Fraunhofer
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FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM

ANNUAL REPORT 2020

Precision work! Using a mechanically assisted micromanipulator, researchers from the Regensburg-based Fraunhofer ITEM Division of Personalized Tumor Therapy isolate disseminated cancer cells individually. By using molecular biological analyses of these cells, they aim to better understand the process of metastasis and thereby to enable the development of novel therapies – not only to make the fight against metastasis more effective, but to actually prevent metastasis formation right from the beginning.

FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM

PERFORMANCE AND RESULTS

ANNUAL REPORT 2020

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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.

FOREWORD

Dear Reader,

The year 2020 was shaped by the COVID-19 pandemic, especially by the tremendous efforts to cope with the pandemic. This has also impacted our research. We at Fraunhofer ITEM – as pioneers for sustainable health – have taken on this challenge with great commitment, creativity and perseverance. Our competence, capacity and ability to work have stayed intact during the pandemic. In particular, the consistently high motivation of all employees at all three locations – in Hannover, Braunschweig and Regensburg – has been a decisive factor of success and stability at Fraunhofer ITEM. I would like to take this opportunity, also on behalf of the complete management team, to sincerely thank all employees for their high commitment, even under difficult conditions, both in the institute's facilities and in their home offices.

"Fraunhofer vs. Corona" is the motto governing many of our projects. What is an appropriate method to characterize the exposure to infectious aerosols in different environments? What is the best way to accompany and accelerate the development of a vaccine or an antiviral drug up to proof of concept? How can ventilators be manufactured using a 3D printer? Our institute has been working on the fundamental principles of these pivotal research questions for years, if not decades, and we are now applying models and procedures we have developed to coronavirus research. For example, our researchers have developed an approach for bioprocess development and first GMP manufacturing of a passive vaccine against SARS-CoV-2 for use in clinical trials. They are collaborating in drug repurposing projects aimed at quickly identifying drugs against COVID-19. They are developing complex in-vitro models and test systems that can also be used for other medical conditions, as well as new ventilators and innovative technologies for air purification. However, despite the pandemic, we have also continued to develop other areas of research. By establishing the Attract Group for Bioinformatics, we are enhancing the use of modern bioinformatics methods in the medical field. Major advances have also been achieved in Regensburg: researchers of our Division of Personalized Tumor Therapy have found crucial clues to factors that promote metastatic outgrowth of disseminated cancer cells.

Highly dynamic project lists, a lot of time pressure, tension, and a very strong spirit of research were the hallmarks of our activities in the year 2020. To ensure that the institute is well positioned for the future as well, we have continued our change and strategy process. A top-level external team of executives from academia and industry audited our strategy. The auditors were "impressed with the institute's capabilities." In their opinion, the institute can be proud of its scientific excellence, including its publications. And they made some very valuable recommendations. In 2021, we will continue our strategy development together with Prof. Thomas Thum – joining the institute's management team – in a continuous, structured and motivated manner. Already in the near future, we will expand the orientation of our institute: in addition to the institute's existing focus on airway research, cardiovascular research will henceforth play an important role at Fraunhofer ITEM.

I would like to take this opportunity to thank our partners from industry, academia and government for their unwavering confidence in us during the crisis and look forward to continuing our fruitful collaboration based on the values and goals we share.

Yours,

Norbert Krug
Institute Director

PROFILE OF THE INSTITUTE

Research for human health is the central topic at Fraunhofer ITEM – with a focus on the lungs and airways. The emphasis is on protecting health from potentially harmful substances, airborne substances in particular – be they gases, aerosols, particles, fibers, or nanomaterials – and also on investigating and developing novel diagnostic and therapeutic approaches in the fields of inflammatory and allergic respiratory conditions, both at the preclinical and clinical levels. Complementing these thematic focuses, Fraunhofer ITEM also engages in other subject areas, such as development and manufacturing of biopharmaceuticals, tumor therapy, and translational biomedical engineering.

Health protection

Environmental, occupational and consumer protection are essential elements of health protection. Fraunhofer ITEM supports industry and public authorities in the early identification and prevention of health hazards from new products and processes. In this context, Fraunhofer ITEM scientists investigate novel products and processes whose potential health hazards are as yet unknown, such as different nanomaterials. They evaluate the human exposure situation and develop suggestions on how to reduce or eliminate the potential hazards. For the experimental part of risk assessment, Fraunhofer ITEM has at its disposal the necessary know-how and toxicological test methods. A focus is on inhalation toxicology. For the required tests, we can generate complex atmospheres and test aerosols at laboratory scale and reproduce the exposure scenario for in-vitro or in-vivo studies. Special computerized mathematical exposure models are also developed and used for this purpose.

Reliable 21st-century assessment of chemical safety

Integrated approaches to testing and assessment of chemicals are becoming more and more important in toxicology. This means that the scientists are breaking new paths towards mechanism-based toxicological assessment. Human-relevant in-vitro and in-silico methods play a crucial role in this context. In-silico approaches today are no longer limited to deriving the toxicity of a substance from its structure, but also include toxicity and effect profiles.

Preclinical testing of candidate drugs

As researchers in translational medicine, working at the interface of basic research, clinical application, and drug regulatory requirements, we aim to translate scientific results into benefits for patients. The institute offers a broad range of drug efficacy and safety studies, for which we use diverse in-vitro test systems and models of inflammation, asthma, lung infection, and pulmonary fibrosis. In particular the use of human tissue in in-vitro and ex-vivo test systems allows us to obtain human data at an early stage already – data of pivotal importance above all in the testing of biopharmaceuticals.

Throughout the entire research and development process, Fraunhofer ITEM scientists keep an eye on the ethical principle of the "3 Rs" – they are well aware of their great responsibility for the well-being of the laboratory animals. The three Rs stand for Replacement – the use of alternative methods that avoid or replace the use of animals –, Reduction – strategies that will result in fewer animals being used – and Refinement – modification of husbandry or experimental procedures to minimize pain and distress. Research at Fraunhofer ITEM is geared to using less animals to answer research questions, to consistently improving research methods, and to replacing animal experiments by alternative methods whenever possible. Fraunhofer ITEM scientists, therefore, participate in different projects aimed at developing non-animal methods – in vitro, ex vivo, and in silico – and at validating these as test systems for drug safety assessment and registration.

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Clinical trials for efficacy and tolerability testing of novel drugs

Efficacy and tolerability testing of novel drugs in humans is the critical step in medical translational research. Fraunhofer ITEM performs clinical trials to this end – in particular for the therapeutic areas allergy, asthma, COPD, and pulmonary fibrosis, but also atopic dermatitis and inflammatory diseases. The focus is on proof-of-concept studies, conducted by highly qualified physicians in compliance with GCP guidelines. The Clinical Research Center Hannover (CRC Hannover) with its state-of-the-art infrastructure offers optimal conditions for performing this step.

With the Fraunhofer Challenge Chambers, special facilities for controlled challenges are available. The efficacy of novel medications to treat allergies, asthma, or airway inflammation can be tested here under controlled conditions. By setting up a sleep laboratory, Fraunhofer ITEM has extended its diagnostic possibilities in clinical research.

Biopharmaceutical manufacturing from cell line to investigational medicinal product

In the institute's facilities in Braunschweig, Fraunhofer ITEM scientists develop manufacturing processes for novel biopharmaceutical agents – simple proteins, antibodies, and complex viruses such as bacteriophages. They cover the whole process chain from recombinant production cell lines, master and working cell banks to bioprocess development and scale-up, manufacturing of pilot batches of the novel agents, and sterile fill and finish of investigational medicinal products in the form of infusion solutions or in vials or ampoules – in compliance with GMP guidelines.

Bringing medical devices from the laboratory into clinical trials

In the field of translational biomedical engineering, we aim to bring medical devices from the lab into phase I of clinical development and to support clients in particular with the implementation of the European Medical Device Regulation (MDR). The High-Performance Center Translational Biomedical Engineering is aimed at making the translation process still easier and more efficient. In this High-Performance Center, Fraunhofer ITEM is collaborating with the Lower Saxony Center for Biomedical Engineering, Implant Research and Development (NIFE).

Personalized tumor diagnosis

The focus of the Fraunhofer ITEM Division of Personalized Tumor Therapy is on the development of diagnostic tests and innovative models to enable detection of disseminated cancer cells early in the disease and prediction of the response to therapy of metastatic progenitor cells. The division closely collaborates with the Chair of Experimental Medicine and Therapy Research of the University of Regensburg.

Bioinformatics for better health and chemical safety

Processing large quantities of data is likely to remain a major challenge in the future, in the life sciences in particular. The individualization of medicine will lead to an increasing demand for evaluation of individual data sets, and in the regulatory area, both for drugs and chemicals, it will also become increasingly necessary to analyze large amounts of data. Furthermore, the continued development of novel methods, such as high-throughput technologies and omics analyses, is closely

1 The Clinical Research Center Hannover (CRC Hannover) offers researchers and physicians optimal conditions for conducting clinical trials – proof-of-concept studies in particular.
2 In the Braunschweig-based Division of Pharmaceutical Biotechnology, Fraunhofer ITEM scientists develop manufacturing processes for biopharmaceutical agents.
3 Personalized tumor therapy is the focus of research and development at Fraunhofer ITEM in Regensburg's Biopark.

linked to the availability of efficient bioinformatics methods. In fall 2019, the Project Group for Bioinformatics was set up at the institute. With its key expertise, its position is directly at the interface between research and the industrial application of newly developed methods for data analysis.

GXP – quality assurance according to international standards

Fraunhofer ITEM is committed to meeting high quality standards with the services and products offered and to ensuring maximum safety for study participants in clinical trials performed at the institute. The relevant legal regulations are strictly complied with and the regulatory requirements, in line with the state of the art in science and technology, are consistently taken into account. To guarantee that the work performed at Fraunhofer ITEM satisfies internationally accepted quality standards, the institute has implemented the GXP quality assurance systems. These include Good Laboratory Practice (GLP), Good Clinical Practice (GCP), and Good Manufacturing Practice (GMP). With their respective scopes of application, these quality assurance systems cover the translational approach in the institute's spectrum of activities. The central service unit "Quality Assurance" is responsible for putting into practice the relevant quality assurance programs.

Lighthouse projects

Our lighthouse projects are dedicated to topics that are of particular relevance for the health of individuals and society at large – topics that are, therefore, important to us.
www.item.fraunhofer.de/en/lighthouse-projects

Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD
Translation of innovative ideas and identified targets into individualized therapies for immune-mediated diseases.

German-Australian iCAIR® project
iCAIR® (Fraunhofer International Consortium for Anti-Infective Research) is a research cooperation for the development of anti-infective therapies.

EU-ToxRisk
An integrated European "flagship" program driving mechanism-based, animal-free toxicity testing and risk assessment for the 21st century.

EU project MDOT
Development of an open-innovation test bed to support small and medium-sized manufacturers of medical devices in the conformity assessment of their products.

Phage4Cure
Aimed at establishing bacteriophages as an approved drug.

What turns cells into killer cells?
Searching for approaches for novel diagnostics and personalized treatments against cancer.

High-Performance Center Medical and Pharmaceutical Engineering (previously Translational Biomedical Engineering)
Aiming to close the gap between basic research on medical devices and first clinical trials – with an emphasis on safety aspects.

TWENTY YEARS OF CLINICAL RESEARCH AT FRAUNHOFER ITEM

The year 2020 was a very special year for Fraunhofer ITEM – not only because of the corona pandemic, but also because it was the 20th anniversary of "Clinical Airway Research" at the institute. Exactly 20 years ago, Fraunhofer ITEM set up its own clinical research department in Hannover, with a special focus on inflammatory and allergic diseases of the lung. The aim was to advance translational research, i.e. to bring findings from applied and preclinical research into clinical trials – in a one-stop shop.

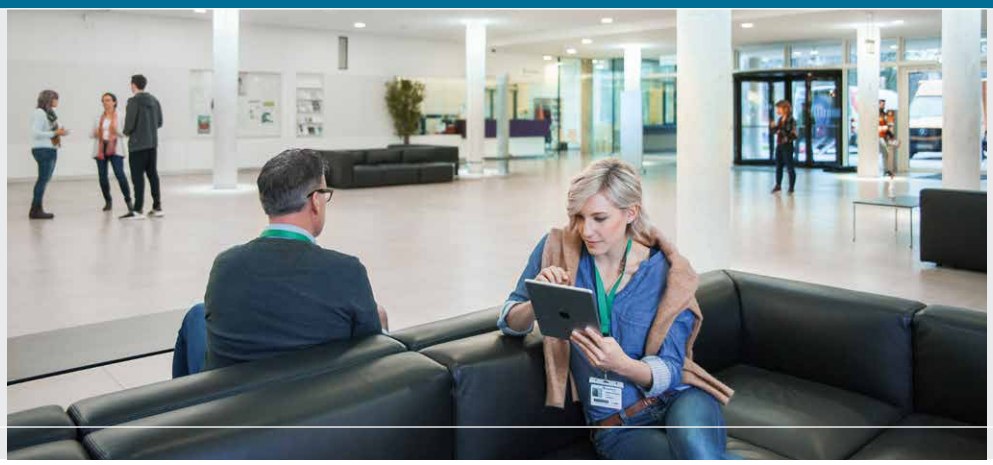
Already in 1981, when the institute was founded, the lung and the airways were the focus of research at the institute, although then rather under aspects of environmental and occupational toxicology. Using in-vitro and in-vivo methods, the ITEM researchers studied the effects of airborne substances that enter the body via the respiratory tract. "Initially, we wanted to extend our spectrum to allow us to investigate the effects of airborne substances on human health directly. One example is an experimental study with dust from an industrial area in eastern Germany. We were able to show in this study that metal-containing fine dusts from the environment induced airway inflammation in healthy subjects," says Prof. Jens Hohlfeld, Division Director of Airway Research. The pulmonologist played an active role in setting up this division 20 years ago. "Because allergies were on the rise, we were also interested in natural allergens such as pollen and their effects on human health – and in treatment options in particular. We, therefore, extended our research to include clinical trials with novel drugs for treating asthma and allergies." In the beginning, it was mainly the pollen challenge chamber, also called the "meadow in the lab", that caused an increase in clinical drug trials, especially of those targeting allergies. With their many

Veit Erpenbeck MD Ph.D., Therapeutic Area Leader Respiratory, F. Hoffmann-La Roche Ltd.

"The high-level scientific expertise and quality in performing clinical as well as preclinical studies has made Fraunhofer ITEM a reliable partner for industry. In particular, the mix of academic and industry-funded research is a recipe for success."

Dr. med. Cornelia Faulenbach, specialist in internal medicine and pulmonology, Department of Clinical Airway Research, Fraunhofer ITEM

"As an investigator, I can dedicate a lot of time to each study participant during our clinical trials. Due to the personal attention they get, the individual medical consultation and comprehensive examinations, study participants feel that they are in good hands here. That's why many of them return to participate in new studies!"



years of expertise, our aerosol technologists played a key role in setting up our pollen challenge chamber – and their know-how is also crucial to our current development work," says Prof. Hohlfeld.

While the division started in 2000 with just a handful of staff headed by Prof. Norbert Krug and Prof. Jens Hohlfeld, today a team of more than 50 physicians, scientists, project managers, nurses, physician assistants, documentalists, medical and biological laboratory assistants, and students take care of patients and healthy study participants.

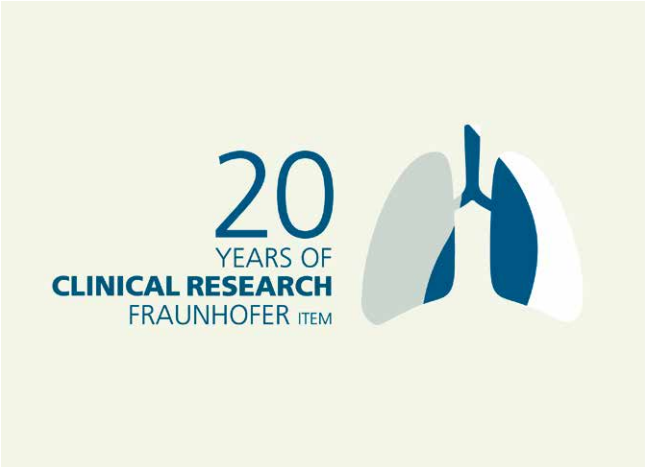
The buildings have also become larger over the years: After two expansions of the clinical facility in 2004 and 2006, a new building was eventually constructed to allow for further enhancement of the institute's clinical research and to place the focus on early-phase clinical development with an expanded range of therapeutic areas. The Clinical Research Center Hannover – CRC Hannover for short – was thus planned as a new facility and institute extension of Fraunhofer ITEM, designed for collaborative work with the neighboring partners Hannover Medical School and Helmholtz Centre for Infection Research under one roof. The new building was inaugurated with an opening ceremony in the fall of 2014. With the availability of a phase-I ward, overnight beds and interdisciplinary diagnostic equipment including MRI imaging, the focus of clinical research at Fraunhofer ITEM has shifted towards experimental medicine and early-phase clinical development. "Our broad range of challenge methods with different allergens, endotoxin, rhinovirus, ozone, dusts or hypoxia in combination with invasive and non-invasive diagnostics within a quality-assured and custom-designed infrastructure make us an important and highly demanded partner for clients from the pharmaceutical industry," says Prof. Hohlfeld. Meanwhile, the initial focus has broadened: from the lungs to nearby organ systems such as the skin and the immune system. And last

Dr. Diana Sims-Silbermann, Senior Trial Manager Early Development and Clinical Pharmacology, Janssen-Cilag GmbH

"As Senior Trial Manager for Early Development and Clinical Pharmacology trials for Janssen since 2007 I have had the opportunity to work with Fraunhofer ITEM on several phase I clinical trials in the recent past. The trials were performed with utmost professionalism and the quality of documentation was excellent. Site staff was responsive, attentive and performed the required protocol activities without deviation. The Principle Investigator exercised his oversight responsibility and was at all times available, cooperative and well-informed on the progress of the trial. I can highly recommend this site for any clinical trials within their therapeutic area of expertise."

but not least, the corona pandemic has shown the importance of research on infectious diseases. Following the appointment of the new institute director Prof. Thomas Thum, cardiac diseases will also play a major role in clinical and translational research at Fraunhofer ITEM in the future.

"We would have loved to celebrate our 20th anniversary with an international symposium, but unfortunately, like so many other events, this one also fell victim to the pandemic," regrets Prof. Hohlfeld. Hopefully, celebrations will be possible again in 2021, because the whole institute will then have the opportunity to celebrate – the 40th anniversary of Fraunhofer ITEM!



Dr. med. Philipp Badorrek, specialist in clinical pharmacology, Head of Department of Clinical Airway Research, Fraunhofer ITEM

"At Fraunhofer ITEM, we have excellent possibilities to conduct clinical research in an academic environment. This means that we are not limited to the common standard, but can develop new techniques and models in our studies, contribute our own ideas, and use the excellent infrastructure of the CRC Hannover. Here, we have access to an MRI scanner for research only and an excellently equipped biomarker laboratory, which we have used very successfully in many of our studies."

Silvia Monden, assistant medical technician for lung function measurements, Fraunhofer ITEM

"I have been part of the team from the beginning and still enjoy working at Fraunhofer ITEM in the Division of Airway Research. Even though my specialty is lung function measurement, my job involves a lot of different activities, which is very motivating! For example, I was able to help establish new methods for specific and non-specific inhalations as well as the hypoxia chamber and the sleep laboratory, establish three new generations of lung function measurement software and hardware, write the corresponding SOPs, and train many colleagues in these procedures. It is exciting to work in such a dynamic environment."

