Fraunhofer
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FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM

ANNUAL REPORT 2018

FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM

PERFORMANCE AND RESULTS

ANNUAL REPORT 2018

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FOREWORD

Dear Reader,

The world is changing – more than ever before. Nobody knows exactly what the future will look like. We could just wait and see what happens. Or we take the future into our own hands. This is exactly the motto of the Fraunhofer-Gesellschaft, which is celebrating its 70th anniversary in 2019, and this is also what drives the individual Fraunhofer Institutes: the ambition to shape the future!

In order to help shape and also be able to serve tomorrow's markets, we need to continuously invest in a future-oriented corporate strategy and organization. With the comprehensive strategy process Fraunhofer ITEM is going through at present, we are on the right track. We explore new topics and new fields of activity, further enhance existing competencies or realign these in anticipation of trends and developments. This also includes the optimization of our internal working processes. To this end, we restructured our divisions in 2018, to adapt to a changing reality. The institute's divisions in Hannover are now "Chemical Safety and Toxicology", "Preclinical Pharmacology and Toxicology", "Airway Research", and "Translational Biomedical Engineering". The divisions of "Personalized Tumor Therapy" in Regensburg and "Pharmaceutical Biotechnology" in Braunschweig have remained unchanged. We will, of course, continue to support our clients with the same proven expertise and, based on this strong foundation, will keep developing new areas of expertise.

Our driving forces are our fascination for research and our ambition to find answers to questions and solutions for problems that are currently relevant to society in the field of human health. For this Annual Report, we have picked three topics of strong interest that we discussed in more detail in interviews with our scientists: our approaches at Fraunhofer ITEM to find answers to the red-hot question of future treating options for infectious diseases, of the airways in particular – keyword: increasing antibiotics resistance –, our contribution to the development of new-approach methodologies in toxicology, aimed at making maximum use of existing data from animal experiments, and our capabilities to help clients bring their medical devices from the lab into clinical trials as smoothly as possible.

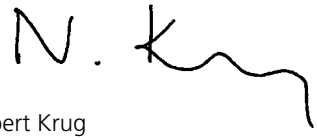
We are constantly striving to become even better. One way to accomplish this goal is joint research, because problems are being solved increasingly in collaboration with other scientists from different disciplines and institutions. Important network structures for us are local cooperations, such as here in Hannover the High-Performance Center Translational Biomedical Engineering, and research alliances within the Fraunhofer-Gesellschaft, in which some institutes temporarily join forces in collaborative projects.

The Fraunhofer Clusters of Excellence are also joint research projects. One of them is the Fraunhofer Cluster for Immune-Mediated Diseases CIMD, in which Fraunhofer ITEM is involved. With this research cluster, the Fraunhofer-Gesellschaft is expanding its activities around the 4 Ds of health research: drugs, diagnostics, data, and devices. In a kind of virtual institute, the Fraunhofer Institutes ITEM, IZI, and IME closely collaborate to advance the translation of innovative ideas and identified targets into individualized therapies for immune-mediated diseases and to bridge the existing gap from research

on novel medications to what is actually available to patients. The aim is not just to temporarily collaborate in a single project, but rather to follow a road map for the long-term development of a complex technological trend.

Frequently, joint research projects are also performed in an international setting, as in our German-Austrailan research project iCAIR®. The Australian Institute for Glycomics of Griffith University, the Hannover Medical School, and Fraunhofer ITEM have teamed up and set themselves the ambitious goal of developing new anti-infective drugs against viral, bacterial, and fungal pathogens – with a focus on respiratory infections. In the long term, iCAIR® is planned to be established as a pre-clinical development platform for new anti-infective agents that can also be used by external partners. It is only with a network that you can have lasting success and further develop things to ultimately achieve excellence.

To use Aristotle's words: "Excellence is an art won by training and habituation. We do not act rightly because we have virtue or excellence, but we rather have those because we have acted rightly. We are what we repeatedly do. Excellence, then, is not an act but a habit." If excellence is a habit, we will be happy to cultivate this good habit – together with the institute's staff, without whom our successful work would not be possible. With this Annual Report, we are offering you, dear reader, some insights into our current research and development topics. I hope you will enjoy reading it.



Norbert Krug
Executive Director


Fraunhofer IEM

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, firstly, on protecting health from potentially harmful, in particular airborne substances – be they gases, aerosols, particles, fibers, or nanomaterials – and secondly, on investigating and developing 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 scientific expertise and toxicological test methods – in the field of inhalation toxicology in particular. 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. The use of human tissue in in-vitro and ex-vivo test systems in particular 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 are keeping an eye on the ethical principle of the "3 Rs" – they are well aware of their great responsibility for the well-being of the animals they use in their experiments. 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.

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. 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. Fraunhofer ITEM has extended its diagnostic possibilities in clinical research: At the end of 2017, a sleep laboratory was set up in the phase-I unit of the CRC Hannover.

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: from recombinant production cell lines, master and working cell banks to bioprocess development and scale-up, manufacturing of pilot batches of the novel biopharmaceutical 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.

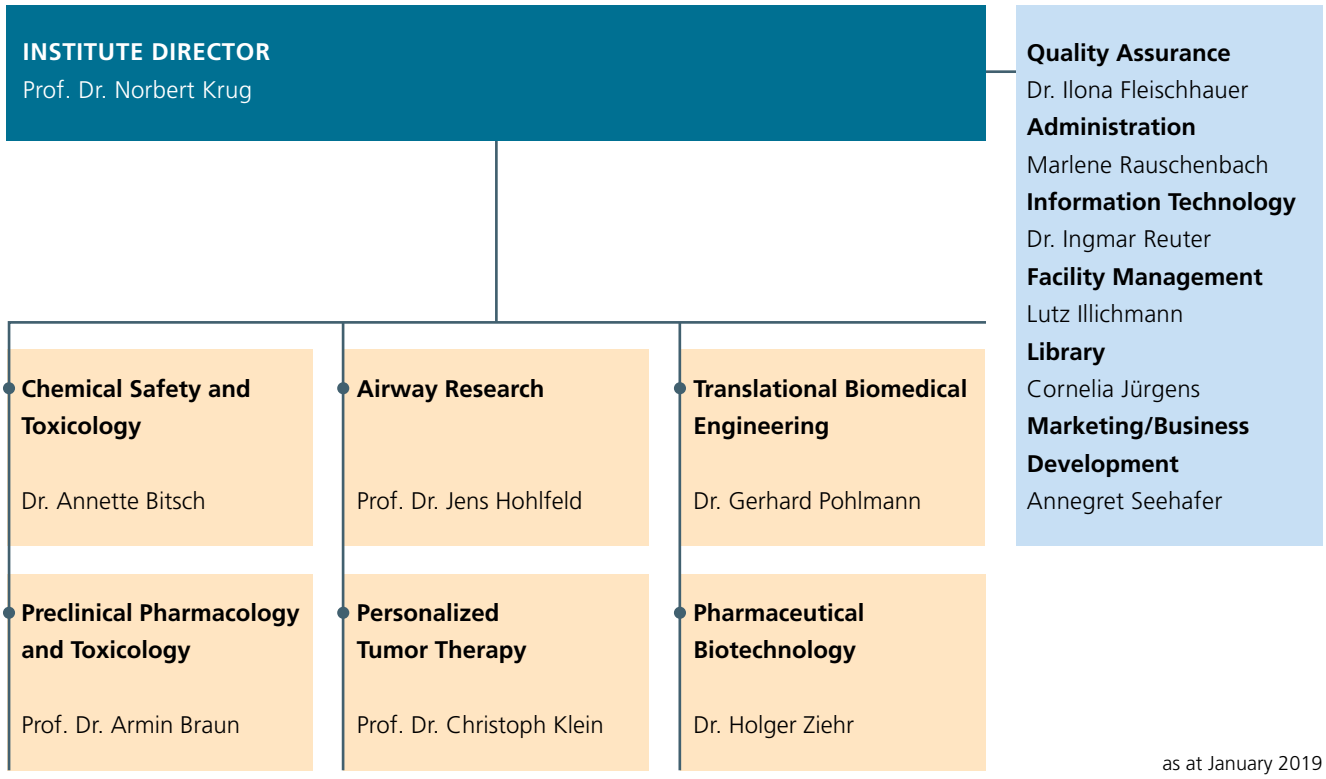
Bringing medical devices from the laboratory into clinical trials

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 new EU-wide Medical Device Regulation (MDR). To enable more efficiency in the translation process, the High-Performance Center Translational Biomedical Engineering was established in spring 2017. In this High-Performance Center, Fraunhofer ITEM collaborates 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.

ORGANIZATIONAL STRUCTURE



as at January 2019

The institute is managed by Prof. Dr. Norbert Krug. Under the Institute Director, Fraunhofer ITEM is organized in six divisions, which have pooled their expertise in three business units: Drug Development, Chemical Safety and Assessment, and Translational Biomedical Engineering.

The Fraunhofer ITEM headquarters are in Hannover, 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.

GXP – QUALITY ASSURANCE ACCORDING TO INTERNATIONAL STANDARDS

Fraunhofer ITEM is striving to meet high quality standards with the services and products offered and to ensure maximum safety for trial subjects in clinical studies performed at the institute. Not only are the relevant legal regulations strictly complied with, but state-of-the-art regulatory requirements are invariably taken into consideration. To guarantee that the work performed at Fraunhofer ITEM satisfies internationally accepted quality standards, Fraunhofer ITEM 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.

GLP compliance of non-clinical safety studies

To ensure reliability and traceability of the data generated in non-clinical health and environmental safety studies, the GLP principles include, among others, the following requirements:
– Clear assignment of responsibilities within the test facility
– Meticulous planning and qualified performance of every study
– Complete documentation of all procedures and preparation of comprehensive reports

By means of study-based and facility-based inspections, the service unit "Quality Assurance" continuously monitors compliance with these principles in the institute's departments that are concerned with toxicology, safety pharmacology, and analytics. For more than two decades, the competent authorities have performed regular inspections and have certified the institute's GLP compliance for a broad range of studies. The most recent inspection in December 2017 was also successful. On the occasion of a re-inspection in September 2018, the authorities furthermore confirmed GLP compliance of the test facility including the Department of Biomarker Analysis and Development. The established quality assurance system thus guarantees to all sponsors an internationally recognized quality standard in the institute's departments performing non-clinical studies.

