Fraunhofer ITEM

Annual Report 2021

Fraunhofer ITEM – pioneers for sustainable health

At Fraunhofer ITEM, we use viable lung tissue slices prepared from human lung tissue, also known as precision-cut lung slices (PCLS for short), to study respiratory diseases. PCLS can also be used for efficacy testing of drug candidates. This ex-vivo model is particularly useful to address translational research questions: Is the target relevant in the disease model? Does the drug substance exhibit a disease-relevant effect in human tissue?

PCLS contain nearly all cells that are normally present in the lung: epithelial cells, endothelial cells, smooth muscle cells, fibroblasts, immune cells and nerve fibers. The cells are biologically active, which means that they communicate with each other and respond to cell-specific stimuli. PCLS remain viable in culture for several days. Human PCLS are entirely in line with the 3Rs principle: they help replace, reduce, and refine animal experiments.

Annual Report 2021

Fraunhofer ITEM – pioneers for sustainable health

To our readers

With this Annual Report we look back on a successful year marked by numerous changes, new ideas and a spirit of research. But at the same time, this was also a stressful and strenuous year, again under the influence of the pandemic with the resulting changes in our working habits and a focus on coronavirus research.

Executive Director Prof. Norbert Krug

Director Prof. Thomas Thum

Since January 1, 2021, we – Norbert Krug and Thomas Thum – have managed Fraunhofer ITEM in tandem. With Prof. Thomas Thum joining the institute management and the establishment of a new Division of Cardiovascular Research, Fraunhofer ITEM has gained expertise in cardiovascular as well as RNA research. Together, we are setting the course for our research and are enhancing our transfer competence. The establishment of this dual leadership in the institute management is a gain in many respects.

While the focus at Fraunhofer ITEM used to be on the lungs and the respiratory tract, it is now being expanded to include the cardiovascular system. Thomas Thum's scientific core competence, which is RNA research, and his success in using non-coding RNA molecules as a therapeutic target for patients with heart failure also offer promising starting points for further research and development throughout the institute – read more about this in an interview with him in this Annual Report. The enhancement is both a challenge and a great opportunity for our institute. In the past year already, our scientists were able to make use of synergies: The method of precision-cut tissue slices (PCTS for short), well established for the organs lungs and airways as well as liver, will now also be used for the heart.

The translation from bench to bedside is the key parameter of success for Fraunhofer's innovative strength in health research, which ultimately describes the added value of our research work for humankind. The fact that this transfer competence manifests itself in a unique way in the work of Fraunhofer ITEM and its partners was also acknowledged by Lower Saxony's Minister of Science and Culture Björn Thümler on the occasion of the institute's 40th anniversary, celebrated in 2021. In a panel discussion in July 2021, which was streamed live, we discussed health research in Lower Saxony and the future relevance of cardiopulmonary research in Hannover as a center of scientific activity with him and a few other stakeholders.

We would like to take this opportunity to cordially thank our employees at all three sites – in Hannover, Braunschweig and Regensburg – for their extraordinary commitment in another year under difficult conditions. We would also like to say thank you to our partners from industry, academia and government for their confidence in us. We are very optimistic about the future and look forward to further developing Fraunhofer ITEM together.

Prof. Dr. Norbert Krug

Prof. Dr. Dr. Thomas Thum

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Profile

Human health at the focus of research


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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 the institute is thus focused on human health – and from the 2021 perspective this has been so for 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. For the institute's clinical trials, the Clinical Research Center Hannover (CRC Hannover) with its state-of-the-art infrastructure offers optimal conditions. While in the past the focus at Fraunhofer ITEM used to be on airway research, the institute entered the fifth decade of its existence with a major new research field: cardiovascular research and development of diagnostics and therapeutic approaches based on RNA.

This new research field was brought to Fraunhofer ITEM by Prof. Thomas Thum with his joining the institute's management at the beginning of 2021. Linking cardiovascular research with lung and airway research offers enormous potential for translational research at Fraunhofer ITEM.

At the institute's headquarters in Hannover and at the branch offices in Braunschweig and Regensburg, the Fraunhofer ITEM employees work in the business areas Drug Development, Chemical Safety and Assessment, and Translational Biomedical Engineering. The areas of research and development expertise – cardiopulmonary research, toxicology, infection research, malignant disease research, immunology, medical device development, and bioinformatics and AI, in addition to RNA research, which is in the process of being established as a research expertise – are geared towards translation into commercial applications and provide the basis for the three business areas.

Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD

In the Fraunhofer CIMD, several Fraunhofer institutes dedicated to health research 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. Next to the Fraunhofer institutes ITMP and IZI, Fraunhofer ITEM is one of the core institutes of the cluster. It 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 Group for Health Research

Health research at Fraunhofer addresses the four major areas of medical science – drugs, diagnostics, devices and data, 4D for short. 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.

"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.

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.

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 provides an ideal basis for accelerating scientific developments in medical and pharmaceutical technologies to provide state-of-the-art applications for patients.

Fraunhofer Nanotechnology FNT

Fraunhofer Nanotechnologie 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.

www.item.fraunhofer.de/network

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.

Start with new perspective – interview with the institute director

Prof. Thomas Thum joined Fraunhofer ITEM as institute director on January 1, 2021. He has since been managing the institute together with Prof. Norbert Krug. Prof. Thum is a specialist in cardiology and bioscience, with a clear research focus on the functional characterization and translational potential of novel therapeutic RNA strategies. He is head of the Institute for Molecular and Translational Therapy Strategies at the Hannover Medical School (MHH), is holding a concurrent professorship in "Translational validation of innovative therapeutics" at MHH that is associated with the post of Fraunhofer institute director, and a guest professorship at the Imperial College London. Furthermore, he is CSO of his spin-off from MHH, the Hannover-based clinical-stage company Cardior Pharmaceuticals GmbH.

With this short interview, we would like to give an insight into the expertise that Prof. Thum has brought to the table and into how this is opening up new perspectives for Fraunhofer ITEM.

Prof. Thum, you are one of the world's leading experts in the field of non-coding RNA, cardiologist, successful entrepreneur, university professor and now also Fraunhofer institute director. You literally live applied medical research wholeheartedly – as the heart is your specialty. Will you also introduce this field of research to Fraunhofer ITEM?

In fact, the heart, or more precisely cardiovascular research, is my passion. The focus of research at Fraunhofer ITEM is on the lungs. The heart and lungs are close to each another, not only in terms of position in the body, but the two organs also mutually influence each another and their pathological interplay is complex. It is thus only logical to bring cardiovascular research to Fraunhofer ITEM and thereby profitably complement the institute's traditional focus on lung and airway research. In addition, my team and I study the causes of organ fibrosis and therapies for this condition, which is a connective tissue remodeling of organs after stress or disease. This topic also fits in perfectly with the interests of Fraunhofer ITEM and will continue to be a central focus of our work. The key players in all our subject areas are RNA molecules.

What important role do RNA molecules play in research and medicine?

Many people by now are aware of RNA as an innovative therapeutic in the form of a COVID-19 vaccine. But vaccines are only one use case. In many organ diseases, altered gene expression signatures are known to influence disease progression. This is where RNA therapy comes in, specifically targeting pathophysiological processes with RNA therapeutics. The key to developing a targeted, RNA-based therapeutic strategy is to understand the alterations in gene expression. In this context, bioinformatics is essential to identify important molecules known as "switch molecules". Bioinformatics builds a bridge, so to speak, between patient data and application-oriented research. In addition, RNA molecules are not only important for treating diseases, but also for diagnosis.

What opportunities and challenges do you see for Fraunhofer ITEM?

In cooperation with our ITEM colleagues, we have already been able to identify promising synergies and potential, which we are going to develop together. It is certainly a challenge to expand the focus of Fraunhofer ITEM to include the organ system of the heart as well, but it is also a great opportunity. I am very much looking forward to taking on this challenge and opportunity together with my team and in this way to further developing the institute's research and development competence in the field of RNA. The expertise of the ITEM colleagues in toxicology and preclinical pharmacology and in regulatory affairs plays a very important role here.

Prize for outstanding pharmacological research

In 2021, Prof. Thum received the Paul Martini Prize for the design and first clinical testing of an antisense RNA for treating chronic heart failure. The non-profit Paul Martini Foundation, sponsored by the German Association of Research-Based Pharmaceutical Companies, each year awards a prize worth 50,000 euros for outstanding achievements in the field of clinical pharmacology.

In addition, Prof. Thum was one of the 6600 most frequently cited scientists worldwide in 2021. This analysis is published yearly by the U.S. company Clarivate and includes researchers from all disciplines.

Concurrent professorships are part of the concept for success of the Fraunhofer institutes. You are also holding a concurrent professorship at MHH. What does this mean for research and development at Fraunhofer ITEM?

Cooperation with MHH has been inherent to this Fraunhofer institute ever since its foundation in 1981 – one of the founding fathers, Prof. Ulrich Mohr, was Professor of Experimental Pathology at MHH and with his expertise brought a basic competence for application-oriented toxicological research to Fraunhofer ITA, now ITEM.

My own focus is on transfer and translation. With my concurrent professorship, I would like to strengthen the ties between university and Fraunhofer research. The strengthened ties with MHH and the intensified translation from bench to bedside will be a benefit to Fraunhofer's innovative strength in health research and eventually also to humankind. Linking cardiovascular research with lung and airway research offers enormous potential for translational research at Fraunhofer ITEM. I look forward to firmly establishing these ties at the institute.

Prof. Thum, what is your personal wish for Fraunhofer ITEM?

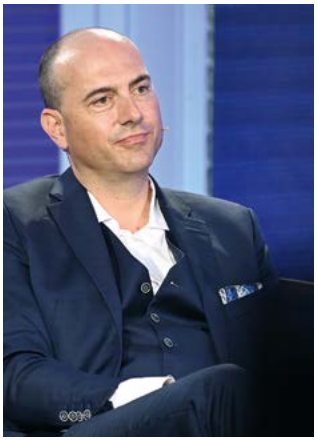
That all employees together will be heading for the future with a lot of fun and enthusiasm about innovative research for the benefit of all human beings.

The heart complementing the lung – 40 years of Fraunhofer ITEM in Hannover

Aerosol research, toxicology, translational medicine – for 40 years now, Fraunhofer ITEM has been making decisive contributions to advancing health research and developing health solutions for people. After Prof. Thomas Thum's joining the institute management, Fraunhofer ITEM entered the fifth decade of its existence with a major new research field – cardiovascular research and development of diagnostics and therapeutics based on RNA. Linking this with lung and respiratory research, the subject area in which Fraunhofer ITEM in Hannover (Germany) specialized for the past 40 years, has great potential.

On the occasion of the institute's 40th anniversary, the two directors of Frauhofer ITEM, Prof. Norbert Krug and Prof. Thomas Thum, hosted a panel discussion on July 13, 2021. Together with Lower Saxony's Minister of Science and Culture Björn Thümler, Prof. Michael Manns, president of the Hannover Medical School, and Prof. Ulrike Köhl, director of the Fraunhofer Institute for Cell Therapy and Immunology IZI in Leipzig (Germany), they discussed how the institute's traditional focus on respiratory research and the future area of cardiovascular research fit together, what this means for the city of Hannover and the state of Lower Saxony as a center of science, and how people will benefit from this research.

Due to the pandemic situation, the panel discussion was streamed live and a video recording (in German language) is available on Youtube: **https://youtu.be/70pVgX02kU0**



"The link between cardiovascular research and the traditional focus on the lungs and respiratory tract at Fraunhofer ITEM offers enormous potential for translational research made in Lower Saxony."

Prof. Dr. Dr. Thomas Thum
Fraunhofer ITEM director

"With the MHH professor Thomas Thum joining the institute management of Fraunhofer ITEM, we have come a substantial step closer to my vision of a Hannover Health Science Campus."

Prof. Dr. Michael P. Manns
President of the Hannover Medical School (MHH)

"The link between complementary disciplines for the benefit of medical research is a decisive unique selling point of health research at Fraunhofer."

Prof. Dr. Dr. Ulrike Köhl
Fraunhofer IZI director

"Fraunhofer ITEM makes important contributions, also in the fight against the corona pandemic. Our research could scarcely be more relevant than it is at present."

Prof. Dr. Norbert Krug
Fraunhofer ITEM director

"In Lower Saxony, the transfer of health research into business and the translation into applications serving people are manifest in a singular way in the research work performed by Fraunhofer ITEM and its partners."

Björn Thümler
Lower Saxony's Minister of Science and Culture

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.

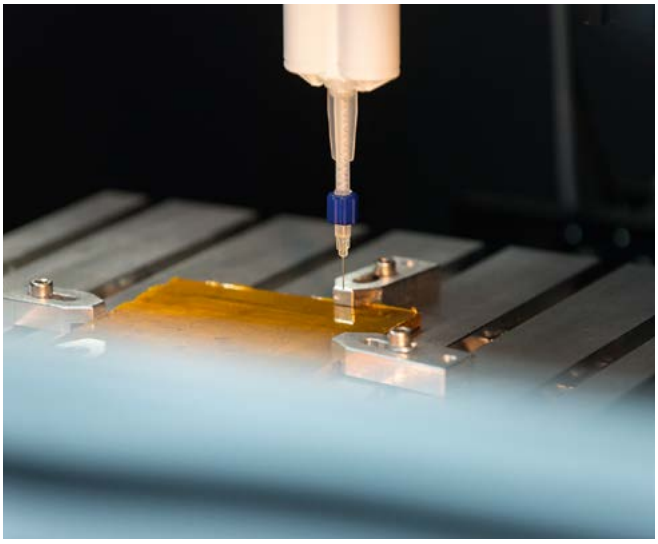
In the field of device development, our focus is on neural implants and on conducting and assisting the development of novel technologies for administration of therapeutic aerosols towards smart drug/device combination products.

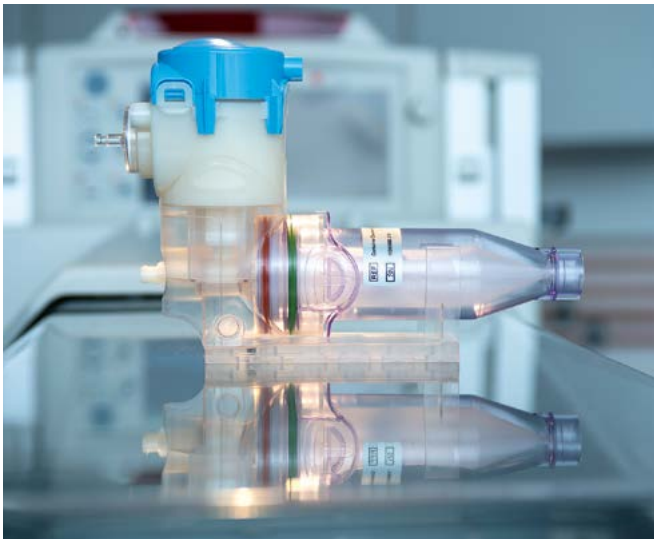
Numerous collaborations with both internal and external development partners from industry and academia enable flexible responses to project-specific requirements. We can thus comprehensively assist our clients in the medical device development process, including biocompatibility testing according to 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.