BIOINFORMATICS FOR BETTER HEALTH AND CHEMICAL SAFETY

Processing large quantities of data is a major challenge of our era, in the life sciences in particular. The individualization of medicine will lead to an increasing demand for individual data sets to be evaluated. In addition, bioinformatics is playing an increasingly important role in regulatory toxicology, for example for the processing of large quantities of data for computer-based modeling approaches to risk assessment. 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. In fall 2019, the Project Group for Bioinformatics was set up at Fraunhofer ITEM as a Fraunhofer Attract Group headed by Prof. Lena Wiese. This grant program offers outstanding external scientists the opportunity to further develop their ideas in a market-oriented environment at the interface between business and science and with a focus on actual applications. In this interview, Prof. Wiese explains the work and goals of the Attract Group "Bioinformatics" and how it complements the research and development activities at the institute and thus the institute's research portfolio.

Prof. Wiese, how did you learn about the "Fraunhofer Attract" grant program?

After several years of academic work at different universities in Hildesheim, Salzburg, Göttingen and now also at the Goethe University in Frankfurt/Main as well as my very theory-laden research at the National Institute of Informatics in Tokyo, I was looking for a new environment that would allow me to work closer to industry and, at the same time, to dare take a step towards more interdisciplinarity in research. In my search, I came across the Fraunhofer Attract program.

Setting up the partly Attract-funded research group at Fraunhofer ITEM gives me the opportunity to further develop my projects with a clear focus on their application – and thus to achieve real benefits for clients and patients through smart and reliable analysis of medical data. In particular, the funding provided by the Fraunhofer Attract program shows how important the topic of digitization in medicine is also for applied and industry-related research.

Human health is the central topic at Fraunhofer ITEM. What is the role of bioinformatics in health research?

The digital transformation in health research will change the way of treating diseases in the future. Reliable methods for medical data analysis are a fundamental prerequisite for this. Biomedical data can be used, for example, to identify health risks or adverse effects of drugs, or ideally to reduce side effects of drugs through new developments. Especially in this medical context, it is my ambition to develop user-friendly and intelligent data analysis systems that are interpretable.

You are currently setting up a working group at Fraunhofer ITEM. What is your focus here?

In very abstract terms, the aim of the working group is to apply modern informatics methods to real data collected at the institute for specific biomedical uses. The challenge is always to cope with what is known as "data wrangling" in a real-world environment. This means that before the actual analysis, we have to ensure that the collected data are usable – by correcting input errors, removing outlier data, or selecting relevant features. A major hurdle here is the lack of data format standards, making automated evaluation much more difficult and requiring comprehensive development of transformation modules in each case. These modules then allow the data available in a variety of input formats to be converted to a newly developed efficient data format. But also for the actual data analysis, it should be noted that usually there can be no one-size-fits-all solution: for each experimental problem, a suitable tailored solution must be developed, which pursues a different optimization goal in each case.

Hannover with its manifold biomedical research facilities offers an ideal environment for the Attract Group. Here, I have been able to network with the Center for Individualized Infection Medicine, the Hannover Medical School, the Lower Saxony Center for Biomedical Engineering, Implant Research and Development (NIFE), Leibniz University, and the University of Veterinary Medicine, and I have already submitted joint proposals together with colleagues from these institutions.

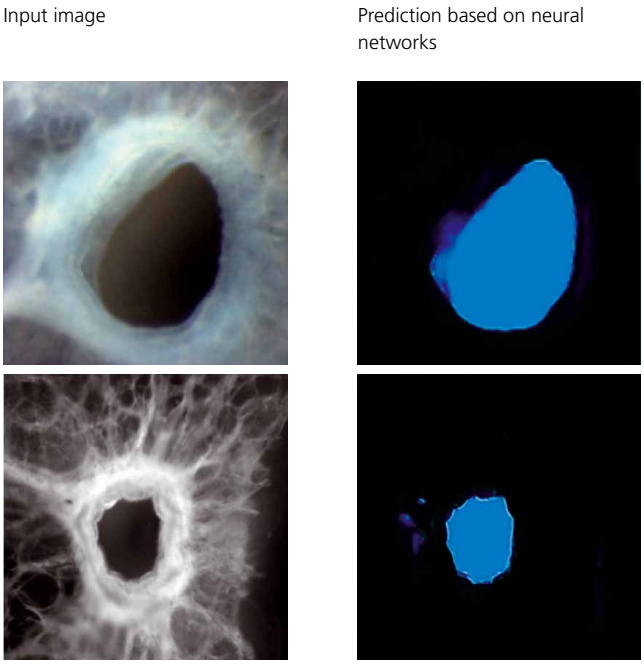
The aim of Fraunhofer Attract is, on the one hand, to promote the scientist heading the group and, on the other hand, to bring new know-how and thus new expertise to the Fraunhofer Institute through the scientist's activities. What ideas would you like to introduce and implement at Fraunhofer ITEM?

Many new methods and tools for data analysis have been developed in the past few years. Among these, there is also a broad range of open source software in particular, which can be used and adapted as required. In order for Fraunhofer ITEM to benefit from these latest developments, one of my team's goals is to adapt and further improve the available tools for specific medical applications. A major focus of the Attract Group in this regard is to offer comprehensive data preparation functions and a combination of several data analysis methods, and then to identify ideal configurations for analysis in a comparative evaluation.

Could you give some examples of practical application?

Individual configuration is enabled by the development of user-friendly interfaces. Therefore, we develop web-based dashboards – that is, a graphical user interface used to visualize the data and allowing the underlying analysis pipelines to be controlled. For example, we have been focusing on airway microscopy images, which our colleagues use for their preclinical research and which we analyze by means of neural networks. To this end, we develop specialized procedures, such as boundary refinement, which sharpen the airway boundaries against the surrounding tissue in the output image in order to improve the accuracy of analysis. Another area we are working on is analyses of multivariate time series from electronic patient data to monitor disease progression. For this purpose, we are developing an end-to-end analysis platform that integrates all processing steps, including data transformation, normalization, imputation, feature selection and dimensionality reduction, clustering, classification, explainability, and visualization. In addition, for gene expression analyses, we develop methods to compare gene expression profiles across different study datasets.

Furthermore, my group is involved in setting up a new hardware infrastructure at the institute, so that the analysis pipelines we develop can benefit from optimization for specific hardware, such as multi-core processors or graphics cards, through appropriate parallelization.



Airway recognition in microscopy data by means of neural networks. Based on a microscopic image of an airway (input image, left column), neural networks allow prediction of the airway lumen (right column).

Your work will also expand the range of R&D services offered by Fraunhofer ITEM.

That's right. Just as for the groups within the institute, we can also develop special procedures for external clients to enable efficient and validated analyses. A high level of automation and modularization in our software development also allows us to customize the data analysis process to meet specific customer requirements. With the help of specialized services, data analyses can be improved and preprocessed data can be made available to support new research findings.

What are the goals you are striving for with your work and what do you think your research will look like in the future?

On a technical level, it is very important to me that good software development techniques are also used for research software. For Fraunhofer ITEM, this means implementing good software engineering practices in the development of modern data analysis pipelines for Medical Data Science, for example, functionality tests and error handling as well as reproducibility of data preprocessing and data analysis. This is just as important as adhering to GXP quality standards. Unfortunately, this aspect has been neglected in much of the available research software so far, since research projects usually allow neither time nor money for that.

In terms of expertise, I aim to create and use synergy effects between my work as a university professor and as a Fraunhofer working group manager, thereby creating a bridge between basic and applied research. This also means that I want to continue to involve students in my research at Fraunhofer ITEM by supervising their research-oriented theses.

As a forward-looking vision for my research, I would like to enable a significant increase in the efficiency of medical data analysis by using cutting-edge technologies – even to the point of real-time data analysis. Such efficient real-time analysis would of course be highly attractive for use in routine clinical practice: in the long term, it will enable the application of analytical procedures on a mobile device directly at the patient's bedside.

What I am particularly keen to see is more women involved in shaping digitization – and not just in the medical field. With activities within Informatica Feminale and Girls' Day, I try to help young women discover their interest in computer science and the joy of programming.

CONTACT

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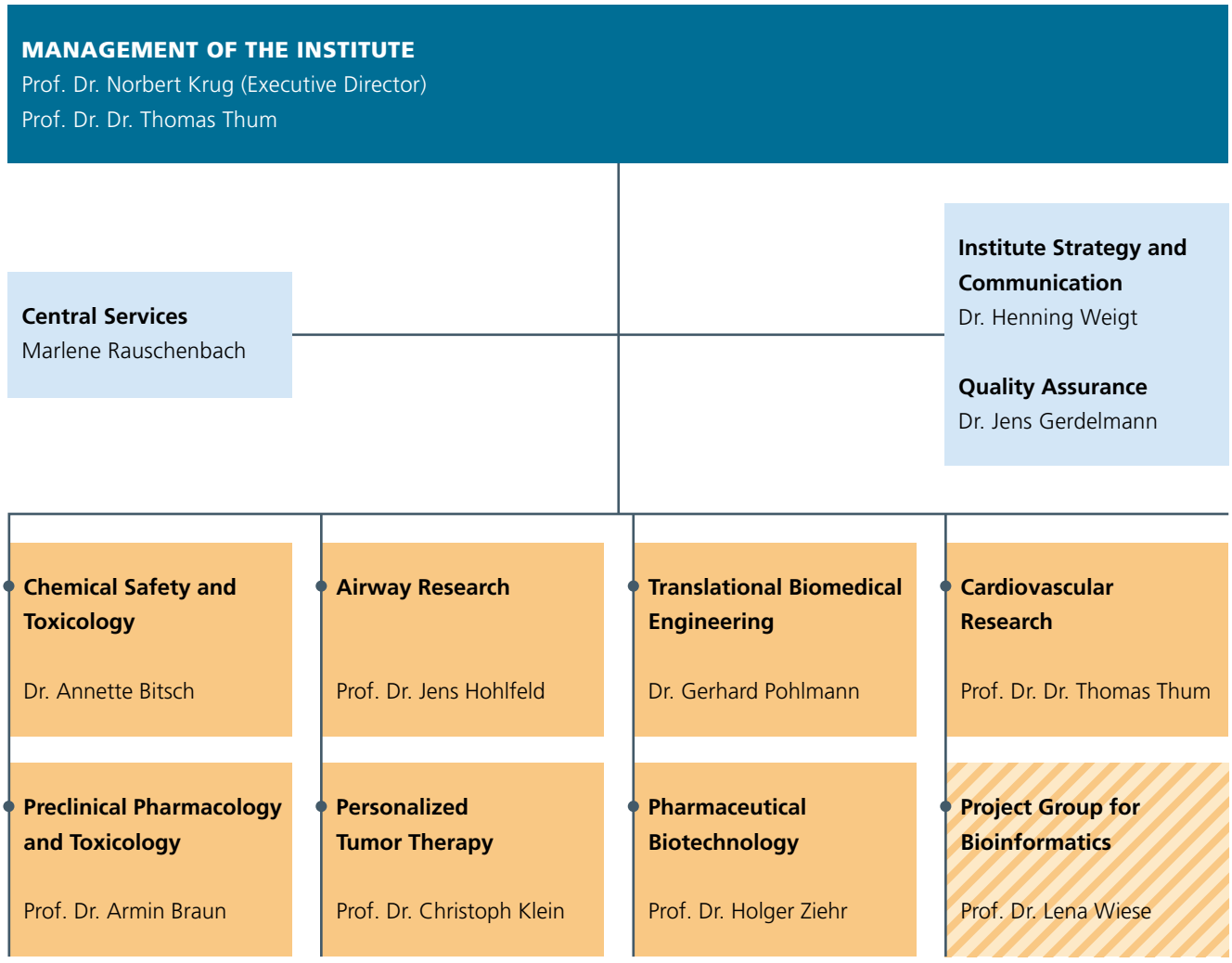
ORGANIZATIONAL STRUCTURE



As at January 2021.

The institute is managed by Prof. Norbert Krug as executive director. In January 2021, Prof. Thomas Thum joined Fraunhofer ITEM as co-director. Under the institute directors, Fraunhofer ITEM is organized in seven divisions, which have pooled their expertise in three business areas: Drug Development, Chemical Safety and Assessment, and Translational Biomedical Engineering. Special expertise that is relevant for all business areas comes from the Project Group for Bioinformatics. The Fraunhofer ITEM headquarters are in Hannover (Germany), whereas the institute's Division of Pharmaceutical Biotechnology has its facilities in Braunschweig on the "Science Campus Braunschweig-Süd" and the Division of Personalized Tumor Therapy is based in Regensburg's BioPark.

CONTACT PERSONS

The R&D services offered in the business areas Drug Development, Chemical Safety and Assessment, and Translational Biomedical Engineering are based on the expertise available in the institute's seven divisions and the Project Group for Bioinformatics. These divisions are supported by business developers and various departments including "Central Services", "Quality Assurance", "Library" and "Institute Strategy and Communication".

Below, please find our contacts for the different research topics and services offered. Please do not hesitate to contact these persons directly.

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Airway Research

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STAFF AND INSTITUTE BUDGET PERFORMANCE

At the end of 2020, Fraunhofer ITEM staff at all three sites – Hannover, Braunschweig and Regensburg – altogether amounted to 394 persons, with a female proportion of 61 percent. People from 16 countries work and do research together at Fraunhofer ITEM.

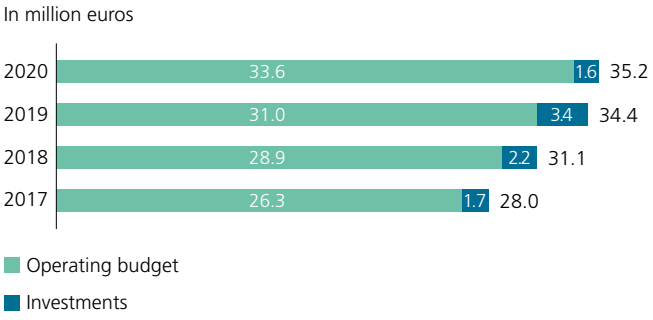
The institute's staff in 2019 included:
318 scientific, technical and administrative staff
22 Ph.D. students
38 students (bachelor's and master's programs)
12 apprentices
4 interns

In 2020, the institute's budget reached a level of approximately 33.6 million euros. Financing by acquired funding amounted to 69 percent. The share of industrial income in the institute's budget was 44 percent.

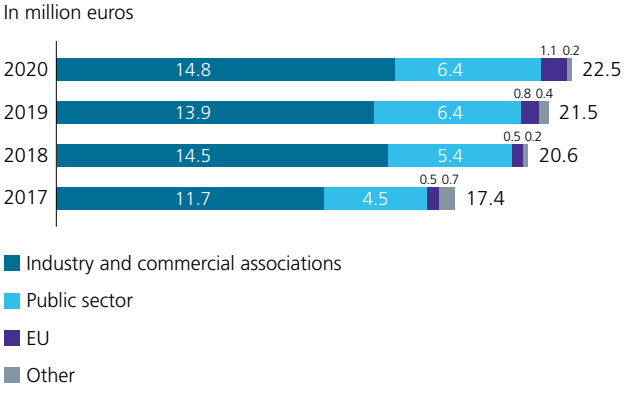
Investments of Fraunhofer ITEM amounted to approximately 1.6 million euros.

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.

We would like to take this opportunity to express our special thanks to the chairman of our board of trustees, Dr. Eckhard von Keutz, for his long-standing and dedicated commitment. Dr. von Keutz was Head of Translational Sciences of Bayer AG until the end of 2020. He became a member of the institute's board of trustees in July 2004 and has been its chairman since 2010. In all these years, he has supported the researchers and directors of Fraunhofer ITEM in matters of thematic orientation and structural and strategic change. Among the major milestones in the institute's development in which he was involved during his chairmanship were the following: He accompanied the establishment of our "Personalized Tumor Therapy" in Regensburg – from a funded project group to a Fraunhofer ITEM division included in the Fraunhofer financing model. Dr. von Keutz was involved in the strategic planning of the CRC Hannover, the unique study center for early-phase clinical trials and for patient-oriented translational medicine, where three strong partners do research under one roof: the Hannover Medical School, the Helmholtz Centre for Infection Research, and Fraunhofer ITEM. The establishment of an in-house clinical research division was a very special step in the Fraunhofer-Gesellschaft at the time, opening up a much broader research perspective to Fraunhofer ITEM and enabling new research services to be offered. Another milestone was the establishment of the Division of Translational Biomedical Engineering,

Dr. Eckhard von Keutz, chairman of the board of trustees, has served Fraunhofer ITEM with great dedication over many years.

a very future-oriented research area. Furthermore, Dr. von Keutz was a member of the nomination committee for the Fraunhofer ITEM co-director, eventually resulting in the successful appointment of Prof. Thomas Thum, and he chaired the external strategy audit in fall 2020.

Today, Fraunhofer ITEM is very well positioned to face the future as a pioneer for sustainable health – in accordance with its vision. Thank you very much indeed, Dr. von Keutz, for your great support!

As from July 2021, Prof. Dr. Paul-Georg Germann, Head of Global Non-clinical Safety at Merck KGaA, will be chairman of the board of trustees.

Members of the Fraunhofer ITEM board of trustees in 2020:

Chairman
Dr. Eckhard von Keutz
Head of Translational Sciences, Bayer AG

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

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

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, Mestag Therapeutics Ltd. (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 Division 614 – 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
Guest in the board of trustees, 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

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

“FRAUNHOFER VS. CORONA“

A new topic began to emerge at the turn of the year 2019/2020. It has since taken center stage in the public discourse and in the personal experience of individuals. The novel virus that the World Health Organization (WHO) calls “severe acute respiratory syndrome coronavirus type 2” (or SARS-CoV-2) has interfered with all aspects of public life. The WHO declared the outbreak of this virus a “public health emergency of international concern.” The COVID-19 pandemic is taking a toll on day-to-day life, on people’s health, on businesses, on the domestic economy and on global trade.

Working at the forefront of the fight against the pandemic under the motto “Fraunhofer vs. Corona”, Fraunhofer experts are supporting the efforts of industry and society to cope with the immediate effects and the consequences to come. As an institute with decades of experience in infection and airway research, drug development, biomedical engineering, and in the field of chemical risk assessment, Fraunhofer ITEM can make an important contribution to scientific progress in the fight against the new coronavirus.

www.item.fraunhofer.de/coronavirus-research

BEAT-COVID: advanced therapy strategies against the pandemic

The present SARS-CoV-2 pandemic with all its effects on society – both on health and the economy – highlights the urgency of developing new therapies for COVID-19 treatment. At the same time, it demonstrates the necessity to become well prepared for new virus infections we may be facing in the future. In the project BEAT-COVID, Fraunhofer researchers are developing independent novel therapy strategies and are building up platform technologies that will enable rapid and targeted development of new drugs against as yet unknown pathogens that may emerge. Based on their expertise in preclinical and clinical drug development, five Fraunhofer Institutes (IZI, ISC, IAP, IZM, and ITEM) and cooperating universities, coordinated by Fraunhofer ITEM, have addressed the following objectives: prevent the virus from entering host cells, combat the virus itself, and control the excessive immune response triggered by the virus.

redCMC: regulatory-technical shortcut for a passive vaccine against SARS-CoV-2

Before a new vaccine reaches the stage of clinical application, it has to go through defined development phases in line with regulatory and process-related technical requirements. Using a passive vaccine against SARS-CoV-2 as an example, Fraunhofer ITEM closely collaborated with its project partner Corat Therapeutics GmbH and Paul-Ehrlich-Institut to develop an approach aimed at drastically reducing the time required for bioprocess development and first GMP manufacturing of an investigational medicinal product for clinical trials – from previously more than 15 months to less than 6 months. The principle can generally be used for the development of new biopharmaceuticals, thereby accelerating their translation from bench to bedside. In future pandemics, new vaccines can thus be expected to be available faster.