GCP standard of clinical trials

The ethical principles for biomedical research laid down in the Declaration of Helsinki form the basis of the GCP principles describing the quality standards to be met in clinical trials. At Fraunhofer ITEM, long-established quality assurance measures ensure that these requirements are met in trials performed on behalf of international sponsors and in clinical research projects. The service unit "Quality Assurance" assists the clinical investigators in fulfilling their responsibilities by closely monitoring implementation of the quality-relevant processes under aspects of GCP and by routinely checking the corresponding documentation. The institute's sponsors have rated the quality level reached as GCP-compliant.

In the Clinical Research Center Hannover (CRC Hannover), cooperated as a Fraunhofer research institution by Fraunhofer ITEM, the Hannover Medical School (MHH) and the Helmholtz Center for Infection Research (HZI), the service unit "Quality Assurance"

performs cross-project and coordinating tasks in the field of quality assurance, thereby maintaining a high level of uniform quality standards in the CRC Hannover facilities. The synergies resulting from the scientific cooperation of the partners in the CRC Hannover thus go hand in hand with guaranteed maximum protection of all trial subjects and fulfillment of sponsors' quality requirements.

GMP quality standard

The Division of Pharmaceutical Biotechnology in Braunschweig has comprehensive expertise and a long track record in the development of GMP manufacturing processes for biopharmaceuticals. For this purpose, the division has established a GMP quality assurance system to ensure compliance with the German Drug Act, the German Ordinance on the Manufacturing of Medicinal Products and Active Ingredients (AMWHV), and the European Union GMP Guidelines. Other guidelines are also taken into account, e.g. those of the ICH (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use).

The division operates clean rooms of grades D to B according to Annex 1 of the EU GMP Guide, subdivided into different zones satisfying the respective hygiene and pressure requirements. Steam and water quality meets the requirements of the European Pharmacopoeia. All critical equipment for the manufacture of medicinal products has been qualified in compliance with Annex 15 of the EU GMP Guidelines. An automated filling machine enclosed in a restricted-access barrier system (RABS) of clean-room grade A in a clean-room grade B environment is available for manufacturing of small batches of sterile investigational medicinal products (IMPs) for use, for example, in clinical trials or stability testing.

The division has been repeatedly inspected by local and national authorities – the most recent inspection was successfully completed in March 2018 – and holds a manufacturing and importation license for microbial or animal cell culture biopharmaceutical APIs and for IMPs.

Biopharmaceutical products can thus be developed in collaboration with industrial and academic partners and can consistently be manufactured to the required quality – from initial cell line development and manufacturing of master cell banks to the optimization of production steps and the released IMP.

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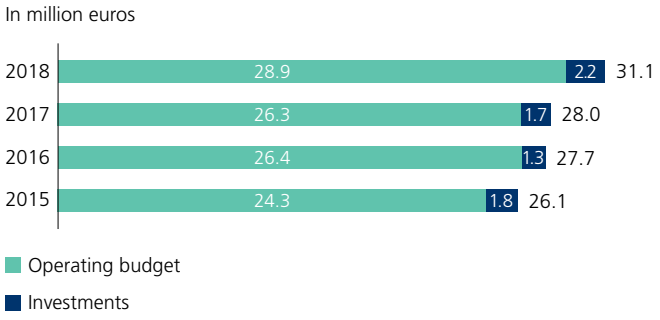
STAFF AND INSTITUTE BUDGET PERFORMANCE

At the end of 2018, Fraunhofer ITEM staff amounted to 357 persons:
7 apprentices
44 students (including Ph.D. students)
306 scientific, technical, and administrative staff

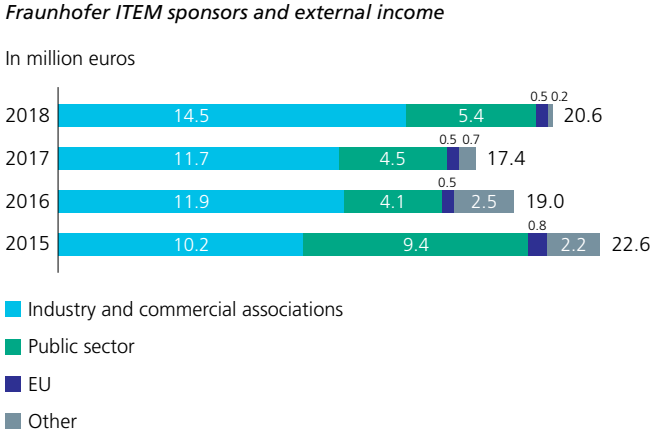
In 2018, the institute's budget reached a level of 28.9 million euros. Financing by acquired funding amounted to 71 percent. The share of industrial income in the institute's budget was 50 percent. Investments of Fraunhofer ITEM amounted to approximately 2.2 million euros.

Fraunhofer ITEM staff

Fraunhofer ITEM total budget



Fraunhofer ITEM sponsors and external income



BOARD OF TRUSTEES

The boards of trustees of the individual Fraunhofer Institutes act as purely advisory bodies to their institute's management. The members come from academia, industry, and government agencies. In 2018, the Fraunhofer ITEM board of trustees was made up of the following members:

Dr. Eckhard von Keutz
Chairman of the board of trustees
Senior Vice President, Head Translational Sciences,
Bayer AG

Prof. Dr. Christopher Baum
Deputy Chairman of the board of trustees
President and member of the Presidential Council
responsible for the Division of Research and Teaching of the
Hannover Medical School

Dr. Marcus Beiner
Deputy Head of the Department Research and Innovation,
Head of the Division of Life Sciences, Humanities,
Social Sciences, and Sustainable Development,
Lower Saxony Ministry of Science and Culture

Prof. Dr. Paul-Georg Germann
Head of Global Non-clinical Safety, Merck KGaA

Prof. Dr. Edith M. Hessel
Vice President and Head Refractory Respiratory Inflammation
Discovery Performance Unit,
GlaxoSmithKline UK Stevenage

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

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

Prof. Dr. Hillel S. Koren
Managing Director, Environmental Health, LLC;
former Director Human Studies Division,
United States Environmental Protection Agency;
Research Professor Carolina Environmental Program,
The University of Carolina at Chapel Hill, USA

Dr. Edgar Leibold
Vice President Product Stewardship, BASF SE

Prof. Prof. h. c. Dr. Thomas Lenarz
Director of the Department of Otorhinolaryngology
and Director of Deutsches HörZentrum,
Hannover Medical School

Prof. Dr. Reinhard Pabst
Lower Saxony Professorship in Immunomorphology,
Hannover Medical School

Prof. Dr. Klaus F. Rabe
Medical Director and Executive Medical Officer,
LungenClinic Grosshansdorf;
Endowed Professorship in Internal Medicine/Pneumology,
Faculty of Medicine, Kiel University

Dr. Thor A. Voigt
Medical Director Germany,
Boehringer Ingelheim Pharma GmbH & Co. KG

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

NEWS IN 2018

Gentle treatment for premature babies with lung diseases

Preterm infants who are born before their lungs have finished maturing often suffer from a lack of surfactant – a substance necessary for lung development. They are also particularly susceptible to illnesses of the respiratory organ, which have to be treated by means of inhalation. Available inhalation systems, however, are not geared to the needs of preterm infants and other newborns. Fraunhofer ITEM researchers are working with partners to develop a system that will allow drugs to be administered efficiently using breath-triggered aerosols. This will shorten therapy duration, thereby easing the strain on the infants.

https://www.item.fraunhofer.de/en/press-and-media/press-releases/gentle-treatment-for-premature-babies.html

Successful step in COPD research

In a clinical trial performed at Fraunhofer ITEM, administration of a combination drug from Novartis (indacaterol/glycopyrronium) was shown to improve not only lung function in COPD patients, but to have a significantly positive effect on their heart function as well. The results of this study were published in the renowned journal "The Lancet Respiratory Medicine".

https://www.item.fraunhofer.de/en/press-and-media/news/successful-step-in-COPD-research.html

Biomedical engineering: stakeholders request revision of the regulation

Patient safety is top priority in medicine and biomedical engineering. Aiming to increase patient safety, the EU introduced the European Medical Device Regulation (MDR) in 2017. During a discussion round organized by the Fraunhofer High-Performance Center Translational Biomedical Engineering, it became clear that stakeholders are expecting massive negative consequences from the regulation. They are suggesting specific measures for a revision of the MDR.

https://www.item.fraunhofer.de/en/press-and-media/press-releases/pr-medical-device-regulation.html

Cluster of excellence Hearing4all continued

As a partner in the cluster of excellence Hearing4all of the University of Oldenburg, the collaborating Fraunhofer ITEM scientists were proud that this cluster was selected for funding for the second time. The Excellence Commission published its decision in Bonn on September 27, 2018. In the future, the audiologists want to bundle their work into four research strands that will, on the one hand, map the development chain from basic research to hearing technology and, on the other hand, map the severity of hearing impairment.

https://www.item.fraunhofer.de/en/press-and-media/news/Hearing4all.html

InnoTour 2018: Australian delegation explored the German healthcare sector

In the course of InnoTour 2018, 16 researchers from Australia visited Fraunhofer ITEM on November 8, 2018. In scientific lectures about integrating human tissue into research and development and guided lab tours at the CRC Hannover, the visitors gained insight into the cutting edge of in-vitro toxicology and ex-vivo methods in particular. Organized by the Fraunhofer-Gesellschaft, InnoTour 2018 presented the large portfolio of applied research and corporate landscape in Germany and promoted networking between the German and Australian actors.

https://www.item.fraunhofer.de/en/press-and-media/press-releases/innotour-2018.html

Fraunhofer Science Campus: stepping stone into a scientific career for female students of STEM disciplines