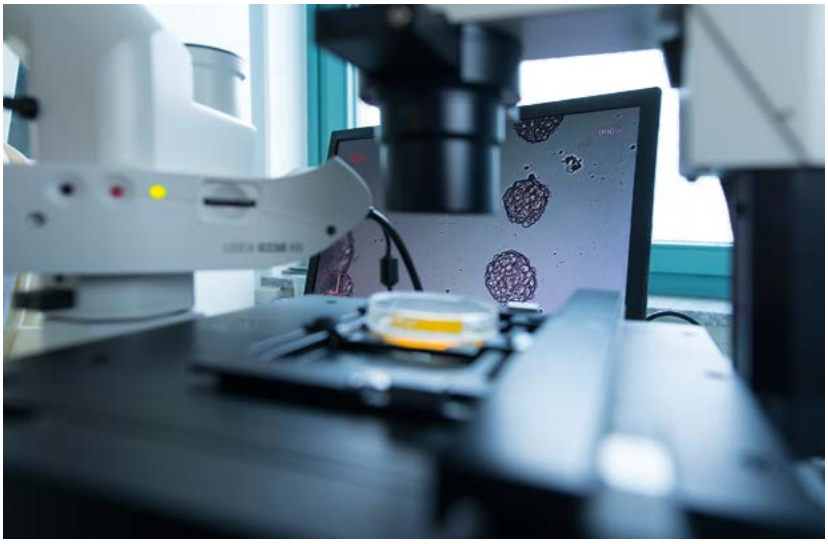
We have special expertise in the comprehensive characterization of circulating or disseminated cancer cells. These can be collected as circulating tumor cells by taking ordinary blood samples (also referred to as "liquid biopsy") from patients or they can be isolated from lymph node tissue or bone marrow 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

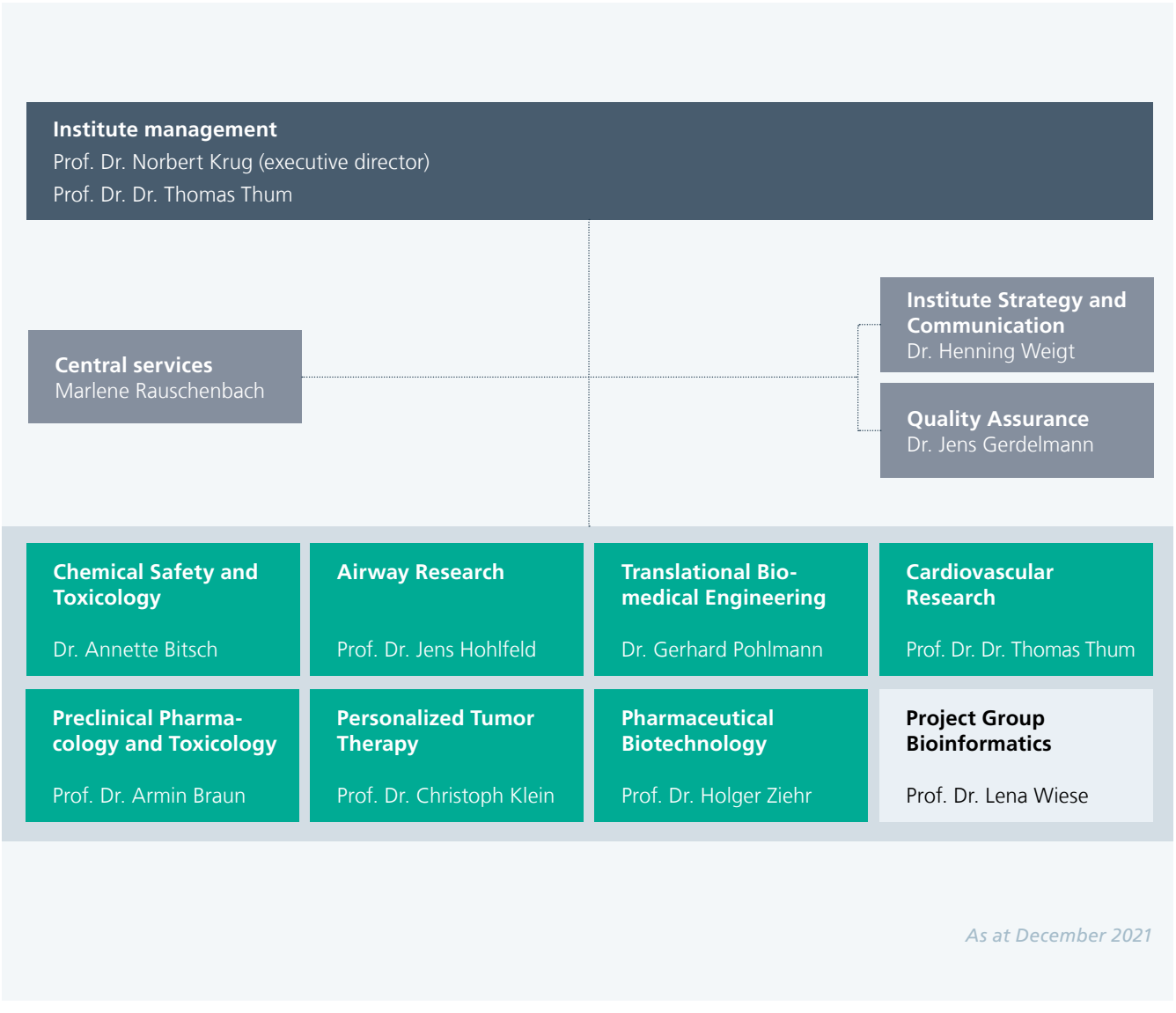
www.item.fraunhofer.de/tumor-therapy



Organizational structure

Headed by the institute directors, Fraunhofer ITEM is organized in seven divisions and three additional units. The Division of Cardiovascular Research of Prof. Thomas Thum, who has been managing Fraunhofer ITEM together with Prof. Norbert Krug since January 2021, is in the process of being established. Special expertise that is relevant for all our thematic areas, namely in bioinformatics, comes from the corresponding Project Group.

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.



As at December 2021

Staff and institute budget performance

At the end of 2021, Fraunhofer ITEM staff at all three sites – Hannover, Braunschweig and Regensburg – altogether amounted to 441 persons, with a female proportion of approximately 61 percent. People from 22 countries work and do research together at Fraunhofer ITEM.

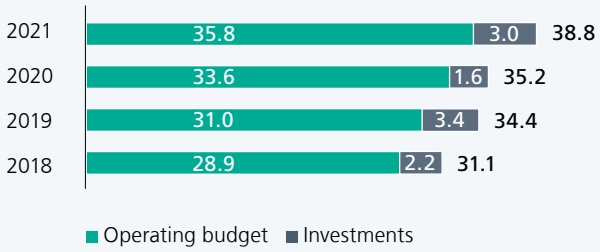
The institute's staff in 2021 included:

- 356 scientific, technical and administrative staff
- 24 Ph.D. students
- 43 students (bachelor's and master's programs)
- 14 apprentices
- 4 interns

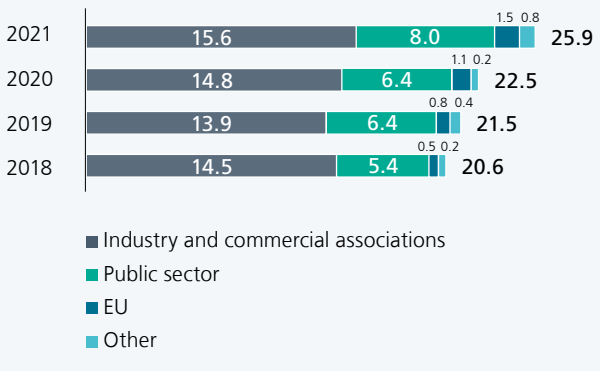
In 2021, the institute's budget reached a level of approximately 35.8 million euros. Financing by acquired funding amounted to 72 percent. The share of industrial income in the institute's budget was 44 percent. Investments of Fraunhofer ITEM amounted to approximately 3 million euros.

Fraunhofer ITEM staff

Fraunhofer ITEM total budget



Fraunhofer ITEM sponsors and external income



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 2021:

Chairman (until June 30, 2021)
Dr. Eckhard von Keutz
Head of Translational Sciences, Bayer AG

Chairman (as of July 1, 2021)
Prof. Dr. Paul-Georg Germann
Global Head of Chemical and Preclinical Safety (CPS), Biopharma, R&D, Discovery and Development Technologies, Merck Healthcare KGaA

Dr. Marcus Beiner
Deputy Head of the Department of Research, Innovation, Europe, Head of the Division of Europe and International Affairs, Lower Saxony Ministry of Science and Culture

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)

Prof. Dr. med. Julia Carolin Stingl
Full academic professor in Molecular Pharmacology, full professor and Director of the Institute of Clinical Pharmacology, University Hospital Aachen

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

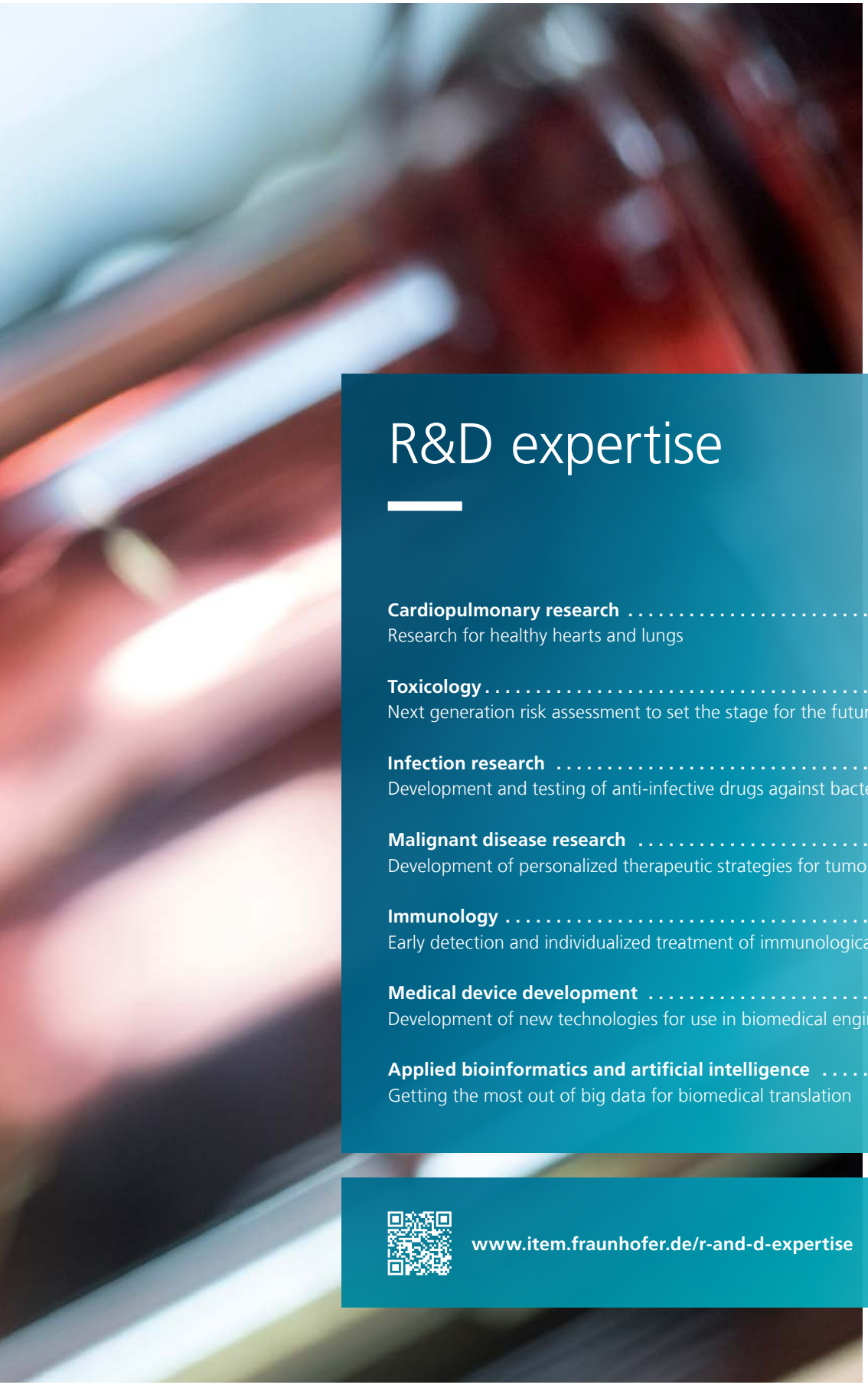
The Fraunhofer-Gesellschaft based in Germany is the world's leading applied research organization. Prioritizing key future-relevant technologies and commercializing its findings in business and industry, it plays a major role in the innovation process. A trailblazer and trendsetter in innovative developments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

With a view to the needs of tomorrow, our research and development expertise represents the focus of our work. We transfer findings and know-how into values, services and products for society and humankind, pursuing our vision of being 'pioneers for sustainable health'."

Prof. Dr. Norbert Krug
Fraunhofer ITEM director



R&D expertise

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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.

Establishment of a university-affiliated Division of Cardiovascular Research in 2021 has generated new methodological and scientific overlaps at Fraunhofer ITEM. As a result, the long-standing expertise in lung research is experiencing 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.

Candidate drugs can be tested at the institute for their 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

Systematic in-silico analyses as well as in-vitro experiments in human lung fibroblasts have revealed a novel regulatory miRNA-506-QKI axis that contributes to IPF pathogenesis.

MicroRNA-506-Quaking axis – novel molecular mechanism contributing to IPF pathogenesis

A team of scientists of Fraunhofer ITEM, the Hannover Medical School and Friedrich-Alexander-Universität Erlangen-Nürnberg has discovered a novel molecular regulatory axis that plays a decisive role in the pathogenesis of idiopathic pulmonary fibrosis (IPF). The focus is on the RNA-binding protein Quaking (QKI) and its functional interplay with microRNAs (miRNAs). Systematic in-silico analyses of the molecular network around QKI and QKI-regulating miRNAs as well as in-vitro experiments in human lung fibroblasts revealed a novel regulatory miRNA-506-QKI axis that contributes to IPF pathogenesis. These findings, which were published in Nature's "Scientific Reports" (DOI 10.1038/s41598-021-89531-7), open up new options for IPF therapies, for example based on antagonizing RNA therapeutics or small molecules interacting with the QKI network.

Results of this work have demonstrated significantly lower QKI expression in lung tissue of IPF patients compared to healthy individuals. Next, researchers identified miRNA-506 as a regulator of QKI protein expression. This miRNA also plays a cell type-specific role in cardiovascular research. Endogenous miRNAs are a class of highly conserved, short, non-coding RNAs that are part of a complex network of gene regulation. They regulate gene expression with a high degree of specificity at the posttranscriptional level by inhibiting protein expression or facilitating mRNA degradation. For translational IPF treatment, inhibition of relevant micro-RNAs that regulate QKI expression may thus be an elegant strategy to restore the loss of QKI protein expression. The aim is now to make use of these findings to develop new therapeutic approaches in the fields of RNA therapeutics or innovative small molecules. For this purpose, researchers will also apply human precision-cut lung slices, which scientists at Fraunhofer ITEM have used for preclinical studies for a long time.

Development of innovative RNA therapeutics in the Fraunhofer CIMD

The translation of innovative ideas and identified molecular targets into novel therapies for immune-mediated diseases is the primary goal of the Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD. Two interdisciplinary competence platforms have been established for this purpose: "Alternative methods to animal testing" under the leadership of Fraunhofer ITEM and "New drug classes" with the sub-platform "RNA therapeutics" that is equally led by Fraunhofer ITEM.

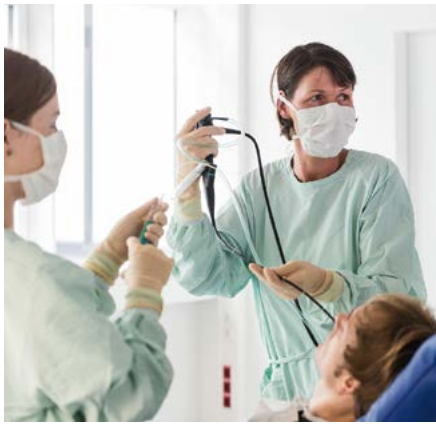
Innovative therapeutics based on ribonucleic acid (RNA) have become known to a broad public in the context of vaccine development. But RNA-based vaccines are only one use case. In many organ diseases, altered gene expression signatures are known to influence disease progression. This is where RNA therapy comes in: The targeted use of coding or non-coding RNA sequences enables a tailored response of the specific target cells under certain pathological conditions.

Fraunhofer ITEM has access to a broad range of techniques and methods, partly by cooperating with other Fraunhofer institutes and academic partners, and these are used to explore and develop for example short siRNA molecules for the treatment of pulmonary fibrosis and other chronic immune diseases. One focus is on model systems based on human cells and tissues, which are being further developed within the Fraunhofer CIMD sub-platform "RNA therapeutics". Furthermore, special administration technologies, both at the molecular and equipment level, play a key role. The pooled expertise in bioinformatics-based target discovery and characterization, preclinical pharmacology and toxicology, targeted delivery and eventually clinical translation is already available for research collaborations and joint activities with industry partners.

