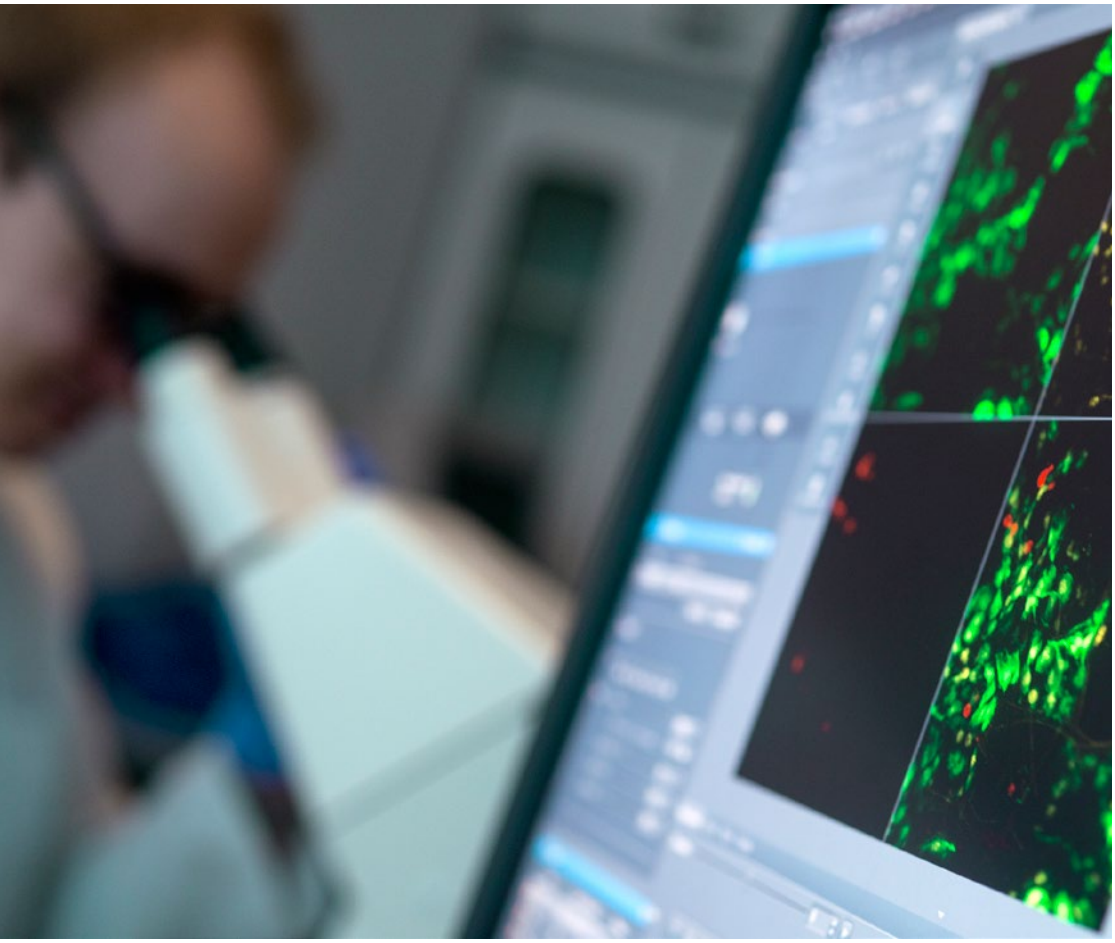


Precision-cut lung slices that have been infected with parainfluenza virus (viruses are shown in red, cell nuclei in blue, ciliae in green).



In the iCAIR® project, scientists are breaking new paths in the development of anti-infective therapies, such as against parainfluenza. For efficacy testing of new anti-infective agents, they use, among other models, viable human lung tissue slices.

iCAIR® – internationally visible platform for the development of anti-infectives

Infectious diseases continue to be among the most serious global threats to human health, due to both evolving drug resistance and newly emerging diseases. Scientists keep searching for new drugs, however, there is still a wicked gap between the discovery of new agents in the lab and their further development into usable therapeutics by industry – often referred to as "valley of death".

The International Consortium for Anti-Infective Research iCAIR® aims to close this gap in anti-infective research and development. For this purpose, iCAIR® is receiving a competitive 5-year funding. During this period, iCAIR® is to be developed into a well-defined brand in Australia, pooling the complementary expertise of the consortium partners – Institute for Glycomics of the Australian Griffith University, Hannover Medical School, Helmholtz Centre for Infection Research, and Fraunhofer ITEM. As an internationally visible platform, iCAIR® will develop its own drugs – for example, against parainfluenza –, collaborate with academic institutions and networks, and perform contract research on behalf of industry. iCAIR® will remain committed to adding maximum value towards licensing of both its own compounds and partner products by providing the preclinical proof of safety and efficacy, thus offering a complete preclinical package that will enable and support applications for subsequent clinical trials.

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Designer immune cells to assess drug safety, potency, and efficacy

To meet the ever-increasing demand for immune cells and immune cell preparations, biomedical researchers are exploring alternative ways of obtaining immune cells by means of novel bioprocesses, as well as methods for propagating such cells. A team of researchers led by Prof. Nico Lachmann is making use of the capacity of induced pluripotent stem cells (iPSCs) to continuously divide and differentiate. They have successfully produced mature immune cells, such as macrophages, in scalable systems, i.e. from laboratory scale to industrial application.