Along with the career program TALENTA, the Science Campus is one of numerous measures aimed at increasing the share of female scientists at Fraunhofer. Fraunhofer ITEM actively supported this initiative in Braunschweig and Hannover: in September 2018, female students of STEM disciplines were given the opportunity to get an insight into the manufacturing and testing of candidate drugs.

https://www.item.fraunhofer.de/en/press-and-media/press-releases/science-campus-2018.html

Prediction of survival in patients with idiopathic pulmonary fibrosis

In a Fraunhofer study, Prof. Antje Prasse identified a signature in bronchoalveolar lavage that is predictive of survival in patients with idiopathic pulmonary fibrosis. In addition, the results suggest a hitherto unknown role of airway basal cells, which are progenitor cells of airway epithelium, in the pathogenesis of idiopathic pulmonary fibrosis.

https://www.item.fraunhofer.de/en/press-and-media/news/ipf.html

Battling infection and resistance in a German-Australian collaboration

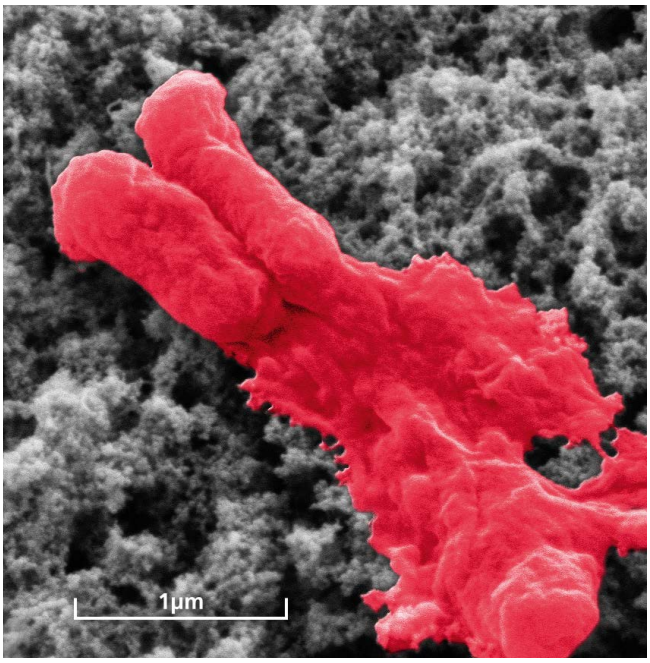
In the "Fraunhofer International Consortium for Anti-Infective Research"– iCAIR® in brief – researchers from Fraunhofer ITEM have teamed up with colleagues from the Hannover Medical School and Griffith University's Institute for Glycomics in Gold Coast, Australia. They have set themselves the ambitious goal of developing new anti-infective drugs. On January 18, 2018, representatives from academia, industry, governmental institutions and from the Australian embassy got together at Fraunhofer ITEM to celebrate the official launch of this pioneering collaboration. It is planned for the Helmholtz Center for Infection Research to also contribute its expertise to the consortium as a partner.

https://www.item.fraunhofer.de/en/lighthouse-projects/icair-project.html

No chance for bacteria on implants

Hip and dental implant operations are routine. But not entirely risk-free. They may result in infection that is difficult to control with oral or intravenous antibiotics. In such cases, the implant will normally need to be replaced. As part of the project Synergy-Boost, researchers of the Fraunhofer Institutes IFAM, IME, IZI, and ITEM have together developed a technique for preventing further infection: they can now apply a precisely matched drug directly to the implant while significantly increasing the effectiveness of the antibiotic via a synergism with silver ions.

https://www.item.fraunhofer.de/en/press-and-media/press-releases/synergy-boost.html



First study on a new antidepressant drug candidate at the CRC Hannover

Fraunhofer ITEM has extended the diagnostic possibilities in its clinical research by setting up a sleep laboratory with four beds in the phase-I unit of the CRC Hannover. In collaboration with the Department of Psychiatry, Social Psychiatry and Psychotherapy of the Hannover Medical School, a multi-center clinical trial started in February 2018. The aim is to investigate the effects of a new antidepressant drug candidate on the symptoms of depressive patients, but also on sleep disorders and other psychosomatic problems such as anxiety.

https://www.item.fraunhofer.de/en/press-and-media/news/sleep-study1.html

Fraunhofer researcher Prof. Christoph Klein received the "Fidler Innovation Award"

Prof. Christoph Klein (left in the photo), Fraunhofer ITEM Division Director of Personalized Tumor Therapy and Senior Professor of Experimental Medicine and Therapy Research at the University of Regensburg (Germany), has been given the international "I.J. 'Josh' Fidler Innovation in Metastasis Research Award". Prof. Klein received this award for his innovative contributions to metastasis research.

https://www.item.fraunhofer.de/en/press-and-media/press-releases/fidler-award-for-christoph-klein.html

TransPlaMed: translational manufacturing platform for innovative medical devices

In the publicly funded project TransPlaMed (NBank), the Institute for Microtechnology (IMT) of Technische Universität Braunschweig, the Lower Saxony Center for Biomedical Engineering, Implant Research and Development (NIFE), the University of Applied Sciences and Arts in Göttingen (HAWK), and the Fraunhofer Institutes IST and ITEM are collaborating to develop a translational manufacturing platform for innovative medical devices.

https://www.item.fraunhofer.de/en/press-and-media/news/transplamed.html

November of Science in Hannover: Open house day at Fraunhofer ITEM

On November 3, 2018, visitors got the chance to learn how approximately 300 Fraunhofer ITEM employees each day work on the early detection of airborne pollutants, on assessing the risks of such pollutants to human health, on diagnosing respiratory diseases, and on developing novel medications. A highlight for children was a mini hands-on training in the chemistry lab. The open house day at Fraunhofer ITEM was offered as part of the "November of Science", a project of the Initiative Science Hannover, in which eight universities in Hannover and Fraunhofer ITEM have been involved since its beginning in 2007.

Faster from the laboratory to the patient

In the development of new medications and smart medical devices, there is a gap between the discovery of potential active ingredients and products and their further development into drugs and medical devices by the industry. The Fraunhofer-Gesellschaft has joined forces with the Helmholtz Association and Deutsche Hochschulmedizin (the peak organization of German university hospitals and medical schools) to promote translational pilot projects in the health sector. In this so-called Proof-of-Concept Initiative, Fraunhofer ITEM is playing a major role in the project "Nanoparticles against pulmonary hypertension".

https://www.item.fraunhofer.de/en/press-and-media/press-releases/proof-of-concept-initiative.html

"Models of Lung Disease": new developments in lung research

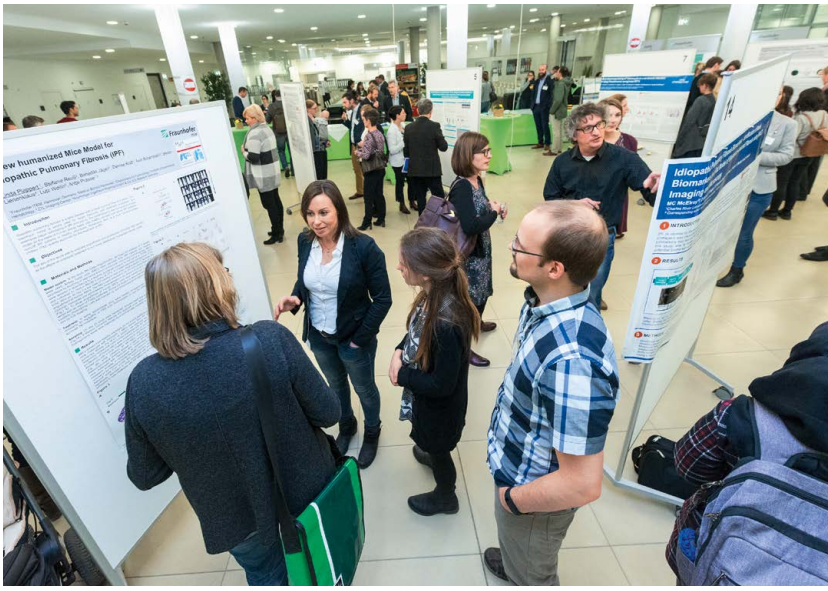
In January 2018, Fraunhofer ITEM organized the 17th seminar of the series "Models of Lung Disease". This event has long become a tradition at Fraunhofer ITEM and is one of the institute's flagships. Different phases of translational research were addressed in excellent presentations from the subject areas COPD, asthma, lung infection and exacerbation, tumor development, fibrosis, and new technologies.

https://www.item.fraunhofer.de/en/events/lungws_2019/documentation-models-of-lung-disease-2019.html

CRACK IT Challenge 2017: funding for two Fraunhofer ITEM projects

Two Fraunhofer ITEM project teams have been awarded funding for their research projects in the 2017 CRACK IT Challenge competition. The CRACK IT Challenge is the NC3Rs' response to the changing environment in the biosciences. The NC3Rs is a UK-based scientific organization dedicated to replacing, refining and reducing the use of animals in research and testing. Dr. Sylvia Escher was successful in the RespiraTox challenge with her project "In-silico model for predicting human respiratory irritation" and Dr. Tanja Hansen in the DoCE challenge with her project "Towards a differential dosing strategy covering diverse chemical classes and different exposure routes".

https://www.item.fraunhofer.de/en/press-and-media/news/crack-it-challenge-2017.html



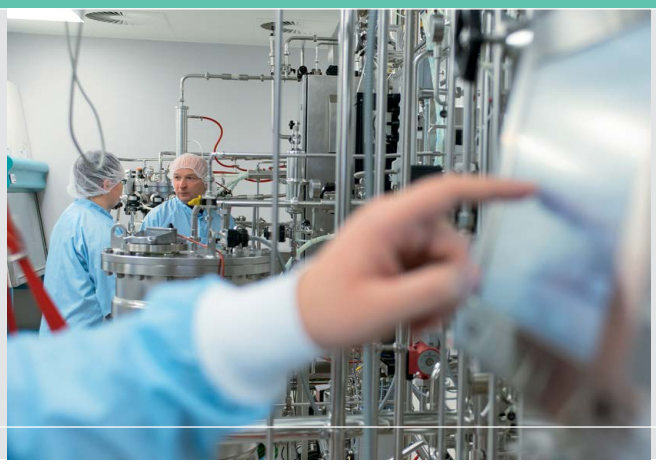
DRUG DEVELOPMENT

OUR SERVICES: 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.