Please refer also to the project report "Top-speed development of an antibody against SARS-CoV-2" on page 44.

InnoCoV: automation technologies in medical research

The COVID-19 pandemic once again has shown the tremendous challenges arising in the context of the development and subsequent production of specific vaccines. As a pioneer in applied research, the Fraunhofer-Gesellschaft is bringing together the expertise of 23 Fraunhofer Institutes to develop new development and production technologies for innovative cell and gene therapeutics, as well as vaccines, in the "Production for Intelligent Medicine" innovation cluster. The cluster is combining biological and medical know-how with expertise in automation technologies and the autonomous control of industrial processes. As part of the fight against the pandemic, Fraunhofer ITEM biotechnologists have designed a completely new production strategy for a coronavirus vaccine, which substantially shortens the process development time for the production of investigational medicinal products for clinical trials. In addition, Fraunhofer ITEM is bringing in its comprehensive know-how on the biology, production, and differentiation of stem cells and on lung macrophages. Based on this know-how, quality characteristics and risk profiles will be developed for these cell types and will then be used as a basis for automated production processes.

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

Fraunhofer ITEM in Regensburg is cooperating with the University of Regensburg and the company 2bind GmbH, aiming to identify drug candidates that prevent the replication of SARS-CoV-2. Packaging of the viral genome is an essential process in the viral life cycle, during which the nucleocapsid protein (N-protein) specifically binds to viral genomic RNA and organizes its packaging into viral particles. Specific RNA binding and dimerization domains of the N-protein are crucial for the packaging. The project partners want to develop a target- and cell-based compound screening to identify selective small molecules targeting the RNA binding and dimerization domains. The functional effects of these molecules on RNA binding, dimerization and packaging will be analyzed using biophysical methods and their impact on SARS-CoV-2 replication and infectivity will be investigated in cellular systems. This intertwined "screening pipeline" will enable rapid, targeted identification of novel active compounds that inhibit SARS-CoV-2 replication and have the potential to be further developed into novel therapeutics. The Bavarian Research Foundation is funding this project for a period of one year starting in December 2020.

iCAIR® makes use of synergies to develop new medications against SARS-CoV-2

Researchers of the international consortium iCAIR® are working on the development of novel anti-infective agents to treat or prevent clinically significant diseases of the respiratory tract caused by bacteria, fungi, and viruses. In May 2020, they started a project aimed at developing therapeutics to combat SARS-CoV-2. Because of the typical long drug development timelines, the approach of the iCAIR® consortium is based on drug repurposing – the use of drugs that have already been approved for other therapeutic purposes. To begin with, the researchers are screening substance libraries for suitable drug candidates that have a virostatic effect on SARS-CoV-2, which means they are able to inhibit replication of this virus inside cells. Efficacy and tolerability of the identified drug candidates will be evaluated in sophisticated cell-based infection models and human precision-cut lung slices (PCLS). The most promising drug candidates will eventually be developed further for inhaled administration.

DRECOR: development of new inhalation therapies by drug repurposing

To quickly identify drugs and develop therapies for COVID-19 treatment, the DRECOR project uses the drug repurposing approach. The following major goals are being addressed: First of all, the scientists want to identify suitable candidate molecules targeting the lungs and airways and formulate these for inhaled or systemic administration. For inhaled administration of these drugs, a prototype of a smart medical device for use in clinical trials will be created in addition.

For more information on this part of the project, please also refer to the report "Novel micro-nebulization system for pharmaceuticals" on page 62.

Furthermore, the team will set up complex in-vitro models and test systems that will also be available for use in other projects targeting different therapeutic areas. In the long run, DRECOR is aimed at establishing a multidisciplinary drug formulation and delivery network and process, so as to be better prepared for future pandemics. Several Fraunhofer Institutes (IME, IGB, ISC, EMFT, and ITEM) and the Fraunhofer Project Center for Drug Discovery and Delivery at The Hebrew University in Jerusalem (Israel) are collaborating in the DRECOR project.

RENACO: repurposing of nafamostat for COVID-19 treatment

In the RENACO project, scientists of Fraunhofer ITEM and the German Primate Center (DPZ) in Göttingen have joined forces to investigate, among other things, whether the anti-pancreatitis drug nafamostat provides protection against SARS-CoV-2 infection. To speed up the development of new medications against SARS-CoV-2, existing drugs that have already been approved for treatment of other conditions are tested for their efficacy against the new coronavirus. One of these drugs is nafamostat. It inhibits the enzyme TMPRSS2 that plays a crucial role for viral entry into the host's lung cells and has shown promising results in the first tests. The German Federal Ministry of Education and Research (BMBF) is funding this project with 1.6 million euros.

Immunovid-19: preventing SARS-CoV-2 from entering cells

One of the therapeutic targets in the context of SARS-CoV-2 infection is to prevent the virus from entering host cells. This is the development concept Fraunhofer ITEM and Helmholtz-Zentrum Dresden-Rossendorf as a partner are pursuing in the project Immunovid-19. The partners have joined forces to develop a therapeutic approach aimed at preventing the coronavirus from entering cells. The goal of the collaboration is to develop a recombinant CHO production cell line that can be used for the production of a fusion protein whose structure corresponds in part to the soluble domain of the human ACE2 protein. Given that SARS-CoV-2 uses ACE2 as a receptor for its entry into host cells, the purpose of the fusion protein is to prevent the virus from binding to and entering cells in a manner analogous to a neutralizing antibody.

SARS-CoV-2 infections can also affect the heart

SARS-CoV-2 infections not only cause stress on the lungs, but also massively affect the cardiovascular system. A research group led by Prof. Thomas Thum, director of Fraunhofer ITEM and of the Institute for Molecular and Translational Therapy Strategies at the Hannover Medical School (MHH), has detected micro-RNA biomarkers in seriously ill COVID-19 patients that have also been associated with inflammatory processes in heart diseases. In collaboration with the MHH Departments of Cardiology and Angiology and of Pneumology, the research team examined blood samples from COVID-19 patients who were treated and ventilated in intensive care. For comparison, the researchers also examined the blood of influenza patients with acute respiratory distress syndrome who also had to be ventilated, as well as blood samples from a healthy control group. The concentration of the microRNA markers in blood serum of COVID-19 patients was significantly higher than in healthy individuals. It also differed significantly from the values found in influenza patients. The researchers now want to find out whether the microRNA markers enable prediction of the course of disease. In addition, microRNAs could provide new therapeutic targets in the fight against COVID-19.

Corona-Access: a lung tissue-based SARS-CoV-2 infection model for drug research and testing in S2 labs

Research on SARS-CoV-2 and efficacy testing of candidate drugs against this virus using lung infection models with the active virus can be performed only in safety level 3 (S3) laboratories. Not all research institutions, however, have access to S3 laboratories, and working under S3 conditions is very challenging. In the project Corona-Access, non-infectious virus-like particles are used for a SARS-CoV-2 infection model, allowing work in this context to be performed at the lower safety level 2. For efficacy testing of drug candidates for COVID-19 treatment, the Fraunhofer ITEM scientists want to use tissue slices from human lung explants, also referred to as precision-cut lung slices (PCLS). These slices remain viable for several days in ex-vivo cultures and perfectly mimic the natural responses in the lung. This model will be used to test drug candidates and also to study risk factors for severe courses of COVID-19 in vulnerable patient groups.

Safe-AntiCorona: pharmacokinetics and safety of monoclonal antibodies against SARS-CoV-2

Virus-specific, neutralizing antibodies derived from blood plasma of recovered COVID-19 patients are able to inactivate SARS-CoV-2, representing a promising treatment option for COVID-19. Classically, such antibodies or convalescent plasma, i.e. plasma from the blood of recovered patients, are administered intravenously. Since these neutralizing antibodies must specifically reach the site of SARS-CoV-2 infection, i.e. the lungs, one aim of this project is to clarify whether inhaled administration of neutralizing antibodies is a way to increase their concentration in the lung. Fraunhofer ITEM scientists are using the isolated perfused rat lung (IPL) model to investigate the safety, bioavailability and kinetics of such a neutralizing antibody against SARS-CoV-2. This method represents an alternative ex-vivo organ model and offers the possibility to measure important lung function parameters (tidal volume, compliance, and resistance). Thus, acute adverse effects after antibody administration can be identified without using animal experiments.

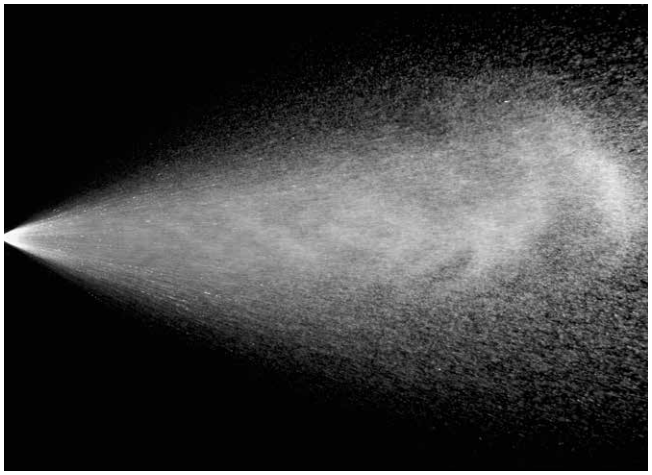
AVATOR – Anti-Virus-Aerosol: Testing, Operation, Reduction

Aerosols – tiny exhaled droplets which are smaller than 10 µm in diameter, remain airborne for a long time and may be loaded with viruses – play a major role in the transmission of SARS-CoV-2. In the project AVATOR (Anti-Virus-Aerosol: Testing, Operation, Reduction), scientists of the Fraunhofer Institutes IBP, EMI, ITWM, ICT, LBF, IAP, IMM, IFF, IPM, IGD, IFAM, IGB, and ITEM are, therefore, investigating how to monitor and reduce the risk of infection from aerosol-borne virus in indoor areas. In addition to simulation-based methods for air dispersion assessment, the project is aimed at developing air purification technologies involving both trapping and inactivation of the virus. Based on these data, the scientists will derive hygiene concepts for different applications, including means of transport such as airplanes or trains as well as production facilities and meeting rooms, but also classrooms and open-plan offices.

For further information, please refer to the corresponding project report on page 57.

CoClean-up: controlling the spread of SARS-CoV-2 by means of highly efficient indoor air disinfection

Aerosols exhaled by infected individuals are considered the main vector spreading the coronavirus SARS-CoV-2. In the project CoClean-up, Fraunhofer ITEM is assisting Fraunhofer IKTS in its development of a system for purification of the air extracted from enclosed indoor spaces. The system is based on electrochemical total oxidation, a technology allowing complete elimination of organic substance. No endotoxins or other substances resulting from incomplete degradation of airborne pollutants can thus get into the indoor air, in particular in ventilated or air-conditioned indoor areas. After successful development of a prototype, the scientists intend to rapidly pursue the market entry. It is intended to use this highly efficient indoor air disinfection technology also in the future to prevent viruses from spreading.



Give-a-Breath Challenge: non-invasive ventilator for COVID-19 patients

In the global call for ideas "Give-a-Breath Challenge", Munich Re and Fraunhofer started seeking concepts for emergency ventilation systems and related equipment in March 2020. The subchallenge for ventilators was won by two teams – one of which was the team SmartCPAP, consisting of the Fraunhofer Institutes IAPT and ITEM and the company AC Aircontrols GmbH. The team developed a non-invasive ventilator that can be produced inexpensively anywhere and used in a wide range of conditions. The device has some special features that make it particularly suitable for COVID-19 patients. For example, it assists patients very flexibly with breathing in and out spontaneously, thereby providing support for as long as possible without intubation. Intensive care beds can thus be kept free for even more serious cases.

For more information on this project, please refer to the report "Biomedical technology for fast local manufacturing of non-invasive ventilators" on page 63.

Filter4Flow: intelligent viral filter for SARS-CoV-2 patients

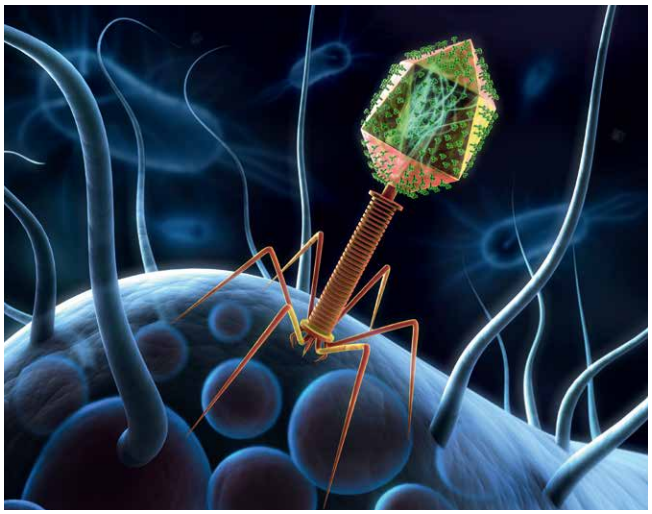
Patients experiencing a severe course of COVID-19 often require ventilation, some of them with a non-invasive method, but others in an intensive care unit. In either case, the patient's lung function and respiratory parameters have to be monitored. Patients and the health-care staff should be provided with the best possible protection from a viral infection. An intelligent viral filter for use with both non-invasive and

invasive ventilation is aimed at enabling this high level of protection. In the project Filter4Flow, Fraunhofer scientists are collaborating with the companies AC Aircontrols, ELK and Christoph Manegold MT-Consult to develop such a smart viral filter – a novel combination of a viral filter and fast sensor elements for measuring the flow rate, pressure and inhaled gas. The signals are digitized and transmitted quickly and wirelessly to a ventilation or patient monitoring system (e.g. an app). The intelligent viral filter allows precise, reliable and at the same time cost-effective breath monitoring in numerous patients, while also providing a filter function that protects both patients and staff from infection. This can also help prevent the dreaded shortage of ventilation resources.

QUELLE: tracking the risk of airborne infections

Exhaled aerosols – tiny liquid droplets (< 5 µm) that remain suspended in the air for a long time – are a major route of SARS-CoV-2 transmission. Fraunhofer ITEM experts want to use existing, appropriate measurement techniques to systematically investigate the proportion of fine aerosol particles in exhaled air and whether the face masks currently in use provide efficient protection against exhaled aerosols. The researchers hope that their results will contribute to a better understanding of coronavirus transmission and will help to better assess the relevance, suitability and prioritization of corresponding protective measures, in particular in the health and geriatric care sectors. In addition, they aim to evaluate the efficiency of passive protective measures, such as ventilation of indoor areas.

NEWS IN 2020



New agents to fight multidrug-resistant germs

January 2020: Resistance to antibiotics is on the rise worldwide. Fraunhofer scientists have joined forces with partners in the Phage4Cure project to explore alternative therapies. One objective is to vanquish multidrug-resistant pathogens with viruses called bacteriophages. Another is to see these phages approved to treat the dreaded hospital germ *Pseudomonas aeruginosa*, the most frequent bacterial cause of pneumonia.

www.item.fraunhofer.de/multidrug-resistance

Thematic forum at Fraunhofer ITEM: new impetus for biomedical engineering in Germany

January 2020: During the thematic forum on biomedical engineering, organized by Fraunhofer ITEM and the Lower Saxony Center for Biomedical Engineering, Implant Research and Development (NIFE), stakeholders from industry and academia discussed topics such as sustainment of innovation power, acceleration of innovation, and recent developments regarding a biomedical engineering data space. Furthermore, they compiled requirements and criteria aimed at enabling and promoting an effective implementation of the European Medical Device Regulation in Germany.

www.item.fraunhofer.de/thematic-forum-2020

19th Fraunhofer seminar "Models of Lung Disease"

February 2020: At the already 19th Fraunhofer seminar "Models of Lung Disease", participants from academia and industry enjoyed excellent presentations about COPD, asthma, lung infection, fibrosis and new technologies, addressing different phases of translational research. In a total of 23 lectures, more than 120 participants from 14 different countries discussed new developments and findings and presented innovative models for lung research.

www.item.fraunhofer.de/models-of-lung-disease-2020

Fraunhofer Research consortium iCAIR®: collaborative development of new medications against SARS-CoV-2

May 2020: Researchers of the international consortium iCAIR® are working on the development of novel anti-infective agents to treat or prevent clinically significant diseases of the respiratory tract caused by bacteria, fungi, and viruses – in May 2020, they started a project aimed at developing therapeutics to combat the new coronavirus SARS-CoV-2.

www.item.fraunhofer.de/icair-corona-project

Additive manufacturing using medical-grade silicone rubber

May 2020: In the webinar "Additive Manufacturing" held during the Industry Days 2020 of the Industrial Generation Network, experts from Fraunhofer ITEM and industry got together and exchanged ideas. Prof. Theodor Doll, Head of Department of Implant Systems in the Division of Translational Biomedical Engineering, addressed several topics there, such as the role of additive manufacturing in personalized medicine, 3D printing of medical-grade silicone rubber in the production of patient-specific implants, as well as additive medicine and MDR (Medical Device Regulation)-compliant certification.

www.item.fraunhofer.de/industry-days-2020

Hunting down life-threatening metastases

June 2020: What turns tumor cells into killer cells? Fraunhofer ITEM scientists in Regensburg are investigating the mechanisms of metastasis formation and are searching for approaches for new treatments in the fight against cancer. Among other things, the team of reseachers has developed a method enabling them to analyze entire lymph nodes.

www.item.fraunhofer.de/life-threatening-metastases

Emergency use authorization of disinfectants

June 2020: Disinfectants play an important role in preventing infectious diseases. The outbreak of the SARS-CoV-2 pandemic resulted in an increased need of disinfectants with at least "limited virucidal" activity, i.e. substances that are effective against enveloped viruses such as SARS-CoV-2. In compliance with the exemption authorization for certain biocidal products enabled by ECHA and the national authorities of the EU, Fraunhofer experts provide support regarding regulatory issues and the efficacy of biocidal products.

www.item.fraunhofer.de/disinfectants

ISO certification of our Division of Translational Biomedical Engineering

June 2020: Certified with EN ISO 13485 for contract design and development of medical devices for inhalation treatment and implants, the Fraunhofer ITEM experts can provide customers with ideal support in tapping market opportunities.

www.item.fraunhofer.de/iso-biomedical-engineering

Pancreas drug nafamostat for COVID-19 treatment

July 2020: In the face of the pandemic spread of SARS-CoV-2, there is an urgent need for effective drugs and vaccines. To speed up this process, existing drugs that have already been approved for treatment of other conditions are tested for their efficacy against SARS-CoV-2. To investigate the efficacy of nafamostat in the RENACO project, scientists of the German Primate Center in Göttingen (Germany) and of Fraunhofer ITEM are receiving 1.6 million euros from the German Federal Ministry of Education and Research.

www.item.fraunhofer.de/renaco-nafamostat

Teaching sustainable chemistry

July 2020: Fraunhofer ITEM scientists are contributing to professional training and education in the new master's program M.Sc. Sustainable Chemistry at Leuphana University Lüneburg. The program was developed at Leuphana's Institute of Sustainable and Environmental Chemistry (ISEC) in collaboration with the International Sustainable Chemistry Collaborative Centre (ISC3).