Pharmacokinetics of inhaled and systemic drugs directly from the lungs: a clinical evaluation

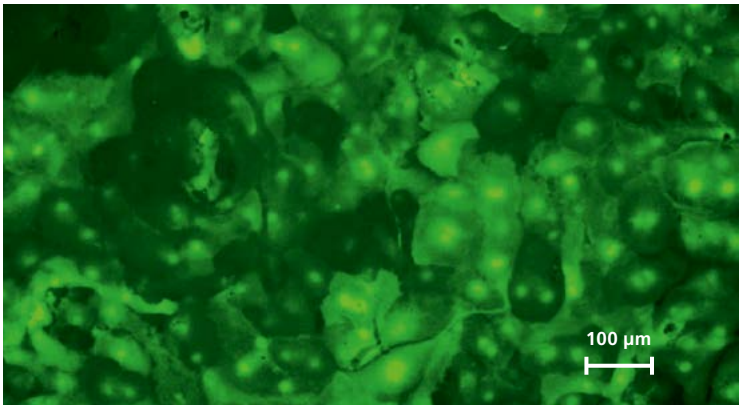
Pharmacokinetic studies of lung-targeted drugs in humans are typically limited to measurements of systemic plasma concentrations, which provide no direct information on lung target-site concentrations. The aim of a study performed at Fraunhofer ITEM was to investigate whether spatial pharmacokinetic studies in human lung are feasible. To this end, the lung pharmacokinetics of commonly prescribed drugs was evaluated by sampling different lung compartments after inhalation and oral administration.

The results have shown that pharmacokinetic studies in human lung are, indeed, feasible: After inhaled administration, considerably higher drug concentrations were found in the lungs – in the bronchial mucosa and in the bronchial and peripheral epithelial lining fluid – than in plasma. This result is of particular importance for clinical pulmonary pharmacokinetic studies with novel drugs targeting the lung, as target tissue concentrations can thus be determined more accurately and the therapeutic dose and dosing interval can be better estimated. The researchers are now already exploring a diagnostic method to collect epithelial lining fluid without bronchoscopy. To this end, they analyze the pharmacokinetics in exhaled particles. The obtained data will be presented at the annual congress 2022 of the European Respiratory Society.



Bronchoscopy is an important method for sampling of different lung compartments in clinical pharmacokinetic studies of lung-targeted drugs.

With the help of a novel nanoparticle transfer system, messenger RNA (mRNA) encoding green fluorescent protein (GFP) can be delivered into human cardiomyocytes.

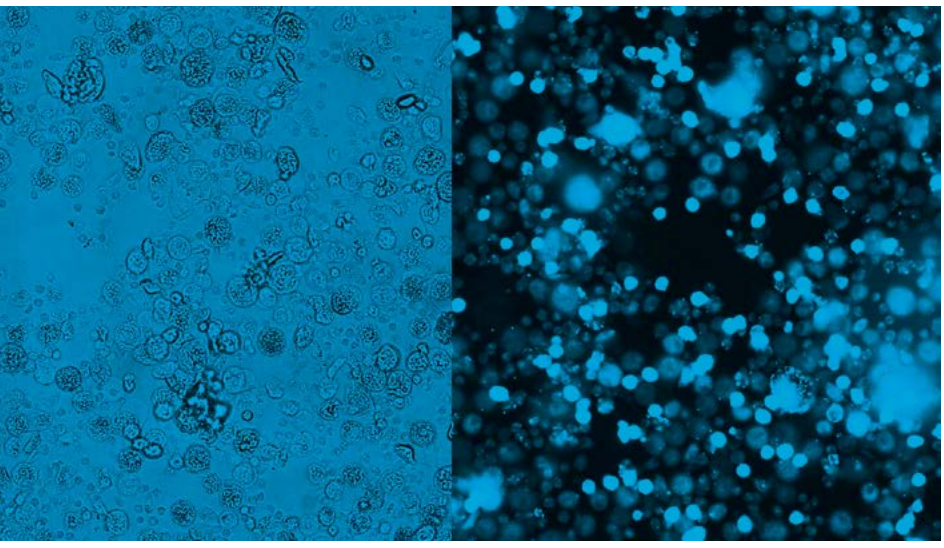


Chip cytometry: chip-based cell analysis in induced sputum and BALF

Why some people develop chronic lung disease during their lifetime and others do not is poorly understood. What is known, however, is that inflammatory immune cells in the lungs play an important role in the development and progression of these diseases. To understand the relationship between clinical pictures and inflammation, analysis of the cellular composition of bronchoalveolar lavage (BAL) and induced sputum samples is very important. These analyses are used for example in clinical trials to monitor and evaluate the drug response. To this end, it is necessary to gain as much information from a sample as possible.

In a clinical proof-of-concept study performed by Fraunhofer ITEM researchers, it was possible to demonstrate that chip cytometry can also be used to analyze BAL fluid or induced sputum. This method enables even multiple repeated analyses of cells. In view of the fact that biological samples can typically be collected only in small quantities, this is a true benefit. The researchers have optimized chip cytometry for the analysis of BAL fluid and induced sputum, as these samples contain morphologically very heterogeneous cell populations and often also numerous cell debris and large squamous cells from the oral mucosa, making it difficult to identify and differentiate cells. The performance of chip cytometry was evaluated in a clinical trial using endotoxin challenge of healthy subjects. The results showed that chip cytometry is a valuable addition to the current spectrum of methods for characterizing and quantifying cellular changes in the major cell populations in BAL fluid and sputum. And it is particularly well suited for use in multi-center clinical trials: The valuable samples from patients can be stored in refrigerators for months and can be investigated for further parameters, if new issues become relevant during the course of a trial – and they are easy to transport.

Cell populations within a sputum sample, for example macrophages and granulocytes, differ from each other morphologically and biologically. Chip cytometry enables direct comparison between a morphological transmitted-light image and fluorescence stainings at the single-cell level.



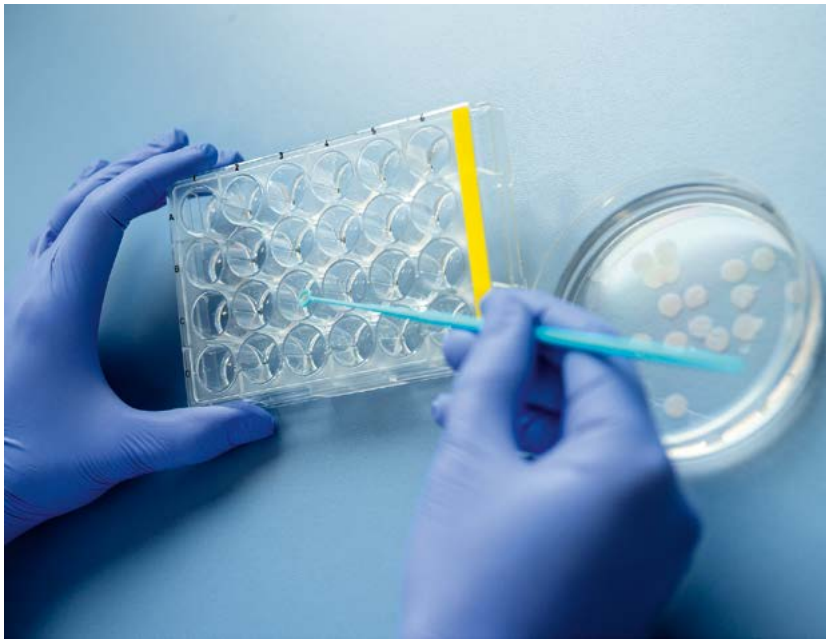
Alternatives to animal models: advances in medicine through human-relevant disease models

Worldwide, there is growing belief that biomedical sciences can advance with less animal testing by replacing in-vivo experiments with in-vitro models based on human cells or tissues. However, when it comes to elucidating disease mechanisms, especially at the organ and system levels, or to testing the efficacy and safety of drugs and medical devices, animal models are as yet indispensable. This is why Fraunhofer ITEM researchers are working to develop new human-relevant disease and test models according to the principle of the 3Rs, both in vitro and ex vivo.

In an effort to provide guidance to researchers on the translation of research findings from the laboratory into clinical applications, the European Society of Cardiology has published a position paper. Its main author and chairman of the ESC Working Group Myocardial Function is Prof. Thomas Thum, director of Fraunhofer ITEM. The authors are pointing out the recent progress that has been made in attempting to use alternative methods to reduce the number of experimental animals in cardiovascular research. The paper mentions stem cell-based cell models, in-situ modeling of features of the heart, bioinformatic models and improved animal models currently in use that exhibit clinically relevant signs observed in patients with cardiovascular disease.

Studying early events in the pathogenesis of respiratory diseases in human lung tissue

For improved prediction of chemical toxicity and adverse drug reactions as well as for safety assessment in line with the principle of the 3Rs, other models than animals are needed. The aim of the 3Rs principle is to avoid animal experiments altogether (replacement), to reduce the number of animals per experiment (reduction) and to keep animal distress to an absolute minimum (refinement). As an adverse outcome induced by an agent (such as a chemical or drug) can be linked to molecular initiation events, it is possible to investigate early events in the pathogenesis of acute and chronic respiratory diseases by measurement of key events at the cellular or tissue level.



Precision-cut lung slices (PCLS for short) are a useful method for assessing the safety of drugs and chemicals. PCLS can be exposed to chemicals, proteins or complex mixtures such as cigarette smoke, also at the air-liquid interface.

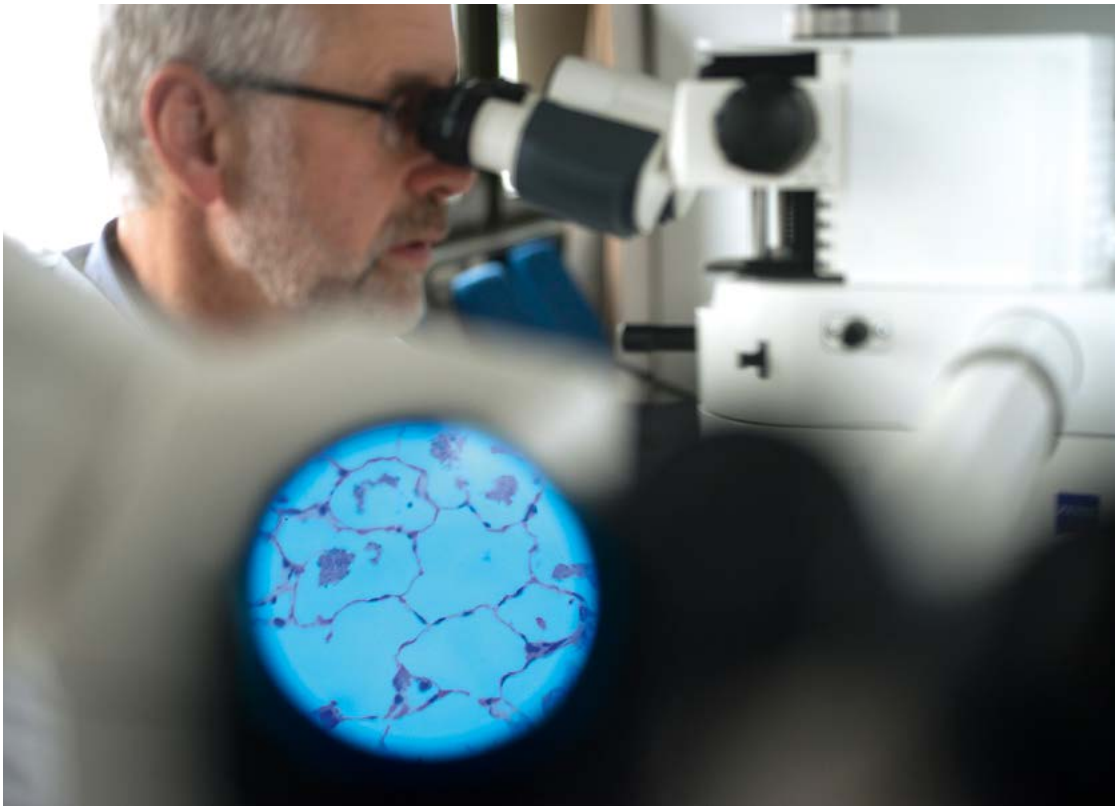
Human lung tissue is complex, it contains many different cell types and resident immune cells. As a result, injuries are often associated not only with increased release of intracellular enzymes but also with release of pro-inflammatory cytokines and chemokines such as TNF-α, IL-1β and others that serve as markers, for example of inflammation and fibrosis. Fraunhofer ITEM receives human lung tissue from two hospitals in Hannover and ensures the high quality of these samples through a standardized approach to tissue collection and appropriate quality controls. From these lung tissue samples, the Fraunhofer ITEM researchers prepare precision-cut lung slices (PCLS), which can subsequently be exposed to different test items, either in submersion culture or at the air-liquid interface. The combination of different techniques as well as the use of both healthy and end-stage diseased tissue enables the identification of chemical-changed biomarkers and pathways.

Over the past years, Fraunhofer ITEM scientists have built up expertise to advance the discovery and safety of drugs and chemicals by the use of human tissue. First publications on this topic defined a new standardized approach for using lung tissue ex vivo to assess lung injury and inflammation[1]. This approach was then used to develop disease-related models of asthma[2], COPD[3], fibrosis and infection[4]. By using these disease models, it was possible to show for example how pharmaceutical immunosuppression can lead to an increased risk for infection with influenza[5]. In this context, human lung tissue increases the predictive validity of disease models and provides a reference point that can be correlated with clinical symptoms. Nevertheless, integrating human tissue into research and development remains a significant challenge.

1 Neuhaus et al., 2018: DOI 10.3791/57042
2 Danov et al., 2018: DOI 10.1371/journal.pone.0207767
3 Obernolte et al., 2022: DOI 10.1007/s00441-021-03553-1
4 Wronski et al., 2021: DOI 10.1165/rcmb.2020-0337oc
5 Danov et al., 2020: DOI 10.3389/fmed.2020.571003

Toxicology

Next generation risk assessment to set the stage for the future



Fraunhofer ITEM stands for toxicology testing and risk assessment of chemicals, active substances and drugs – with a focus on inhalation toxicology. 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 non-genotoxic tumorigenic substances or to allow these methods to be used for the development of medical devices as well.

Our highlights

In the EU, new medicines are required to undergo an environmental risk assessment (ERA) as part of the authorization process. In some cases, the available data is insufficient. In the PREMIER project, Fraunhofer researchers are developing a read-across approach aimed at closing data gaps by extrapolating relevant data from related compounds.

The PREMIER project: managing the environmental risks of medicines

Active ingredients from medicines can get into the environment through a variety of routes and can potentially be harmful to wildlife and ecosystems. In the EU, therefore, new medicines are required to undergo an environmental risk assessment (ERA).

In the IMI project PREMIER, Fraunhofer ITEM is collaborating with numerous partners from the public and private sectors, aiming to deliver a better framework for assessing and characterizing the environmental risks of active pharmaceutical ingredients (APIs). This framework could be used to prioritize older ("legacy") APIs that have never been through an ERA for further investigation. It could also be used to ensure early detection of potential environmental risks in new APIs that are still under development. One part of the project is to set up a database containing ecotoxicological studies and environmental fate studies on active pharmaceutical ingredients and allowing this data to be made available for the development of models that can be used for prediction of environmental data. A team of the Fraunhofer ITEM Division of Chemical Safety is in charge of evaluating the quality and relevance of the data in this database. This is to ensure reliability of the data for their use in environmental risk assessment in the future. Another task is to prepare technical assistance guidelines for stakeholders on how to use the database to meet different needs. In this project, Fraunhofer researchers are furthermore developing a read-across approach for chemical compounds that is aimed at closing data gaps by extrapolating relevant data from related compounds. In addition, the possibilities of interspecies extrapolation will be investigated. PREMIER hopes its work will contribute to greener drug design in general and will help to make environmental data on APIs more visible and accessible to all stakeholders.

Preclinical studies for repurposing of Aloxistatin

Infection with SARS-CoV-2 can lead to severe courses of COVID-19. Effective therapies that limit mortality from this disease and thereby also help maintain a well-functioning healthcare system continue to be in high demand. Aloxistatin (E64D) is a cysteine protease inhibitor that has been known for many decades and was originally developed for treating neurodegenerative diseases and muscular dystrophy. In addition, Aloxistatin has shown efficient inhibition of SARS-CoV-2 replication in in-vitro experiments, making this drug, which has already undergone clinical testing, a candidate for drug repurposing for COVID-19 treatment.

Under the BMBF funding call "Investigation of COVID-19 following the outbreak of SARS-CoV-2", inhalation toxicology studies under GLP conditions were performed at Fraunhofer ITEM to prepare for regulatory approval of the cysteine protease inhibitor Aloxistatin. The studies included safety pharmacological and histopathological endpoints as well as blood tests. Given the successful toxicological characterization of Aloxistatin, a phase-I inhalation trial with Aloxistatin in healthy volunteers has now been initiated at the University Medical Center Freiburg im Breisgau, Germany.