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 and cells. 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 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 inhalation toxicology and immunotoxicology.

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 testing of drug candidates we offer the following services and expertise:

- In-vitro studies (genotoxicity, molecular toxicity, screening assays)
- Ex-vivo studies (e.g. precision-cut lung slices)
- 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

IN THE SPOTLIGHT

RESPIRATORY INFECTIONS: FRAUNHOFER ITEM IS ESTABLISHING A NEW RESEARCH FOCUS

The focus at Fraunhofer ITEM is on respiratory research. Over several decades, the institute's scientists have built up their expertise in research on respiratory diseases such as asthma and COPD and successfully performed projects both on behalf of and with clients. A topic of growing importance is that of infectious diseases of the lung – not least because they cause acute worsening of symptoms, termed exacerbation, especially in asthma and COPD patients. In addition, antibiotic resistance is drastically increasing, making previously treatable bacterial infections a serious threat again. Chronic, biofilm-associated and also viral lung infections are particularly difficult to treat. Dr. Sabine Wronski, manager of the Working Group on Infection and Immunology, explains how Fraunhofer ITEM research teams are facing up to the challenges in infection research.

Dr. Wronski, it is known that bacteria and viruses are constantly changing and can thus adapt to new conditions. Will this continue to be a race in which therapy development is always "one step behind"?

We think that we need to change our strategy to win this race, or to at least be able to find appropriate responses. For example, it is not conducive to count by all means on directly antiviral or antibacterial therapeutics, because these increase the selection pressure and thus promote the development of resistances. Instead, researchers are now trying to develop drugs that will keep pathogens from spreading in the host or will make them less dangerous for humans, for example by means of virulence blockers. Another approach is not to focus on the pathogens themselves, but to support the human immune system in its defense.

What is the approach Fraunhofer ITEM scientists are pursuing?

First, we need to better understand how viruses and bacteria adapt to the human body and how they interact with our immune system. Traditional development of anti-infective drugs often fails to take this into account. This is exactly our starting point. With our precision-cut lung slices model, PCLS for short, we are developing infection models with bacteria and viruses that allow us to study the infection directly in human lung tissue. Our aim is to mimic the situation in patients as closely as possible in our test systems, to eventually obtain results and also insights that will enable prediction with the best possible accuracy of what actually happens in the human body.

With PCLS, you thus have a method available that enables much more predictive studies. Where are you using this method?

We are already using this model in studies on behalf of pharmaceutical companies, for example to test whether potential drug targets actually play a role in human tissue during infection and whether their modulation can positively change the

course of the infection or the immune response. Furthermore, in the international project iCAIR®, our cooperation partners from the Institute for Glycomics in Australia are very successfully developing drugs against influenza and parainfluenza, which we in turn test directly in human PCLS.

Above all, we are very interested in establishing PCLS models of respiratory infections as a genuine alternative to animal studies.

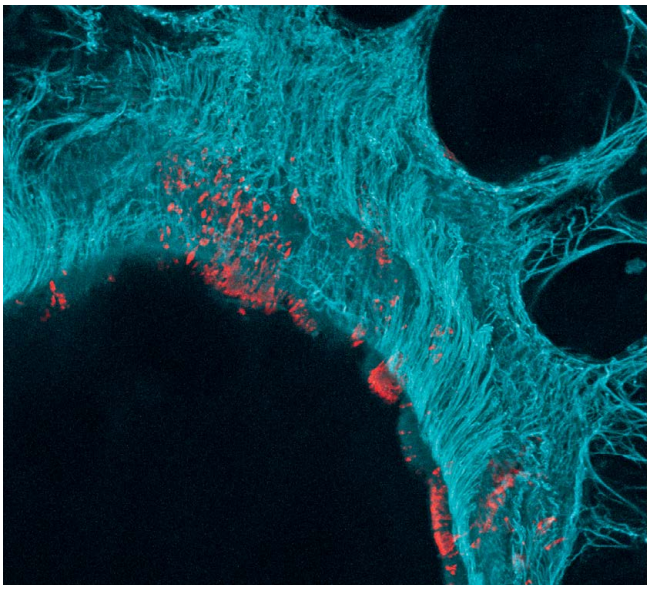
Inhaled administration of drugs is a standard treatment for patients with asthma. What role does this route of administration play in infectious diseases of the lung?

The benefit of inhalation therapies is that they deliver the active ingredient directly to the site of action. This leads to higher concentrations of the active agent in the lungs, as this route circumvents the barriers resulting from drug absorption via the gastrointestinal tract, losses due to insufficient transport into the lungs, metabolization or degradation of the active substance. In addition, systemic exposure is avoided and the risk of side effects is reduced. The development of inhalation therapies requires not only an intact tissue architecture, but furthermore, the route of exposure, i.e. inhalation, and aerosol distribution in the human lung must be taken into account. This is particularly important for lung areas with damaged tissue or that are difficult to access due to infection and inflammation. Unfortunately, these aspects so far can be covered only in animal experiments. Animal infection models, however, are associated with a high burden on the animals and, moreover, have no relation to the human organism. This is why we want to develop alternative models for the testing of inhalable antibiotics.

In the project InhalAB, funded by the German Federal Ministry of Education and Research, we are developing human-based in-vitro models, PCLS, and the ex-vivo model of the isolated perfused rat lung as a complete, intact organ. We then combine these components to enable best possible predictivity regarding drug efficacy, but also substance distribution in healthy vs. damaged lungs. Using standard-of-care antibiotics, we are trying to determine whether and to what extent the combined use of these models will enable a predictive statement about the effect in humans. If we manage to achieve this goal, this will allow us to use these alternative models for future testing of inhalable anti-infectives and will thus reduce animal testing in line with the 3Rs principle.

In which direction is infection research going?

For example, new active substances are being developed from insects. They have an antibacterial effect but are less prone to induce development of bacterial resistance. These substances thus have great potential as new antibiotics. In the projects Triple-IN and 4-IN, both funded by the German Federal Ministry of Education and Research, we are testing such insect-based anti-infective agents developed by Fraunhofer IME.



Human parainfluenza virus (hPIV3), displayed in red here, infects airway epithelial cells in human precision-cut lung slices, PCLS for short. Due to its autofluorescence, the lung tissue appears blue.

Interestingly, yet another, totally different trend is becoming apparent, namely a revival of the interest in research on traditional plant extracts. First of all, these are better accepted by patients, especially for treating mild colds, which affect millions of people every year and cause considerable economic damage. And secondly, such complex herbal medicines can, indeed, be more effective, as their various components act in a multifactorial manner, making it almost impossible for pathogens to develop resistance. We are observing a growing interest of companies to scientifically investigate the observed effects of complex medicines and to elucidate their mechanisms of action.

Another resurgent trend is research on phages, which is becoming more and more interesting due to the growing antibiotics crisis. Phages are viruses that specifically infect and kill bacteria. In eastern Europe in particular, phages have been successfully used as an alternative or complementary treatment to traditional antibiotic therapy. In the European Union, however, they have not yet been approved as drugs. This is due, among other reasons, to missing quality standards for bacteriophage production, a sine qua non for drug approval by the authorities. Furthermore, systematic clinical trials first have to be performed to demonstrate the safety, tolerability, and efficacy of treatment with phages. Our colleagues in the institute's Braunschweig-based Division of Pharmaceutical Biotechnology initiated the much-noticed project Phage4Cure, aimed at establishing bacteriophages as an approved drug for treating bacterial infections. To this end, they have teamed up with Leibniz Institute DSMZ-German Collection of Microorganisms and Cell Cultures GmbH, Charité – Universitätsmedizin Berlin, and Charité Research Organisation GmbH. The inhalation toxicological tests will be performed here in Hannover. We are developing the necessary nebulizing system for this and will perform the tests for persistence of phage activity.

What vision of modern infection research do you and your colleagues have?

Our vision is to use state-of-the-art methods in infection research to advance the development of new anti-infectives in order to effectively combat infectious diseases. To reach this goal, we have to think beyond the classical methods in infection biology and take into account the host or, more precisely, the host's immune response as an essential factor. With our approach of investigating infections in human PCLS, we are already getting much closer to this goal. Problems in this context are limited availability of the material and a substantially higher effort compared to other methods. If we succeed in optimizing new technologies such as tissue-on-a-chip, organ-on-a-chip, or artificial lymph nodes to the point that we can reproduce human tissue in its full complexity and function, this would be a quantum leap that would considerably advance the development of effective drugs. And, in principle, this holds true not only for infection research. But that is still a long way off, maybe another 10 to 20 years, before we will have reached this point. We hope to get there by collaborating with our strong partners, to decisively advance the development of new drugs that are effective again.

What do you reckon are the biggest hurdles to the development of new anti-infective drugs?

Despite the increasing threat from infectious diseases, anti-infective research has been at a low point for several years in recent decades, due to the withdrawal of large pharmaceutical companies. Consequently, research on and development of new active agents have been advanced above all by universities, start-ups, and SMEs. These, however, lack the financial means to bring the new active substances to market approval, as this requires expensive preclinical toxicological and, above all, clinical studies.

Fortunately, politicians have recognized the threat infectious diseases pose to public health as one of the most pressing problems of our time: the EU and Germany's federal government meanwhile are providing more money for infection research and have initiated numerous funded projects. Likewise, the large pharmaceutical companies have recognized that precompetitive collaboration is a key to success. Experts must team up and share resources instead of everyone doing their own thing. At present, this is being practiced only to a limited extent, but I believe that this is the only way to overcome the hurdles, especially considering the massive investments that are needed to bring even a single pharmaceutical to the market.

It seems logical that an application-oriented research institute such as Fraunhofer ITEM can help facilitate the transfer of research results into practical applications, given its commitment to translational medicine. Is that right?