This method of standardized immune cell production is very helpful for investigating and evaluating candidate drugs, whose safety and efficacy can thus be tested directly in human target structures. The aim is to advance the development and validation of these tests under the Fraunhofer Attract program in the project "IMMUNITY – designer cells: novel immune cell platforms for health research". In addition, it is planned to establish cell-based potency assays measuring the biologic activity of biologics and bioengineered drugs. Such assays play an important role in GMP quality control and release testing of active pharmaceutical ingredients and medicinal products. Based on this key technology for continuous production of macrophages from iPSCs, the researchers also want to develop novel manufacturing processes for different fully standardized immune cell products and cell-based immunotherapies. The Fraunhofer Attract project will be funded with 2.5 million euros over a period of five years.

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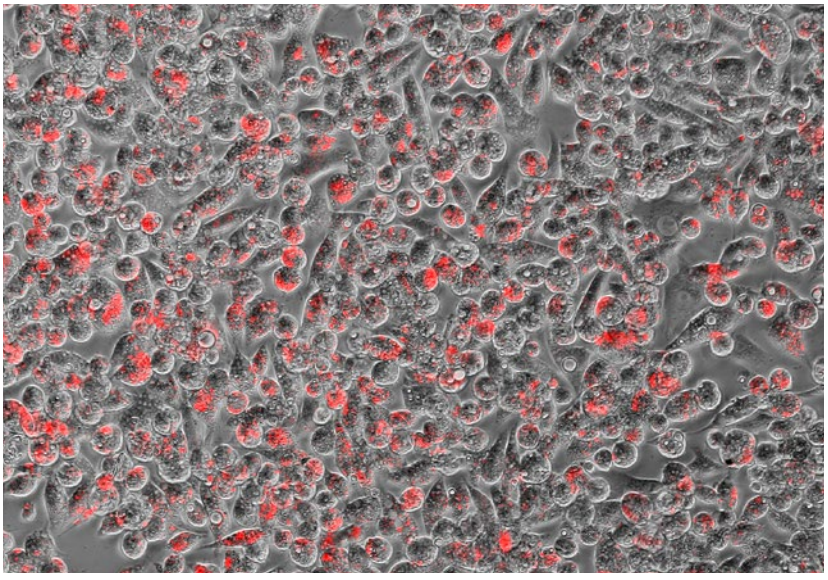

Macrophages produced from induced pluripotent stem cells fight bacteria (red).

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

Fraunhofer ITEM researchers characterize single cells, for example, from liquid biopsies, and make use of the information thus obtained to identify biomarkers.

Single-cell sequencing: methodology for establishing biomarkers of systemic chronic diseases

During many years of research on malignant diseases, scientists at Fraunhofer ITEM in Regensburg have gained special expertise in analyzing single cells from liquid biopsies. With some minor adjustments, they can apply – and have already applied – the established, partly automated technologies for single-cell DNA and RNA analysis from clinical samples to other cell types in order to characterize these in more detail and to make use of the information thus obtained, for example to identify biomarkers. The Fraunhofer researchers are also using this expertise to identify prognostic biomarkers for Alzheimer's disease in the project ADIS – Early Diagnosis of Alzheimer's Disease by Immune Profiling of Cytotoxic Lymphocytes and Recording of Sleep Disturbances. Fraunhofer ITEM is one of seven partners in the ADIS project, which is being funded by the EU Joint Program for Neurodegenerative Diseases Research (JPND) for three years with a budget of 1.3 million euros.

Alzheimer's disease and related dementias are heterogeneous, multifactorial diseases in which several etiopathogenic mechanisms lead to neuronal cell death and loss of cognitive function. The disease is believed to begin decades before diagnosis, posing a significant treatment challenge. Therefore, the identification of prognostic biomarkers for Alzheimer's disease is of great importance. There is growing evidence that the systemic immune system is involved in the pathophysiology of Alzheimer's. Using a multidisciplinary approach to multi-omics profiling of the immune system in conjunction with AI and agent-based modeling (ABM), novel signatures of the immune system and digitally recorded physiology shall be identified to facilitate early prediction of the disease. The aim is to enable improved therapies in the future.

Researchers at Fraunhofer ITEM in Regensburg will thoroughly characterize peripheral blood mononuclear cells (PBMCs) derived from samples taken from Alzheimer's patients, healthy volunteers, and patients with mild cognitive impairment, and will analyze their functional status. They will use combined single-cell immune repertoire and transcriptome sequencing for this. Two main analyses will be conducted to this end: (1) standardized combined generation and quality control of single-cell sequencing libraries for whole-transcriptome analysis and T cell receptor analysis, and (2) single-cell RNA sequencing of PBMCs to identify immune subpopulations that are uniquely associated with Alzheimer's disease, with a focus on natural killer cells and effector memory cells.

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Extending the liquid biopsy concept to brain tumor diagnosis

Primary and secondary tumors of the central nervous system (CNS) continue to be associated with an unfavorable prognosis. Among other reasons, this is also due to the fact that taking tissue biopsies of inoperable tumors and tumor relapses poses considerable risks for patients because of the tumor location in the CNS. Researchers of the Regensburg-based Fraunhofer ITEM Division of Personalized Tumor Therapy have joined forces with physicians of the study groups "Primary and secondary malignant brain tumors" and "CNS tumors in children and adolescents" of the Bavarian Cancer Research Center (BZKF) to improve the situation for patients by means of new approaches to analyzing cerebrospinal fluid (CSF).

Using technologies that were originally developed for analyzing circulating tumor cells (CTC) and cell-free nucleic acids in blood, the partners are collaborating on strategies to extend the liquid biopsy concept to the analysis of CSF to facilitate the diagnosis of brain tumors. In addition to methods for the detection of single tumor cells and genetic analyses of DNA and RNA, a special focus is on the development of preanalytical standards. Through this research, a framework has been established that allows this innovative approach to be used in multicenter clinical trials.