www.item.fraunhofer.de/sustainable-chemistry

"Production for Intelligent Medicine" innovation cluster

August 2020: 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. As a first step of this project, a concept for a modular pilot plant for automated production of such therapeutics is to be developed. Fraunhofer ITEM is involved in designing the production and quality control of ATMPs (Advanced Therapy Medicinal Products) and vaccines.

www.item.fraunhofer.de/intelligent-medicine

Disseminated breast cancer cells use bone marrow growth factors for metastasis

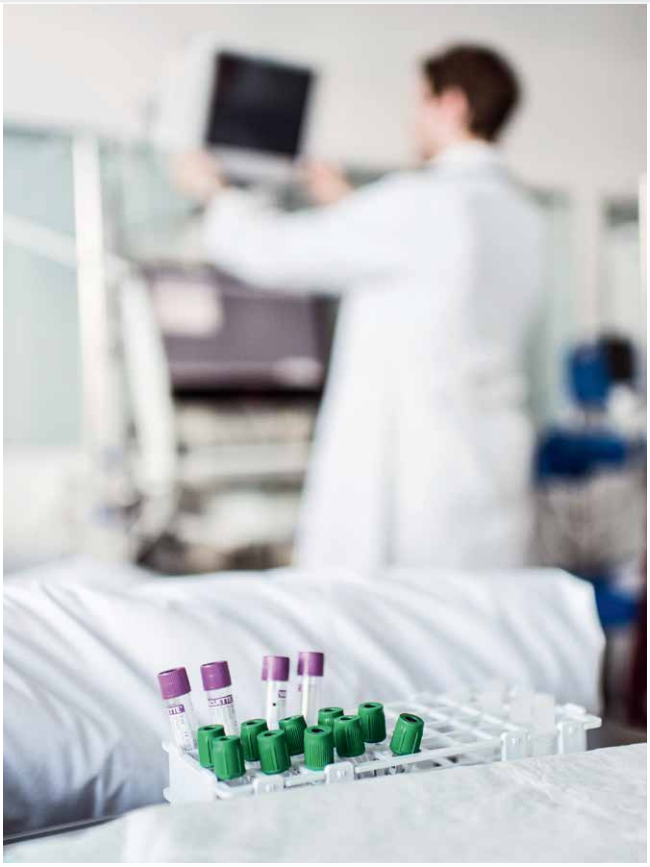
October 2020: Researchers of the University Hospital Regensburg and of Fraunhofer ITEM in Regensburg published new findings on the mechanism of metastatic spread in "Nature Communications". The researchers demonstrated that disseminated cancer cells can acquire stem cell-like properties by interpreting signals from the bone marrow environment, enabling them to form metastases.

www.item.fraunhofer.de/nature-metastasis

BEAT-COVID – advanced therapy strategies against the pandemic

October 2020: To help control the current pandemic and brace for novel pathogens that may cause future pandemics, Fraunhofer researchers initiated the project BEAT-COVID to develop independent novel therapy strategies and build up platform technologies that will enable rapid and targeted development of new drugs against as yet unknown pathogens that may emerge.

www.item.fraunhofer.de/beat-covid-project



New SFB/Transregio approved to investigate metastasis

November 2020: In the new Collaborative Research Center/ Transregio (SFB/TRR) 305, scientists of the German universities of Regensburg and Erlangen and of the Fraunhofer-Gesellschaft will investigate the mechanisms of metastatic organ colonization and aim to develop novel systemic therapies.

www.item.fraunhofer.de/SFB-cancer-therapy

Top-speed antibody development

December 2020: A decade or more can elapse between the discovery of a new protein-based active ingredient and the approval of a new drug. As a rule, it takes between 18 months and two years to even produce an investigational medicinal product for use in clinical trials. Researchers of the Braunschweig-based Fraunhofer ITEM Division of Pharmaceutical Biotechnology have developed a novel production strategy that reduces this step to just six months.

www.item.fraunhofer.de/antibody-development

Development of a drug screening pipeline for discovery of novel COVID-19 therapeutics

December 2020: Fraunhofer ITEM in Regensburg is cooperating with partners from the University of Regensburg and the company 2bind GmbH, 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 Bavarian Research Foundation is funding this project for a period of one year.

www.item.fraunhofer.de/covid-drug-screening-pipeline

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 development strategies, we support our clients in process development for and manufacturing of active biopharmaceutical ingredients and sterile investigational medicinal products, in preclinical testing – both pharmacology and toxicology – and in 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.

www.item.fraunhofer.de/drug-development

Development and manufacturing of active biopharmaceutical ingredients

A multidisciplinary team of biologists, chemists, pharmacists, engineers, and technicians assists our clients on their way from the idea for a new biotherapeutic via development of a production cell line to GMP manufacturing of the investigational medicinal product (IMP) released for use in clinical trials. This team guides you along the entire regulatory pathway to your approved IMP dossier. Our clients benefit from our profound knowledge accumulated over 25 years from a broad range of biopharmaceutical candidates – from simple proteins to complex structures such as viruses, e.g. bacteriophages. Our service portfolio includes:

- Technical and regulatory consultancy for biopharmaceutical development projects, in particular on recombinant proteins and antibodies
- Engineering of recombinant mammalian and microbial production cell lines
- GMP manufacturing, cell banking and storage of master and working cell banks
- Development of complex upstream and downstream sequences with subsequent upscaling
- GMP manufacturing of API pilot charges
- Release testing of biopharmaceutical APIs and IMPs
- Aseptic filling and quality-assured release of IMPs (liquid dosage forms)

Regulatory research and risk assessment in drug development

Fraunhofer ITEM has combined its expertise in drug research and development with its experience in registration and risk assessment of chemicals. With these forces joined, the institute is uniquely positioned to support clients in regulatory affairs in the drug development process. Our expertise allows experimental studies for risk assessment and registration of substances to be kept to a minimum. Our scientists explore, develop, and validate new approaches to manufacture, characterize, and test innovative medicinal products. Furthermore, we ensure regulatory input on these approaches and implement them in product development in cooperation with the client. Our service portfolio includes:

- Preparation of a regulatory strategy to take products from lab to market
- Interaction with regulatory authorities
- Preparation of the required documentation
- Risk assessment
- Regulatory research

Preclinical testing

For preclinical development of a drug candidate we offer a broad spectrum of disease-relevant and toxicological models. Our outstanding expertise, many years of experience with partners from the pharmaceutical and biotech industries, and state-of-the-art equipment provide the foundation for our scientific solutions and custom-tailored services. Our special focus is on preclinical models of respiratory diseases, on inhalation toxicology, immunotoxicology, and respiratory infections.

For efficacy testing of drug candidates we offer disease-relevant models for all therapeutically relevant diseases of the respiratory tract such as COPD, asthma, pulmonary fibrosis, infections, and tumors. We are committed to enabling reliable prediction of the efficacy of drug candidates – by constant development of new methods in collaboration with academic institutions and research centers. For toxicology and pharmaceutical efficacy testing of drug candidates we offer the following services and expertise:

- In-vitro, ex-vivo, and in-vivo studies in models of asthma, COPD, pulmonary fibrosis and infection
- Transcriptome analyses in different biological samples
- Invasive lung function measurement in disease models
- In-vitro studies (genotoxicity, molecular toxicity, screening assays)
- Ex-vivo studies in precision-cut slices from lung (PCLS), liver, lymph nodes, or tumors; studies in isolated perfused rat lungs (IPL)
- In-vivo studies (relevant species, single-dose and repeated-dose toxicity)
- Safety pharmacology (core battery)
- Testing strategies to accompany clients during scientific advice and registration processes
- Track record including biopharmaceuticals, oligonucleotide-based therapeutics, and ATMPs
- Study performance according to OECD GLP, where applicable

Clinical trials

Finding the most appropriate model for your proof of concept and the most suitable study design are challenges we can successfully handle with our excellent medical expertise and strong academic background. We support clients in the development of drugs targeting respiratory and allergic diseases and do patient-oriented research to help people suffering from these conditions. A broad range of challenge models is available for clinical studies on respiratory diseases such as asthma, allergic rhinitis, COPD, and interstitial lung diseases (idiopathic pulmonary fibrosis in particular). A new sleep laboratory was set up in 2018, extending our study portfolio. The Fraunhofer Sputum Core Facility offers validated methods for sputum analysis in multicenter studies. In the state-of-the-art clinical research center CRC Hannover, we perform our studies with a highly qualified and dedicated team of physicians, study nurses, and medical documentation specialists, accompanied by an independent quality assurance unit. The following services and infrastructure are available:

- Fraunhofer Challenge Chambers: challenge chambers for proof-of-concept studies with sophisticated study designs, enabling exposure of test subjects to natural pollen, allergen extracts, ozone, or hypoxia challenge
- Inhaled allergen challenge
- Segmental challenge during bronchoscopy
- Exercise testing (spiroergometry)
- Collection and analysis of human samples with subsequent storage in the biobank at the CRC Hannover
- Biomarker analysis
- Imaging: non-invasive MRI techniques
- In-house GMP laboratory for production of intravenous dosage forms of IMPs
- Patient/volunteer database

PROJECTS

Top-speed development of an antibody against SARS-CoV-2

Worldwide, research into therapeutics and vaccines to combat SARS-CoV-2 is in full swing. The pandemic has underlined once again how important it is to get pharmaceuticals quickly to the patient. But the development of a suitable bioprocess and pilot production of a protein-based drug candidate, such as an antibody, typically takes between 18 and 24 months, which seemed too long in the face of the pandemic dynamics. The division of Pharmaceutical Biotechnology, therefore, took a completely new path with its fast-track approach and, together with an industrial partner, developed and manufactured a clinical antibody preparation in just six months. This fast-track approach was agreed upon in advance with the national regulatory authority, the Paul-Ehrlich-Institut. Classically, recombinant antibody production is performed using a cell clone isolated from a pool of transfected CHO cells that produces sufficient amounts of the desired antibody. Since clone selection is an extremely time-consuming process, it was decided to omit this step and instead cultivate and further process the entire cell pool. In just six months, a large quantity of pharmaceutical-grade antibodies could be harvested and 3500 doses for clinical trials prepared. This fast-track development process can be adopted for a wide range of pharmaceutical-grade proteins, providing much faster access to clinical investigational products and opening up a completely new business model for the institute's division of Pharmaceutical Biotechnology.

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Using ex-vivo lung tissue to test drugs for parainfluenza treatment

The COVID-19 pandemic has added a new dimension to the global health threat from respiratory viruses. But there are also other viruses that infect millions of people every year. In the iCAIR® consortium, Fraunhofer ITEM is collaborating with Griffith University in Australia, the Hannover Medical School and the Helmholtz Centre for Infection Research to develop new, urgently needed agents targeting respiratory infections. Besides the influenza virus, this research consortium is also targeting the parainfluenza virus, which is less well known and for which no drugs are available to date. To enable a better understanding of the parainfluenza infection and the related immune response and, consequently, the identification of therapeutic targets, laboratory testing methods are needed that are able to mimic the infection in the human lung as closely as possible. Using human precision-cut lung slices (PCLS), i.e. viable and immunocompetent lung tissue, the parainfluenza infection has now been successfully mimicked for the first time, allowing a detailed analysis of the biological and immunological responses to the virus. Increased viral replication, which is critical for the severity of the disease, has been observed in PCLS under suppression of the T-cell immune response. This unique human model is thus suitable to test the efficacy of new drugs in the immunocompromised, infected lung. A new inhibitor developed by the Australian partner has already shown promising antiviral activity.

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Fill and finish of a SARS-CoV-2 antibody preparation for use in clinical trials. A fast-track strategy allowed the development of the investigational medicinal product to be reduced from 24 to just 6 months.

Toxicology testing of an innovative RNA therapeutic for heart failure treatment

Heart failure is a frequent complication after myocardial infarction and represents a major health problem. It is a chronic, progressive and mostly irreversible disease. Currently available pharmaceutical therapies are often purely symptomatic and at best can slow down disease progression. A novel RNA-based therapeutic agent for heart failure treatment has been developed by Cardior Pharmaceuticals and preclinical and first toxicological studies necessary for obtaining regulatory approval of this drug have been successfully performed at Fraunhofer ITEM. In a first clinical trial, this innovative RNA-based therapy proved to be well tolerated and safe. In addition, first indications of efficacy warrant further clinical trials to confirm the favorable pharmacodynamic effects of the novel therapeutic agent for treating heart failure. As part of this cooperation with Cardior Pharmaceuticals, a chronic toxicity study will be performed at Fraunhofer ITEM according to GLP standards. Cardior Pharmaceuticals is a biopharmaceutical company focused on the discovery, development and clinical validation of non-coding RNA therapeutics targeting cardiovascular diseases.

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Replacing animal experiments: alternative models for testing of inhalable antibiotics

To date, preclinical data on inhaled antibiotics have been generated mainly in animal studies, but acute in-vivo infection models in particular place a heavy burden on the welfare of the experimental animals used. The aim of the project InhalAb, funded by the German Federal Ministry of Education and Research, was to combine biologically relevant in-vitro, ex-vivo and in-silico lung models to gain direct insights for non-clinical development of inhaled candidate drugs. To enable antibiotic testing for toxicity, efficacy, and pharmacokinetics without animal experiments, Fraunhofer ITEM researchers established a combination of alternative models based on human cell lines, precision-cut lung slices (PCLS), and isolated perfused rat lungs (IPL). In human PCLS, comparative toxicity and efficacy analyses demonstrated good mapping of the therapeutic window: in the non-toxic range, a dose-dependent reduction of bacterial counts after infection with *Pseudomonas aeruginosa* was observed. Systemic availability was evaluated in vitro in human lung epithelial cells and ex vivo in the IPL model after exposure to antibiotic aerosols. Based on a PBPK* model of inhalation exposure developed at Fraunhofer ITEM, the researchers predicted a systemic concentration-time profile that agrees very well with published human data. Predictive preclinical data sets on the efficacy, toxicity, and pharmacokinetics of inhaled antibiotics can thus be generated without the need for direct animal testing.

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* PBPK = physiologically based pharmacokinetics model describing the uptake, distribution and degradation of a substance in the human organism.

Well combined: phase-I trial – to evaluate the safety, tolerability and pharmacokinetics of a candidate drug – with biomarker analyses to gain insights into its immunological efficacy.

Phase-I trials with specialized analyses – safe even under pandemic conditions

Starting at the end of 2019, researchers of the Department of Clinical Airway Research have conducted two comprehensive phase-I studies aimed at testing the safety, tolerability and pharmacokinetics of one drug for treating COPD and another one for treating asthma. About 80 healthy volunteers and 100 asthmatics will be participating in the course of these two trials. For a period of eleven days, the study participants are staying as inpatients at the study center, since the highest doses in both studies are first-in-human trials and therefore require enhanced monitoring of the participants. The studies are being accompanied by specialized analyses in the institute's own biomarker laboratory. To this end, blood cells obtained from the study participants are stimulated in order to gain first insights into the immunological efficacy of the new drugs. This combination of operative conduct of a phase-I study and complex biomarker analyses is a unique selling point of Fraunhofer ITEM and distinguishes it from typical phase-I centers. Even during the COVID-19 pandemic, the trials are being continued, subject to increased safety measures. These include corona swab testing before inpatient admission, single occupancy of bed rooms, social distancing between study participants, and the wearing of face masks. These measures have allowed the trials to be continued safely and successfully, so that development and testing of new innovative drugs is possible even under pandemic conditions.

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Lung deflation in COPD – effects on heart, airways and sympathetic nervous system

Obstruction of the small airways in chronic obstructive pulmonary disease (COPD) leads to what is known as "air trapping" due to impaired expiration, resulting in lung hyperinflation. Inhalation of a bronchodilator improves lung function by widening the bronchi and thereby reducing airway constriction. This allows the lungs to be deflated, at least partially. Fraunhofer researchers are interested to learn how a one-time or two-week treatment affects particles in the patients' exhaled breath, their cardiac output, and sympathetic tone. Since June 2020, they have been investigating this in an investigator-blinded, sequence-randomized, monocentric cross-over study involving the drug Spiolto® Respimat® (Boehringer Ingelheim). After administration of a single dose of Spiolto® Respimat® or isotonic saline, the investigators examine the overall 48 study participants with COPD and pulmonary hyperinflation by micro-neurography (sympathetic tone) and MRI (including hyperpolarized xenon) and measure exhaled particles and the patients' lung function. Thereafter, the test subjects use the spray at home for two weeks to comparatively measure the effects of lung deflation over a longer period of time. The study is scheduled to be completed by the end of 2021 and is being conducted in collaboration with the German Aerospace Center in Cologne and the Institute for Radiology of the Hannover Medical School. It was initiated by Fraunhofer researchers and is being funded by the Fraunhofer-Gesellschaft.

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Search for early predictors of acute exacerbation of COPD

It is currently not well understood how physiological parameters in COPD patients vary prior to an acute exacerbation (AECOPD). Early predictors could enable a rapid adaptation of treatment and potentially avoid the development of an exacerbation or result in a milder course. In a three-year project funded by the German Center for Lung Research and pharmaceutical companies, 350 patients will be tightly monitored during their physical rehabilitation. It is estimated that about fifty of these patients will develop an AECOPD during their stay at the rehabilitation clinic. In this setting, it will be possible to gain information about a broad spectrum of physiologic changes prior to AECOPD. Fraunhofer ITEM researchers are responsible for breath analysis in these patients. Breath samples are collected using a ReCIVA sampler system previously optimized by Fraunhofer and are shipped to Fraunhofer ITEM once a week for analysis by GC-MS (gas chromatography coupled with mass spectrometry) in cooperation with the Department of Bio- and Environmental Analytics. Due to the coronavirus pandemic the study had to be interrupted during the summer, but by October 2020, thirty patients had been included. The data is constantly monitored and will be analyzed on a yearly basis for potential AECOPD breath biomarkers.

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Therapeutic modulation of Th17.1-driven chronic immune diseases by siRNA

In the Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD, Fraunhofer ITEM has teamed up with the Fraunhofer Institutes IZI and IPA to address the therapeutic modulation of Th17.1-driven chronic immune diseases. TH17.1 cells are T helper cells that produce both TH17 and TH1 cytokines, such as IL-17, IL-21, IFN-γ, and TNF-α. Th17.1-driven diseases include sarcoidosis and chronic inflammatory bowel diseases. Based on a single-cell RNA-sequencing dataset derived from bronchoalveolar lavage (BAL) cells of sarcoidosis patients and healthy volunteers, we identified key signal transduction pathways of TH17.1 cells. Subsequently, small interfering RNA (siRNA) molecules were developed, aimed at turning off these TH17.1 signal transduction pathways. Using BAL cells from sarcoidosis patients, the effect of the developed siRNA molecules was then first tested in vitro for inhibition of the secreted cytokines. The siRNA molecule candidates that had successfully inhibited TH17.1 cell production were then tested in murine models of sarcoidosis and inflammatory bowel disease. For this purpose, the siRNA molecules have to be packaged in nanoparticles to avoid creating non-specific and undesirable off-target effects. The long-term goal is to develop packaged siRNA as a novel therapeutic for the above diseases and advance it to the stage of clinical testing.

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Multiplex immunofluorescence to detect B and T lymphocytes and subpopulation-specific antigens in immune cells from mouse spleen (photo on the left: 4x magnification; photo on the right: 40x magnification).