COVID-19 treatment: preclinical studies on the active substance nafamostat mesylate

The availability of newly developed drugs for COVID-19 treatment is limited. Drug repurposing – the use of already approved drugs for other therapeutic purposes – could open up new treatment options in the shortest possible time. The aim of the BMBF-funded research project RENACO has been to test the efficacy and toxicity of the active substance nafamostat mesylate in the treatment of SARS-CoV-2 infections and thereby provide relevant data for the conduct of a clinical trial.

Nafamostat mesylate is a drug that has been used for years for intravenous treatment of pancreatitis. In addition, the substance exhibits high antiviral activity and could help prevent the spread of SARS-CoV-2 infection in the lungs when administered by inhalation. In a translational approach, preclinical studies on this issue were performed at Fraunhofer ITEM. The Fraunhofer scientists investigated the cytotoxicity of the compound in vitro in lung cells. In addition, they demonstrated high efficacy of the treatment in precision-cut lung slices that had been infected with SARS-CoV-2. The effect of nafamostat mesylate on lung function was studied ex vivo in isolated perfused lungs. Finally, the toxicity of the anti-SARS-CoV-2 treatment was investigated in an inhalation study in rats. Performance of the GLP-compliant toxicity study had been previously coordinated with the competent authority. In the RENACO project, Fraunhofer ITEM was able to generate valuable data in a broad range of test systems – in vitro, ex vivo and in vivo. Taken together, they provide a firm basis for the design of a clinical trial in patients.

For drug repurposing, active substances for treating SARS-CoV-2 infections also have to undergo efficacy and toxicity testing. In-vitro and in-vivo studies are performed for this purpose.

How can alternative, new-approach methodologies (NAMs) be integrated into regulatory hazard and risk characterization of chemicals in food and feed? As a result of this EFSA-funded project, scientists have recommended several research activities.

Roadmap for the integration of new-approach methodologies into risk assessment

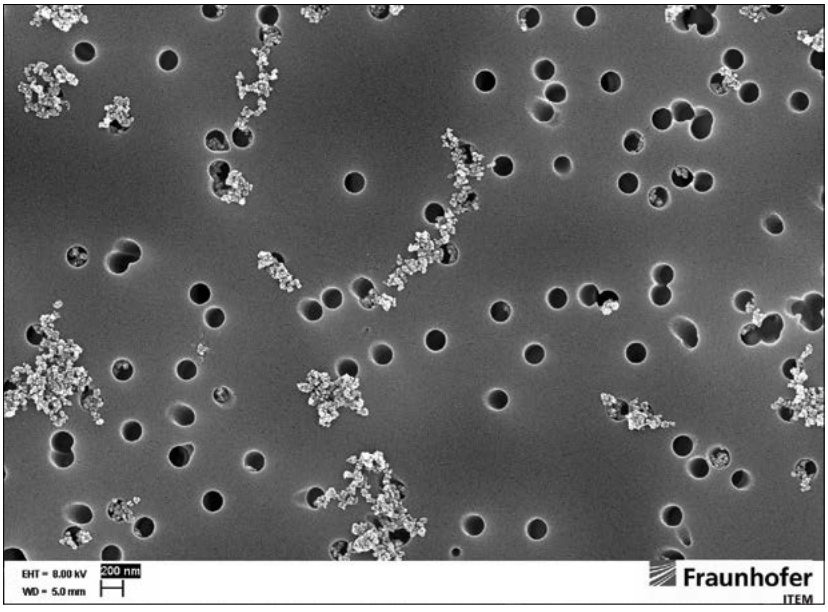
Results from animal studies, which are often requested for risk assessment purposes, are of little or no use in corroborating the observed toxicity with insights into the underlying mechanism at the molecular level. Alternative, new-approach methodologies (NAMs) combining human-relevant in-vitro methods and computational (in-silico) approaches hold much promise to fill this gap.

The main objective of a project on behalf of EFSA is to propose priorities regarding the incorporation of NAMs into regulatory hazard and risk characterization of chemicals in food and feed. For this purpose, focuses were identified from five relevant research areas, namely toxicodynamics, toxicokinetics, exposome, susceptible human subpopulations and data integration. Special attention was paid to the degree of estimated regulatory readiness of the various alternative methods and concepts, starting from the research level to acceptance by the authorities via in-situ validation. To analyze the impact of the five research areas on the reduction, refinement and replacement of animal testing (3Rs), challenges and blockers were identified as well as data gaps, some of which were significant.

The result was the recommendation of seven research activities required for NAMs to be implemented in EFSA's scientific assessment process. The recommended measures include a number of proof-of-concept studies benchmarking the readiness of specific technologies and models with regard to the toxicodynamics and toxicokinetics of compounds, but also enabling hazard assessment for particularly susceptible human subpopulations. In addition, the applicability domain of these models is planned to be extended to compounds in food and feed. The case studies have been specifically designed to build confidence in NAM-based risk assessment and thus to improve the use and acceptance of these technologies.

Toxicokinetics of carbon black

Carbon black is a black, finely dispersed powder containing nanoscale particulates of pure elemental carbon. This technical soot takes the form of aggregates (100-1000 nm) that make up agglomerates with diameters in the range of 1-100 µm.



Carbon black, also referred to as technical soot, is virtually pure elemental carbon in the form of particles that are industrially produced by incomplete combustion or thermal decomposition of gaseous or liquid hydrocarbons under controlled conditions. This technical soot is a black, finely dispersed powder containing nanoscale particulates, taking the form of aggregates (100-1000 nm) that make up agglomerates with diameters in the range of 1-100 µm. A large proportion of carbon black is used in the rubber industry, especially in tire manufacturing, and also as a component of paints, inks, coatings and plastic products. The toxicokinetic behavior of nanoscale particles after pulmonary or oral deposition is of great scientific interest because, due to their tiny size, they might have a potential for migration into the bloodstream and thus systemic exposure.

The toxicity of different types of soot, for example diesel soot from engine exhaust, has been studied comprehensively, but soot particles may also be contaminated, for example with polyaromatic hydrocarbons. Such soots are produced during all incomplete combustion processes of carbonaceous materials. The major health concern with soot is its effect on the lungs as a result of inhalation exposure. Studies in rats have shown that particle deposition in the lungs above certain concentrations leads to an overload

of the lung clearance processes. This, in turn, leads to persistent inflammation, production of reactive oxygen species, depletion of antioxidants and impairment of other defense mechanisms and, in the worst cases, can eventually result in the development of lung tumors. Besides the primary target organ, the lungs, translocation of carbon black could also result in other organs experiencing toxic effects. Whether carbon black remains in the lungs after its deposition or can reach other parts of the body was to be elucidated in a study requested by the European Chemicals Agency ECHA.

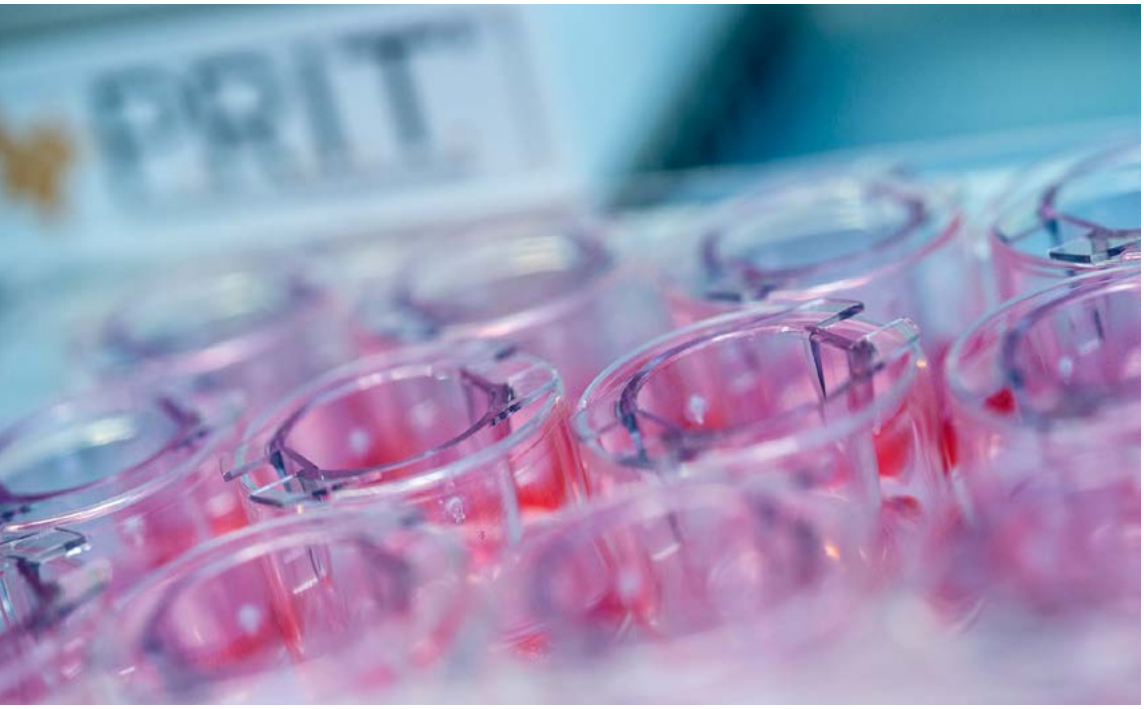
The aim of the toxicokinetic study conducted at Fraunhofer ITEM was to determine whether and to what extent carbon black can be absorbed in the body or systemically distributed. In this animal study, both pulmonary and oral uptake were evaluated, as these are the two major routes of exposure. The scientists found that carbon black acted as microscaled agglomerates of aggregates, not as free, nanoscale particulates, and displayed no potential for translocation. Carbon black was not systemically available after deposition in the lungs or stomach. Publication of the results of this study is currently being prepared.

With a view to the food chain: screening and evaluation of emerging risks from industrial chemicals

Aiming to identify new emerging chemical risks in the food chain, researchers from the Wageningen Food Safety Research institute (project lead), the University of Chemistry and Technology in Prague and Fraunhofer ITEM (Division of Chemical Safety and Toxicology) are collaborating in the EFSA-funded project "Screening for emerging chemical risks in the food chain" (OC/EFSA/SCER/2020/02). In previous projects, 212 industrial chemicals registered under REACH were already prioritized as "potential emerging risk" substances that could possibly be present in the food chain. In the present project, screening methods for detecting these compounds will be developed following a tiered approach and will be used for their

detection and quantification in food raw materials from different countries. In addition, the foodstuffs will be screened for unknown halogenated organic chemicals by using a non-targeted screening strategy. Experts from Fraunhofer ITEM are working to establish targeted detection limits based on the toxicity of the substances. They will perform a preliminary human health risk assessment for selected substances identified in the foodstuffs to evaluate the significance level of occurrence. Furthermore, they will assess the potential intake and compare it to toxicological points of departure in a margin-of-exposure approach.

New, as yet unknown risks can also emerge from already known industrial chemicals and can have an impact on the food chain. Fraunhofer ITEM scientists are investigating and assessing these risks in an EFSA-funded project.



In-vitro models are a part of next generation risk assessment: The exposure system P.R.I.T.® ExpoCube® allows the effects of volatile substances on human lung cells and tissue to be studied at the air-liquid interface. The situation in human lung can thus be mimicked in vitro.

Human-based testing strategies for next generation risk assessment

A primary goal of modern risk assessment is to better understand the mechanisms leading to toxic effects in humans and susceptible human subpopulations. The animal tests used so far are, therefore, increasingly being replaced by human in-vitro and in-silico approaches, in line with the principle of the 3Rs ("reduce, refine and replace animal testing"). The development and further improvement of these new integrated testing strategies is the focus of the European project RISK-HUNT3R. Coordinated by Prof. Bob van de Water of Leiden University (The Netherlands), 37 partners from industry (40%), academia (55%) and regulatory authorities (5%) are cooperating in the project consortium.

The vision of RISK-HUNT3R is to develop, validate and implement integrated approaches to pave the way for next generation risk assessment (NGRA). Innovative mechanism-based novel methods (NAMs) relevant to human health will be exclusively in vitro and in silico. Through systematic and iterative evaluation of the NAM toolbox, the project will optimize a strategy for chemical exposure assessment, toxicokinetics and toxicodynamics. Fraunhofer ITEM scientists will contribute substantially to the development of an exposure model that combines external human exposure with internal concentration modeling via physiologically based pharmacokinetic (PBPK) approaches. Among others, in-vitro ADME models will be developed to address the absorption, metabolism and distribution of inhaled substances in the respiratory tract. Another focus is the integration of NAM data and models into regulatory risk assessment and decision-making.

ERA of veterinary medicinal products: evaluation of an active-substance-based system

Both scientific and policy discussions have been ongoing for decades on the shortcomings of the currently mandatory product-based environmental risk assessment (ERA) of veterinary medicinal products in the EU and the nature of potential alternatives. In the MONO4ERA project, Fraunhofer ITEM performed a feasibility study on behalf of the European Commission. In this study, researchers of the Department of Regulatory Affairs (Division of Chemical Safety and Toxicology) identified, collected and analyzed information to assess the feasibility of an active-substance-based approach, referred

to as "monograph system", and other potential alternatives. The monograph system as defined in the literature and two alternatives presented by two industrial associations were examined for their possible impacts, efficiency and effectiveness in achieving the objectives of Regulation (EU) 2019/06, namely to reduce the administrative burden, enhance the internal market, increase the availability of veterinary medicinal products, while guaranteeing the highest level of public and animal health and protection of the environment. Especially in view of the EU goals, the study came to the conclusion that a monograph system would be justified, proportionate and also affordable in the long run. In addition, in its final report, the project consortium presented a comprehensive proposal for a legislative amendment to introduce a monograph system under the existing Regulation (EU) 2019/06.

Detecting and avoiding pollutants in water

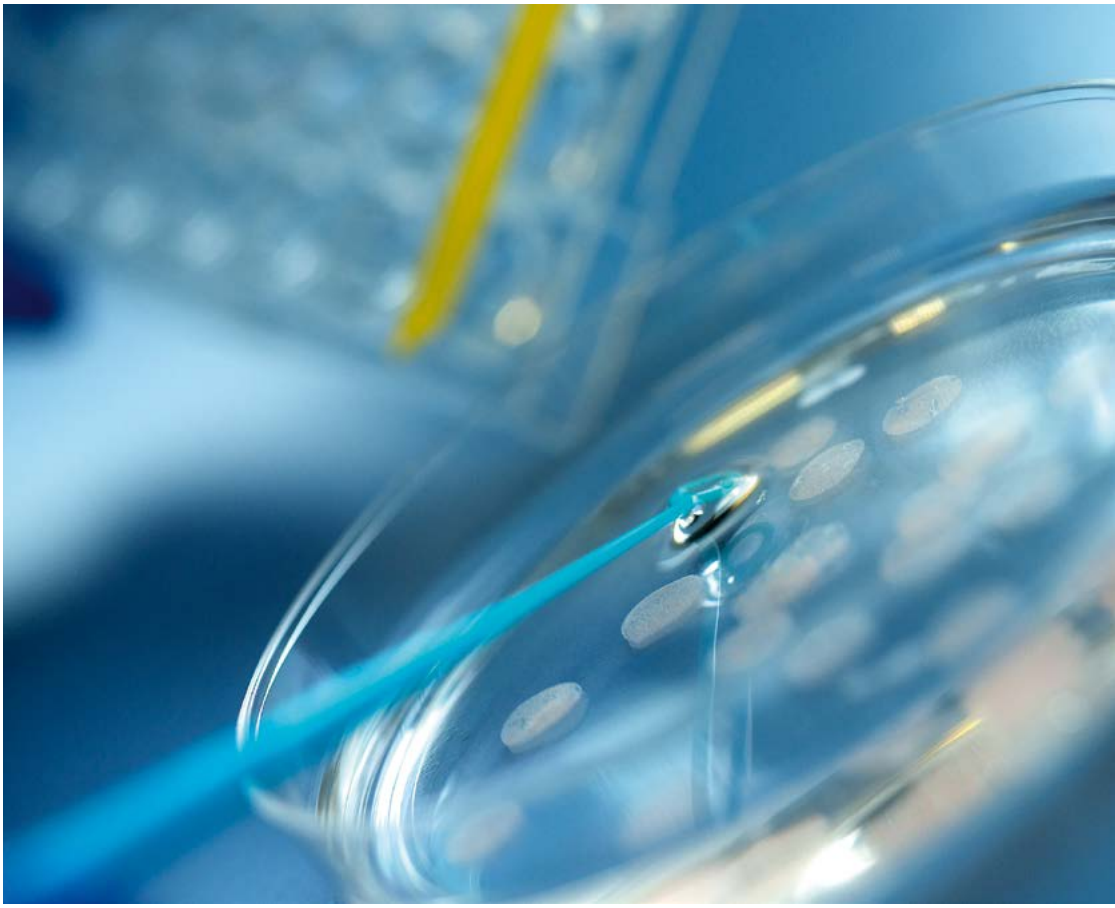
Our drinking water is at risk of contamination by certain chemicals that are not only poisonous, but also particularly long-lasting and mobile. This contamination can be irreparable, because these persistent, mobile substances (PM for short) get through filters and withstand drinking water purification processes. PM are often used in the manufacturing of functional textiles, but also in the paper industry and in plant protection products. In the EU project ZeroPM, researchers from Fraunhofer ITEM are collaborating with 15 partners under the leadership of the Norwegian Geotechnical Institute to develop effective means of protecting human health and the environment. The Fraunhofer ITEM team aims to identify and characterize the hazard of PM substances. To this end, the researchers will model the uptake and distribution of these substances in the human organism. By assessing the risks of the toxic effects, the researchers hope to help develop prevention and remediation strategies. At the same time, they want to contribute to new dangerous materials being identified more quickly and avoided in the future.