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Disparities in personalized oncology – a joint approach of the German WERA consortium

In Molecular Tumor Boards (MTBs), clinicians and researchers discuss the results of molecular analyses of tumor samples from individual patients to find suitable therapies. MTBs have therefore become key elements of precision oncology programs. Residents living in urban areas with specialized medical centers can easily benefit from MTBs, however, dedicated efforts are necessary to ensure equal access for patients from rural/underserved areas. To address this challenge, Fraunhofer ITEM scientists Dr. Florian Lüke and Prof. Tobias Pukrop joined forces with partners from the four German Comprehensive Cancer Centers in Würzburg, Erlangen, Regensburg, and Augsburg, which together form the CCC WERA Alliance, and collectively measured the regional outreach of their respective MTBs. Not surprisingly, the highest MTB patient numbers were found close to the four Comprehensive Cancer Centers, however, peaks in absolute MTB patient numbers could also be observed in specific rural centers. After weighting the absolute numbers depending on the local population densities, the researchers were able to identify "white-spots", representing areas from which, relative to the population density, comparatively few cases are presented in MTBs.

In conclusion, the study represents a hands-on approach for assessing the regional efficacy of a precision oncology program (Lüke et al., 2022: DOI 10.3390/cancers14205040). In the future, this analytical approach can easily be transferred to other regions and clinical applications.

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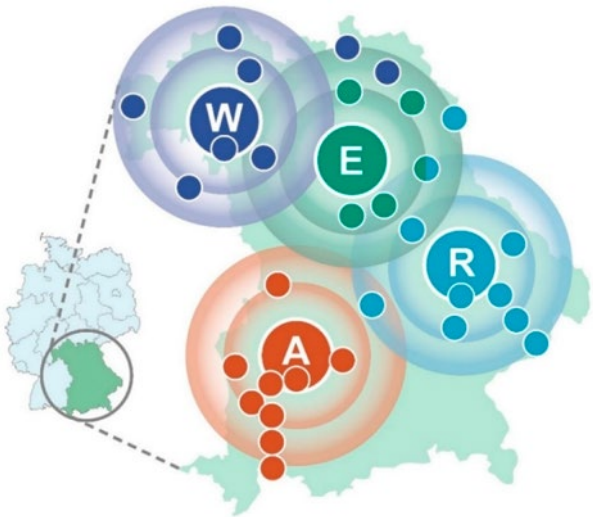
Using technologies such as single-cell analysis, researchers are developing strategies to extend the liquid biopsy concept to the analysis of cerebrospinal fluid for brain tumor diagnosis.



Regional catchment area of the WERA cancer center alliance in the Federal State of Bavaria in Germany, containing Würzburg (W), Erlangen (E), Regensburg (R), and Augsburg (A) as regional hubs, with cooperating regional hospitals (colored smaller dots).

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.

Another 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.

In addition, Fraunhofer ITEM researchers explore the field of additive manufacturing of individualized implants. In order to allow the long-term durability of such implants to be evaluated, the researchers develop novel test methods tailored to specific requirements, such as testing of the osseointegration of orthopedic 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.

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. This approach is all the more relevant in view of the current regulatory requirements for medical devices: The earlier the regulatory strategy is established, the less problematic the performance of the necessary conformity assessment and the shorter the time to market. A comprehensive database of requirements and materials for optimized (re)certification of medical devices is being set up.

Our highlights

A method with great potential: breath-triggered delivery of medical aerosols to preterm neonates (shown on a preterm baby doll in this photograph).

Innovation for preterm neonates: breath-triggered delivery of medical aerosols

Inhalation therapy is an effective method for pharmacological treatment of respiratory diseases. A drawback of continuous drug delivery is the waste of (expensive) medication during exhalation. Development of a breath-triggered drug delivery system can significantly reduce this waste. To date, however, there is no such technology available for preterm infants and neonates, due to their challenging respiratory parameters. Researchers of the Fraunhofer ITEM Division of Translational Biomedical Engineering have developed a system that optically detects neonatal breathing and releases the aerosol directly at the patient interface in a breath-triggered manner. The hallmarks of this system are:

- Up to 300 ms faster detection of the inhalation and exhalation phases compared to a flow sensor (gold standard)
- Integration of a fast (< 25 ms) aerosol valve at the patient interface and thus close to the patient
- Release of aerosol boluses at different inhalation time points, targeting different lung regions

Compared to the clinical standard system, this system can achieve a 4.2-fold higher dose efficiency. This is to be confirmed in a clinical trial with the glucocorticoid budesonide in preterm infants as part of the EU MDOT project in early 2023. The new method has great potential for use in preterm infants and neonates in the future. In view of both economic and ecological improvements, the technology may also be used in adults.

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Personalized finger joint implants based on AI

Finger joint dysfunction due to an accident or medical condition requires surgical intervention. The common therapies very often result in stiffening of the joint, interfering with hand function and daily life activities.

A new therapy for these patients applies custom-fit prostheses that preserve mobility of the joint while ensuring the necessary stability, achieving remobilization. The FingerKIt consortium, an interdisciplinary collaboration involving the institutes Fraunhofer MEVIS, IKTS, IWM and ITEM and the research institution Fraunhofer IAPT, is developing individually adapted joint implants manufactured by 3D printing based on AI. Fraunhofer ITEM is responsible for the validation of the osseointegration and certification compliance. To ensure lifetime functionality for patients, the implant properties must be evaluated. For this purpose, a newly developed test bed forces implants out of bone models while measuring the applied force and acoustic emission, to enable detection of even tiny microcracks (hairline cracks).