Use of the basophil activation test for drug testing in clinical trials

Stimulation of cells of the immune system as a biomarker is an important tool in drug development to test a substance for efficacy and associated molecular mechanisms. An example is the basophil activation test (BAT), which in clinical practice is used as a diagnostic biomarker for an allergic response. In this test, expression of the inflammation-related markers CD63 and CD203c on basophil granulocytes after allergen-induced stimulation is analyzed in whole blood by flow cytometry. Researchers of the institute's Department of Biomarker Analysis and Development have evaluated whether this test can be used as a biomarker in clinical trials. A prerequisite was the establishment and validation of the test in both healthy and asthmatic subjects, as it was not assured that the method could be validly applied to sample material from asthmatics. The results of this work have shown that the method is suitable for measurements in sample material from asthmatics and that there is a correlation between allergy-relevant antibody concentrations in blood and BAT reactivity. As a result, it was possible to make use of the BAT in a clinical trial at Fraunhofer ITEM to test an inhibitory substance. In the future, the BAT can be used as a valid biomarker to investigate the immunological response after allergen stimulation in clinical trials.

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Development of innovative model systems for evaluating immunomodulatory therapeutics

Currently existing nonclinical models do neither adequately represent the complexity of the immune system nor accurately reflect the diversity of clinical responses to new therapies for immuno-oncology and immuno-inflammatory diseases. Therefore, a constant refinement of existing and development of new nonclinical models are of high importance and are the main vision of the EU project imSAVAR (Immune Safety Avatar). In this project, a consortium of 28 partners from university and non-university research institutions, pharmaceutical and biotechnology companies and regulatory authorities from 11 countries has joined forces to develop a platform for integrated nonclinical assessment of the safety and efficacy of immunomodulatory therapies. As part of the imSAVAR project, Fraunhofer ITEM aims to characterize undesired effects of high-dose IL-2 in a first case study, to allow these effects to be prevented in future therapies. To this end, immune-related adverse outcome pathways (irAOPs) were determined based on information drawn from literature. As a result, possible cellular and molecular key events involved in the induction of skin rash and pulmonary toxicity as two adverse events induced by IL-2 therapy were identified. These key events will serve as potential markers to evaluate the suitability of the chosen test systems.

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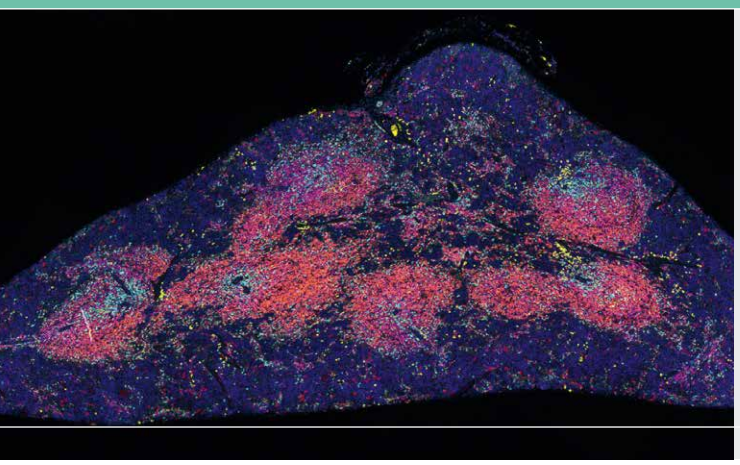

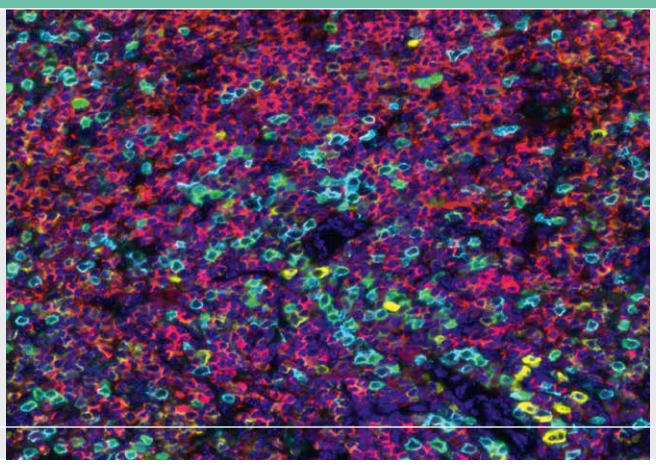

Alternative ex-vivo test method for surfactant release testing

Infant respiratory distress syndrome is a frequent condition resulting from a lack of surfactant in the immature lungs of premature infants. Surfactant replacement therapies with exogenous surfactant preparations represent an efficient treatment option. Before releasing the product, the efficacy of each batch must be approved. The required testing is routinely performed in laboratory animals. This is done using either animal models with endogenous surfactant deficiency (immature lungs in premature infants) or models with secondary surfactant deficiency in adult animals (washout of endogenous surfactant or chemical disruption). The main parameter tested for efficacy approval is the ability of a batch to restore the partial pressure of arterial oxygen in the animals. As an alternative model, Fraunhofer ITEM scientists are also investigating the ex-vivo model of the isolated perfused rat lung (IPL) for surfactant batch testing. In this model, surfactant deficiency is induced by repeated bronchoalveolar lavages and the efficacy of different surfactant batches is then assessed in terms of recovery of respiratory parameters such as tidal volume, dynamic lung compliance, pulmonary arterial pressure and arterial oxygen concentrations. The IPL is a promising model – with regard to the 3R principle (Replace, Reduce, Refine) – for surfactant efficacy testing for the purpose of batch release.

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Multiplex staining: immunohistochemical detection of antigen colocalization in tissues

As part of the research project "Childhood leukemia: study on the impact of magnetic fields on the immune system," the Fraunhofer ITEM Department of Pathology developed a method enabling detection of any six surface, cytoplasmic, or nuclear antigens in formalin-fixed, paraffin-embedded organs. In a mouse model, this method enabled detection of lymphocyte and tissue epitopes in different immune organs and liver, partly in the same cells, by signal-enhanced immunohistochemistry and seven different fluorophores in a single multiplex stain. The histological organ slides are subsequently scanned with a 7-channel fluorescence scanner. The researchers are currently evaluating the digitized fluorescence slices using a whole-slide image analysis tool. This meanwhile automated multiplex staining method can be used species-independently in all projects involving the labeling of several antigens in organ tissue sections and where serial slices do not allow elucidation of antigen colocalization issues. In contrast to FACS analysis, this method can be used to ascertain not only the presence and localization of antigens in cells of tissue sections, but also their presence in cells of specific organ compartments. What makes this technique so special is that it allows both the position and the relationship of antigen-presenting cells to each other and to other cell types to be visualized and evaluated by microscopy.

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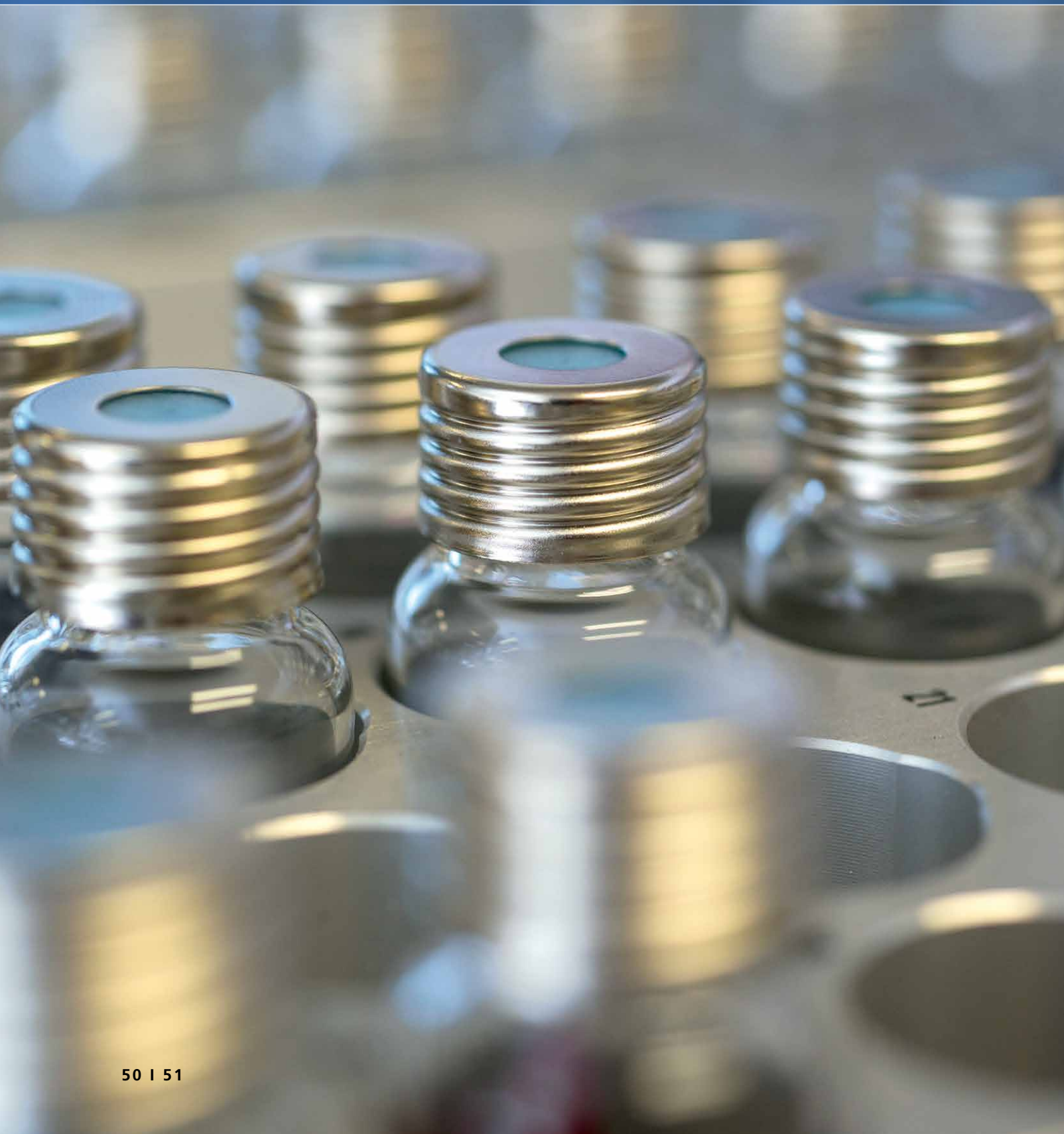
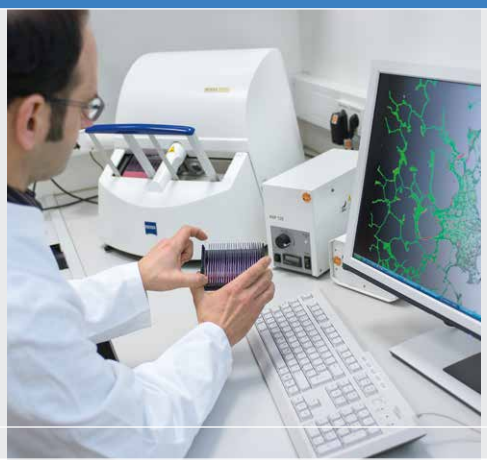
CHEMICAL SAFETY AND ASSESSMENT





FROM RISK ANALYSIS TOWARDS SAFE PRODUCTS

Our commitment is to assess the potential risk from chemical substances, including 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. 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.

The services offered by Fraunhofer ITEM can assist you on the way from risk analysis towards safe products.

www.item.fraunhofer.de/chemical-safety

Development of test methods and analytical procedures

We offer our clients comprehensive consulting and expert opinions in analytical issues that are often beyond the scope of commercially available routine analyses. In close contact with our clients, we develop custom-tailored analytical strategies. In addition, we offer research and development projects in the field of aerosol research, employing methods of physics, process engineering, and physical chemistry. For problem-solving that meets the client's specific requirements, we offer:

Analytical chemistry

- Development of analytical methods and validation in compliance with the relevant guidelines
- Analytical studies (both GLP and non-GLP) required for registration and authorization
- Targeted metabolomics and both target and non-target analysis of inorganic and organic compounds (e.g. aldehydes/ketones, dyes, pharmaceuticals, BTX, PAHs, pesticides, VOCs, SVOCs, metals, and compounds typical of explosives)
- Characterization of complex mixtures in environmental samples and biological matrices
- Structural elucidation of drug substances and natural products and of their metabolites
- Biomonitoring – determination of the bioavailability of pharmaceuticals and food contaminants and, if applicable, their metabolites, (heavy) metals and other chemicals, and test substances from production and development scenarios
- Protein mass spectrometry, structural elucidation of modified proteins, de-novo sequencing

Aerosol research

- Development of instruments and methods for measurement, collection, and generation of aerosols
- Development of methods and technologies for studies with controlled inhalation exposure to different atmospheres

Toxicology testing of chemical substances

We offer a broad range of toxicological tests enabling assessment of potential risks from chemicals, particles, complex mixtures, and nanomaterials. Depending on our clients' specific requirements, we develop appropriate testing strategies and, if required, conduct toxicology studies with different routes of administration – with a focus on inhalation toxicology and characterization of inhalable substances. Our service portfolio includes:

- Regulatory assessment by means of standard toxicological tests in compliance with international guidelines (OECD, EU, EPA, or FDA)
- Focus inhalation toxicology:
  - Nose-only and whole-body exposure of rodents
  - Toxicokinetics of inhaled particles
  - Specific lung toxicity measurements including bronchoalveolar lavage
  - Inflammatory reactions in the lung
- Focus (nano)particles and fibers:
  - Deposition and retention
  - Particle clearance by using radiolabeled tracers
  - Biopersistence of fibers
  - Bioavailability of metals from solid material particles
- P.R.I.T.® exposure system for in-vitro exposure of cells and tissues to airborne, soluble, and particulate test substances at air/liquid interfaces
- Characterization of molecular mechanisms of action
- Use of our own toxicological databases (RITA, *go*RENI, *Dev*Tox)

Exposure characterization

To characterize occupational, indoor, and environmental human exposure to gases and aerosols/particles, inhalation exposure in particular, we combine state-of-the-art measurement technology with mathematical modeling tools. Whenever necessary, we provide adaptations to customize a solution to a client's specific needs or to guarantee its compliance with relevant regulations. We use the following methods for this purpose:

- Physical and chemical measurement of emissions from aerosols (e.g. dusts, (nano)particles, sprays, oil mists, vapors, and microorganisms) and gases (volatile and semivolatile organic compounds)
- Inhalation exposure modeling:
  - Dispersion of pollutants (SprayExpo, e.g. for biocides; quantification of particle deposition and resuspension for indoor air models)
  - Lung deposition and absorption (interspecies comparison; clearance and solubility)
- Development of custom-tailored measurement and process technology:
  - Measurement technology for dusts and aerosols (PM_{10}, $PM_{2.5}$, exhaust gases, nanoparticles)
  - Aerosol generation methods (calibration aerosols, nebulization, dry dispersion)
- Process development (development of test methods and analytical procedures)
- Design of relevant exposure scenarios and calculation of the exposure – also by using commercially available models
- Development of new exposure models in collaboration with regulatory agencies and/or industrial clients

Regulatory research and risk assessment of chemical substances

To assess the potential risk from chemical substances – industrial chemicals, biocides, food additives, and human and veterinary medicinal products – including their use in specific products, we use a tiered approach, referred to as integrated testing strategy. 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, animal studies in particular. Examples of such projects are elucidation of structure-activity relationships ((Q)SAR), category approaches such as read across, the setting up of databases (e.g. RepDose, FedTex, PaFTox), and further development of the TTC concept. For risk assessment of chemicals and their registration for a particular use, we offer:

- Data gap analysis and literature search: in cooperation with the sponsor, we determine what data are available and whether additional studies are necessary, and we check whether there is information publicly available about the substance in question.
- Preparation of dossiers: we prepare IUCLID-5 datasets for the studies, perform exposure and risk assessments, and prepare a chemical safety report (CSR) and the registration dossier.
- Consulting and support to develop a registration strategy tailored to your situation
- Experimental investigations, e.g. for toxicology testing, can be performed directly at Fraunhofer ITEM or are subcontracted to other testing institutes. If an external partner is needed, we can assist you in selecting an appropriate partner and in the monitoring of your studies.
- Risk assessment and expert reports: in the form of expert reports, we document the (eco)toxicological properties of substances and assess their risks to human health and the environment, for example for REACH registrations, for biocides, and for contaminations or chemical residues in foods and products.

PROJECTS

Updating registration dossiers – new regulation in force

The quality of REACH registrations largely depends on the information in the dossiers being up to date. In the past, dossiers had to be updated "without undue delay". In the Commission Implementing Regulation (EU) 2020/1435 of October 9, 2020, the meaning of this requirement has now been clarified. Changes in the tonnage band, for example, must be reported within three months. Deadlines of up to twelve months apply for changes in the classification and labeling of a substance and in the guidance on its safe use. Since the dossiers always have to be submitted in the latest version of IUCLID, additional work may sometimes be required to complete a REACH-compliant dossier. This should always be kept in mind when planning for a deadline. In addition to the electronic checks in the "technical completeness check" (TCC), ECHA also introduced a manual check of certain items in the dossiers in 2016. When updating a dossier, the most recent literature can be reviewed in addition. Furthermore, it is possible to check whether the models used for exposure assessment are up to date and to make any necessary adjustments. Many years of experience are an asset when it comes to adequately considering all these points. Based on such long experience and special toxicological expertise, Fraunhofer ITEM supports its clients with all scientific and regulatory issues. This also includes the collection of data to update the dossiers of industrial chemicals.

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Health effects of exposure to electromagnetic fields

Due to the rapidly advancing development of technology, from wireless telecommunication to power grid expansion and a multitude of industrial applications, exposure of the public to electromagnetic fields (EMF) of all frequency ranges is steadily increasing. In view of the most recent deployment of the 5G mobile network technology and increasing wireless connectivity of household appliances to the Internet, there is growing concern among both the general public and experts about potential health consequences of EMF exposure. At present, there is no evidence for biophysical mechanisms that may result in health hazards, other than thermal effects and the excitation of nerve cells observed after exposure above thresholds. The existence of such mechanisms, however, cannot be ruled out. To precisely assess a possible influence of EMF exposure on two of the major endpoints in this context, namely fertility and oxidative stress, Fraunhofer ITEM has started a project aimed at reviewing the most relevant findings in this field. Supported by the German Federal Office for Radiation Protection and the World Health Organization, the project envisages three highly comprehensive, systematic reviews intended to support decision-making with regard to radiation protection and eventually to be implemented in the WHO health recommendations on EMF exposure.

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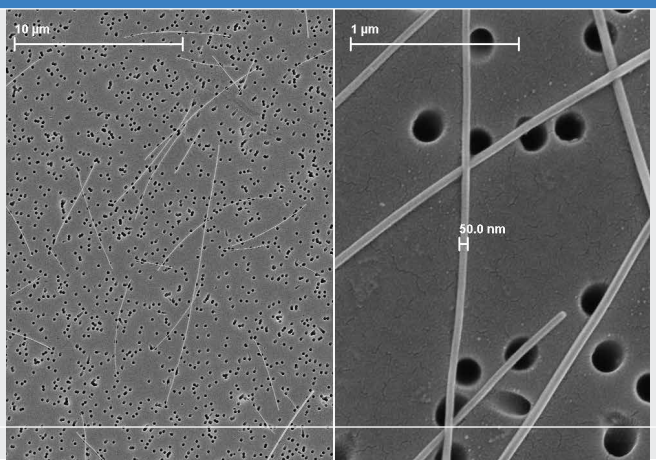

To date, there is hardly any toxicological data available for fibrous innovative nanomaterials such as the silver nanowires shown here (SEM image). The aim of the project MetalSafety is to develop an in-vitro model for the toxicological evaluation of different metal-based compounds that differ in bioavailability.