It certainly is. We as Fraunhofer scientists live our commitment to precompetitive collaboration, not only by actively participating in a broad range of consortia funded by the EU and the German Federal Ministry of Education and Research, but above all by our proactive attitude. In the iCAIR® consortium, we have joined forces with the Australian Institute for Glycomics as a leading institute in the development mainly of antiviral drugs and, together with the Hannover Medical School, have pooled our resources there to develop new anti-infectives.

For anti-infectives in particular, finding an economically viable way is a necessity in view of their very low return on investment. The financial imbalance can be improved, among other things, by earlier go or no-go decisions. By using custom-made infection models closely mimicking the real-life situation, we want to enable the quickest possible and highly predictive selection of drug candidates for further development and thus facilitate the transfer from bench to bedside.

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PROJECTS

Hypoxic chamber as a challenge model of pulmonary hypertension

High blood pressure in the pulmonary arteries, usually referred to as pulmonary hypertension, is a severe disease for which no adequate treatment is available yet. Using a hypoxic chamber, Fraunhofer ITEM researchers have developed a challenge model of pulmonary hypertension that allows efficacy testing of novel medications for treating this disease. A rise in pulmonary arterial blood pressure can be induced in healthy volunteers by exposing them to hypoxic conditions. This rise is a normal physiological response to a low-oxygen atmosphere, like at high altitudes. Decreasing oxygen levels result in a contraction of pulmonary blood vessels and increasing pressure – temporary pulmonary hypertension is thus induced. At present, a first clinical drug trial in 25 volunteers is performed in the hypoxic chamber. The test subjects are administered either the drug candidate or placebo. Changes in heart ultrasound are used to measure the rise in pulmonary arterial pressure in response to the hypoxic conditions. Only volunteers with a leaking heart valve between the right ventricle and the pulmonary arteries have been included in this trial. Due to this defect, some blood flows back from the pulmonary artery into the ventricle after each contraction, and this regurgitation increases with rising pressure. Heart ultrasound allows the resulting slight differences to be measured. The aim of the present study is to demonstrate whether or not the candidate drug is able to prevent the hypoxia-induced rise in pulmonary arterial blood pressure. If so, this would provide the proof of concept.

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Validation of soluble biomarker measurement in nasal samples after an allergic response

Measurement results for soluble biomarkers in different sample materials cannot be assumed to be correct by all means – they may be biased due to the interference of soluble compounds such as proteins, lipids, or salts present in the investigated samples. Another interfering factor can be differences in binding strength of the analyzed proteins to the filter material and the resulting reduced solubility into the eluate during sample processing. In the collaborative project described in this report, absorption filters were used to collect the nasal liquid released after allergen challenge in the noses of allergic patients. The medium-term aim of this research is to be able to measure the concentration of early biomarkers of the allergic response and cytokines in this matrix, in order to enable efficacy testing of drug candidates. Corresponding ELISA and Multiplex systems are being validated to this end, with a view to recovery after eluation of the proteins pipetted into the filters and to measurement variance. Suitable measurement systems for biomarker measurement have been identified, allowing characterization of the early allergic response in the nose via the endpoints tryptase and histamine and enabling measurement of endpoints suitable to study the ongoing response in the nose via different pro-inflammtory cytokines such as interleukin-6, 4, and 5 as well as eotaxin.

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The hypoxic chamber as a challenge model of pulmonary hypertension – enabling efficacy testing of new drugs for treating this condition.

BAL cell gene expression is predictive of survival in IPF patients

Idiopathic pulmonary fibrosis (IPF) is a fatal disease with a variable and unpredictable course. A study under the direction of Fraunhofer ITEM was performed to determine whether bronchoalveolar lavage (BAL) cell gene expression is predictive of survival in IPF. The transcriptome of BAL cells from three independent IPF cohorts in Freiburg (Germany), Siena (Italy), and Leuven (Belgium) were analyzed, including 212 patients in total. BAL cells from 20 healthy volunteers, 26 patients with sarcoidosis stage III or IV, and 29 patients with COPD were used as controls. The scientists identified 1582 gene transcripts that were significantly associated with mortality. Many of the gene transcripts associated with mortality in IPF originated from basal cells of the airway epithelium. Basal cells are stem cells of the airways, and further analyses by gene expression, flow cytometry and immunohistochemistry showed an increase in airway basal cells in the lung tissue of IPF patients compared to healthy controls, but not in COPD or sarcoidosis patients. This study has demonstrated that a certain BAL transcriptome signature enables very good prediction of IPF-related mortality. Furthermore, the results suggest a hitherto unknown role of airway basal cells in the pathogenesis of IPF.

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Electron beam treatment of NK cells

Administration of genetically modified immune cells is an innovative approach to treating tumors. Such immune cells are able to specifically detect and destroy tumor cells. Besides T cells, natural killer (NK) cells can be used for this purpose. Their benefit is that they barely induce any adverse immunological responses, so that NK cells of non-related donors can be administered as well. Furthermore, it is possible to use NK cell lines that can be produced in unlimited quantities. Cells that are administered to patients, however, must not proliferate without control. Nevertheless, they must be able to kill tumor cells. Today's standard inactivation methods such as gamma or X-ray irradiation are not entirely suitable for this purpose. They damage the cells to such an extent that these are no longer functional. The radiation process thus needs optimizing. An innovative alternative to the method used so far is electron irradiation, which is fast and puts less stress on the cells. The result are cells that are fully functional but no longer able to proliferate without control. The Fraunhofer-Gesellschaft is funding the market-driven pre-competitive research project aimed at laying the foundations for electron beam-based inactivation of NK cells and their use as anti-tumor therapeutic agents. Partners collaborating in this project are the Fraunhofer Institutes IZI, FEP, IPA, and ITEM. Over the next three years, novel cellular immune therapies for treating cancer will thus be developed.

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Fraunhofer iCAIR®: German-Australian anti-infective alliance

Infectious diseases cause several million deaths per year worldwide – existing anti-infective drugs are increasingly losing their efficacy due to drug resistance development. Novel therapeutics are thus urgently needed; unfortunately, they often fail in the preclinical phase. Determined to tackle this issue, three partners founded the international consortium iCAIR® in September 2017: the Institute for Glycomics (IfG) of Griffith University in Gold Coast, Australia, the Institute for Clinical Biochemistry of the Hannover Medical School, Germany, and Fraunhofer ITEM. At present, the iCAIR® team is working on five collaborative pilot projects to develop novel active agents against viral, bacterial, and fungal pathogens, with a focus on respiratory diseases. In the long term, iCAIR® is aiming to establish itself as a preclinical anti-infective development platform that can also be used by external partners. First results were presented in January 2019 during the well-established Fraunhofer seminar Models of Lung Disease. Olga Danov of Fraunhofer ITEM and Patrice Guillon of IfG presented data demonstrating that parainfluenza infections of the lower airways can be successfully mimicked ex vivo. For the first time, this model enables detailed investigation of the immune response in human lung tissue. The active agents developed at IfG had a clear effect on the parainfluenza infection in airway epithelium and in precision-cut lung slices – they are promising candidate drugs for further development.

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Human lung tissue for efficacy testing of new anti-asthmatic drugs

Subgroups of patients with severe asthma are insensitive to inhaled corticosteroids and require novel therapies on top of standard medical care. IL-13 is considered one of the key cytokines in asthma pathogenesis. To enable the development of new therapy approaches, Fraunhofer ITEM scientists performed a study aimed at assessing the effect of IL-13 in human lung tissue. For the purpose of comparison, lung tissue from non-human primates (NHP) and rodents was investigated as well. The scientists prepared precision-cut lung slices (PCLS) and observed the effects of IL-13 on inflammation, induction of mucin, and airway constriction. In human PCLS, IL-13 induced release of the proinflammatory cytokines eotaxin-3 and TARC. Anti-inflammatory treatment with different inhibitors significantly attenuated the IL-13-induced inflammation. Contrary to this, IL-13 did not induce airway hyperresponsiveness (AHR) in human and NHP PCLS, although it was effective in rodent PCLS. Overall, this study has demonstrated that IL-13 stimulation induces production of mucus and biomarkers of allergic inflammation in human lung tissue ex vivo, but no AHR. The results of this study show a more distinct efficacy in human lung tissue than known from animal models and a clear discrepancy in AHR induction.

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The iCAIR® team develops and tests novel active ingredients, e.g. for treating parainfluenza infections. German and Australian members of the iCAIR® team met at Fraunhofer ITEM in January 2019 during the well-established Fraunhofer seminar Models of Lung Disease: (from left to right) Carla Seegers (Hannover Medical School), Prof. Mark von Itzstein (IfG, Australia), Prof. Armin Braun, Dr. Katherina Sewald, Olga Danov, Dr. Patrice Guillon (IfG, Australia), Dr. Jana Führing (Hannover Medical School/Fraunhofer ITEM), and Dr. Sabine Wronski.

Alternative to antibiotics: establishing bacteriophages as an approved drug

With the long-term aim of establishing bacteriophages as an approved drug for treating bacterial infections, Fraunhofer ITEM, Leibniz Institute DSMZ, Charité in Berlin, and Charité Research Organisation GmbH are collaborating in the project Phage4Cure. The initial goal is to produce three phages against the bacterium *P. aeruginosa* for an inhalable drug product. *P. aeruginosa* is often associated with hospital-acquired infections and cystic fibrosis. The project partners each are working on different aspects. DSMZ has isolated and selected suitable candidate bacteriophages. At Fraunhofer ITEM, *P. aeruginosa* strains are cultivated and infected with the selected *P. aeruginosa*-specific phages. The phages thus obtained are purified by chromatography. The current focus at Fraunhofer ITEM is on creating a platform-like production process where only a few parameters have to be adapted for successful purification of different types of phages. After establishment of the purification process, the whole process sequence will be performed in compliance with pharmaceutical quality requirements, i.e. GMP. Once phages are available as purified pharmaceutical ingredients, they will be tested in preclinical studies at Fraunhofer ITEM in Hannover and Charité Berlin. After completion and evaluation of the preclinical studies and the required regulatory approval, Charité Research Organisation will test the phages in first human clinical trials.