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Medical device certification fostered by an open-innovation test bed

The implementation of the European MDR 2017/745 has caused resource-intensive challenges in terms of product safety documentation and performance for medical device manufacturers. The inherent complexity poses a risk to numerous small and medium-sized enterprises (SMEs) in Europe, leading to supply gaps in patient care. The EU project "Medical Device Obligations Taskforce", MDOT for short, addresses this issue: An open-innovation test bed shall support SMEs in their conformity assessment and at the same time improve quality and regulatory compliance in medical device development. With a focus on neural implants, prostheses and inhalation technologies, the project partners are developing test methods for conformity assessment according to MDR standards.

The final project phase will begin in 2023. To further reduce the MDR-related burden on SMEs, commercialization options have been discussed and analyzed. The most effective approach is commercialization through one network partner as single-entry point (SEP). This means that a company of the network with international representation will be the link to roughly 15 partners from 7 countries and coordinate all processes and customer inquiries. The aim is to secure know-how of the companies, make it available, communicate it, and ensure efficiency. The SEP represents the network externally and promotes coherence and cooperation within the network.

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The FingerKIt implants are manufactured using special 3D printing methods – with a high level of attention to details and with different surface qualities.

In the EU project MDOT, an open-innovation test bed shall support SMEs in their conformity assessment.

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

Technology of the future – DNA for data storage

The global volume of data has doubled in the past three years alone – a large part of this data, however, is archived after 90 days. Especially for data that is accessed comparably infrequently, there is a need for secure, long-term but inexpensive storage. DNA is not only a medium for storing genomic information but can also be used to store data – a future technology that, so far, has been little explored in Europe. An essential prerequisite for the development of a biological mass data storage system with extremely high storage density and aging resistance is a significant improvement of DNA synthesis – there is as yet no high-throughput technology available for this.

A consortium of the four institutes Fraunhofer FEP, IPMS, IZI-BB and ITEM is now addressing the potential of this research field: In the BIOSYNTH project, Fraunhofer researchers are designing a platform for writing software-defined nucleotide sequences based on conventional microchip manufacturing technologies. In the future, this platform will enable highly parallel and high-throughput production of mass data storage devices by amplification in the volume production processes of the microelectronics industry. The platform is expected to allow today's space-filling synthesis devices to be replaced in the future with portable, low-power, low-cost systems through miniaturization, thus enabling commercial biology-based data storage. In addition, it may provide an important component for other applications such as bio-computing or individualized therapies. The Fraunhofer ITEM Project Group for Bioinformatics is developing special coding processes to enable data storage on this new platform.

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MyDeepLearn for use in the medical field – an end-to-end web application for image analysis using neural networks

Analyzing large sets of image data takes a lot of effort and is still a manual process that requires expert knowledge, especially with biomedical images. Convolutional neural networks (CNNs) have an enormous potential in the medical field due to their ability to extract important features automatically. To make this technology available to a broad spectrum of end users, Fraunhofer researchers have developed the intuitive, web-based end-to-end pipeline MyDeepLearn: It supports users almost from the beginning with a partly automated, easy-to-access pipeline with high usability that reduces the amount of time and manual work. The end-to-end web application enables, for example, detection of skin alterations in melanoma images and classification of skin cancer using neural networks.

MyDeepLearn links the CNNs in the back end with the web application in the front end. It provides users with a vector-based editing tool to post-process predictions or generate annotations, in addition to visualizing the data and providing different evaluation methods. It helps researchers and physicians to evaluate large sets of image data and supports early diagnosis – in particular in situations where there are only few annotated data available, as is often the case in the medical domain.

The web application can improve the CNNs iteratively with an interactive "human-in-the-loop" approach, which means that the user is involved in the evaluation and can actively change it. The workflow thus provides users with constantly improving technology, while continually expanding the data set to make this technology even more accurate.

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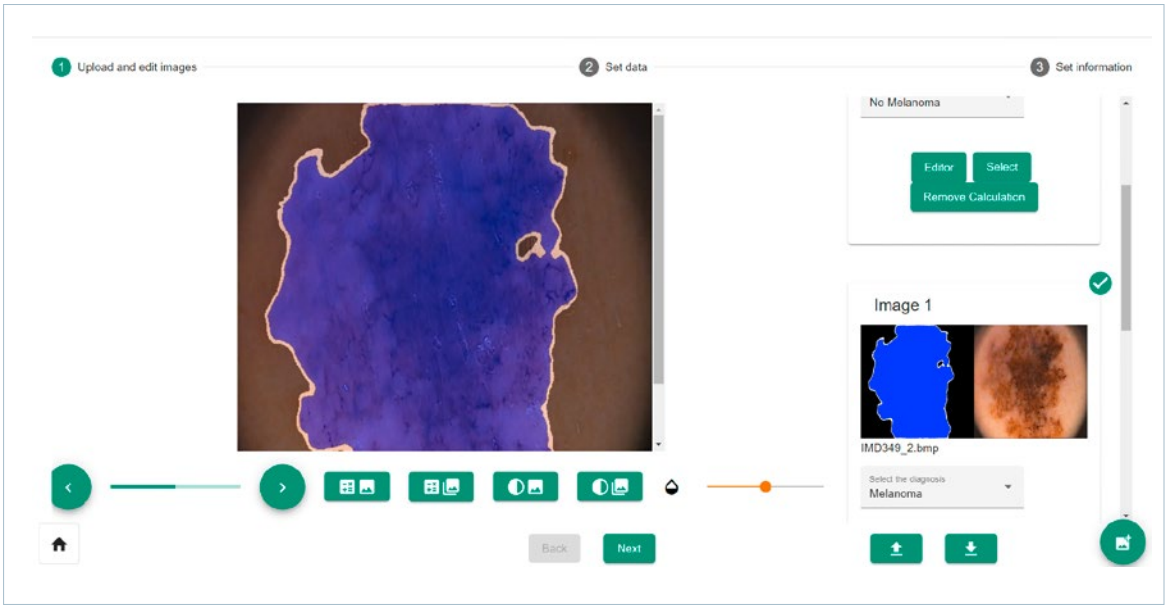
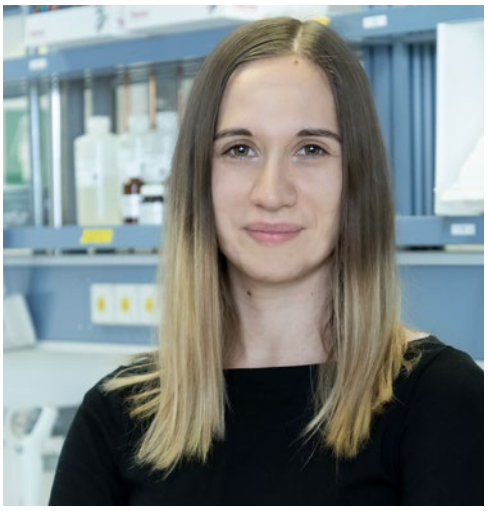
Based on convolutional neural networks, MyDeepLearn can detect the shape of a skin lesion in images and classify the lesion. This screenshot of the web application shows the prediction and classification of the uploaded images.