MetalSafety – new evaluation concepts for metals and metal compounds

Metals and metal compounds are essential in our daily life. They are used in automotive and aircraft engineering and in numerous innovative processes such as optoelectronics, medical diagnostics, and inks for 3D printing. Aiming to develop an in-vitro model for the toxicological evaluation of different metal-based compounds that differ in bioavailability, Fraunhofer ITEM is collaborating with Karlsruhe Institute of Technology (KIT) and BASF SE in the project MetalSafety. One focus in this project is on investigating the toxicological profiles of metal-based nanowires compared to the respective nano-scaled granular compounds, since there is hardly any toxicological data available for these innovative materials. The project is thus also making an important contribution to occupational safety and the safe handling of these materials. The aim of the ex-vivo and in-vivo studies conducted at Fraunhofer ITEM is to validate the in-vitro results with regard to their predictiveness of the toxicological potential, underlying modes of action, and dose-response relationships. The ex-vivo toxicity studies will be performed in precision-cut lung slices (PCLS) generated from rat lungs and patient samples to address potential species differences. To verify the results of the in-vitro and ex-vivo studies under physiological conditions and ideally to fully validate the screening models, selected materials will also be tested in vivo.

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Exposure-based adaptation of information requirements under REACH

Exposure-based adaptation (EBA) is a tool to avoid unnecessary animal testing and may be applicable when human or environmental exposure is absent or so low that additional effects information will not improve risk management. ECHA has developed a guidance for EBA under REACH, however, it does not include a quantitative metric for accepted exposure levels. The technical guidance to justify EBA is also lacking. As part of the PetCo initiative, Concawe and Fraunhofer ITEM prepared a framework concept evaluating various approaches, criteria and essential elements to address and justify EBA for repeated-dose toxicity testing. They developed an enhanced version of the flow diagram from the ECHA guidance R5 that can help registrants select the most appropriate approach for developing robust science-based EBA justification. It integrates several quantitative elements in a weight of evidence approach to be followed when no reliable DNEL (derived no-effect level) is available. The concept was presented at the joint workshop of ECETOC, Concawe and EPAA on October 14, 2020, where scientific feasibility of EBA in regulatory settings was discussed. The challenge of ambiguous terminology within the REACH legal text was also highlighted and the potential use of a threshold of toxicological concern (TTC) for determining "low" or "negligible" exposure was discussed.

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e:ToP collaborative project ExITox II – Explain Inhalation Toxicity II

The aim of the project ExITox II, funded by the German Federal Ministry of Education and Research, was to develop an integrated testing strategy for the assessment of inhalable chemicals. To this end, scientists investigated five read-across groups of compounds that share structural properties and had comparable adverse outcomes in the respiratory tract in in-vivo studies. The investigated substance categories included volatile organic compounds and nanoparticles. Using human in-vitro and ex-vivo models, the researchers were able to show that different mechanisms of action can be distinguished for these substances at the gene expression level. In this project, cells and lung tissue slices were exposed using an air-liquid technology available with the Fraunhofer ExpoCube®. Gene expression was analyzed by means of the TempOSeq® technology. In addition, the scientists developed a lung PBPK model for the respiratory uptake. PBPK stands for a physiologically based in-silico model describing the uptake, distribution and degradation of a substance in the human organism. Both components, namely similarity based on the biological profile and information about toxicokinetic differences between the substances, will be taken into consideration in the integrated approach to testing and assessment (IATA). The researchers in the ExITox II project have thus made a major contribution to reducing in-vivo studies, especially complex animal experiments such as repeated-dose studies.

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Sound and safe exposure estimates for consumer products

Consumer products are an integral part of our everyday lives. Their composition and active ingredients vary depending on their intended use. Direct human exposure to such products can be either intentional (e.g. cosmetics) or should best be avoided (e.g. biocides). In either case, the exposure route and frequency as well as the exposure dose are critical factors that determine the risk for the consumer associated with hazardous compounds found in a given consumer product. "Real-life" exposure simulations and systematic investigations are essential for exposure assessment. At Fraunhofer ITEM, numerous model rooms, ranging from 0.1 to 160 m³ in size, are available for this purpose. Our scientists bring in the required extensive experience in designing, setting up and conducting suitable model scenarios, with an emphasis on inhalation exposure. Such experimental data in concert with exposure modeling are the key tools for the generation of sound and safe exposure estimates for consumer products. Exposure assessment and subsequent risk assessment for the intended use of a consumer product is an interdisciplinary task bringing together the expertise of the Fraunhofer ITEM departments of Aerosol Technology and Biophysics, Bio- and Environmental Analytics, and Regulatory Affairs.

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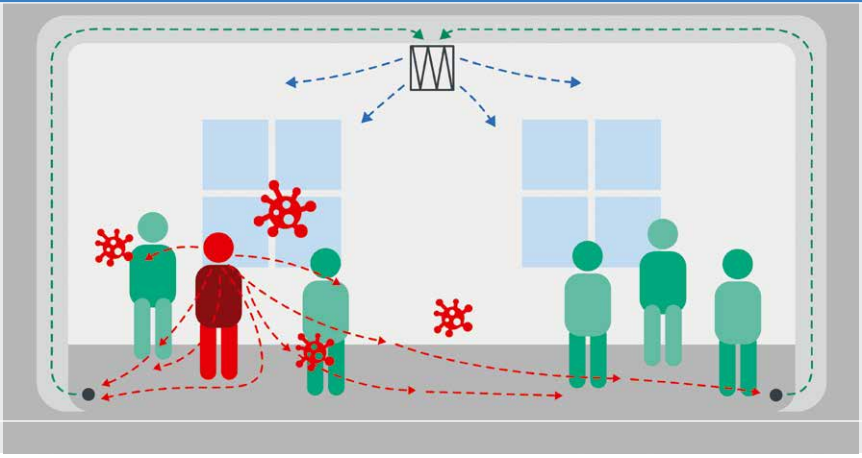

Aerosol-borne viruses in indoor areas: in the AVATOR project, scientists are investigating how to monitor and reduce the risk of infection.

AVATOR – Anti-Virus-Aerosol: Testing, Operation, Reduction

According to the current state of research, aerosols play an important role in the transmission and spread of the coronavirus SARS-CoV-2. Tiny droplets which are smaller than 10 µm in diameter – referred to as aerosols – can remain airborne for a long time. Human beings emit aerosols, for example, when they breathe, speak, sneeze or cough. These aerosol droplets are composed of saliva and lung fluid and provide a habitat in which the coronavirus can survive for several hours. Aerosols can be dispersed in the air over distances of several meters, and via this route, an infected person can infect others with SARS-CoV-2. In the project AVATOR (Anti-Virus-Aerosol: Testing, Operation, Reduction), scientists are investigating how to monitor and reduce the risk of infection from aerosol-borne viruses in indoor areas. The project uses two interlocking approaches: firstly, development of indoor air purification and disinfection technologies, and secondly, modeling of aerosol spread to derive hygiene concepts for different scenarios. Computer simulations are used to determine the airborne virus spread in exemplary real-world environments and exposure scenarios are developed. A risk model will be created for these defined scenarios to determine the risk of infection in the simulated use cases and evaluate the impact of different protective measures. Furthermore, by using agent-based simulations, i.e. methods for simulating complex systems, additional effects of movements and actions of the different individuals in the room, e.g. teachers and students in a classroom, will be taken into account. Overall 13 Fraunhofer Institutes working in a wide range of research areas are collaborating very closely in this project. Fraunhofer ITEM is involved at several important interfaces, for example in the collection of data on aerosol distribution, in the development of the risk model, and in the (efficacy) testing and toxicological evaluation of several air purification and disinfection technologies.

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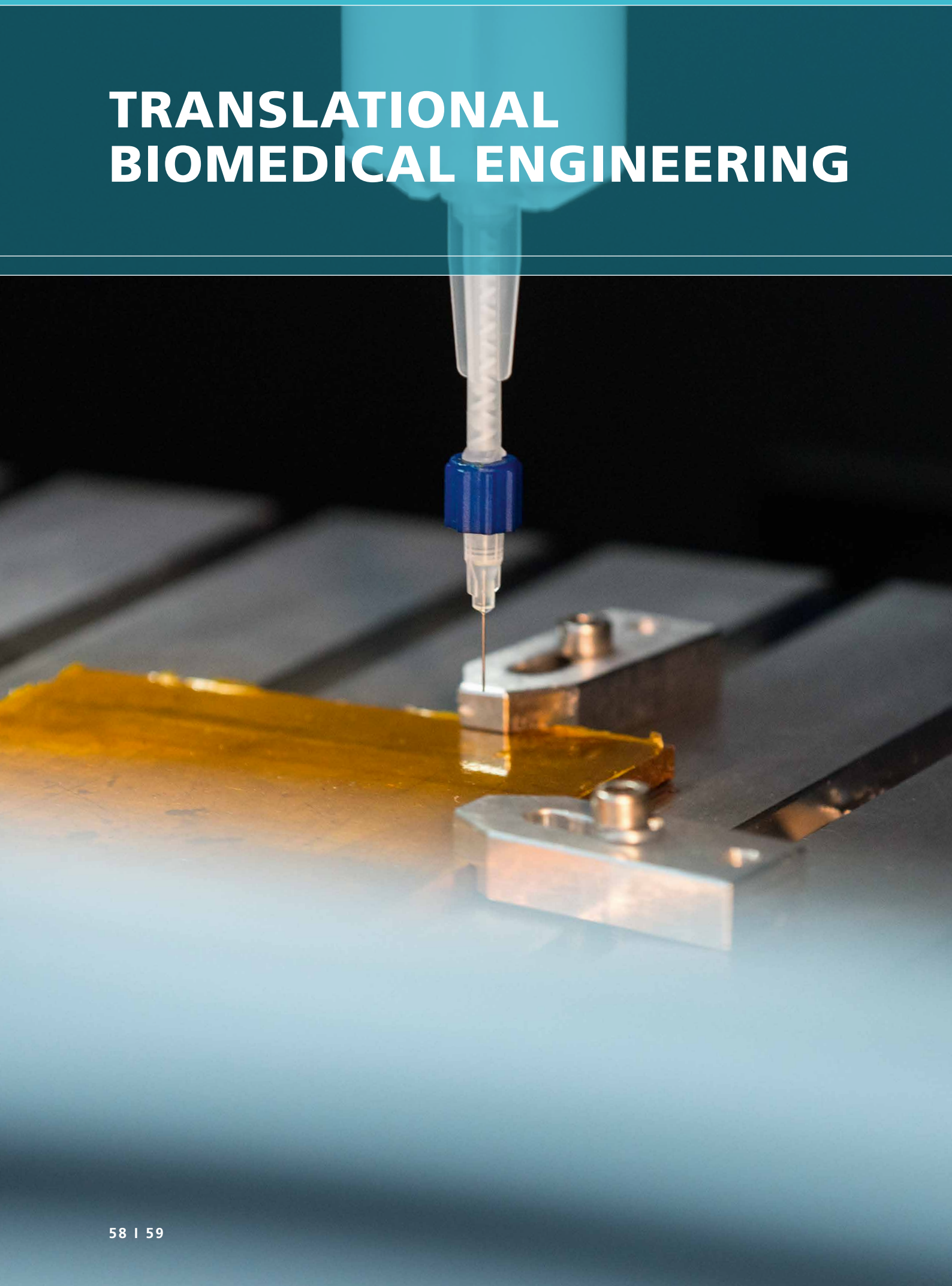
TRANSLATIONAL BIOMEDICAL ENGINEERING



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 administration technologies for medical aerosols towards smart drug/device combination products.

By cooperating with both internal and external development partners from industry and academia, we quickly find flexible solutions for project-specific requirements. We can thus comprehensively assist our clients in the medical device development process, including biocompatibility evaluation according to ISO 10993. In the fields 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.

The services offered by Fraunhofer ITEM can assist you on the way from idea to safe medical device.

www.item.fraunhofer.de/biomedical-engineering

Device development and manufacturing processes

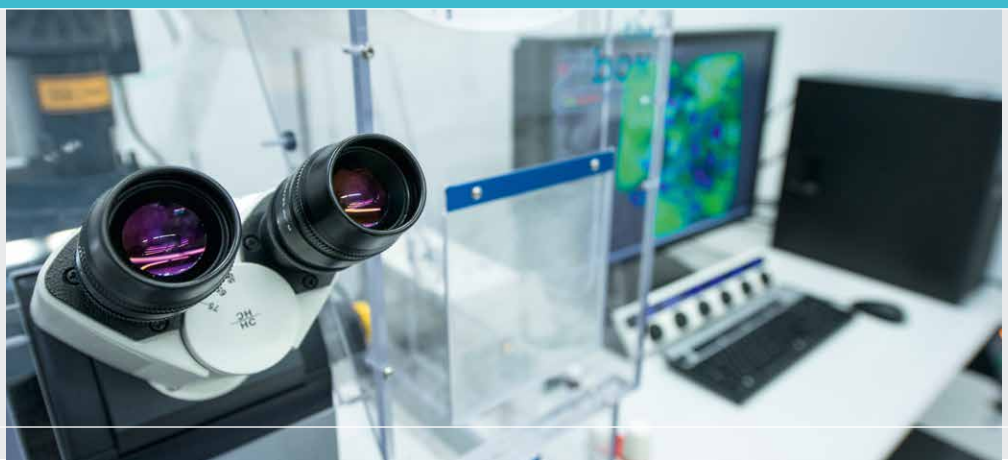
Our services allow our clients to substantially reduce the obstacles encountered during development of innovative medical devices and the risk of technology transfer failure. We can perform device development as contract research or support the client's own device development in a targeted manner through simultaneous development of custom-fit test benches and test methods. At Fraunhofer ITEM, products and test benches are developed to the point of meeting the requirements for use in first clinical investigations or as validated measurement systems. We are thus able to make an important contribution to your development process: from initial explorative research via prototype manufacturing and verification to first clinical investigations. In particular small and medium-sized enterprises and spin-offs from research institutions will benefit from our support in their development projects.

Area of expertise "Medical inhaler devices": The development of medical inhaler technology is increasingly evolving towards intelligent, breathing-controlled combination products for inhalation treatment with pharmaceuticals. Development of novel systems and formulations for the generation of inhaler medications, however, is a very complex process taking place in a highly regulated environment. Supporting clients with novel technologies for high-dose drug administration, enabling also continuous release of controlled high doses of dry powder and breath-triggered aerosol administration to neonates, infants and small children, is one of our areas of expertise.

Area of expertise "Implants": In addition to manufacturing individualized implants from medical-grade silicone rubber by using additive production methods, we do research on life cycle testing of implants. In order to evaluate the long-term durability of implants, we develop novel test methods tailored to specific requirements. These also include methods to test the osseointegration of orthopedic implants and testing of active implants in particular. For example, we investigate silicone delamination from interfaces with metallic conductors and explore methods for evaluating the long-term performance of neural implants in vivo.

Testing and test methods

Testing of medical inhalers: Conformity assessment of novel medical devices with the existing standard test methods is often not possible. This is why the relevant standards leave scope for action. ISO 20072, for example, does not exactly stipulate the test method to be used for testing of inhaler devices. To test novel systems for inhalation therapies, in many cases it is necessary to use new approaches and adapt existing or develop new test methods. We use standard methods as



well, but our focus is on testing novel devices and especially devices used in inhalation circuits for adults, neonates, infants and small children. This includes not only measurements of device performance, but also investigation of any impact the delivered substance may have on the whole ventilator circuit. This might be, for example, blockage of filters or other air-conducting pathways, such as nasal prongs of neonates.

Testing of implants: Modern implants are designed to last for a 100-year life span after implantation. To ensure that these requirements are already met in the development phase, custom-fit test methods must be employed. Whilst exposure to elevated temperatures has been a viable method of durability testing for many applications, thin-film polymer implants soon reach their limits with a pure temperature increase, e.g. when it comes to reliability. To solve this problem, we develop novel test methods, such as a multi-parameter model involving elevated and alternating pressures and artificial body fluids at high concentrations. Since testing according to the relevant standards for implants often does not guarantee long-term functionality, we also develop standardized in-vivo methods as well as modern test benches with extended testing features for implants.

Regulatory support

A pillar for success in the development of medical device technology is the regulatory strategy. The earlier it is established, the more smoothly the necessary conformity assessment can be performed, thus reducing the time to market. The present European MDR and IVDR (In Vitro Diagnostic Regulation) define quality and safety standards for medical devices and compliance with these is mandatory for a successful market entry or marketing authorization. Manufacturers have to prepare technical documentation to prove compliance with the general safety and performance requirements. Documented risk management to evaluate and minimize potential risks and clinical evaluation of medical devices in accordance with MEDDEV 2.71 have been regulated in detail and are essential in achieving compliance. Over a product's life cycle, there must be processes in place covering the identification and evaluation of technical, biological, and chemical risks.

In the business area Translational Biomedical Engineering, we have pooled our expertise in medical devices with our long-term experience in chemical risk assessment, nanomaterials, and biocompatibility. Medical device manufacturers will get optimal support in their development of innovative medical devices or in making adjustments to existing products required to achieve compliance with the new regulations. We devise a risk management strategy according to (DIN EN) ISO 14971, perform biological evaluation of the medical device as part of the risk management process, and identify and offer relevant in-vitro and in-vivo tests from the (DIN EN) ISO 10993 series of standards. Clinical evaluation is performed primarily based on literature and, if required, can be complemented by clinical investigation.

PROJECTS

Novel micro-nebulization system for pharmaceuticals

There is an urgent need for drugs for treating patients infected with SARS-CoV-2 and the COVID-19 disease it causes. In the DRECOR project, scientists from several Fraunhofer Institutes are seeking to rapidly identify new pharmaceutical agents against SARS-CoV-2 and develop therapies for COVID-19 by means of drug repurposing, i.e. by using existing pharmaceutical agents with known safety profile or drugs already approved for other medical conditions to fight this new disease. The researchers began by searching for suitable active molecules targeting the respiratory tract and lungs, which will then be formulated for systemic or inhaled administration. To enable testing of the identified drug candidates, they are developing complex in-vitro models and test systems that will also be applicable to other therapeutic areas in other projects.

For inhaled drug delivery, the researchers intend to develop a prototype of a smart medical device for micro-nebulization for use in clinical trials, aimed at enabling targeted deposition of very small amounts of drugs in both the throat and the nose, because these are the sites often colonized first by SARS-CoV-2. This requires adaptation of the conventional nebulizing technology. In addition, it is a special challenge to develop both delivery modes (to the lungs and nose) based on the same nebulizer platform. To develop the prototype, the Fraunhofer ITEM Division of Translational Biomedical Engineering has teamed up with Fraunhofer EMFT and the company Nebu-Tec. In the development of the micro-nebulizer, the researchers coordinate with Fraunhofer ISC, which is developing the drug formulation. A functioning demonstrator is scheduled to be available by mid-2021.

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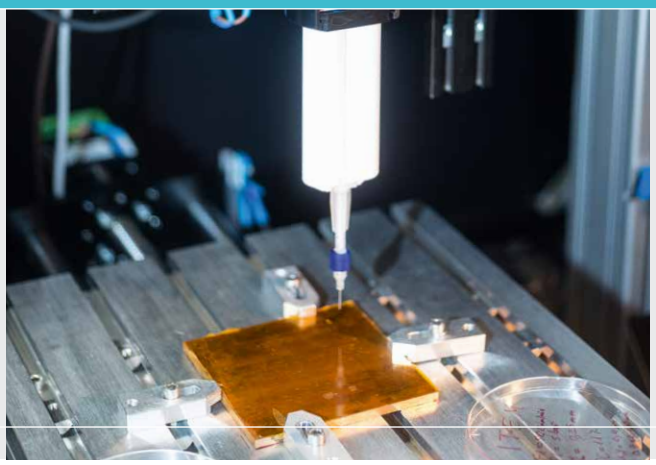

The custom-developed 3D printer enables processing of medical-grade silicone rubber and conductor materials to produce individualized neural implants.