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Cultivation strategy for mammalian cell lines optimized by glucose limitation

The primary energy source for mammalian cell cultures is the carbohydrate glucose. In degenerated or tumor cells, glucose is converted to chemical energy mostly by glycolysis. Through the so-called Warburg effect, the cells transform glucose to pyruvate and then to lactate, resulting in an acidification of the extracellular space. This effect also occurs during cultivation of mammalian cell lines, leading to acidification of the culture medium. It can be counteracted by adding alkaline compounds such as NaOH or Na_2CO_3, however, with the adverse side effect of an increase in osmolality, which is unfavorable for the cell culture. A different approach is to limit the cells' supply of glucose. This can be achieved by continuously adjusting the glucose feed rate to the cells' current demand. Glucose availability is thus limited and the cells have no choice but to use the glucose entirely for energy production, without producing lactate. With this kind of process control, Fraunhofer ITEM scientists were able to prevent lactate production, thereby avoiding the addition of alkaline compounds and the resulting increase in osmolality. The results were prolonged cell growth and substantially increased cell productivity. This and other modifications to the cell culture medium and process control lead to a considerable increase in the yield of the target product and reliable prediction of the cultivation process.

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CHEMICAL SAFETY AND ASSESSMENT

OUR SERVICES: 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 assist you on the way from risk analysis towards safe products.

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

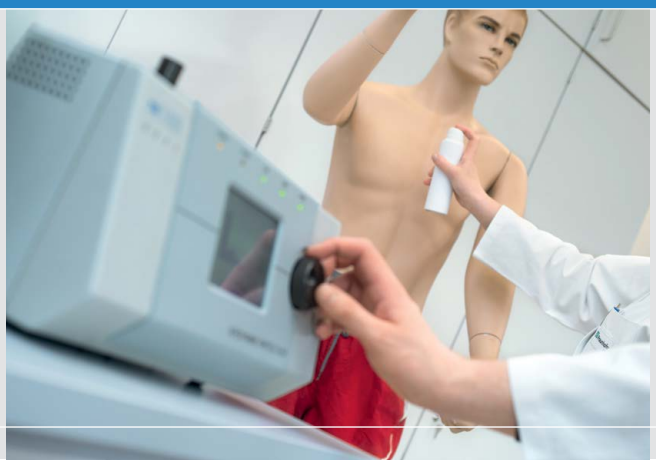
Aerosol research

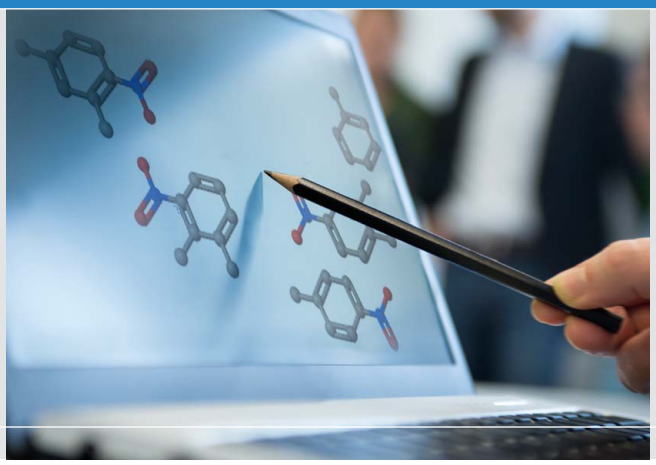
- Development of instruments and methods for measurement, collection, and generation of aerosols
- Development of methods and technologies for controlled inhalation studies with different atmospheres

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 incl. 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, 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. 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.

IN THE SPOTLIGHT

REPLACING ANIMAL TESTING: FRAUNHOFER ITEM ADVANCES THE DEVELOPMENT OF NEW-APPROACH METHODOLOGIES

Humans are exposed to chemicals all their lives: in the environment, at work places, and using household and care products. Human safety assessment is performed to assess the risk of these chemicals to human health. At present, this is done based on data from in-vivo animal testing. But a paradigm shift is underway and Fraunhofer ITEM researchers are contributing their expertise in this area as well. The scientists Dr. Sylvia Escher, head of the Department of In-Silico Toxicology, and Dr. Tanja Hansen, head of the Working Group on In-Vitro Test Systems, provide answers to questions of current interest.

Dr. Escher, in which direction is the paradigm shift in risk assessment going?

A paradigm shift is ongoing, away from traditional risk assessment based on apical findings in animal studies towards a mechanistic risk assessment. Mechanistic risk assessment aims to better understand mechanisms or adverse outcome pathways, AOP for short, leading to adverse toxic effects. It is assumed that a better understanding of these mechanisms will enable the design of specific human test systems which might be able to replace or at least reduce the amount of de-novo animal testing.

Dr. Hansen, what can the Fraunhofer ITEM scientists contribute?

Our working groups are involved in several projects aimed at replacing or reducing in-vivo animal testing by new-approach methodologies, NAMs for short. Such NAMs include in-vitro testing batteries and computer-based modeling approaches, termed in-silico models.

Dr. Escher, could you give us an example of a project?

In the EU-ToxRisk project, we recently completed a case study assessing the toxicity of a branched carboxylic acid by using a combination of in-vitro and in-silico models. We used a read-across approach with ten structural analogues. In addition, in-vivo data from three structurally related analogues were available. A team of partners from 14 academic institutions was involved in the design of the testing strategy. Based on the available in-vivo data, we assumed that the target compound 2-ethylbutyric acid (2-EBA) is a liver toxicant with special concern for hepatic steatosis. The NAM data proved this read-across hypothesis wrong by showing a consistent trend with regard to toxikokinetics and toxikodynamics within the grouped compounds.

To characterize the toxicodynamics, published signaling pathways leading to steatosis were compiled from literature and described in an AOP network. Two high-throughput models were used to measure some of the described molecular initiating events, MIEs for short. Furthermore, three liver models were used to measure lipid accumulation, which is seen as a direct in-vitro surrogate for in-vivo steatosis. It was shown that the

The ExpoCube® allows cell and tissue cultures on standard 12-well plates to be exposed directly at the air/liquid interface (ALI technology).

number of activated MIEs and induction of lipid accumulation increases with the side chain length of the tested carboxylic acid, whereas short-chain analogues like 2-EBA remained inactive. This finding is in very good agreement with the in-vivo data.

The next question that arises is how to derive a dose, based on in-vitro tests, below which there is no risk to human health. For this purpose, a human PBPK model was used in the EU-ToxRisk project. By means of this PBPK model, an equivalent

human dose was calculated based on the minimal-effect concentrations from all available in-vitro assays, a process known as quantitative in vitro to in vivo extrapolation. The results of this successful case study are currently being reviewed by toxicologists from national and international regulatory authorities. They are planned to be published in 2019.

Dr. Hansen, how can in-vitro test systems from your working group contribute to alternative risk assessment?

In the project ExITox-2 – Explain Inhalation Toxicology – funded by the German Federal Ministry of Education and Research, we are collaborating with three partners from academia and industry to develop NAMs for the assessment of inhalable compounds. By exposing a human alveolar epithelial cell line and human precision-cut lung slices at the air-liquid interface, we are investigating the hazard of five classes of compounds that share structural properties and specific adverse outcomes in in-vivo studies. The compound classes tested in ExITox-2 include volatile organic compounds (VOCs) and nanoparticles.

The most common approach used to mimic the exposure situation of the epithelium in the in-vivo lung is the air-liquid interface (ALI) technology based on cell cultures on microporous membranes. Fraunhofer ITEM scientists have developed a patented exposure device, the P.R.I.T.® ExpoCube®, facilitating the use of ALI cultures for testing of different classes of inhalable substances with high reproducibility and sufficient dose control. The ExpoCube® enables exposure of ALI cultures of cells or tissues directly in 12-well plates, prevents second-route exposures via the culture medium and ensures efficient particle deposition by thermophoresis. It thus provides the technological basis for new experimental designs.

In the ExITox-2 project, five read-across compound groups were tested for cytotoxicity in the human lung epithelial cell line A549 using the ExpoCube®. Secondary amines are known to cause pulmonary inflammation in in-vivo animal studies. An adverse effect on lung cells could also be demonstrated for these substances in the in-vitro model.

How will you perform in vitro to in vivo extrapolation in ExITox-2?

For this purpose, among others, we have developed a three-compartment lung PBPK model. It will enable a better estimate of the uptake of compounds via the respiratory tract.* The transport through the pulmonary epithelium is considered an important rate-limiting step for the systemic uptake of inhaled compounds. The transepithelial transport is thus investigated for different compound classes and the resulting permeability coefficients are used as input parameters for the lung PBPK model.

Dr. Escher, what exactly does this work mean for the risk assessment of the future?

We think that the above mentioned case studies from the EU-ToxRisk project and the results of the ExITox project will contribute to a better understanding of integrated testing strategies and their applicability to human risk assessment. Such illustrative case studies are needed to gain regulatory acceptance. We do believe that our in-vitro test systems in particular will help advance the paradigm shift towards alternative assessment methods for inhalable chemicals.

* Editor's note: For more information, please refer to the report "New in-vitro and in-silico tools for lung absorption and pharmacokinetics" on page 41.

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PROJECTS

Validated toxicity data for graphene nanoplatelets

Carbon-based nanoplatelets are a new class of 2D nanomaterials. Generation of valid toxicity data was the aim of the project PLATOX, funded by the German Federal Ministry of Education and Research. A variety of commercially available single-layer, multi-layer, and modified graphenes were selected as model substances that were first tested in vitro. Primary rat alveolar macrophages (AM) and primary human lung fibroblasts were used as cell models for this in-vitro screening. The endpoints measured were membrane damage, metabolic activity, proliferation, DNA damage, cytokine release, and eicosanoid release. AM proved to be the more predictive cell model. The single-layer graphenes showed the highest (geno)toxic and pro-inflammatory potential. To generate further data, two graphenes with the highest (i.e. single-layer) and lowest (i.e. multi-layer) toxicity potential were investigated in a 28-day inhalation study. The analysis of bronchoalveolar lavage fluid in the high-dose single-layer group showed a moderate inflammatory response with mild effects still four weeks after treatment, while the values in the multi-layer groups were at control level. In the oxidative comet assay performed 28 days after treatment, concentration-dependent induction of DNA strand breaks and a tendency to oxidative DNA damage were visible for single-layer but not multi-layer graphenes. Accordingly, moderate and weak inflammatory reactions, respectively, were observed in histopathology. The in-vivo results confirmed validity and predictivity of the in-vitro data obtained with the primary AM model.