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, three ITEM employees serve as representatives of the many others who work at Fraunhofer ITEM with enthusiasm and great commitment.



From top left to bottom right:
Annika Klauke, Marvin Thienel, Selina Schrader

Annika Klauke

Laboratory technician in the Fraunhofer ITEM Department of Preclinical Pharmacology and In-vitro Toxicology in Hannover

Accurate and clean work with tiny amounts of genetic material is part of Annika Klauke's daily routine. She is a laboratory technician in the Fraunhofer ITEM Department of Preclinical Pharmacology and In-vitro Toxicology. Together with her colleagues, she has delved deeply into molecular biological work with RNA and DNA over the years, thereby building up the in-depth expertise that is essential to obtain valid research results in this field – especially when it comes to analyzing complex samples.

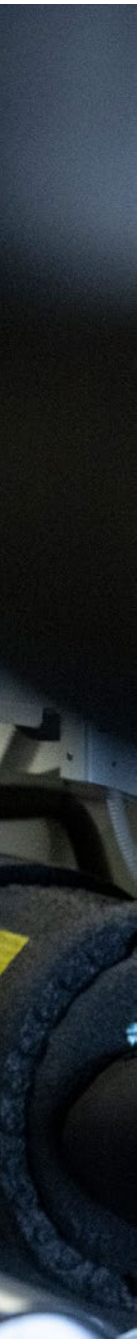
It was at quite an early age that Annika Klauke discovered her passion for molecular biology – first through a brief internship with her aunt, who was working on her doctorate as a biologist in a molecular biology laboratory at the time, and then during her apprenticeship as an agricultural laboratory technician. As an apprentice, she learned things like how to visually identify a good laying hen, but what really fascinated her was the molecular biological work in the lab. Right after her apprenticeship, at just 17 years of age, she started working at Fraunhofer ITEM as a molecular biology laboratory technician. "I loved working in the very well-equipped labs in a really great team – even if it did get late sometimes. And to this day, we teammates from back then are still close friends," she says. She much enjoys doing a useful job as part of a large team, such as in the major project ExITox-II – Explain Inhalation Toxicity II. This project, funded by the German Federal Ministry of Education and Research, was aimed at developing an integrated testing strategy for human health risk assessment of repeated-dose toxicity after inhalation exposure so as to replace de-novo animal testing. A variety of analyses were performed to this end, including genome-wide transcriptome analyses in human precision-cut lung slices and cell cultures. In the course of this project, Annika Klauke and her team colleagues had the chance to directly compare three analytical methods – RT-qPCR, HTS methods, and microarrays – using the same sample material. They were able to show that the data obtained with all three methods of analysis were in perfect agreement, which means that the team had generated absolutely valid data.

A completely different aspect of Annika Klauke's work is her role as an instructor of apprentices. For more than ten years, she has been in charge of the biological laboratory technician apprentices at Fraunhofer ITEM. In addition, she is a member of the examination board of the Chamber of Industry and Commerce in Hannover. Her job there is to examine biological laboratory technicians, but also interns from other countries who wish to have their qualifications recognized – among these some Syrians and Ukrainians who did an internship at Fraunhofer ITEM.

"In contrast to working in the lab, which is rather small-scale and extremely clean, I also much enjoy putting my hands in the soil," Annika Klauke says about her hobby, which is gardening at home in her own garden, designed to be close to nature and insect-friendly, as well as at a solidarity farm, where she grows and harvests organic vegetables together with others. This hobby is a nice counterbalance – and something she also considers useful, like her work in the lab.

"I want to pass on my knowledge and to enthuse young people about the multifaceted and exciting job of a laboratory technician."

"My team and I together provide the technical environment that allows our scientists to do their research as smoothly as possible."



Marvin Thienel

Head of Technical Infrastructure at Fraunhofer ITEM

As Head of Technical Infrastructure, Marvin Thienel, with a team of ten technicians, is in charge of all building services and facilities of Fraunhofer ITEM and the Clinical Research Center Hannover (CRC Hannover). The institute facilities in Hannover encompass a floor area of about 32,000 m², including laboratories, offices, technical areas, and some special facilities such as S2 labs, laboratory animal facilities, and imaging units. Furthermore, as Construction Officer, he oversees Fraunhofer ITEM construction projects in Hannover and Braunschweig.