Natural barriers in the water cycle, such as soil filtration, cannot stop persistent, mobile substances.

An objective of the MONO4ERA project was to assess the feasibility of an active-substance-based approach – a monograph system – and of other potential alternatives for environmental risk assessment of veterinary medicinal products.

Infection research

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



Research in the field of infectious diseases became particularly important with the outbreak of the SARS-CoV-2 pandemic. At Fraunhofer ITEM, funding programs of the Fraunhofer-Gesellschaft and the German Federal Ministry of Education and Research as well as contract research commissioned by industry helped to get numerous projects up and running within a very short time. The aims were to better understand the infectivity and transmissibility of SARS-CoV-2, to develop corona-specific active and passive vaccines and to evaluate the safety and efficacy of therapeutics for treating COVID-19. The findings from a broad range of research projects performed at Fraunhofer ITEM have made a valuable contribution to the fight against the corona pandemic and help to generate knowledge for potential future pandemics. For example, researchers of the Division of Pharmaceutical Biotechnology managed to manufacture neutralizing antibodies against SARS-CoV-2 as an investigational medicinal product in record time: The IMP was advanced to the stage of clinical testing in less than seven months.

Urgently needed drug substances against respiratory infections and new preclinical infection models are being developed in research collaborations, for example in the German-Australian iCAIR® consortium. The formulation and mode of delivery of anti-infective substances is also a research topic of current interest at the institute. The competence in formulation development, therefore, will be further expanded and the development and production of anti-infectives for inhaled administration as drug aerosols will be 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.

Our highlights

Preparing for the future with novel RNA therapies and platform technologies

The SARS-CoV-2 pandemic has highlighted the urgency of developing new therapies for COVID-19 treatment and at the same time has demonstrated the necessity to become well prepared for new virus infections we may be facing in the future. To help control this pandemic and also brace for novel pathogens that may cause future pandemics, Fraunhofer researchers collaborated in the BEAT-COVID project funded under the Fraunhofer vs. Corona program to develop novel RNA-based therapy strategies and build up platform technologies. These will support the manufacturing, development, testing and marketing authorization of novel therapeutics for the treatment of infectious diseases, at present primarily COVID-19.

Coordinated by Fraunhofer ITEM, the consortium included four more Fraunhofer institutes (IAP, ISC, IZI and IZM), in addition to the universities of Leipzig and Würzburg as well as the Hannover Medical School as cooperators. By pooling Fraunhofer-wide expertise in preclinical and clinical drug development, BEAT-COVID addressed three objectives: prevent the virus from entering host cells, combat the virus itself and control the excessive immune response triggered by the virus. The focus was on the development of RNA therapeutics including their viral and non-viral packaging as well as on the development of the antibody palixizumab for COVID-19 treatment. Recently, the researchers successfully published part of the results obtained (Friedrich et al., 2022: DOI 10.3389/fbioe.2022.801870). By establishing platform technologies, the researchers aimed to enable rapid and targeted development of new drugs against other viruses and infection-causing pathogens that may yet emerge.

To enable rapid and targeted development of new drugs against as yet unknown pathogens, researchers have developed independent novel therapy strategies and built up platform technologies.

Setup of a “screening pipeline” for the development of novel COVID-19 therapeutics

The COVID-19 pandemic has brought together scientists with different expertise to work on the prevention and treatment of this disease. Current vaccine and drug development is often focused on the well-known spike protein that is relevant for binding of the virus to host cells. Rapid changes of the viral RNA genome within relatively short time intervals, however, have taught us that a single strategy will not be sufficient to successfully combat the pandemic in the long term. Aiming to identify drug candidates that specifically inhibit packaging of the SARS-CoV-2 genome into virus particles and thereby prevent replication of the virus, the working group on High-Throughput Drug and Target Discovery

at Fraunhofer ITEM in Regensburg is cooperating with partners from the University of Regensburg and the company 2bind GmbH. The project is being funded by the Bavarian Research Foundation.

The team of Prof. Gernot Längst from the University of Regensburg has developed a new strategy to block virus replication by targeting the assembly of viral particles in infected cells. A key element in this process is the binding of viral RNA to the nucleocapside protein (N-protein), which organizes packaging of the viral genome into viral particles and is thus necessary for assembly of the mature viral particle. Unlike the spike protein, the N-protein is essential for virus replication and is therefore not mutation-prone. This process is the "Achilles' Heel" of the viral infection, and it can be targeted by interrupting the interaction of viral RNA and N-protein.

To identify compounds that can block RNA/N-protein assembly, the consortium tested a library comprising 2.5 million compounds in silico. Out of these, the Fraunhofer researchers in Regensburg investigated 500 compounds in the laboratory. The screening was performed by using a specifically designed automated and upscaled biochemical assay. In this assay, formation of biomolecular condensates of RNA and N-protein can be measured during liquid-liquid phase separation (LLPS) after treatment with chemical compounds. Size and morphology of the condensate were analyzed using automated high-content screening microscopy. In addition, the scientists selected 20,000 compounds with maximal diversity for biochemical screens. The identification of compounds targeting viral replication may direct the development of novel therapeutic strategies with high economic potential.

In their search for drug candidates that specifically inhibit packaging of the SARS-CoV-2 genome into virus particles and thereby prevent replication of the virus, the Fraunhofer ITEM scientists in Regensburg make use of high-throughput screening technology.

Viable human lung slices as test system for COVID-19 drug development

By the end of 2021, the pathogen "severe acute respiratory syndrome coronavirus 2", SARS-CoV-2 for short, had caused 450 million confirmed infections and more than 6 million deaths (www.worldometers.info/coronavirus). The disease this virus triggers in humans has been named COVID-19. Without treatment at an early stage, about 10 to 15 percent of patients develop a severe course of COVID-19, which can be fatal. Regardless of the vaccines now available, there continues to be a need for new antiviral drugs and treatment strategies. Fraunhofer ITEM is actively involved in the search for new active substances for COVID-19 treatment.

The Fraunhofer scientists use human-relevant, predictive ex-vivo systems such as viable precision-cut lung slices (PCLS) for target identification and lead optimization of new drugs. For these studies, conducted in cooperation with universities and other institutes, PCLS are prepared from human lung tissue and infected with SARS-CoV-2 in an appropriate laboratory. The results have shown that the virus replicates in these tissue slices and triggers the release of inflammatory

Fraunhofer scientists study the antiviral effects of different compounds in human precision-cut lung slices infected with SARS-CoV-2.

mediators. Simultaneous treatment with drugs such as cyclosporine A[1], fluoxetine[2], nafamostat or camostat[3] allows the antiviral effects of these drugs to be studied. Drugs demonstrating safety and efficacy in this and other models are now being further developed for treating COVID-19 patients.

1 Sauerhering et al., 2022: DOI 10.1164/rccm.202108-1830LE

2 Zimniak et al., 2021: DOI 10.1038/s41598-021-85049-0

3 Hoffmann et al., 2021: DOI 10.1016/j.ebiom.2021.103255

Aerosols in the pandemic: their role and the development and evaluation of protective measures

Aerosols play an important role in the transmission and spread of the coronavirus SARS-CoV-2. When humans breathe, speak, sneeze or cough, they emit tiny droplets – smaller than 10 up to 20 µm in diameter – which can remain airborne for a long time. These droplets are composed of saliva and lung fluid and provide a habitat in which the coronavirus can survive for several hours. Aerosols can spread over long distances, which means that a person infected with SARS-CoV-2 can infect others in the immediate vicinity but also further away. In view of this situation, Fraunhofer ITEM researchers have developed steps for a prevention strategy in a variety of projects. A total of 16 Fraunhofer institutes with a broad range of expertise has participated in different projects funded by the Fraunhofer-Gesellschaft: AVATOR, CoClean-up and QUELLE.

The research activities in these projects addressed a great diversity of topics – from the characterization of virus or particle emission by an infected person via a possibility for indoor air disinfection to the determination and evaluation of the risk of infection in a defined scenario. The ITEM researchers have developed a method for generating defined atmospheres with viral aerosol enabling efficacy testing of air purification methods, explored methods to test the efficacy against corona surrogate viruses and worked on a strategy for risk assessment under specific exposure conditions.

As part of these projects, a novel system for air purification in indoor areas, based on electrochemical total oxidation, has been developed under the leadership of Fraunhofer IKTS. After the successful development of a prototype, the scientists intend to further optimize the system and pursue the development of a marketable product. Furthermore, a model for determining and assessing the risk of infection has been developed by using the example of workers in industrial manufacturing settings in two different companies. An asset in this process was the Fraunhofer ITEM expertise in aerosol emission and distribution

and in characterizing specific exposure situations. The good results in the different projects were enabled by the interplay of the different expertises in the fields of determination of the emission of potentially infectious droplets, indoor aerosol dispersion simulation, agent-based simulation of people's movement patterns and risk modeling.

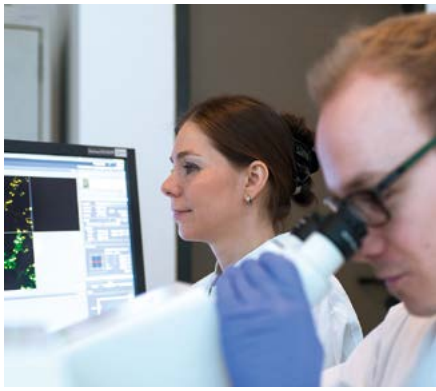
Drug repurposing to speed up the development of new medications

Specific drugs for treatment of COVID-19 infections continue to be largely unavailable. Given the long time it takes to develop new pharmaceuticals, alternatives are needed, especially in acute situations such as the COVID-19 pandemic. Drug repurposing, which is the use of drugs that have already been approved for other therapeutic purposes, may offer a fast track to making effective therapeutics available.

In the international iCAIR® consortium and in the Fraunhofer projects DRECOR (Drug Repurposing for Corona) and RENACO (Repurposing Nafamostat Mesylate for COVID-19 prevention), Fraunhofer ITEM scientists are collaborating with external partners, such as the German Primate Center, the Helmholtz Centre for Infection Research and the Australian Griffith University, to investigate the possibilities of drug repurposing.

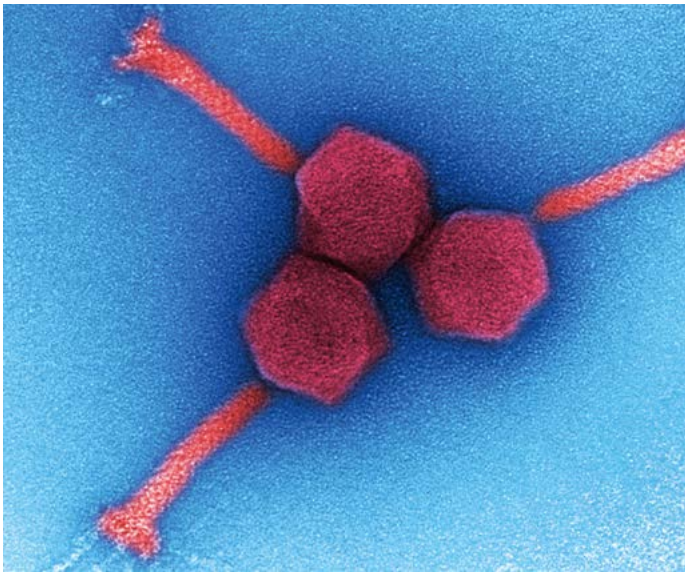
In the search for suitable drug candidates, the scientists screened substance libraries. The active pharmaceutical ingredients camostat and nafamostat, approved in Japan for treating pancreatitis, were shown to prevent SARS-CoV-2 from entering host cells. Experiments in cell cultures and in human tissue models confirmed the safety and efficacy of both compounds. Their efficacy also against possible new SARS-CoV-2 variants is intended to be investigated in the future.

To optimize the efficacy and reduce potential adverse effects, targeted release of the active ingredient at the site of infection is planned to be realized. For this purpose, the top candidate nafamostat is being further developed for inhaled administration. To make nafamostat available as an inhaled therapeutic for COVID-19 patients, Fraunhofer ITEM scientists are conducting in-vivo GLP inhalation toxicology studies and are developing device prototypes to enable inhaled administration of the drug in clinical trials.



Drugs that have already been approved for other therapeutic purposes also have to undergo safety and efficacy testing. Fraunhofer ITEM researchers use human lung tissue, among others, for this purpose.

In the corona project QUELLE, Fraunhofer ITEM scientists aimed to track the risk of airborne infection.



In the PhagoFlow project, E. coli bacteria are among the target pathogens of phage therapy. The picture shows E. coli-specific phages in red (stained electron micrograph; courtesy M. Rohde, Helmholtz Centre for Infection Research).

Practicability of phage therapy in Germany

The aim of the project PhagoFlow is to determine the infrastructural requirements for magistral production of phages in Germany to enable treatment of patients with wound infections of the extremities. This project, initiated by the Federal Joint Committee and funded by the Innovation Committee of the German Bundestag, is a collaboration of Fraunhofer ITEM, Leibniz Institute DSMZ and the Bundeswehr Hospital in Berlin.

As a first step, DSMZ identified 12 phages targeting different WHO prioritized pathogens based on their biological properties: complementary host range, high lytic activity and absence of undesired genes. These phages then were to be produced for magistral use. The challenge in this context, however, is the lack of a regulatory guideline and drug monograph. The ITEM researchers, therefore, focused at first on the definition of minimum requirements for quality control testing, GMP aspects and the purity of phage preparations and on discussing these with the competent authorities. The aim was to combine a high level of patient safety with cost-effective and time-saving production.

This was followed by pilot production of the most promising phages based on the previously established GMP and pharmaceutical quality requirements. Subsequently, individualized phage preparations shall be formulated by the Bundeswehr Hospital Pharmacy in Berlin based on phagograms (phage susceptibility tests against pathogens) and are planned to be administered to selected patients in the Department of Trauma Surgery.

Bacteriophages: new therapies with “old” anti-infective agents

The aim of the project Phage4Cure is to establish bacteriophages (phages for short) as anti-infective drugs against bacterial infections with *Pseudomonas aeruginosa* – a bacterium that has been associated with hospital-acquired infections and cystic fibrosis. Using phages previously selected by Leibniz Institute DSMZ, the Braunschweig-based Fraunhofer ITEM Division of Pharmaceutical Biotechnology is developing manufacturing processes to supply these phages as active pharmaceutical ingredients of a future drug for inhaled administration. The manufacturing process includes cultivation of the production strain, phage replication in the production strain and harvesting, purification by chromatography, formulation, and fill and finish of the investigational medicinal product. The aim is to develop a largely standardized, platform-like production technology that will later allow the manufacturing process to be adapted to other phages by adjusting only a few parameters.

The scientists managed to produce the specific phages in the required quantities and pharmaceutical quality as active ingredients and to deliver them to the project partners at Charité Berlin and Fraunhofer ITEM in Hannover for preclinical pharmacology and toxicology studies. Pharmaceutical-grade phage-based investigational medicinal products have been manufactured for phase-I clinical trials in compliance with the GMP quality assurance system. The first clinical trial with bacteriophages in Germany is expected to start in the second half of 2022.