Laser-facilitated 3D printing of biocompatible materials for neural implants

Fabrication of individualized neural implants by means of 3D printing is considered a promising sector of biomedical engineering. Due to the strong regulatory requirements, however, biomedical engineering is facing major challenges with regard to materials and manufacturing processes, as patient safety must be guaranteed by all means. Engineers and scientists collaborating in the High-Performance Center Translational Biomedical Engineering in Hannover have been working on a 3D printer for medical-grade silicone rubber since 2014. Based on this collaboration, researchers from the Lower Saxony Center for Biomedical Engineering, Implant Research and Development (NIFE) and Fraunhofer ITEM have now demonstrated that the printing process developed can be used to print both medical-grade silicone rubber and conductor materials. The printing process does not affect the biocompatibility of the raw materials and can thus be used for a wide range of manufacturing purposes. Furthermore, neurosensors produced with this method have electrical properties that are compatible with the intended neurological application in patients. The results have been published in the scientific journal "Sensors" (Behrens et al. 2020, DOI 10.3390/s20226614).

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Biomedical technology for fast local manufacturing of non-invasive ventilators

The "Give-a-Breath Challenge" launched by Munich Re and Fraunhofer-Gesellschaft in March 2020 actually had two winners in the sub-challenge category for non-invasive ventilators, who shared the award – one of them was the team SmartCPAP. The aim of the challenge was to develop equipment that could be manufactured anywhere in the world using 3D printing or other fast manufacturing processes to enable faster support in regions severely affected by the COVID-19 pandemic, independently of international supply chains. The SmartCPAP team, a cooperation of the Fraunhofer Institutes ITEM in Hannover and IAPT in Hamburg and the company AC Aircontrols GmbH, developed a prototype of a non-invasive ventilator that can be produced inexpensively and can be used in a wide range of conditions. The SmartCPAP ventilator has been designed for patients suffering from respiratory insufficiency induced by SARS-CoV-2. The device offers the possibility to supply the patient's lung with oxygen from three different sources:

- From the ambient air
- From a high-pressure source
- From a low-pressure source

Oxygen levels above room concentration can be achieved via either the high or low oxygen pressure supply lines. This allows the operator to adjust the oxygen level to the desired oxygen range between 21 and 50 percent FiO_2 (= inspiratory oxygen fraction). By making use of this ventilation system, intensive-care beds can be reserved for more serious cases. The team is now working hard to further develop the device to the point of being ready for market entry.

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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 (CTCs) 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 (DCCs). Our expertise also includes the analysis of cell-free, tumor-derived blood components (circulating tumor-DNA, microvesicles) and innovative tissue-based analytical methods (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", "Innovative molecular technologies and biomarker discovery", "Preclinical therapy models", "Disease modeling", and "High-throughput drug and target discovery", we work on a broad variety of topics in the fields of liquid biopsy and rare cell populations. Our in-house data management and comprehensive bioinformatics enable custom-fit analyses of the generated data. The Division of Personalized Tumor Therapy has been certified by TÜV Süd according to DIN ISO 9001:2015 and thus complies with international standards.

The services offered by this division can assist you on the way from molecular analysis to personalized tumor therapy.

www.item.fraunhofer.de/tumor-therapy

Single-cell analysis

Enrichment, isolation and molecular analysis of rare cells

Our commitment is to drive innovative therapeutic approaches by decoding the underlying mechanisms in complex diseases on a single-cell level. The focus is on solid cancers, e.g. the analysis of circulating tumor cells (CTCs) and disseminated cancer cells (DCCs), however, our technologies can be adjusted to different application areas, such as stem cell therapy. Our expertise ranges from the development and implementation of individual enrichment and staining strategies to the isolation of pure cell populations, down to a single target cell. As an accredited single-cell laboratory and through our cooperation with the University of Regensburg, we have access to a sample biobank generated from single CTCs/DCCs of patients with different cancer types. We use these for biomarker research and target validation, and for many samples a correlation with the clinical follow-up can be established. We thus work in a perfect environment for translational research within clinical studies.

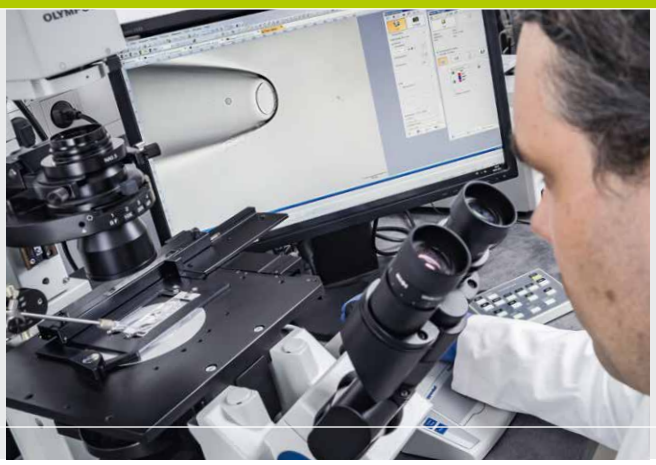
Decoding of single cells

For the development of tailored solutions for single-cell or rare-cell analysis, we offer expert knowledge in next-generation sequencing (NGS) and microarray technologies, in particular at the single-cell DNA and RNA levels. Our in-house developed workflows are optimized for the analysis of clinical low-input or single-cell samples, e.g. cancer cells isolated from body fluids, fine-needle aspirates and tissue specimens. Our workflow integrates quality control assays for optimal sample selection, technical implementation, and bioinformatics evaluation.

Innovative tumor models

In-vitro and in-vivo drug testing

For efficacy testing of drugs in innovative preclinical models representing systemic cancer disease, we offer experience in the generation of cellular models for functional analysis of rare cancer cell populations from fluids, organs, and primary tumors. To this end, we have established technologies allowing expansion of few DCCs or CTCs despite their extremely low abundance. Such preclinical models allow us to perform



individualized pharmaceutical drug tests, both in vitro and in vivo, and provide the opportunity to comparatively test drugs on cancer subpopulations. To support our clients in the discovery of novel drugs and drug targets, we use these in-vitro models in automated high-throughput screenings against approved cancer drugs, in addition to bioactive and diversity compound libraries.

Advanced preclinical PDX models

Preclinical animal models only partially represent the patient situation. We develop optimized PDX (patient-derived xenograft) models allowing more representative preclinical drug testing. Our advanced models are based on patient-derived metastatic precursor cells (DTCs) or CTCs. In addition, we concomitantly generate a human immune system in these models, which infiltrates the human tumors and develops phenotypes (e.g. tumor-associated macrophages) that have been described in patient samples. This allows both the tumor development and the dissemination of cancer cells into different organs to be followed in the presence of human immune cells. Our services include development of individualized preclinical in-vivo models to test in particular immunomodulatory drugs on target cells of systemic disease.

Mathematical modeling and bioinformatics

Multi-level disease modeling

Data analysis and biological process modeling are necessary to facilitate development of innovative therapies and support their clinical application. Therefore, we offer our clients profound data analysis and result visualization as well as aim-oriented mathematical modeling of biological mechanisms, disease progression, and therapeutic effects. We can also assist in experimental planning and statistical evaluation of experiments and patient trials. Our spectrum of methods ranges from feature selection, pattern recognition, machine learning, and network analysis to population dynamics, probability theory, and predictive modeling.

Bioinformatics services

Complex biological questions normally cannot be addressed by generalized "one-fits-all" approaches. Our commitment is to provide tailored bioinformatics solutions that provide a comprehensive yet specific answer to your experimental questions. We offer our clients expertise in bioinformatic analysis of high-throughput data from next-generation sequencing or microarray experiments. The Fraunhofer ITEM bioinformatics experts in Regensburg are focused on analyzing human single-cell omics data. Our expertise ranges from simple gene expression via complex genome reconstruction analyses to the development of novel algorithms and applications. Clients are invited to use our counseling services.

PROJECTS

Bioinformatics and disease modeling: essential for personalized tumor therapy

According to the current state of knowledge, cancer is not a uniform disease, but varies greatly between patients in terms of cause, course and treatment options. Therefore, therapy personalization is necessary. For this purpose, classical clinical data are increasingly complemented by high-dimensional molecular characteristics, referred to as multi-omics data. These methods require high-precision work, which is why strict quality standards (ISO 9001 certification) must be met from sample collection to secure data storage and data analysis.

At Fraunhofer ITEM in Regensburg, two working groups (WGs) perform data analysis and data modeling. The researchers of the WG on Bioinformatics and Data Management analyze various RNA- and DNA-based omics data. By automating the analysis workflows to the greatest possible extent, they ensure that the high demands on quality and reproducibility are met. The WG on Mathematical Disease Modeling is involved in numerous cross-disciplinary projects. The focus here is primarily on biostatistical evaluation of molecular biological and clinical data and on modeling tumor evolution and metastasis. In co-operation with the WGs on High-Throughput Drug and Target Discovery and on Preclinical Therapy Models, the researchers analyze data from tests with different pharmaceutical agents. The research and analysis activities are embedded in a data protection concept that takes into account the strict European and national guidelines for personal data and protects patients from possible re-identification.

The WG on Bioinformatics offers protocol-optimized routine analyses for bulk and single-cell sequencing data (mRNA, miRNA, CNV profiles, MSK-IMPACT) and develops solutions addressing new scientific problems. The scientists have thereby been able to contribute, for example, to the description of new cellular phenotypes.[1] With regard to methodology, they are currently working on improving the identification of disseminated cancer cells. The project work of the WG on Mathematical Disease Modeling has been reported in relevant publications, e.g. on tumor evolution and metastatic colony formation[2-5], on the characterization of mechanisms of metastatic growth[1] and on the introduction of novel diagnostic methods.[6,7] Other research performed by this WG addressed embryonic cell division[8] and the identification of stochastic biological systems.[9]

Looking ahead, the researchers want to develop innovative analysis methods and largely automate established processes. Based on modeling and the use of machine learning and artificial intelligence, they aim to gain a better understanding and quantitative estimate of tumor evolution, disease progression, and the efficacy of therapies. The best way to achieve these goals is through regional and international collaborations, which is why the team of researchers is further expanding its scientific network, for example by cooperating with the new Faculty of Informatics and Data Science at the University of Regensburg, the Bavarian Center for Cancer Research, and other Fraunhofer Institutes.

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1. Werner-Klein (2020): DOI 10.1038/s41467-020-18701-4; **2.** Hosseini (2016): DOI 10.1038/nature20785; **3.** Werner-Klein (2018): DOI 10.1038/s41467-017-02674-y; **4.** Ebinger (2016): DOI 10.1016/j.ccell.2016.11.002; **5.** Schumacher (2017): DOI 10.1038/bjc.2017.233; **6.** Czyz (2014): DOI 10.1371/journal.pone.0085907; **7.** Hoffmann (2018): DOI 10.1002/ijc.31108; **8.** Suzuki (2016): DOI 10.1038/ncomms12676; **9.** Hoffmann (2018): DOI 10.1038/s41540-018-0049-0.

Culture models with patient-derived breast tissue cells help to elucidate the factors that promote or prevent metastatic outgrowth of disseminated cancer cells.

Disseminated breast cancer cells hijack bone marrow growth factors for metastasis

Why is it that sometimes decades pass before first metastases appear in breast cancer patients, even though cancer cells spread to other organs already at an early stage of primary tumor development? And why do not all patients with disseminated cancer cells (DCCs) develop metastases, despite the early spreading? To find answers to these questions, Prof. Christoph Klein's teams at Fraunhofer ITEM in Regensburg and at the University of Regensburg's Chair of Experimental Medicine and Therapy Research have joined forces in their research. They have found indications of which factors promote or prevent metastatic outgrowth of disseminated cancer cells[1].

The research team was able to show that cancer cells disseminated into the bone marrow respond to the growth factor interleukin-6 (IL-6), which is present at high levels in the normal bone marrow environment. Using cell culture models with breast tissue cells from healthy donors, the researchers have demonstrated that IL-6 signaling causes DCCs to acquire stem cell properties that may be essential for metastasis formation. These findings may have revealed an Achilles' heel of DCCs and could enable entirely new therapeutic approaches, for example by disrupting signals from the microenvironment of the site the DCCs have colonized. Furthermore, this research work has shown that certain niches exist in bone marrow where DCCs are unable to receive the IL-6 signal. This could explain why some patients do not develop metastasis at all or only after a very long time, even though thousands of cells had already spread into the bone marrow from the primary tumor before it was surgically removed. Comparison of cancer cells from patients with and without metastasis suggests that DCCs acquire genetic alterations during their evolution in bone marrow, allowing them to become independent of environmental signals in the bone marrow and thus increasingly malignant.

The researchers' findings have important implications for the development of new adjuvant therapies aimed at early elimination of DCCs after removal of the primary tumor to prevent lethal metastatic disease from developing. In the early stages of cancer, a weakness of cancer cells may be their dependence on signals from the microenvironment to support their survival and proliferation. It may also be that at this early stage of the disease, DCCs are more sensitive to already approved drugs if in addition they are deprived of growth factors from the microenvironment or if growth activation by the bone marrow is systematically suppressed. The researchers hope that, if things go well, formation of metastases in breast cancer patients can one day become preventable and recurrence of the disease can be forestalled.

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1. Werner-Klein (2020): DOI 10.1038/s41467-020-18701-4.

FRAUNHOFER-WIDE NETWORK

Successful research requires scientific exchange – one of the reasons why Fraunhofer ITEM is well networked within the Fraunhofer-Gesellschaft. Fraunhofer Institutes that conduct research in related subject areas cooperate in Fraunhofer Groups, Alliances and Clusters of Excellence dedicated to specific topics to coordinate the development of appropriate solutions along the entire value chain. The Fraunhofer Clusters of Excellence promote the cooperative development and processing of system-relevant topics through an inter-institute research structure, corresponding to a "virtual institute" spread over multiple locations. In addition, Fraunhofer Institutes cooperate in Fraunhofer research programs, working out a solid basis for contract research geared to practical applications in pre-competitive research projects.

The Fraunhofer-Gesellschaft also plays an active role in the fight against the corona pandemic that began in early 2020. Under the motto "Fraunhofer vs. Corona", several Fraunhofer Institutes including Fraunhofer ITEM have joined forces in numerous projects to conduct joint research on different aspects of the pandemic (see also pages 26-33).

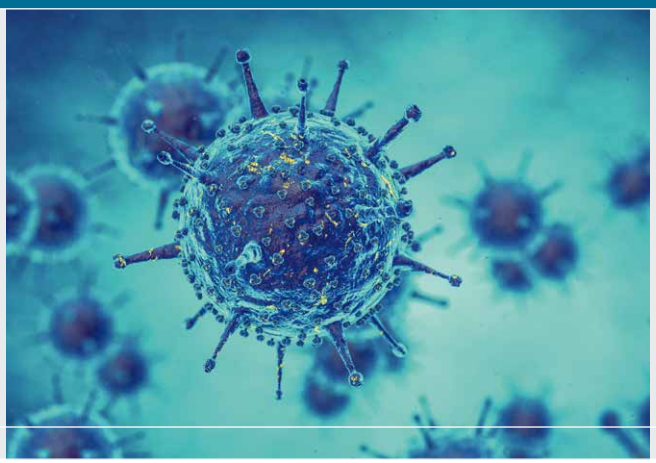
The Fraunhofer-Gesellschaft

Based in Germany, the Fraunhofer-Gesellschaft is the world's leading organization for applied research. With its focus on developing key technologies that are vital for the future and enabling the commercial exploitation of the results of this work by business and industry, it plays a central role in the innovation process. As an innovator and catalyst for groundbreaking developments and a model of scientific excellence, it helps shape society now and in the future. Founded in 1949, the Fraunhofer-Gesellschaft currently operates 75 institutes and research institutions. The majority of its 29,000 staff are qualified scientists and engineers, who work with an annual research budget of 2.8 billion euros. Of this sum, 2.4 billion euros are generated through contract research.
www.fraunhofer.de/en

Fraunhofer Cluster of Excellence Immune-Mediated Diseases CIMD

The primary goal of Fraunhofer CIMD is the translation of innovative ideas and identified targets into individualized therapies for immune-mediated diseases. The aim is to bridge the existing gap from research on novel medications to what is actually available to patients. To this end, three Fraunhofer Institutes dedicated to the life sciences – IME, IZI, and ITEM – have pooled their expertise.

About eight percent of the population worldwide suffer from immune-mediated diseases. These conditions are very heterogeneous and can affect almost any organ or tissue. So far, immune diseases mostly have been treated symptomatically with drugs that non-specifically suppress the patient's immune system. A treatment that fights the cause of the disease and, ideally, is individualized and cures the patient is not available at present. Fraunhofer CIMD is responding to the great need for research by means of translational research – the translation of findings from basic research into practical applications. It addresses the four major areas of medical science, the 4Ds – drugs, diagnostics, devices, and data – in the form of a virtual institute. Fraunhofer ITEM is involved in numerous projects, most of which target respiratory immune diseases such as chronic lung disease, asthma, and pulmonary fibrosis, and is working on the cross-institutional harmonization of clinical research processes and biobank structures.
www.cimd.fraunhofer.de/en



Innovation cluster "Production for Intelligent Medicine"

The "Production for Intelligent Medicine" innovation cluster pools the expertise of 23 Fraunhofer institutions to develop new development and production technologies for innovative 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.
www.item.fraunhofer.de/intelligent-medicine

Fraunhofer Group for Life Sciences

Six Fraunhofer Institutes – IBMT, IGB, IME, ITEM, IVV, and IZI – and the Fraunhofer Research Institution EMB, each having proven in-depth expertise in different areas within the life sciences, have teamed up in the Fraunhofer Group for Life Sciences. Their combined knowledge of biology, chemistry, biochemistry, biotechnology, medicine, pharmacology, ecology, and nutritional science is thus pooled and synergized – to allow solutions to be provided even for clients with complex requirements.
www.lifesciences.fraunhofer.de/en

Fraunhofer Nanotechnology FNT

Fraunhofer Nanotechnologie FNT is a cooperation of several Fraunhofer units that work together in the business and research field of nanotechnology – from application-oriented research to support and consultancy in the implementation of results in industry. Examples are the development of multifunctional layers for optical applications, automotive construction and the electrical equipment industry or the use of metal and oxidic nanoparticles, carbon nanotubes and nanoplatelets as well as nanocomposites as structural and coating materials and for biomedical applications. Furthermore, issues of toxicology and safe handling of nanoparticles are addressed.
www.nano.fraunhofer.de/en.html

Research project TheraVision

The aim of the Fraunhofer project TheraVision is to develop a platform technology for the development, manufacturing and testing of anticancer viruses. The Fraunhofer Institutes IGB, IZI, ITWM, IME, and ITEM want to jointly develop an oncolytic virus enabling targeted treatment of non-small-cell lung carcinoma.

Research project MyCellFight

For this ambitious research project, the Fraunhofer Institutes IGB, IMW, IZI, IOSB, IPA, and ITEM have teamed up. Their aim is to develop an automated immune chip enabling prediction of the specific immunological responses to a drug or chemical of up to 100 individuals at the same time.