"We see ourselves as service providers and create the technical environment that allow scientists, technicians, and administrative staff to work as smoothly as possible," says the department head. The tasks handled by his department are very diverse – from minor repairs via lab modifications to support for the construction of new buildings, in addition to project planning and the overall design of new facilities. Marvin Thienel likes the combination of hands-on work on the one hand and planning and project work on the other. He considers his work to be very multifaceted, requiring not only good planning, but also great flexibility to meet the day-to-day challenges.

It was at an early age that Marvin Thienel discovered his passion for technology – something he shares with his father and grandfather. His apprenticeship to become an industrial electronics technician seemed only logical to him. Thereafter, Thienel studied mechanical engineering and joined Fraunhofer ITEM after completing his bachelor's degree. Construction of the CRC Hannover began at that time, immediately giving him the opportunity to contribute his skills. In parallel to his job, he did a master's degree in mechanical engineering. In addition to heading the Department of Technical Infrastructure, the graduated engineer also serves as Construction Officer and in this role – in collaboration with the Fraunhofer-Gesellschaft in Munich – manages the institute's construction projects, such as most recently the remodeling of the entrance hall, the ongoing renovation of the drinking water network including optimization of fire prevention, as well as renewal of the building control system during ongoing operations. Since 2022, he has been Climate Protection and Climate Neutrality Officer – eventually to ensure that Fraunhofer ITEM also achieves the goal of the entire Fraunhofer-Gesellschaft to become climate neutral by 2030.

"I have a lot of autonomy in my work at the institute – the goal is set, but it is up to me to choose how I get there." In Thienel's opinion, this is an important prerequisite for adequately meeting multiple objectives in an effective manner. In his spare time, he equally likes to work on technical issues, such as integrating solar energy in his private home. Lazing around is nothing he enjoys – there is always something to be done. Yet there are also times when he can do more or less without hands-on work – when he is on vacation, traveling along the Baltic and North Seas in his caravan with his wife, two sons, and dog.

Selina Schrader

Scientist in the Braunschweig-based Fraunhofer ITEM Division of Pharmaceutical Biotechnology

Formulation of the active pharmaceutical ingredients is an important part of the drug development process: A well-designed formulation ensures that the active ingredient is delivered to the therapeutic target in the right dosage and via the appropriate route of administration so as to achieve the desired therapeutic effect and minimize adverse side effects. With the aim to develop formulation systems for various biopharmaceuticals, a corresponding working group is being established at the Braunschweig-based Fraunhofer ITEM Division of Pharmaceutical Biotechnology. Selina Schrader is part of the team.

The graduate biologist started at Fraunhofer ITEM in Braunschweig in the fall of 2021, initially with a project addressing the formulation of bacteriophages. Not least through the Corona pandemic, RNA compounds increasingly came into focus, and the Fraunhofer project RNAuto was launched to develop automated production technologies for mRNA-based pharmaceuticals. In this comprehensive project, Selina Schrader is collaborating with colleagues from six other Fraunhofer institutes. Her part is bioprocess development and mRNA formulation. Packaged in lipid nanoparticles, the RNA molecules are meant to be delivered to the target cells in a safe and targeted manner, shielded from degradation.

After receiving her master's degree in biology, Selina Schrader began working in research and development, but increasingly took an interest in translating research into real-world applications. This led her to Fraunhofer, where the focus is on applied research. At present, Selina Schrader spends a lot of time working in the lab. "Especially now that we are setting up the formulation group, I first go through all the steps myself and optimize them until the process is established," the researcher explains. The processes first have to work at laboratory scale. In the RNAuto project, this is being taken care of by the team led by Dr. Christian Bär, head of the Working Group on Regenerative Cardiology at Fraunhofer ITEM in Hannover. Schrader then scales up the process to a slightly larger scale. Her starting point for this is a template DNA, which forms the basis for enzymatic RNA production. The template DNA is first amplified and transcribed into RNA. The next step is to purify the RNA and develop an optimal packaging for it. Speaking about the project, Selina Schrader says: "It provides a good opportunity to get to know and understand the whole process from the beginning, that is, from the therapeutic molecule to the packaged, formulated and finally filled drug, and thus develop a formulation system that can be used across a wide range of biologics."

She spends part of her working time in the laboratories of Fraunhofer ITEM in Braunschweig and the other part at PVZ, the Center of Pharmaceutical Engineering at TU Braunschweig, which offers excellent equipment and a very good basis for setting up formulation systems. Selina Schrader enjoys working in the "lab" in her free time as well – at home in her kitchen, where she likes to bake macarons and other treats. To make sure these turn out well, she also had to try out many things, much like what her research work in the lab requires.

"It is wonderful and fascinating to be involved in research that holds tremendous potential for the future, such as the development of vaccines and cancer therapies."