Preventing RSV-mediated asthma through novel therapeutic approaches

Respiratory syncytial virus (RSV) usually causes mild airway infections in healthy adults. In infants, however, severe courses are frequent and have been associated with subsequent development of asthma. This relationship has not yet been scientifically elucidated, and effective treatment and prevention options are lacking to date.

Fraunhofer ITEM scientists have established a model that mimics the viral infection ex vivo in viable human lung tissue (precision-cut lung slices – PCLS for short). RSV triggers reactions in these tissue slices similar to those seen in infected patients. First results obtained with infected PCLS have shown not only a marked anti-viral immune response, but also activation of asthma biomarkers in the tissue, which might be a target for specific inhibition by preventive drugs.

In parallel, an interdisciplinary team in the Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD is developing an innovative vaccine that is not only intended to protect against severe respiratory infections with RSV, but could also prevent the consequent development of asthma. To this end, inactivated virus particles are packaged in liposomes and administered into the lungs. The aim is to establish immunity directly in the airways. The scientists make use of PCLS to investigate the tolerability and immunomodulatory effects of the vaccine. Important first data on the use in humans are thus obtained and, furthermore, animal testing is systematically avoided.

Investigating aerosol droplet absorption in an ex-vivo model

Most diseases are treated systemically. In many cases, the affected organs are easily accessible via this route. The lung offers the possibility of direct treatment via the respiratory tract. For relevant substances this enables enhanced efficacy, robustness and effectiveness.

On the other hand, the administration of drugs via the respiratory tract also leads to (undesired) systemic absorption of the substance. To study the transition of a nebulized or aerosolized substance depending on droplet size, Fraunhofer ITEM researchers use the ex-vivo model of the isolated perfused rat lung (IPL). In this alternative model, they studied the transition of a fluorescence-labeled substance into the perfusate, which served as blood substitute in this model. Two different methods were used to generate aerosols with different droplet sizes. The kinetics showed an increase in fluorescence in the perfusate over the duration of the experiment. The absorption of fluorescent substance from larger droplets into the perfusate was higher than from the finer aerosol, and the uptake of small molecules was faster than that of large molecules.

The IPL, therefore, represents a promising model – in the spirit of the 3Rs (replace, reduce, refine animal testing) – for the investigation of airborne substances, their deposition in the lungs and their transition into the bloodstream.

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

Malignant disease research

Development of personalized therapeutic strategies for tumor diseases

Research into metastatic disease, the development of diagnostics and pharmaceuticals is 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.

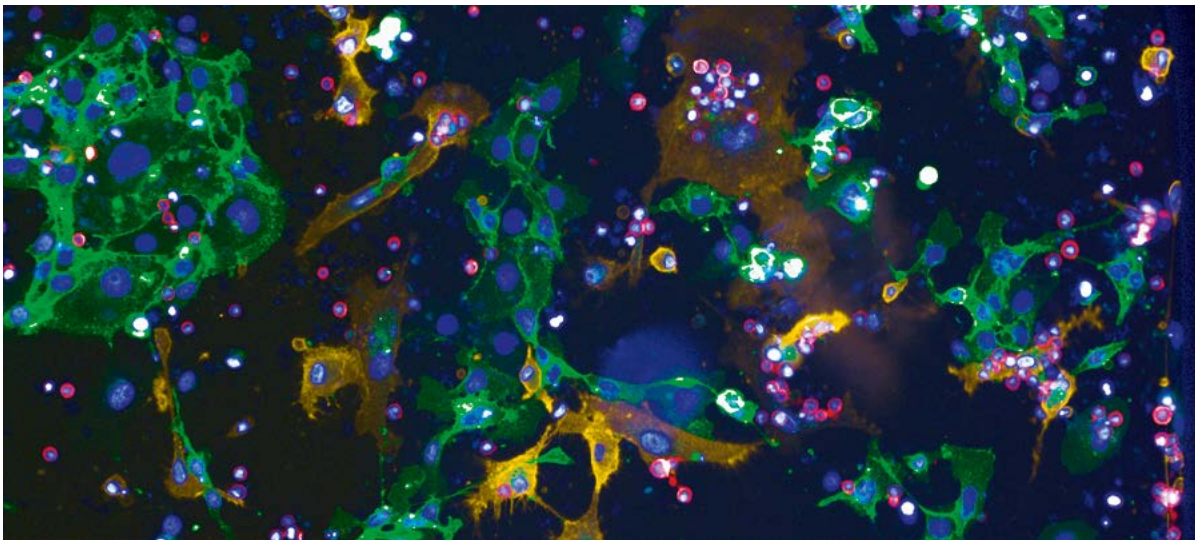
An area of special expertise of the researchers is the molecular biological characterization of single cancer cells, which can be collected as circulating tumor cells by liquid biopsy or isolated from lymph node tissue or bone marrow as disseminated cancer cells. In order to define new treatment monitoring 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.

Bioprocess development and manufacturing of novel active molecules and investigational medicinal products for treating tumor diseases is established at Fraunhofer ITEM in Braunschweig and will be further expanded by setting up a toolbox for the analysis, molecular characterization and development of production cell lines. The focus is on manufacturing processes for small bi-specific single-chain antibodies (BiTEs) that bind to T cells or CART cells and lead to tumor cells being recognized by the immune system (immunotherapy).

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 institute's 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



Multicolor immunofluorescence staining of co-cultured lung, immune and stromal cells. Specific cell types are visualized by a panel of antibodies detecting antigens that are specifically expressed on the surface of human lung cancer cells (green), immune cells (violet) or stromal cells (yellow).

Patient-specific model systems to investigate early metastasis

More than 90 percent of deaths from cancer are not caused by the primary tumor, but by metastases in distant organs. Metastases originate from single disseminated tumor cells that migrate to another organ and form new metastatic colonies there. In the Collaborative Research Center/Transregio (SFB/TRR) 305, scientists are conducting research to better understand the mechanisms of early colony formation of tumor cells and identify specific therapies that can prevent metastasis. Headed by Prof. Christoph Klein, senior professor of Experimental Medicine and Therapy Research at the University of Regensburg and division director of Personalized Tumor Therapy at Fraunhofer ITEM, and Prof. Thomas Brabletz, senior professor of Molecular Oncology and chairman of the Department of Experimental Medicine at the University Erlangen, the SFB/TRR 305 also brings together the expertise of researchers from the Fraunhofer institutes EMFT, IIS, IME and IWS.

Within the SFB/TRR 305, Fraunhofer ITEM scientists are developing novel preclinical models that adequately map the process of colony formation as well as the interactions with the microenvironment of the affected organ. For this purpose, disseminated tumor cells from cancer patients are expanded in organoid cultures and cultured together with the patient's own immune cells under conditions suitable for high-throughput analysis. In addition, to study colony formation in a complex microenvironment, disseminated tumor cells are cultured on tissue slices from the metastatic organs lung, liver and lymph nodes using microfluidic chip systems and are then characterized.

The aim is to use these novel models to investigate the molecular mechanisms involved in colony formation by disseminated tumor cells in different organs and to perform functional testing to identify drugs that can prevent metastasis.

Comparison of single-cell miRNA sequencing methods

The human genome transcribes tens of thousands of small non-coding RNAs. Although they do not get translated into proteins, these molecules make significant contributions to physiological and pathological processes. The best studied are microRNAs (miRNAs) – highly conserved molecules that have a length of 20 to 25 nucleotides and act as important post-transcriptional regulators. They bind to complementary regions on cellular mRNAs, usually leading to degradation of these mRNAs or suppression of their translation. In cancer patients, the transcription of many miRNAs is altered. Thus, they can serve as diagnostic or prognostic biomarkers and represent promising novel pharmaceuticals or therapeutic targets. The promising clinical applications of miRNAs, however, necessitate methods for accurate and reproducible quantification of the overall miRNA expression.

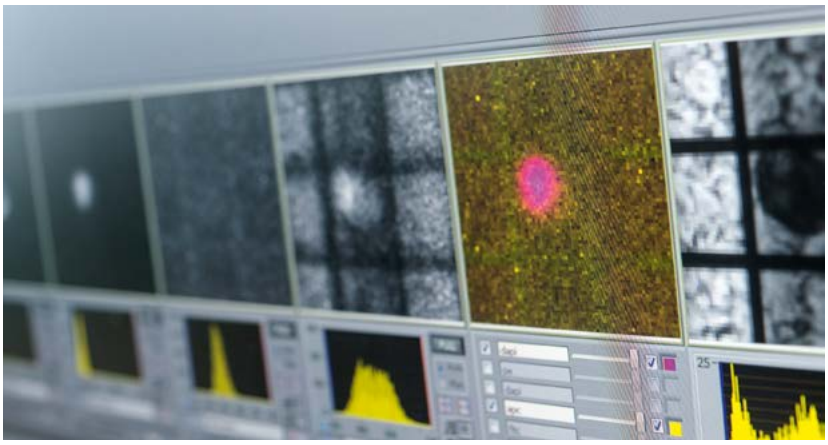
Researchers of the Regensburg-based Fraunhofer ITEM Division of Personalized Tumor Therapy have conducted a study to evaluate 19 different protocol variants with regard to their performance and quality in sequencing miRNAs from single cells of different cell lines. Using the protocol with the best performance, the miRNA profile of individual circulating tumor cells from patients with small-cell lung cancer enabled deduction of the tissue of origin and the disease. The data collected show that single-cell miRNA profiles have the potential to serve as biomarkers. The study was published in "Nature Communications" (Hücker et al., 2021: DOI 10.1038/s41467-021-24611-w).

CSF diagnostics of brain tumors based on single tumor cells

Primary and secondary tumors of the central nervous system (CNS) continue to be associated with an unfavorable prognosis. This is due on the one hand to the cellular heterogeneity and on the other hand to a genetic adaptation and selection of aggressive cell clones under therapy. An additional handicap is that tissue biopsies pose considerable risks for patients because of the tumor location in the CNS, making it difficult to perform molecular characterization at short intervals in the course of the disease.

Scientists of the Fraunhofer ITEM Division of Personalized Tumor Therapy, therefore, are collaborating with the study group on primary and secondary malignant brain tumors in adults of the Bavarian Cancer Research Center (BZKF) to develop technologies for minimally invasive, longitudinal, molecular genetic characterization of such cancers. For this purpose, they analyze cerebrospinal fluid (CSF) collected from patients by means of lumbar puncture in the sense of a liquid biopsy, to detect small numbers of tumor cells and evaluate other relevant biomarkers. The aims of this project are, firstly, to define pre-analytical standards for biomarker studies with CSF and, secondly, to develop molecular genetic tests based on panel sequencing, i.e. sequencing of a set of clinically relevant genes. It is intended to use these tests initially in clinical trials and, in the long term, for predictive diagnostics of CNS tumors.

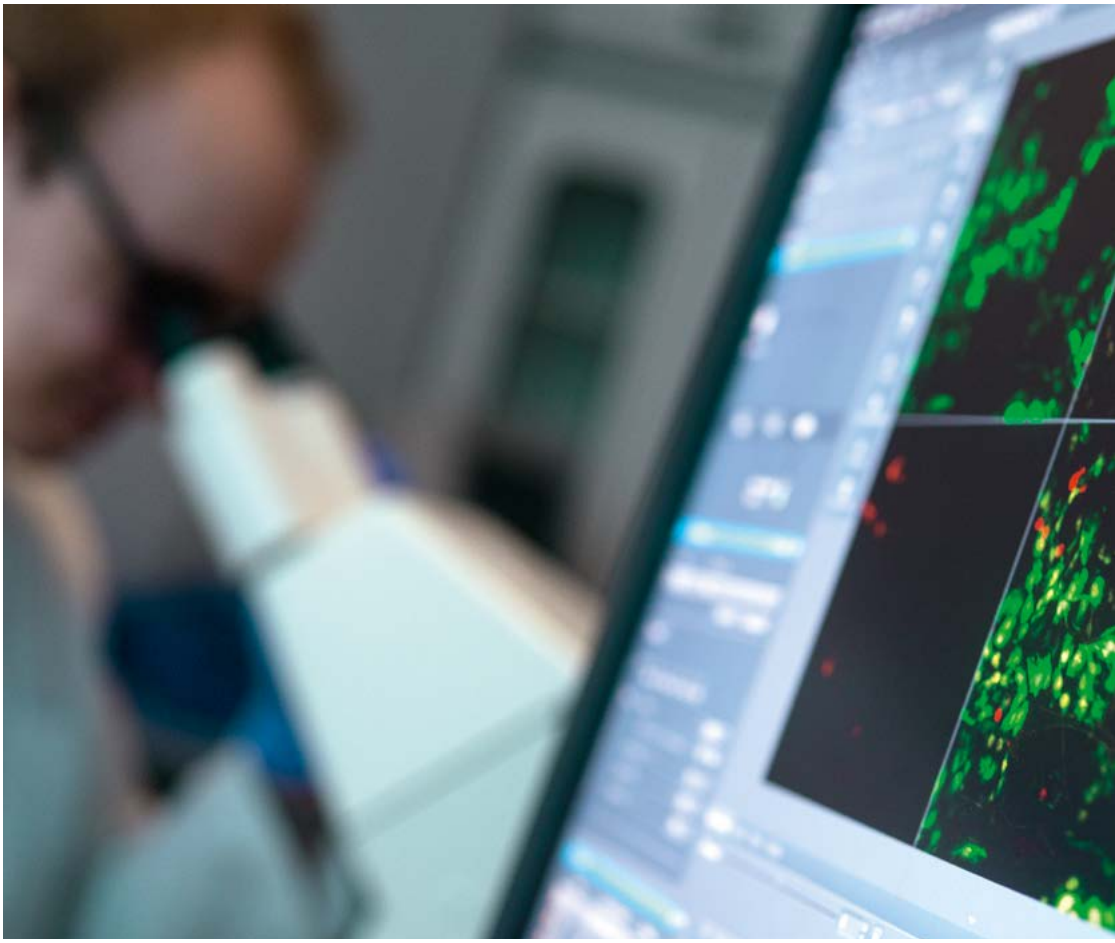
The miRNA profile of individual circulating tumor cells from patients with small-cell lung cancer allows researchers to deduce the tissue of origin and the disease.



The semiautomated DEPArray™ technology enables molecular analysis of single cells.

Immunology

Early detection and individualized treatment of immunological diseases



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.

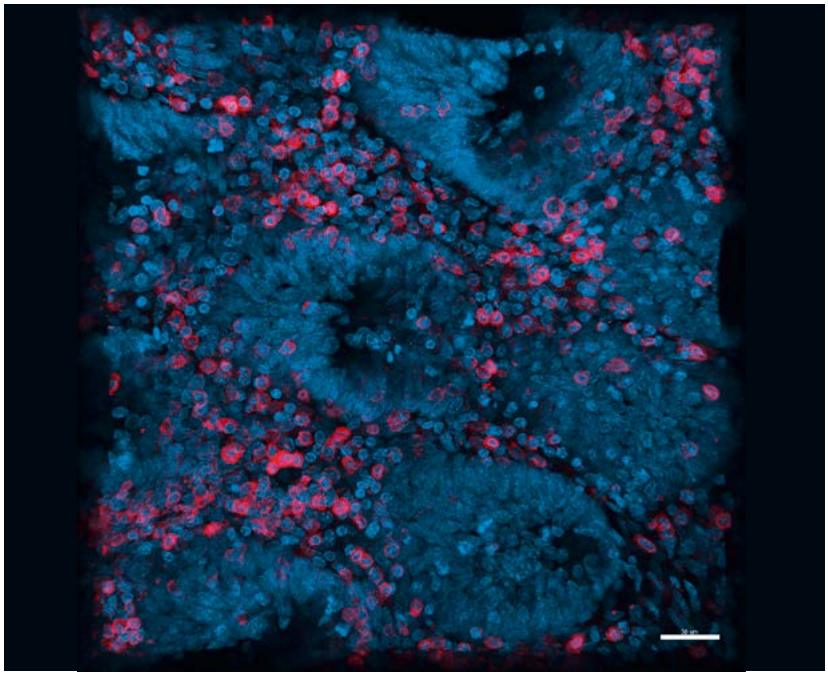
Fraunhofer ITEM has many years of expertise in immunotoxicology and immunopharmacology, centered on the development of biopharmaceuticals and advanced therapy medicinal products (ATMPs) in addition to mechanistic research. The focus here is on diseases of the lungs and airways – especially asthma, chronic obstructive pulmonary disease (COPD), fibrotic lung diseases, allergies and infections. For the investigation of immunomodulatory substances and ATMPs, Fraunhofer ITEM 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.