Research project SynergyBoost

The Fraunhofer project SynergyBoost is aimed at making a significant contribution to the development of strategies for the fight against implant-associated infections. The collaborating Fraunhofer Institutes IME, IZI, IFAM, and ITEM are investigating synergistic combinations of active agents in this project.

Research project ELITE NK Cells

Administration of genetically modified immune cells is an innovative approach to treating tumors. Immune cells such as natural killer cells (NK cells) are able to specifically detect and destroy tumor cells. The Fraunhofer-Gesellschaft is funding the market-driven pre-competitive research project ELITE NK Cells, aimed at laying the foundations for electron beam-based inactivation of NK cells and their use as antitumor therapeutic agents. Partners collaborating in this project are the Fraunhofer Institutes IZI, FEP, IPA, and ITEM.

NAMES, DATES, EVENTS

394 employees

61 percent female staff

38 students (bachelor's and master's programs)

22 Ph.D. students

63 published abstracts

96 publications

44 publicly funded projects, including **12** EU projects

18 employees with activities for international journals

cooperation partners in **20** countries on **5** continents

56 oral presentations

32 congresses, workshops and seminars

25 employees teaching at **13** universities in Germany

23 cooperations with Fraunhofer Institutes

cooperation partners in **15** European and **5** non-European countries

52 cooperation partners outside Germany

34 employees actively participating in committees

6 patent applications

patents in **51** patent families

14 completed theses – **3** doctoral theses, **8** master's theses, **3** bachelor's theses

117 cooperation partners in Germany

2 podcasts

46 scientific posters

Figures are for December 31, 2020

Up to date throughout the year

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 in the field of 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. The figures on the two preceding pages give a first impression of our activities. On the following pages, you will find details of our active participation in committees, an overview of the publicly funded projects in which our scientists were involved in 2020, of our cooperation partners, and of congresses and other events to which we actively contributed in 2020, most of which were held as virtual events due to the coronavirus pandemic.

In addition, our website provides up-to-date information throughout the year:

www.item.fraunhofer.de/annual-report

Active participation in committees

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

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

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

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

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

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

German Center for Lung Research (DZL)

External assessor for international foundations

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

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

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

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

Reviewer in the European Commission's Marie Skłodowska-Curie Actions (MSCA) program, expert in the work packages "Biomedical Technologies" and "Sensors" of the EU Graphene Flagship

ASIIN reviewer for biomedical engineering careers

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

Uta Dörfel
Working groups on GLP analytics "GLP-Analytik" and medical devices "Medizinprodukte" of the German Quality Management Association (GQMA)

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

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

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

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

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

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

External assessor for the Klaus Tschira Foundation (mathematical oncology)

Reviewer for the international journal "Nature Communications"

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

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

Board member of the interdisciplinary allergy center of the Hannover Medical School

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

Dr. Olaf Holz
IABR (International Association of Breath Research) Standardization Focus Group

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

Dr. Kamran Honarnejad
Chair of the Knowledge Content and Delivery Council (KCDC) of the Society for Laboratory Automation and Screening (SLAS)

Reviewer for the journal "SLAS Discovery"

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

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

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

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

Advisory committee of the Pezcoller Foundation-AACR International Award for Cancer Research Committee

Scientific advisory board of the AIRC (Associazione Italiana per la Ricerca sul Cancro) 5x1000 project "Cancer of Unknown Primary (CUP): the archetype of metastatic disease"

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

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

Prof. Dr. Norbert Krug
Scientific advisory committee of the German Society for Allergology and Clinical Immunology (DGAKI)

Chair of the Clinical Trial Board of the German Center for Lung Research (DZL)

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

External assessor for the German Research Foundation (DFG)

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

Advisory board of the expertise network "Asthma und COPD"

Working group "Fraunhofer-Gesellschaft and Deutsche Hochschulmedizin"

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

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

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

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

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

Public relations delegate of the German Society of Toxicology

Dr. Meike Müller
Network of ombudspersons in Lower Saxony

Dr. Neophytos Papamichael
Working committee on quality management "Qualitätsmanagement im VLS" in the Fraunhofer Group for Life Sciences

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

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

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

External assessor for the Swiss Cancer League

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

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

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

Board member of Deutsche Atemwegsliga e. V.

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

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

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

Spokesperson of the Cell Biology Section in the German Respiratory Society (DGP)

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

Associate editor of "PLOS ONE"

Priv.-Doz. Dr. Susanne Rittinghausen

Co-optive member of the European Society of Toxicologic Pathology (ESTP) board: representative for nomenclature

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

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

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

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

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

Dirk Schaudien Ph.D.

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

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

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

Examination board of the European College of Veterinary Pathology

Dr. Stefanie Scheffler

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

Dr. Sven Schuchardt

Treasurer of the German Society for Metabolome Research

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

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

Scientific committee for the EU project FACTS (investigations to find FACTS on the subject of aircraft cabin air quality)

Dr. Florian Schulz

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

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

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

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

Dr. Katherina Sewald

Steering group of the workshop "Respiratory Toxicity"

German Center for Lung Research (DZL)

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

Mentor in the Fraunhofer career program for female scientists TALENTA

External assessor for international research grants

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

Prof. Dr. Lena Wiese

Special interest group "Digital Health" and working group "Data Science and Data Engineering" of the German Informatics Society

Dr. Dorothee Winterberg

Working group "Respiratory Toxicology" of the German Society of Toxicology (DGT)

Association of Inhalation Toxicologists (AIT)

German Center for Lung Research (DZL)

Dr. Sabine Wronski

Reviewer for the international journal "European Respiratory Journal"

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

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

Center for Pharmaceutical Process Engineering (PVZ) at Technische Universität Braunschweig

BioPharma-Translationsinstitut e. V.

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

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

Working group on carcinogenesis "Carcinogenese" of the German Society of Toxicology

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

External assessor for applications submitted to the German Federal Environmental Foundation

German Pharm-Tox Summit program committee

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

Publicly funded research projects

National

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

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

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

Designing nanoparticle-based inhaled antibiotics for the treatment of cystic fibrosis associated biofilms and infections and in vivo studies in a rat model. Project no. 256755002

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

Federal Environment Agency
Relevance of physiological and anthropometric parameters for the standardization and assessment of human biomonitoring results. R&D project 3716 62 214 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: 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: InhalAb
Alternative models for testing of inhalable antibiotics

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 "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 of Nafamostatmesylat for Covid-19 treatment

Federal Ministry of Education and Research (BMBF) funding program "Establishment of Industry-in-Clinic Platforms for the Development of Innovative Medical Devices"
Cooperation of Hannover Medical School, Fraunhofer ITEM and other stakeholders in the field of biomedical engineering, aimed at offering the competencies available in Hannover as a one-stop shop with pooled services

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, Atmungs-triggerung 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 Experten-system für die pädiatrische Intensivmedizin (a learning and interoperable, smart expert system for pediatric intensive-care medicine)

Federal Office for Radiation Protection
Childhood leukemia – influence of the immune system on the development of the disease (experimental study in a suitable animal model)

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

International

EU project: ERA-Net TRANSCAN
Analysis of tumor evolution and identification of relapse-initiating tumor cells in non-small cell lung carcinoma

EU project: eTranSafe (IMI)
Enhancing translational safety assessment through integrative knowledge management

EU project: Eurostars TARGIT
Development of next-generation treatment for allergies: targeted glycan-allergen immunotherapy

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

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

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

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

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

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

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

EU project: 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: ToxRisk (HORIZON 2020)
An Integrated European 'Flagship' Programme Driving Mechanism-based Toxicity Testing and Risk Assessment for the 21st century

Cooperation partners

National

Abbvie Deutschland GmbH & Co. KG

AC Aircontrols GmbH, Kempen

Activoris Medizintechnik GmbH, Gemünden (Wohra)

Adjutem GmbH, Oldenburg

Assay.Works, Regensburg

Augsburg University Hospital

BASF SE, Ludwigshafen

Bayer AG, Berlin and Wuppertal

Bielefeld University

BioMedVet Research GmbH, Walsrode

Boehringer Ingelheim Pharma GmbH & Co. KG

Brain AG, Zwingenberg

Bundeswehr Hospital, Berlin

Cardior Pharmaceuticals GmbH, Hannover

Cellex Patient Treatment GmbH, Dresden and Cologne

Center for Bioinformatics (CBI), Saarbrücken

Center of Allergy & Environment (ZAUM), Munich

Ceres GmbH, Lörrach

Charité – Universitätsmedizin Berlin

Charité Research Organisation, Berlin

Cilian AG, Münster

CORAT Therapeutics GmbH, Braunschweig

Cortec GmbH, Freiburg i. Br.

Cytena GmbH, Freiburg i. Br.

Desitin Arzneimittel GmbH, Hamburg

dysantect, Wiesbaden

Essen University Hospital

European Aviation Safety Agency (EASA), Cologne

European Molecular Biology Laboratory, Heidelberg

Federal Environment Agency, Berlin and Dessau

Federal Institute for Drugs and Medical Devices (BfArM), Bonn

Federal Institute for Occupational Safety and Health (BAuA), Berlin and Dortmund

Federal Institute for Risk Assessment (BfR), Berlin

Federal Office for Radiation Protection (BfS), Salzgitter

Forschungszentrum Jülich

Fraunhofer Center for International Management and Knowledge Economy IMW

Fraunhofer Institute for Cell Therapy and Immunology IZI, Leipzig

Fraunhofer Institute for Ceramic Technologies and Systems IKTS, Dresden

Fraunhofer Institute for Chemical Technology ICT, Pfinztal

Fraunhofer Institute for Digital Medicine MEVIS, Bremen

Fraunhofer Institute for High-Speed Dynamics, Ernst-Mach-Institut, EMI

Fraunhofer Institute for Industrial Mathematics ITWM, Kaiserslautern

Fraunhofer Institute for Integrated Circuits IIS, Erlangen

Fraunhofer Institute for Intelligent Analysis and Information Systems IAIS, Sankt Augustin

Fraunhofer Institute for Interfacial Engineering and Biotechnology IGB, Stuttgart and Würzburg

Fraunhofer Institute for Laser Technology ILT, Aachen

Fraunhofer Institute for Manufacturing Engineering and Automation IPA, Stuttgart

Fraunhofer Institute for Manufacturing Technology and Advanced Materials IFAM

Fraunhofer Institute for Material and Beam Technology IWS, Dresden

Fraunhofer Institute for Mechanics of Materials IWM, Freiburg i. Br.

Fraunhofer Institute for Microelectronic Circuits and Systems IMS, Duisburg

Fraunhofer Institute for Molecular Biology and Applied Ecology IME, Schmallenberg, Frankfurt/Main and Hamburg

Fraunhofer Institute for Reliability and Microintegration IZM, Berlin

Fraunhofer Institute for Silicate Research ISC, Aachen

Fraunhofer Institute for Surface Engineering and Thin Films IST

Fraunhofer Institute of Optronics, System Technologies, and Image Exploitation IOSB, Karlsruhe

Fraunhofer Research Institution for Additive Manufacturing Technologies IAPT, Hamburg

Fraunhofer Research Institution for Microsystems and Solid State Technologies EMFT, Munich

Friedrich Schiller University Jena

GEMoaB Monoclonals GmbH, Dresden

Genewiz Germany GmbH

Georg-August-Universität, Göttingen

German Aerospace Center (DLR), Cologne

German Center for Infection Research (DZIF)

German Center for Lung Research (DZL)

German Primate Center, Göttingen

Giessen University (JLU)

Goethe University Frankfurt, Frankfurt/Main

Hannover Medical School

Heidelberg University Hospital

Helmholtz Center for Infection Research, Braunschweig

Helmholtz Zentrum München – German Research Center for Environmental Health, Munich

HYpharm GmbH, Bernried

IPA – Institute for Prevention and Occupational Medicine of the German Social Accident Insurance at Ruhr-Universität Bochum, Bochum

Kiel University

KOEHLER eClinical GmbH, Freiburg i. Br.

Labor Pachmann, Bayreuth

Leibniz Institute DSMZ – German Collection of Microorganisms and Cell Cultures, Braunschweig

Leibniz University Hannover

Leibniz-Institut für Analytische Wissenschaften – ISAS – e. V., Dortmund

Leuphana University Lüneburg

Ludwig-Maximilians-Universität München (LMU), Munich

LungenClinic Grosshansdorf GmbH

Max Planck Institute for Heart and Lung Research, Bad Nauheim

MDR Competence, Düsseldorf

Merck KGaA, Darmstadt

Molecular Machines & Industries MMI GmbH, Eching

MT-Consult – Consulting Engineers for Medical Technology, Düsseldorf

Nebu-Tec GmbH, Elsenfeld

Ostbayerische Technische Hochschule Regensburg

Research Center Borstel

RWTH Aachen

Saarland University

SanoLiBio GmbH, Munich

Sanum Kehlbeck GmbH & Co. KG, Hoya

Schoen Clinic Berchtesgadener Land

Technische Universität Braunschweig

Technische Universität München (TUM), Munich

Telexos GmbH, Weilheim

TherapeutAix UG, Aachen

TissUse GmbH, Berlin

TRAIN – biomedical translation alliance in Lower Saxony, Hannover

TWINCORE (center for experimental and clinical research on infections), Hannover

Ulm University

Universitätsklinikum Erlangen

University Hospital Cologne

University of Applied Sciences and Arts, Göttingen

University of Bonn

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cellenion SASU, Lyon (France)

CeMM – Research Center for Molecular Medicine of the Austrian Academy of Sciences, Vienna (Austria)

Centro Ceramico Bologna (CCB), Bologna (Italy)

Cidetec, San Sebastián (Spain)

Daiichi Sankyo, Tokyo (Japan)

Demcon (The Netherlands)

ETH Zurich, Zurich (Switzerland)

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F. Hoffmann-La Roche AG, Basel (Switzerland)

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Griffith University, Gold Coast (Australia)

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Hibercell Therapeutics Inc., Chicago, Illinois (USA)

Immunotech SAS, Beckman Coulter Life Scienes, Marseille (France)

Instituto de Tecnología Cerámica, Castellón (Spain)

IT'IS Foundation, Zurich (Switzerland)

Johannes Kepler University Linz, Linz (Austria)

Mathys Ltd, Bettlach (Switzerland)

McMaster University Medical Center, Hamilton, Ontario (Canada)

Medical University of Graz, Graz (Austria)

Menarini Silicon Biosystems, Bologna (Italy)

Nanoconsult, Meerssen (The Netherlands)

Nordic Bioscience, Herlev (Denmark)

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Sentinhealth, Paris (France)

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University of Basel, Basel (Switzerland)

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Exhibitions, congresses, workshops, and seminars

Fraunhofer ITEM presents its research and the services offered at national and international congresses and exhibitions. In addition, the institute itself organizes a variety of seminars and workshops. In 2020, the COVID-19 pandemic made it impossible to hold face-to-face events as of mid-March, but numerous virtual event formats quickly made their way into the world of science as well. The institute hosted or played an active role in the following events (among others) in 2020:

January 22, 2020
Theme forum "Additive Medicine 4.0" and "Advanced Testing – Big Data post MDR"
Hannover (Germany)

January 23-24, 2020
DZL Annual Meeting
9th Annual Meeting of the German Center for Lung Research
Travemünde (Germany)

Januar 24-25, 2020
6th WATL Congress
Congress of the Scientific Working Group for the Therapy of Lung Diseases (WATL)
Berlin (Germany)

January 27-29, 2020
SLAS 2020
International Conference and Exhibition of the Society of Laboratory Automation and Screening
San Diego, California (USA)

January 30-31, 2020
EASA Workshop on future Cabin Air Quality Research
Cologne (Germany)

February 6-7, 2020
19th Fraunhofer seminar "Models of Lung Disease"
Hannover (Germany)

February 19, 2020
Biozide // Keimfrei
One-day training within the professional training series on paint and varnish "FARBE UND LACK Spezial Seminare"
Kassel (Germany)

February 19-20, 2020
10th Berlin Workshop on Developmental Toxicology
Scientific event of the BfR Academy
Berlin (Germany)

February 20-21, 2020
Liquid Biopsy Summit 2020
Lisbon (Portugal)

February 26-28, 2020
14th European Young Investigators Meeting
Scientific meeting endorsed by the European Cystic Fibrosis Society
Paris (France)

March 2-5, 2020
DGPT Annual Conference 2020
Annual Conference of the German Society of Pharmacology and Toxicology and 5th German Pharm-Tox Summit
Leipzig (Germany)

April 2-3, 2020
EPTRI Open Meeting
European Paediatric Translational Research Infrastructure (EPTRI) open meeting
Virtual event

May 3-7, 2020
SETAC SciCon
SETAC Europe 30th Annual Meeting
Virtual event

May 26, 2020
Medical silicone rubber in additive fabrication
Webinar by Fraunhofer ITEM as part of the Industry Days 2020 of the Industrial Generation Network

June 6-8, 2020
EAACI Digital Congress 2020
Annual Congress of the European Academy of Allergy and Clinical Immunology
Virtual event

June 9-30, 2020
SOT 2020
59th Annual Meeting of the Society of Toxicology and ToxExpo
Virtual event

July 12-14, 2020
6th Systemic Sclerosis World Congress
Virtual event

August 5-10, 2020
ATS International Conference 2020
International Conference of the American Thoracic Society
Virtual event

August 24-28, 2020
4th AMR Conference: Novel Antimicrobials & AMR Diagnostics
Virtual event

September 7-9, 2020
ERS International Congress 2020
International Congress of the European Respiratory Society
Virtual event

September 9-12, 2020
German Rheumatology Congress 2020
Virtual event

September 30, 2020
Expert meeting on pulmonary fibrosis
Hannover (Germany)

October 1, 2020
Bio-based economy and sustainable production systems
3rd Symposium within the series of events "Innovations in the Life Sciences" of the Fraunhofer Group for Life Sciences
Virtual event

October 8-9, 2020
The Research & Technology Series: flow cytometry, qPCR & digital PCR, liquid biopsies
Virtual event

October 14, 2020
ECETOC workshop "Scientific feasibility of exposure-based adaptations in the regulatory setting"
Virtual event

November 2, 2020
Immunology Day
Virtual event organized by the Fraunhofer Cluster of Excellence for Immune-Mediated Diseases CIMD

November 2-4, 2020
Clinical Trials Europe
Virtual event

November 4, 2020
Künstliche Mineralfasern, Mineralwolleabfälle – Herausforderungen für die Abfallwirtschaft
Webinar organized by the Austrian Water and Waste Management Association (ÖWAV)

November 9-12, 2020
BioData World Congress & Genomics LIVE 2020
Virtual event

November 11-12, 2020
Tissue engineering – a practical seminar on 3D cell culture for tissue engineering
Online seminar organized by the Fraunhofer Institute for Silicate Research ISC

November 23, 2020
Toxicology in 4D
4D workshop IV of the Fraunhofer Cluster of Excellence for Immune-Mediated Diseases CIMD young scientists program
Virtual event

December 2-4, 2020
InnoHealth China – German R&D Tour
Virtual German R&D tour for interested Chinese researchers, entrepreneurs and innovators

December 8-11, 2020
Training course on in-silico toxicology
Online training course by Fraunhofer ITEM in cooperation with RIVM

Due to the SARS-CoV-2 pandemic, many exhibitions, congresses, workshops, and seminars could only be held in a virtual format or were postponed by one year. Nevertheless, scientists managed to get together and exchange ideas, also with industry representatives – albeit mainly virtually and in entirely new formats that might, in fact, continue to be used and appreciated even after the pandemic.

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