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 an overview of the publicly funded projects in which our scientists were involved in 2022, 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

Publicly funded research projects

National

Bavarian Ministry of Economic Affairs, Regional Development and Energy
Further development of Fraunhofer ITEM in Regensburg

Bavarian Research Foundation
Project: Inhibiting COVID-19 N-protein-mediated infectivity HTP screening to identify inhibitors of N-protein function to interfere with genome packaging of SARS-CoV-2

DFG – German Research Foundation
Selection and adaptation during metastatic cancer progression. FOR 2127, project no. 242727105

Collaborative Reserach Center/Transregio (SFB/TRR) 305: Striking a moving target: From mechanisms of metastatic colonization to novel systemic therapies – subprojects "High-throughput screening assays and readouts for targeting metastatic progression" (A07) and "Novel patient-specific immune competent preclinical in vitro models to study early metastasis" (B17)

Federal Agency for Disruptive Innovation (SPRIND)
iGUARD – integrated Guided Ultrafast Antiviral RNAi Drug Development

Federal Environment Agency
Consideration of disinfection by-products in the context of environmental risk assessment of biocidal products – inventory and development of recommendations for the assessment. R&D project 3718 65 403

Investigation of the pathogenic mechanisms of action of emerging pollen allergens using the example of *Ambrosia artemisiifolia*. R&D project 3720 62 203 0

Federal Institute for Occupational Safety and Health (BAuA)
Mode of toxic action of nanocarbons. Research project F 2376

Advancement and connection of modeling approaches for estimating inhalation exposure during spray applications. Research project F 2492

Federal Joint Committee/Innovation Committee
PTmHBP – Practicability testing of the magistral production of bacteriophages for the therapy of septic infections of the lower extremity (PhagoFlow)

Federal Ministry for Economic Affairs and Energy, central innovation program for SMEs
Development of an ex-vivo rat lung model for quality assurance of surfactant batches without the need to simulate asphyxia

Federal Ministry of Education and Research (BMBF)
Project: ELISE – Ein Lernendes und Interoperables, Smartes Expertensystem für die pädiatrische Intensivmedizin (a learning and interoperable, smart expert system for pediatric intensive-care medicine)

Project: P4D – Personalized, predictive, precise and preventive medicine to improve early detection, diagnosis, therapy and prevention of depression disorders – Establishment and validation of test systems for biomarkers. R&D project 01EK2204D

Federal Ministry of Education and Research (BMBF) framework program "Gesundheitsforschung" (health research)
Collaborative research project: 4-IN
Insect-derived inhalable inhibitors of bacterial virulence for treating lung infections

Collaborative research project: NANOpain
Dendritic NanoAnalgesics without addictive potential for better quality of life for patients with cancer, post-operative and chronic pain. R&D project 16GW0333n

Collaborative research project: Phage4Cure
Developing bacteriophages as approved therapy against bacterial infections

Collaborative research project: TPHiPAH
Tryptophan hydroxylase inhibitors as novel therapeutics for pulmonary arterial hypertension

Federal Ministry of Education and Research (BMBF) funding program "Alternatives to Animal Testing"
Project: Inhal-Prädikt
Universally applicable model for prediction of the local efficacy of (inhaled) anti-infectives in the lungs

Federal Ministry of Education and Research (BMBF) funding program DigitaLung
Digital auscultation system for differential diagnosis of lung diseases using machine learning

Federal Ministry of Education and Research (BMBF) funding program "Erforschung von Covid-19 im Zuge des Ausbruchs von Sars-CoV-2" (research on COVID-19 in response to the SARS-CoV-2 outbreak)
RENACO – repurposing nafamostat mesylate for COVID-19 treatment

Federal Ministry of Education and Research (BMBF) funding program "In-vitro Challenge"
ImmunAVATAR: Make your immune system great again

Federal Ministry of Education and Research (BMBF) funding program "Innovative Stammzelltechnologien für die individualisierte Medizin" (innovative stem cell technologies for individualized medicine)
Project: iCARE
Induced pluripotent stem cells for clinically applicable heart repair

Project: TACTiC
Tailored Application for individualized Cell Therapy with iPSC-derived Cardiomyocytes

Federal Ministry of Education and Research (BMBF) funding program "KMU-innovativ: Medizintechnik" (innovative SMEs: biomedical engineering)
Collaborative project: CTCbySCP
Development of a single cell printer-based method for marker-independent quantification and isolation of vital circulating tumor cells for diagnosis and personalized therapy

Federal Ministry of Education and Research (BMBF) funding program "NanoCare 4.0 – application-safe material innovations"
Project: MetalSafety
Development of evaluation concepts for fibrous and granular metal compounds: bioavailability, toxicological efficacy profiles and comparative in vitro, ex vivo and in vivo studies

Project: NanoINHAL
In-vitro test methods for airborne nanomaterials to investigate toxic potential and uptake after inhalation exposure using innovative organ-on-a-chip technology

Federal Ministry of Education and Research (BMBF), German Centers for Health Research (DZG)
German Centre for Cardiovascular Research (DZHK):
Single-cell RNA sequencing in iPSC-derived nodal and atrial cells from patients with atrial fibrillation

German Center for Lung Research (DZL):
Allergy and asthma
Chronic obstructive pulmonary disease (COPD)
Diffuse parenchymal lung diseases (DPLD)

Federal Office for Radiation Protection
Childhood leukaemia – influence of the immune system on the development of the disease (experimental study in a suitable animal model). AG-R-08313/3616S82440

Influence of the inter-frequency magnetic fields of inductive power transmission during charging of electric vehicles on the behaviour of laboratory rodents. AG-R-08319/3620EMF401

Investigation into the occurrence of leukaemia in predisposed animal models exposed to magnetic fields.
Z4/AG-R-08313/3620S92410

Investigation of biological mechanisms of radiation-induced cardiovascular diseases. R&D project 3621S32210

German Centre for Rail Traffic Research at the Federal Railway Authority
Emissions and immissions from railway traffic – air pollutant monitoring and dispersion modeling

Lower Saxony Ministry of Science and Culture
Collaborative project: FibroOmics
Translating Omics studies into clinically relevant insights for lung fibrosis patients