In view of the importance of immunological diseases, the Fraunhofer-Gesellschaft established the Cluster of Excellence Immune-Mediated Diseases – Fraunhofer CIMD – in 2017, with Fraunhofer ITEM as one of the core institutes.

Our highlights

ImmunAvatar: innovative intestinal immune model system for testing therapeutic options

Immune and inflammatory pathways play a central role in the pathogenesis of chronic inflammatory bowel (IBD) and liver diseases. So far, however, there are no persuasive approaches available that would allow the complex processes to be mapped in vitro. In the ImmunAvatar project, a consortium of researchers from Fraunhofer ITEM, Jena University Hospital, Charité Berlin and the University of Tübingen has taken on the challenge of developing improved immune models. The focus is on the development of a microfluidic multi-organ platform allowing interactions between the liver, fatty tissue and the intestine to be mimicked in vitro. The system will serve as an individualizable platform for personalized testing of different therapeutic options in the treatment of IBD and liver diseases.



Precision-cut intestinal slices, PCIS for short, enable the investigation of pharmacological modes of action and immunoregulatory intestinal networks. The picture shows a micrograph of an immunofluorescence-stained PCIS (nuclear staining of intestinal cells in blue, CD3-positive immune cells in red, 20× magnification).

The focus of the Fraunhofer ITEM researchers in the ImmunAvatar project is on mimicking IBD. For this purpose, among other materials, they use human intestinal tissue from bowel resections to prepare precision-cut intestinal slices, PCIS for short. These ultrathin tissue slices represent a complex, multicellular intestinal structure and are cultured ex vivo. The researchers have already successfully demonstrated that PCIS contain tissue-resident immune cells and respond to mitogens. The use of both healthy tissue and tissue from IBD patients enables the identification of disease-specific differences, which can also be modulated in the model. Thus, PCIS are a promising model to reduce animal testing and have potential for future use in studying pharmacological modes of action as well as immunoregulatory intestinal networks.

imSAVAR: development and assessment of innovative models for biopharmaceutical evaluation

In the treatment of diseases involving dysregulation of the immune system, such as cancer and autoimmune diseases, the focus is increasingly on therapies that modulate the immune system. To enable adequate testing of such immunomodulatory therapeutic approaches already in the non-clinical phase, suitable test systems have to be developed and adapted. This development, aimed at improving the transferability of preclinical safety and efficacy data to first-in-human studies, is at the focus of the "Immune Safety Avatar" platform, imSAVAR for short, funded by the Innovative Medicines Initiative (IMI).

As part of this EU consortium, Fraunhofer ITEM is collaborating primarily in two work packages: “Immuno-oncology models” and “Innovative models for safety assessment of immuno-inflammatory disease therapeutics”.

Interleukin-2 (IL-2) as a treatment option for cancer but also for autoimmune diseases has been selected for a first case study. IL-2 therapy had long been considered a promising treatment. Because of its massive side effects seen in clinical use, however, its usage has been drastically reduced. Due to the lack of nonclinical models accurately reflecting the individual interactions of the human immune system in the pathogenic state, adverse effects such as skin rashes could not be displayed in the nonclinical phase at that time. To enable better assessment of the safety also of future drugs, Fraunhofer ITEM researchers are developing innovative model systems for assessing immunomodulatory therapeutics. Immune-related adverse outcome pathways (irAOPs) provide the basis for combining individual clinical observations into an overall picture. The irAOPs allow the identification of possible key cellular and molecular events and the derivation of potential markers suggesting possible adverse effects.

Innovative model systems are being developed in the imSAVAR project.

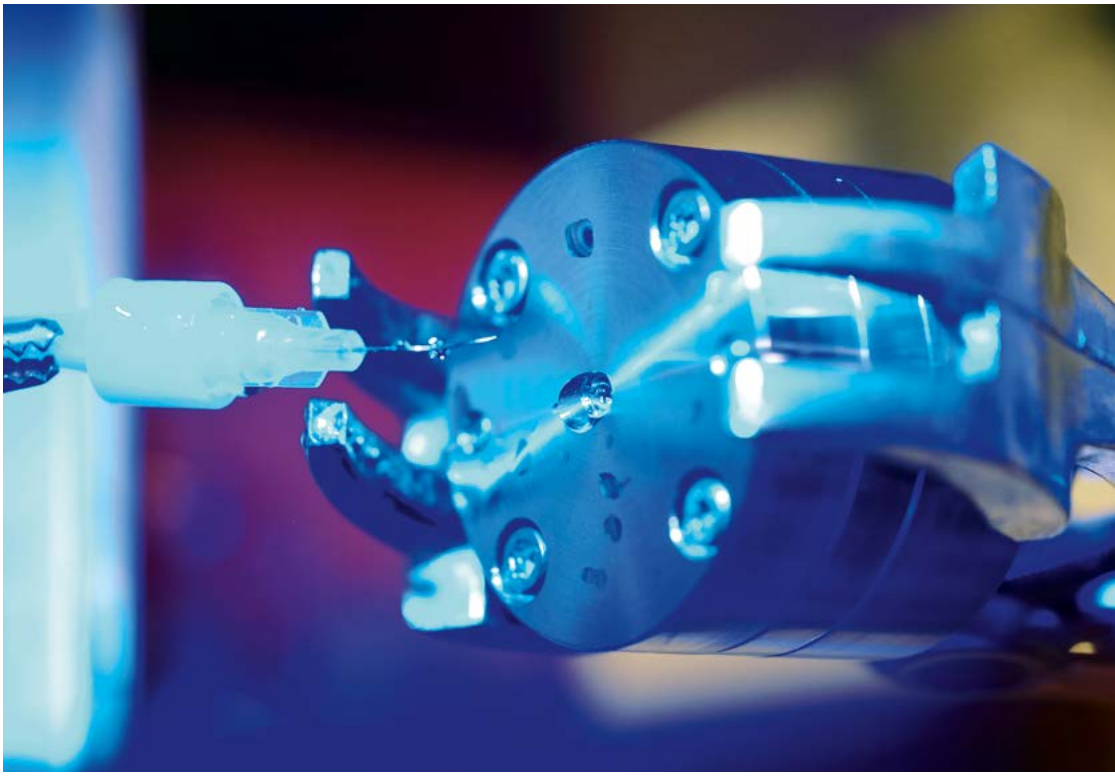
Discovery of a biomarker signature for an adaptive immune response

Every person is unique – also in their immunological response to a drug or chemical. To date, there is no artificial immune system available that can mimic human immune responses in vitro – outside of a living organism. The biotechnological hurdles to this are high: the tissue structure is very complex and dense and the variety of possible biological immune responses too large. In addition, there is huge variability between individuals. The aim of the MyCellFight project is to develop a fully automated immune chip able to predict the specific immune responses of individuals. Seven Fraunhofer institutes (IGB, IMW, IOSB, IPA, ITEM, IWS and IZI) are collaborating in this project. Meanwhile, the research team has successfully accomplished a decisive step: the discovery of a biomarker signature for an adaptive immune response in T lymphocytes. This was achieved by combining the expertise of Fraunhofer ITEM in in-vitro modeling with that of Fraunhofer IZI in next-generation sequencing and bioinformatics. By meta-analysis of publicly available datasets, the biomarker signature was postulated as time-resolved gene expression pattern across different T-cell populations. The signature was subsequently matched with independent RNA sequencing data for verification. Further transcriptome-wide sequencing (next-generation sequencing) is currently in progress and it is expected that in the future it will be possible to better characterize an adaptive immune response in terms of donor and antigen diversity. This sets the stage for the next generation of efficacy and safety research, combined with functional genomics, as well as for animal-free biomedical research and development at Fraunhofer.

In the MyCellFight project, researchers are developing an automated immune chip. Six separate cell chambers are supplied with nutrient medium by the so-called pump chips (left and right) via small tubes.

Medical device development

Development of new technologies for use in biomedical engineering

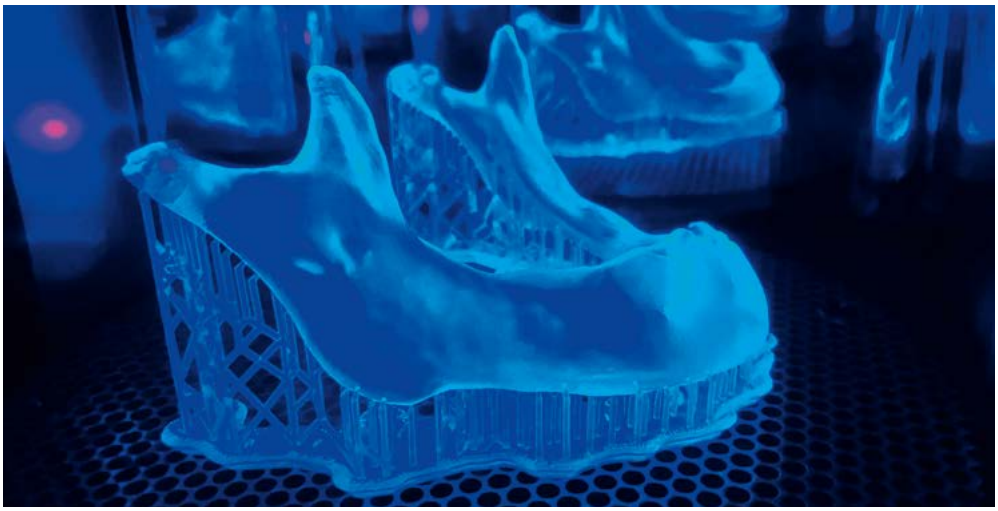


The development of innovative inhalation technologies has always been a priority at Fraunhofer ITEM. The current focus of research is on the development of novel technologies for administration of therapeutic aerosols towards smart drug/device combination products. In addition, Fraunhofer ITEM researchers explore the field of additive manufacturing of individualized implants, for example from medical-grade silicone rubber. In order to allow the long-term durability of such implants to be evaluated, they develop novel test methods tailored to specific requirements. Besides testing of the osseointegration of orthopedic implants, this includes the testing of active implants in particular, such as evaluation of the long-term performance of neural implants. Another research topic are in-vitro and in-vivo systems for toxicity and biocompatibility testing as well as test systems for functional implants, including ones with anti-infective or anti-fibrotic effects.

For the assessment of medical device safety, the researchers use 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.

For in-vitro diagnostics Fraunhofer ITEM is further expanding its existing expertise in the fields of single-cell analysis and liquid biopsy. For example, the researchers aim to gain additional information by separating the RNA and DNA analytes from single cells isolated from the valuable clinical samples and then want to use this information to derive new therapeutic strategies. The combination of multi-omics (metabolome, proteome, transcriptome, genome) and functional data creates novel tailored analysis platforms for this purpose.

Our highlights



Patient-specific implants and respiratory systems as well as individualized pharmaceutical production are at the focus of research and innovation transfer facilitated by the High-Performance Center Medical and Pharmaceutical Engineering.

Platform for research and the transfer of innovations into patient care

As the medical device market grows, so does the demand for quick and professional translation of ideas into practical applications. Therefore, a platform for research and transfer of innovations into patient care was set up with the launch of the High-Performance Center Medical and Pharmaceutical Engineering in March 2021. The focus is on personalized medicine – in particular on personalized implants and respiratory systems as well as individualized drug manufacturing.

The combined expertise of the institutes Fraunhofer ITEM in Hannover, Fraunhofer IST in Braunschweig and the Fraunhofer Research Institution IMTE in Lübeck is complemented by several companies as well as by various local research partners such as the Hannover Medical School, the Leibniz University Hannover, the Lower Saxony Centre for Biomedical Engineering, Implant Research and Development, TU Braunschweig with its Center for Pharmaceutical Process Engineering (PVZ), and the BioMedTec Science Campus in Lübeck with the University of Lübeck, TH Lübeck and the University Medical Center Schleswig-Holstein.

The High-Performance Center Medical and Pharmaceutical Engineering has put the future-oriented field of healthcare at its core. Its service portfolio includes scientific consultancy and development in the fields of neuro- and inhalation technology as well as pharmaceutical process engineering and imaging, complemented by additive manufacturing in medicine, drug formulation and aerosol technology. The partners collaborate in a joint transfer infrastructure to serve as a central entry point for industry and research partners, thus supporting and accelerating the transfer of healthcare innovations for the benefit of all.

RealWorld4Clinic – safety assessment of an implant for clinical research and cardiology

Symptoms of heart failure are often attributed to advancing age and are thus not taken seriously – but heart failure is a serious, life-threatening condition. A particularly high mortality risk is associated with this condition

in conjunction with diabetes: between 25 and 50 percent of these patients die within the following three to five years.

The development of healthcare solutions for people with heart failure is thus of pivotal importance. Only one in ten candidate drugs tested in phase-I clinical trials reach market maturity, at extremely high costs and after a lengthy trial period (up to 15 years). Approved drugs, however, often reveal a lower efficacy in daily healthcare routine than during the clinical trials, a phenomenon referred to as "efficacy-to-effectiveness gap." The AI-powered exploitation of real-world data – data collected in real-life clinical practice – is aimed at making a significant impact on the real-world effectiveness of treatments for heart failure patients and at the same time leveraging savings in the amount of billions of euros.

The RealWorld4Clinic project consortium comprises different European partners from commercial and academic research institutions and university-based maximum-care hospitals. It has been established to develop a medical multi-sensor system (MySentinel) that will enable high-quality collection of real-life cardiorespiratory health data. The class 3 medical device is implanted subcutaneously near the heart and lungs to measure a range of cardiorespiratory parameters. The recorded biomarkers allow conclusions to be drawn about the safety, tolerability and efficacy of an active ingredient under everyday conditions. Another aim is that cardiologists receive data suggesting an aggravation of heart failure at an early stage. In this way, they could gain up to 30 days to initiate interventions that can prevent escalation up to acute hospitalization.

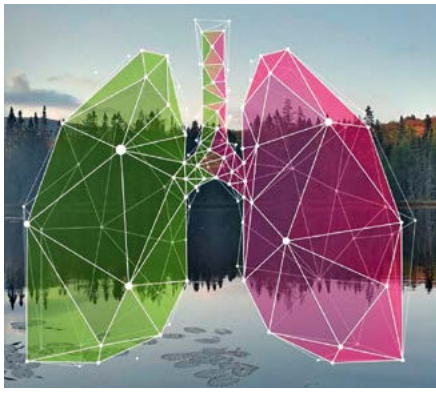
At Fraunhofer ITEM, scientists of the Division of Translational Biomedical Engineering collaborated with colleagues from several other departments of the institute, with external service providers and with the manufacturer of this device to perform assessment and biocompatibility testing for the intended use and position, as required for regulatory approval, within the ISO 13485-certified quality management system. Beyond the mere regulatory requirements of ISO 10933, the researchers performed further studies in a multi-endpoint process to collect additional data on the safety of the active implant when applied in humans, as well as to reduce the manufacturer's commercial risk. Further on in this collaboration, first clinical trials for functionality testing of the implant are planned to be conducted.

REMEDIA: the European research project on the human exposome

Throughout our lives, we are exposed to a variety of factors, both internal and external, which are a function of our lifestyle, behavior and environment. The cumulative measure of all these environmental influences is referred to as "exposome". In the EU project REMEDIA, 15 institutions from 9 countries are working together to determine how and to what extent the exposome influences the severity and morbidity of chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF) throughout the course of these diseases. The partners anticipate to provide key elements for the development of tailored prevention and care programs.

REMEDIA's methodological approach is based on four steps: data integration, experimental work, computational analyses and dissemination of results. Together with the partners Fraunhofer ICT, Fraunhofer IZI-BB and KU Leuven (co-lead), Fraunhofer ITEM is leading a work package of this project. The main goal of this work package is the development and field testing of sensor devices, combining measurements of external exposomes like noise, air pollutants such as particulate matter, organic compounds, nitrogen oxides and ozone with health-related biomarkers in the exhaled air of patients indicating inflammatory processes in the lungs. Comparison of the data is to provide a better understanding of the acute impact of the exposome. The sensor development is almost finalized and the project team is now in the process of planning studies with volunteers.