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Antibiotics – collection of toxicokinetic data to assess uptake pathways

In 2014, the German Federal Institute for Occupational Safety and Health (BAuA) initiated the research project "Pilot study on the assessment of worker exposure to antibiotics in animal husbandry using biomonitoring methods – analyses part", examining feedlot worker exposure to antibiotics. The urine and blood samples analyzed at Fraunhofer ITEM and dust samples from stables provided evidence of the workers' exposure to the antibiotics administered to the animals during the fattening period. However, the concentrations measured in blood and urine did not allow any reliable conclusions on the route of exposure. Collection of toxicokinetic data after exposure via different routes could help improve occupational safety, for example by appropriate risk mitigation measures for workers. The subsequent project "Collection of toxicokinetic data for the assessment of different exposure routes using the example of the antibiotic enrofloxacin" designed by BAuA was aimed at investigating, as an example, the elimination kinetics of the antibiotic enrofloxacin (used in the pilot project) after dermal, oral, and inhalation administration. In this project, Fraunhofer ITEM recruited the test subjects, performed the exposure of human test persons, their biomonitoring for enrofloxacin and its main metabolite ciprofloxacin, and analysis of the toxicokinetic data. The scientists were able to show that ethically acceptable exposure of human subjects using subtherapeutic doses and suitable biomonitoring methods enables rapid identification of the route of exposure.

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The P.R.I.T.® air-liquid exposure system enables valid in-vitro testing of substances or mixtures, even in human cells. This method can be used to test airborne substances, such as the ingredients of cosmetic sprays.

New in-vitro and in-silico tools for lung absorption and pharmacokinetics

At work places and during the use of consumer products, inhalation is an important route of exposure. Due to the lack of in-vivo data describing bioavailable concentrations in humans, in-silico methods are needed for risk assessment. Fraunhofer ITEM has developed a general Physiological-Based Pharmaco-Kinetik (PBPK) model for different types of airborne substances, with a special focus on inhalation as portal of entry. The model simulates substance transport through the lung into the systemic circulation and, in addition, considers further relevant processes for removal of inhaled substances from the lung. The lung PBPK model uses in-vitro parameters to simulate internal doses in human plasma and tissue. Permeation values under air-liquid conditions are derived from human cells, tissue models, or ex-vivo models. In addition, the applicability of other biological and physical parameters determined in vitro, such as intrinsic hepatic clearance or dissolution rates, is being investigated. The final IVIVE lung PBPK model (IVIVE = in vitro to in vivo extrapolation), which is still under development, aims to be universally applicable to gases, liquid aerosols, and (slowly) soluble particles. It can provide useful data for both safety assessment of chemicals and preclinical studies with inhalable pharmaceuticals, e.g. antibiotics. The lung PBPK model will be further developed within the recently started project Cefic-LRI B21.

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Identification of potential chemical risks from REACH-registered substances in food

On behalf of the European Food Safety Authority (EFSA), FoBiG and Fraunhofer ITEM cooperated in a project to apply the method developed in a preliminary project to all substances registered under REACH. Data were evaluated for: (a) environmental release, (b) biodegradation, (c) bioaccumulation in food, and (d) toxicity, e.g. their classification regarding mutagenicity, carcinogenicity, reprotoxicity, and repeated-dose toxicity. The substances were prioritized using defined procedures. For further evaluation, 212 of 2336 substances were identified as priority substances. To confirm the accuracy of this prioritization, 10 substances not listed or assessed in detail by other regulatory bodies were selected for in-depth evaluation. For four of these substances, data on the occurrence in the environment or in food/feed could be found. Enhanced monitoring in food/feed is recommended to enable better assessment of their relevance as emerging risks in the food chain. For the remaining six substances, no data on occurrence are available or existing data were considered uncertain. For these substances, monitoring in relevant environmental compartments is recommended to gain more insight into their relevance as contaminants. Furthermore, a group of 517 substances could qualify as priority substances, if additional toxicology data lead to classification in the future.

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Health effects of phthalate exposure in children and adolescents

Phthalates belong to the class of low volatile organic compounds and most of the phthalates produced industrially in large quantities are used as plasticisers. Phthalates are ubiquitous in the environment and their absorption into the human body is generally possible via all routes of exposure – oral, dermal, or by inhalation. Some chemicals of this category are considered endocrine disruptors, i.e. they can affect the hormonal system and thereby may cause adverse health effects. In a project initiated by the German Federal Environment Agency and funded by the German Federal Ministry of Education and Research, a literature review was performed to identify studies investigating potential health effects of phthalates in children and adolescents up to the age of 21 years. For an evaluation of the most recent and relevant epidemiological studies (most of them cohort studies), the reported potential effects were assigned to the categories growth and metabolism, sexual development and reproductive performance, atopic diseases, neurocognitive development, and other health effects. Due to substantial heterogeneity of the evaluated studies concerning the assessed age groups, analyzed routes of exposure, measured outcomes, and methods of data analysis, a quantitative synthesis of the results was not possible. The qualitative synthesis of the study results provided only initial indications for long-term health effects of phthalates.

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Safety assessment of cosmetic products

Cosmetic products are used as leave-on or rinse-off products. In either case, direct exposure of the human body occurs. There is a wide range of cosmetic products, from hair care products, deodorants, and powder products to lotions and sun screen products. The products are usually evaluated to be safe under "normal" use conditions; however, chemical changes are possible in extreme or very specific use situations, such as hot showering or hot hair drying. Fraunhofer ITEM supports industry and users in the development of specific safety assessment concepts for such products. For this purpose, Fraunhofer ITEM scientists offer comprehensive characterization of inhalation exposure including droplet size analysis and consideration of aged aerosols from spray products as well as chemical analysis of any substances of interest in the aerosol and gas phase. Applying relevant test atmospheres to the P.R.I.T.® air-liquid exposure system, valid in-vitro testing of substances or mixtures can be carried out, even in human cells. Additionally, in-silico approaches such as read-across can be applied and finally, considering all available data, risk assessment tailored to the specific question can be performed.

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Measurements have demonstrated that aircraft cabin air quality is largely comparable to normal indoor air quality.

Perception of oil-related "smell events" in aircraft cabin air

A study commissioned by the European Aviation Safety Agency EASA to investigate cabin air quality was successfully completed in 2016. In this study, the occurrence of airborne contaminants was monitored during a total of 69 flights. Scientists of Fraunhofer ITEM and the Hannover Medical School included 108 additional measurement flights performed in collaboration with Lufthansa in their analysis. In some of these flights, so-called "smell events" were encountered, where the cabin or cockpit crew reported a "smell of oil" with potential adverse health effects. In no case was the olfactory detection of oil confirmed by the measurement results. In contrast, putative contamination with oil, identified via increased organophosphate concentrations (e.g. tricresyl phosphate), was not detected by smell on any occasion. Even in the presence of elevated organophoshate levels, concentrations in cabin air were below the established limit values. In addition, systematic quantitative analysis of the contaminant profiles showed a reduced air exchange rate in the takeoff phase in almost all commercial aircraft. The measurements demonstrated only low contamination of cabin air, in a range that is largely comparable to normal indoor air. The results were published in the scientific journal "Building and Environment" in November 2018 (Schuchardt et al., Vol. 148, pp. 498-507. DOI: 10.1016/j.buildenv.2018.11.028).

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Endocrine disruptors and biocides – new guidance in force

The assessment of endocrine activity of chemicals is receiving much public attention. Clear criteria for their identification, however, had been missing in the past. In 2018, the guidance for the identification of endocrine disruptors (ED) came into force. It lays down the implementation of ED criteria in the context of the Biocidal Products Regulation (BPR). A substance is considered as having ED properties if it shows adverse effects that are linked to an endocrine mode of action, such as estrogen, androgen, thyroid, and steroidogenic (EATS) modalities. The ED properties need to be assessed for both humans and non-target organisms. As a starting point, all relevant information (in-vivo, in-vitro, but also in-silico data) has to be gathered and grouped in tables. Finally, the existing knowledge on EATS-mediated adverse effects has to be addressed in a mode-of-action analysis. As a conclusion, a link between endocrine activity and observed adverse effect(s) has to be established. The new guidance is valid for all biocide applications and addresses biocidal active substances as well as co-formulants in biocidal products. Therefore, applicants have to evaluate an extensive dataset before submitting it to the competent authorities. Fraunhofer ITEM with its specific expertise in toxicology supports its clients in all aspects of scientific and regulatory issues. This also comprises the compilation of data for the evaluation of the endocrine potential of biocides.

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TRANSLATIONAL BIOMEDICAL ENGINEERING

OUR SERVICES: 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 testing.

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 assist you on the way from idea to safe medical device.

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 trials 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 trials. 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 a novel technology for high-dose drug administration, enabling also continuous release of controlled high doses of dry powder, is one of our areas of expertise.