International

EU project: MDOT (Medical Device Obligations Taskforce)
Establishment of a digital platform for simplified conformity assessment and testing of medical devices, including three demonstrator technologies: Inhalation technology, 3D-printed neural implantats, and coatings for orthopedic prostheses

EU project: RealWorld4Clinic
AI-powered health monitoring for clinical research and cardiology
(EIT Health innovation project)

EU project: REMEDIA – RElation exposoME DIseAse
Impact of exposome on the course of lung diseases

EU project (EASA): Cabin Air Quality 3rd Campaign
Cabin air quality assessment of long-term effects of contaminants

EU project (EFSA): Development of roadmaps for action on: New-approach methodologies in risk assessment
(LOT 2; OC/EFSA/ED/2020/01-02)

EU project (EFSA): EFSA Read-Across
Identification of the applicability domain (in terms of toxicological endpoints and chemical space) for the use of read-across in food safety

EU project (EFSA): Emerging Risks III
Screening for Emerging Chemical Risks in the Food Chain

EU project (EFSA): IUCLID training for EFSA

EU project (EFSA): PARC
European Partnership for the Assessment of Risks from Chemicals

EU project (EMA): MutaMind
Better models to shed light on the mutagenicity of N-nitrosamines

EU project (HORIZON 2020): Marie Skłodowska-Curie Innovative Training Networks, Magicbullet :: Reloaded
Development and employment of approaches for selective, targeted delivery of a panel of anticancer drugs for directed tumor therapy

EU project (HORIZON 2020): REMADYL
Removal of legacy substances from polyvinylchloride (PVC) via a continuous and sustainable extrusion process

EU project (HORIZON 2020): RISK-HUNT3R
RISK assessment of chemicals integrating HUman centric Next generation Testing strategies promoting the 3Rs

EU project (HORIZON 2020): TBMED
An open innovation test bed for the development of high-risk medical devices
Translation of the quality-by-design approach of the pharmaceutical industry to biomedical engineering, using several medical devices as examples: bone defect reconstruction materials, keratoprosthesis, and nanoparticles for cancer treatment

EU project (HORIZON 2020): ZeroPM
Zero pollution from persistent, mobile substances

EU project (IMI): eTranSafe
Enhancing TRANslational SAFEty Assessment through Integrative Knowledge Management

EU project (IMI): imSAVAR – Immune Safety Avatar
Nonclinical mimicking of the immune system effects of immunomodulatory therapies

EU project (IMI): PREMIER
Prioritization and risk evaluation of medicines in the environment

EU project (JPND – Joint Program Neurodegenerative Disease Research): ADIS
Early diagnosis of Alzheimer's Disease by immune profiling of cytotoxic lymphocytes and recording of sleep disturbances (collaborative project)

EU research cluster: ASPIS
Animal-free Safety assessment of chemicals: Project cluster for Implementation of novel Strategies

Active participation in committees

Prof. Dr. Christian Bär
MD/Ph.D. commission "Molecular Medicine" of the Hannover Medical School

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

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)

Working groups on Cardiovascular Regeneration & Reparative Medicine and on Cellular Biology of the Heart as well as ordinary nucleus member of the working group on Myocardial Function (WG 4) of the European Society of Cardiology (ESC)

External assessor 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"

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

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. 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
Ph.D. examination board for "Pharmacology, Toxicology and Clinical Chemistry" at the Hannover Medical School

Program committee for the Ph.D. program "Regenerative Sciences" at the Hannover Biomedical Research School (HBRS)

Working group on vascular biology "Vaskuläre Biologie" (AG 4) of the German Cardiac Society (DGK)

Reviewer for international journals in cardiovascular research

Prof. Dr. Edward Geissler
Chair of the Ethics Committee of the University of Regensburg

Executive editor of the journals "Transplantation" and "Transplanation direct"

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. "Integrated Environmental Assessment and Management", "Environmental Science & Technology", "Environmental Toxicology and Chemistry", "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

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 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)

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

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

EU Deputy Representative of the Hannover Medical School

Senate Section II of the Hannover Medical School

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

German Federal Institute for Risk Assessment (BfR) Committee for Contaminants in the Food Chain: panel on perfluorinated and polyfluorinated alkyl substances "Per- und Polyfluoralkylsubstanzen (PFAS)"

Expert panel "Basic module and perfluorinated tensides" of the German Federal Institute for Risk Assessment's MEAL (= meals for exposure assessment and analysis of foods) study within the Total Diet Study (TDS) in Germany

Working committee on regulatory toxicology "Regulatorische Toxikologie" of the German Toxicology Society within the German Society of Clinical and Experimental Pharmacology and Toxicology (DGPT)

Public relations delegate of the German Toxicology Society

Dr. Meike Müller
Network of ombudspersons in Lower Saxony

Dr. Falko Partosch
Advisory board of the German Toxicology Society within the German Society of Clinical and Experimental Pharmacology and Toxicology (DGPT)

Working group on hazardous substances "Gefahrstoffe" of Subcommittee II of the Committee for the Protection of Working Mothers of the Federal Office of Family Affairs and Civil Society Functions (BAFzA)

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

Dr. Bernhard 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")

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

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

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

European Society for Medical Oncology

Priv.-Doz. Dr. Susanne Rittinghausen
Co-optive member of the European Society of Toxicologic Pathology (ESTP) board: representative for nomenclature

"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", "Soft Tissue" and "Special Senses", and working group "Apoptosis"

Ad-hoc working group on inflammatory parameters and inflammatory effects "Entzündungsparameter – entzündliche Effekte" of the DFG Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area (MAK Commission)

Reviewer for the international journals "Toxicologic Pathology" and "Toxicology"

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
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