For high-quality collection of real-life cardiorespiratory health data, Fraunhofer ITEM scientists and their project partners are developing a medical multi-sensor system that can be implanted subcutaneously. The aim is to achieve a substantial improvement in drug development and patient care through data collected in real-life clinical practice.



The European Human Exposome Network is the world's largest network studying the impact of environmental exposure on human health.

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 RNAs 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

Machine learning for pediatric intensive-care medicine

The initiators of the ELISE project, Dr. Thomas Jack (Hannover Medical School) and Prof. Lena Wiese (Fraunhofer ITEM), received the Lower Saxony Health Prize 2021. This award promotes creative ideas and projects that are implemented exemplarily in the fields of disease prevention, health promotion and health care.

In pediatric intensive-care medicine, physicians are confronted with the problem that diseases are sometimes difficult to recognize and may also take a different course. Aimed at supporting the medical staff, the ELISE – "A Learning and Interoperable Smart Expert System for Paediatric Intensive Care Medicine" – research project was initiated. The existing patient data management system already stores important patient data such as recorded vital parameters, laboratory values, medication administration and diagnoses and makes this information available at any time for treatment and nursing. ELISE is able to interpret these values, to recognize pathological conditions and inform the medical staff in critical situations. The project was initiated by the Hannover Medical School (MHH) and Fraunhofer ITEM. The Fraunhofer team has developed a machine learning method for this purpose, with a focus on the development of incremental (i.e. stepwise) and proactive learning algorithms. An explanation component is planned to be included to help users understand the results provided by the algorithms. It is based on the comparative evaluation of a large number of machine learning methods, so that a decision will not be founded on just a single method. This comparative evaluation of different methods based on the available training data as well as flexible data pre-processing methods on the one hand are to identify the most suitable methods and on the other hand to prove the reproducibility, explainability and transparency of the algorithms. The researchers of the Hannover Medical School and of Fraunhofer ITEM have been awarded the Lower Saxony Health Prize 2021 for the ELISE project.

Does the current TTC approach adequately cover non-genotoxic tumorigenic substances?

The Threshold of Toxicological Concern (TTC) is a limit value for substances of unknown toxicity but known chemical structure. Genotoxic substances are currently regulated according to the TTC and are thus subject to a very low daily limit of 0.15 µg per person, because it is assumed that even tiny amounts of these substances can potentially cause mutations and thereby lead to tumor formation. But does this also hold true for carcinogenic substances that do not directly damage DNA? Or should such carcinogens be subject to other regulatory limits, e.g. according to the Cramer classes in the TTC concept? These questions were addressed in a recently completed Cefic LRI project. The researchers initially identified 137 non-genotoxic tumorigenic substances whose threshold limits

could be derived from studies in the Cancer Potency Database and from peer-reviewed publications.

To distinguish the most sensitive point of departure for risk assessment, they plotted the study NOAELs against the effective tumor dose (ETD_{10}) and the benchmark dose level ($BMDL_{10}$) calculated by model averaging using the Proast software. The comparative analysis of NOAEL/EDT_{10} and $BMDL_{10}$ values revealed that bioaccumulating substances and steroids were among the 5 percent most toxic compounds. Exclusion of these compounds led to comparable 5th percentiles for chronic NOAEL/$BMDL_{10}$ values, whereas the 5th percentile EDT_{10} value was about three times higher. A statistically significant difference, however, was not detected. These results were evaluated with regard to the current TTC, supporting the application of Cramer Class thresholds to non-genotoxic tumorigenic substances.

Detecting mutations relevant for treatment decisions in single cells

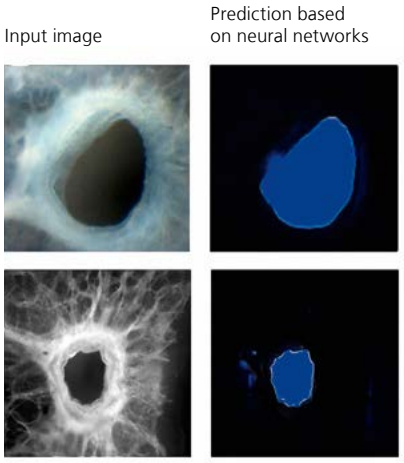
Detection of specific genetic mutations in cancer-associated genes is a prerequisite for the use of numerous targeted therapies. Therefore, knowing the mutation profile of a tumor is a valuable resource when it comes to making the right treatment decision. The FDA-approved MSK-IMPACT assay with its more than 400 cancer-associated genes offers a low-cost approach here. Disseminated and circulating tumor cells differ from the primary tumor. It is thus important for diagnosis and disease monitoring to also screen these cells for mutations and assess their impact. This is why Fraunhofer ITEM researchers in Regensburg, in collaboration with colleagues from the University of Regensburg and the company quantiom bioinformatics, have adapted the IMPACT approach for use with single cells.

In terms of bioinformatics, this was a major challenge, because the cells to be analyzed are so unique that there is no closely related cell population that could be used for corrections to sort out the expected high number of false-positive mutations. Using specific classifiers and combined database queries, the cooperation partners have nevertheless been able to achieve a reliability comparable to that reached with tissues – an important step forward towards getting the method approved.

Using machine learning for easier analysis of tissue slice images

For automated analysis of microscopic images, the Project Group Bioinformatics has developed a web service based on machine learning. The topic "Bronchoconstriction with Machine Learning" addresses the automatic detection (segmentation) of airways in images of lung tissue slices. By entering series of images, it is possible to analyze changes in airway size over a period of time and upon administration of different substances. This allows researchers to study the features of asthma and the efficacy of drugs. Different neural networks have been implemented and evaluated for these automated analyses. With the aim of optimizing the use and significantly speeding up and simplifying existing workflows, a web application has been developed that allows individual images, as well as entire image series, to be uploaded and airway lumens to be determined with the aid of the neural networks. The predictions can subsequently be corrected in the web application using a customized vector-based image processing technique. The developers have created the web application using state-of-the-art software engineering methods tailored to the problem and applying usability principles, and have evaluated it together with the end users.

Disseminated tumor cells differ from the primary tumor. It is therefore important to screen these disseminated single cells (as shown here on the screen) for mutations to allow the therapy to be adjusted accordingly.



Based on a microscopic image of an airway (input image, left column), neural networks allow prediction of the airway lumen (right column).

People in research

From top left to bottom right:
Nataša Stojanović Gužvić,
Otto Creutzenberg, Annika Wittig

“Understanding the molecular basis of human disease and cancer research in particular have fascinated me since my teenage years.”

Nataša Stojanović Gužvić Ph.D.

Project manager in the Fraunhofer ITEM Division of Personalized Tumor Therapy in Regensburg

"Understanding the molecular basis of human disease and cancer research in particular have fascinated me since my teenage years – working on these topics is my passion!" This is how Dr. Nataša Stojanović Gužvić describes her attitude towards her job as a molecular biologist. She studied molecular biology in Belgrade (Serbia) and, supported by scholarships, graduated and completed her doctorate at the Technical University of Munich. She had originally planned to move to vibrant Berlin thereafter, but the career opportunities in unhasty Regensburg were too tempting – a postdoc position in the Fraunhofer ITEM Division of Personalized Tumor Therapy led by Prof. Christoph Klein. She had first met him at a congress during her doctorate and became inspired by his research. In 2015, she joined the Fraunhofer ITEM Working Group on Cellular and Molecular Diagnostics in Regensburg as a postdoc. Four years later, she received the Regensburg Oncology Award for her work on the microfluidic enrichment, isolation and characterization of disseminated melanoma cells from lymph node samples.

After her parental leave, the researcher got the opportunity to establish a new disease model for personalized tumor therapy, namely organoid cultures, in collaboration with the Fraunhofer ITEM working groups on Preclinical Therapy Models and on High-Throughput Drug and Target Discovery. A fantastic project, she reckons. An organoid is an organ-specific microstructure created by growing patient cells using cell culture methods. The scientists in Regensburg generate organoids from disseminated, circulating tumor cells. "These organoids actually reflect the stage of tumor disease of each patient – they harbor the information about the current tumor activity and its vulnerabilities," explains Dr. Stojanović Gužvić. Disseminated tumor cells are genetically different from the primary tumor previously removed from the patient's body, which is why therapy ideally must be individually adapted to the disease stage to make it successful. Organoid cultures derived from patient samples can help identify the drugs that are effective against the relapse. This requires many work steps as well as high-throughput technology, so that using automated processing seemed to be a logical choice to improve these complex workflows.

Her passion for cancer research was thus joined by enthusiasm for automating laboratory processes, a technology that actually belongs to the engineering sciences. When it came to implementing automated sample processing, however, the Regensburg researchers were confronted with problems they were unable to solve with their expertise in the life sciences. At this point, the scientist benefited from the interdisciplinarity within the Fraunhofer world: She discussed her ideas, for example, with colleagues from the engineering-focused Fraunhofer Institute for Manufacturing Engineering and Automation IPA and together they found creative solutions.

"I am dreaming of an automated laboratory that in the future will make it possible to process a large number of samples in a short time, to quickly obtain standardized results and thus ultimately to directly help the patient in the clinic!" summarizes the project manager. She meanwhile enjoys living in Regensburg with her husband and two children, loves yoga as a way to balance her life and whenever possible spends time on the Adriatic coast in her native Montenegro.

Dr. Otto Creutzenberg

Head of the Fraunhofer ITEM Department of Inhalation Toxicology in Hannover

"It seemed exciting to me to be involved in important studies that really help to evaluate the hazards from substances and ultimately minimize the risk to human health," says Dr. Otto Creutzenberg. He is heading the Department of Inhalation Toxicology and has been involved in or even managed numerous toxicology studies. The results have been taken into account by the DFG Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area, also known as MAK Commission, in the derivation of limit values and thus support the safe handling of these substances at workplaces.

It was in 1985, directly after completion of his doctorate, that the chemist embarked upon his first project at the Fraunhofer institute in Hannover – at that time called ITA, today ITEM – in Prof. Muhle's working group: a study on the lung toxicity of toners. The aim of this large industrial project with a contract volume of eight million deutschmarks was to find out whether toner dust and particles pose a similar occupational health risk as was already known for diesel exhaust fumes and particulate matter generated in the mining industry.

Dr. Creutzenberg already took courses in toxicology while he was a student at the University of Münster and he did his doctorate in biochemistry, a subject that was more multifaceted than the chemical synthesis of substances. His interest has always been in living things rather than in plain material science. It was in the early 2000s that the toxicologist truly broke new ground with the Fraunhofer team. The industrial production of nanomaterials experienced a real boom at that time. After all, tiny amounts of these materials were sufficient to achieve the desired effects. In addition, they had special, new features and capabilities and could be used for a broad range of applications. It was still unknown, however, whether nanomaterials might pose a greater risk to humans and the environment than traditional micro-sized particulate matter. "They definitely have the potential to do so: because of their special characteristics, such as their tininess, their large specific surface area and their high reactivity in some cases – but also because of their diverse application areas and high production volumes," explains Dr. Creutzenberg.

Over the years, he has worked on a variety of projects investigating nanomaterials, for example carbon nanotubes, which due to their length and fiber-like structure are suspected to have a similar toxic potential as asbestos fibers. Another project aimed to verify whether the OECD guidelines for micro-scale particulate matter that were valid at the time could also be applied to nanoparticles, such as amorphous silica and zinc oxide particles, or whether amendments were required. Furthermore, together with other Fraunhofer ITEM working groups, he established models to enable testing of modified and well-characterized carbon nanoparticles (e.g. graphene) for toxic effects in the lungs and airways – from simple cell cultures to tissue culture models and validation in animal models.

Dr. Creutzenberg has always been intrigued by the Fraunhofer system: "As a researcher, I have much freedom in my work and it's exciting to find a way to make a project happen and get funding for it." The scientist has always found such a way, even if he had to travel halfway around the world to win customers from Japan. The experiences he was able to make on these occasions have become lasting impressions for him.

“It seemed exciting to me to be involved in important studies that help minimize the risk to human health.”

“The documentation of sensitive health data in clinical research is a critical puzzle piece for progress in medicine!”

Annika Wittig

Project manager and study coordinator in the Fraunhofer ITEM Department of Clinical Airway Research in Hannover

The well-being of the study participants is always top priority in clinical trials. In this context, not only health aspects play a role, but also the informed consent as well as the protection of data, especially of health data. What is called "Good Clinical Practice" (GCP) defines the rules and provides the basis for ensuring the best possible protection of study participants, both under ethical and scientific aspects. Working with sensitive health data requires great diligence and, at least to a certain degree, one must love to pay attention to details. When she was a child, the now 26-year-old Annika Wittig already had a particular liking for tidiness and enjoyed using paper and lists – certainly a good prerequisite for her current job, although today the trend is away from paper and towards digital processes and data storage.

"Fraunhofer ITEM as a renowned research institute attracted me a lot," says Annika Wittig. In 2014, the institute's scientific library offered an apprenticeship for a media and information services specialist. When her application was declined, she decided to study Medical Information Management at the Hannover University of Applied Sciences and Arts. In 2017, she applied again, this time for an internship in clinical research – a field of work which, in terms of documentation and information management, is probably one of the most demanding in the life sciences sector. And she was successful this time. Shortly thereafter, she continued at the institute as a student assistant and in 2019, after her graduation, was offered a permanent position in volunteer recruitment and documentation. Since 2020, Annika Wittig has been project manager, study coordinator and system administrator of the ClinBase™ documentation system in the Department of Clinical Airway Research. "Today, I am very happy that I followed my gut instincts at the time and tried again at Fraunhofer ITEM. My first professional steps were accompanied by many great colleagues and today I am actually in charge of a 40-member study team in an investigator-initiated trial," the Hannover native is proud to say.

A particular challenge and a personal goal of Annika Wittig is to advance the digitization of health data. Her ambition is to record and represent all data of the test persons and related processes in a digital format in the documentation system and ensure that this information can be retrieved, evaluated and verified at any time – or at least pave the way for this.

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 2021, 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
Research consortium on tumor diagnostics for individualized therapy (FORTiTher): Estimation of individual metastasis risk by analysis of disseminated tumor cells

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

Bayern Innovativ, funding program "Biomedical Engineering"
Project: KrEiBl
Method for blood-based cancer diagnosis at the single-cell level: molecular analysis of single cells

Deutsche Krebshilfe (German Cancer Aid) – Priority Program "Translational Oncology"
DETECT CTC: Detection and molecular characterization of circulating tumor cells and cell-free nucleic acids in advanced breast cancer in the context of tumor heterogeneity

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

Identification of tumor-specific peptides for adjuvant immunotherapy of melanoma patients without distant metastasis. Project no. 320058447

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

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) action plan for individualized medicine, funding area "Innovations for individualized medicine"
Collaborative project: TurbiCAR
UniCAR-based treatment of CD123-positive lymphoblastic leukemia – subproject "Production of the anti-CD123 target module"

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 16GW0333

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 FlexMax: flexible active sensor matrix for medical applications
Use of sensor arrays in two different biomedical engineering systems: sub-project "Sensorgesteuerte Atmungsüberwachung, Atmungstriggerung und Inhalation bei Frühgeborenen" (sensor-controlled breath monitoring, breath triggering, and inhalation in preterm infants)

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

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 "NanoCare4.0 – 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 (DGZ)
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 Ministry of Health
ELISE – Ein Lernendes und Interoperables, Smartes Expertensystem für die pädiatrische Intensivmedizin (a learning and interoperable, smart expert system for pediatric intensive-care medicine)

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

Literature study on the influence of electric, magnetic and electromagnetic fields on oxidative processes in humans and in animal and laboratory studies. Z4/AG-R-08313/3619S82464

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

Systematic review on the influence of electric, magnetic and electromagnetic fields on fertility in humans and in animal and laboratory studies. R&D project 3620S82475

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 Task-force)
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 (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 (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): EU-ToxRisk
An Integrated European 'Flagship' Programme Driving Mechanism-based Toxicity Testing and Risk Assessment for the 21st century

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 (SANTE): MONO4ERA
Feasibility study of an active-substance-based review system ('Monographs') and other potential alternatives for the environmental risk assessment of veterinary medicinal products. European Commission, Directorate-General for Health and Food Safety (SANTE), Tender No: SANTE/2020/OP/0001

EU research cluster: ASPIS
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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

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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)

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International associate editor of the "European Heart Journal"

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Reviewer for international journals in genetic toxicology, nanomaterials and quartz (incl. "Regulatory Toxicology and Pharmacology")

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