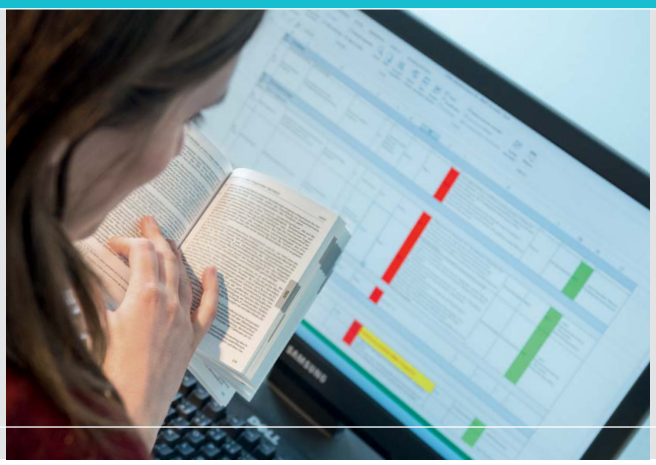
Area of expertise "Implants": Besides cochlear implants with a high number of channels, active positioning in the cochlea, and drug delivery functions, we develop individualized ECoG arrays based on additive manufacturing. In addition, we perform research on accelerated life cycle testing of polymeric implants.

Testing and test methods

In addition to the use of standard methods, we develop new test methods to meet specific requirements. These include above all accelerated-aging models for active implants, which are necessary to allow the required long-term durability of such implants to be determined.

The test systems for medical devices intended for use in inhalation and aerosol therapies follow a risk management approach – the relevant standards such as ISO 20072 do not stipulate the application of particular test methods. Therefore, when it comes to testing novel medical devices, for example for use in neonates, there is a need to develop new test methods, as there are no suitable test systems available.

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 stipulate the test method to be used for testing of inhaler devices. Quite the



contrary, to test novel systems for inhalation therapies in many cases it is necessary to follow a risk-based approach 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 and neonates. 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 active implants: Modern active implants are designed for early childhood implantation and 100-year periods of use. To ensure compliance with these requirements already during development, accelerated testing must be employed. Whilst exposure to higher temperatures has been a working solution for many applications, thin-film polymer implants face reliability limits with a pure temperature increase. To solve this problem nonetheless, we develop new test methods such as a multi-parameter model that makes use of elevated pressure and artificial body fluids at high concentrations. By setting up mathematical modeling in parallel, we can provide the desired long-term life span forecasts for permanent implants with high accuracy.

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 unit 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 testing.

IN THE SPOTLIGHT

HIGH-PERFORMANCE CENTER TRANSLATIONAL BIOMEDICAL ENGINEERING – A FRAUNHOFER ITEM LIGHTHOUSE PROJECT

Medical devices can significantly improve patients' quality of life. To this end, numerous universities and research laboratories are constantly developing new and innovative solutions, which then have to go through a long and often arduous registration process. Aimed at bringing medical devices from the lab into clinical trials and at overcoming scientific and economic hurdles of the development process, the High-Performance Center Translational Biomedical Engineering was established in 2017. It is one of the lighthouse projects of Fraunhofer ITEM. Prof. Theodor Doll explains what exactly the High-Performance Center is and the added value that comes from its activities. He is head of the High-Performance Center and holds a concurrent professorship instituted together by the Hannover Medical School and Fraunhofer ITEM.

Professor Doll, what is a High-Performance Center?

With its High-Performance Centers, the Fraunhofer-Gesellschaft as an organization of applied research supports innovation processes at the regional level. High-Performance Centers organize a strategic topic-based collaboration between several public and private research and development partners. Universities, higher education institutions, Fraunhofer Institutes and other non-university research institutions at a particular location work together with companies and civil society players in a defined subject area and on an application-oriented basis to quickly translate innovations into practical applications. High-Performance Centers stand for excellent infrastructure that is used in a cross-organizational manner, education concepts, and expertise. They bring together appropriate partners and, as innovation guides, advance ideas to market launch. This concept of collaboration in translation-oriented High-Performance Centers has already been put into practice at 17 locations in 11 German federal states.

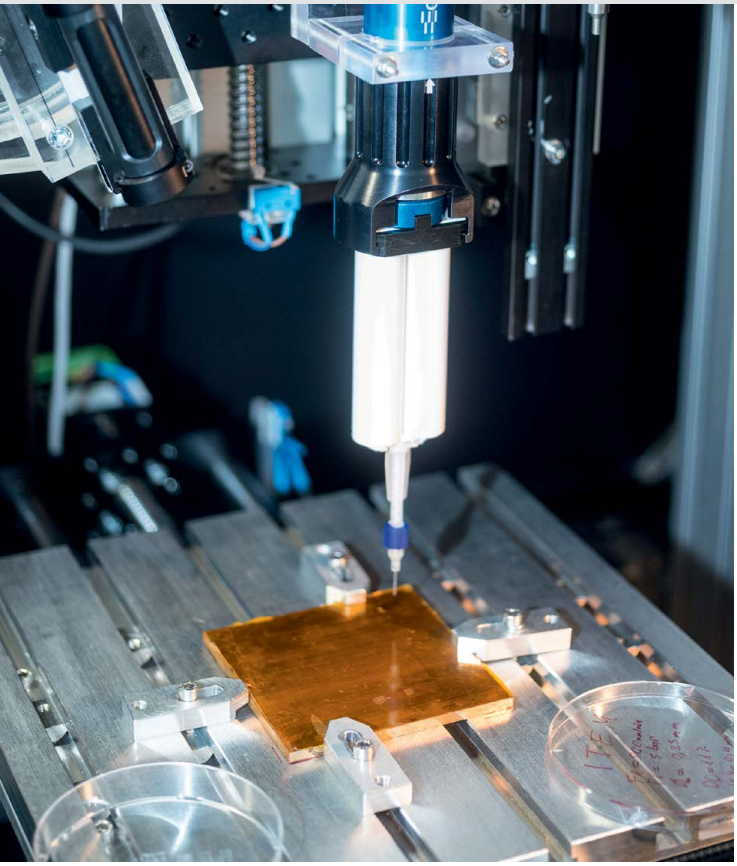
With the High-Performance Center Translational Biomedical Engineering the Fraunhofer-Gesellschaft as an organization at the interface of academia and industry is supporting innovation processes in the biomedical engineering sector in the Hannover area and thus at the location of the Fraunhofer Institute in Hannover. The Center also receives funding from the federal state government of Lower Saxony. Together with our partners, we can provide decisive impetus for future innovations to industry, SMEs and start-ups in the biomedical engineering sector.

Who are the partners in the High-Performance Center Translational Biomedical Engineering?

Fraunhofer ITEM and the Lower Saxony Center for Biomedical Engineering, Implant Research and Development, NIFE for short, are collaborating in the High-Performance Center and also in the Cluster of Excellence Hearing4all.

How does the High-Performance Center support academia and industry?

Our commitment is to close the gap between basic research and the first clinical trial – regarding regulatory support, quality assurance, and manufacturing technology. We place particular emphasis on safety aspects – after all, biomedical engineering products are made for people, for patients. In cooperation with partner institutions we cover the whole chain from innovation to a CE-compliant product.



In the future, individualized implants for each patient are planned to be manufactured from medical-grade silicone using a 3D printing technology.

We equip companies and entrepreneurs with the technical and regulatory support that will allow their innovations to enter and pass clinical testing. This also includes dedicated manufacturing processes that usually represent substantial economic hurdles for companies. These processes can be provided by our partners and are pooled within the High-Performance Center with corresponding quality and risk management structures for medical devices, supplemented by appropriate process logistics to provide a one-stop shop. In addition, we guide clients along the regulatory pathway including the necessary documentation, arrange or conduct the required tests and optimize these according to the requirements of the innovation in close contact with the notified body.

Speaking of registration: How do you think will the new EU-wide Medical Device Regulation affect the biomedical engineering sector?

First and foremost, patient safety is top priority in medicine and biomedical engineering. It is thus a good thing that an EU-wide uniform regulation, the Medical Device Regulation, or MDR for short, was introduced in 2017. Nonetheless, the MDR poses enormous challenges for the biomedical engineering sector. To ensure compliance with the new legislation, manufacturers have to meet increased documentation and testing requirements, also for products that are already on the market. Furthermore, many questions concerning the practical implementation of the regulation are still unanswered. Small and medium-sized enterprises in particular fear that meeting the requirements will be too much for them, also financially, which would reduce the innovative strength of the biomedical engineering sector in Germany in the long term.

Are there figures supporting your concern?

To obtain as complete a picture as possible of the consequences to be expected from the MDR, Fraunhofer ITEM together with the MDR Competence network and Deloitte GmbH performed a market survey that yielded alarming results. Only 15 percent of manufacturers feel sufficiently informed about implementation of the MDR. Fifty percent of the respondents reckon that products or product lines will have to be terminated because of the increased requirements. Over 65 percent of companies feel compelled to shift resources from development to regulatory issues – at the expense of innovation efforts. And 70 percent of companies are feeling uncertain as to whether the notified bodies that have assisted them so far will continue to do so to allow all deadlines to be met.

The consequences for the biomedical engineering sector in Germany and Europe are huge, the more so because small and medium-sized enterprises, SMEs for short, are considered the major innovation drivers in this sector, accounting for 93 percent of all medtech companies. These, however, are particularly affected by the negative effects of the MDR, facing challenges that they can hardly manage. Development costs and time will substantially increase, leading to markedly deteriorating prospects of start-ups and SMEs in this sector. Likewise, it will become much less attractive for investors to invest in innovative medtech developments. The figures give reason to fear that in the medium term the regulation will result in migration towards the FDA-regulated American market and depletion of the innovation hotspot Germany.

How can the High-Performance Center provide support in the implementation of the MDR?

In September 2018, our High-Performance Center invited stakeholders from industry and professional associations in the biomedical engineering sector to a discussion forum dealing with the question "How to survive with the European MDR?" Experts exchanged information regarding the current state of MDR implementation and discussed its impact. Together with the participants of this event, we defined specific measures that could both relieve the current situation and restore confidence in the innovation hotspot Germany for the future. These measures include accelerated accreditation of notified bodies , correction of deadlines for manufacturers, development of implementation guides, introduction of special regulations for conformity assessment, and avoidance of trust-like structures.

With our professional expertise pooled in the High-Performance Center, we offer advanced professional training for executives and junior staff in biomedical engineering companies, especially on regulatory issues.

Precisely speaking, at Fraunhofer ITEM in particular we support clients in their MDR-compliant development of innovative medical devices or in making adjustments to existing products to achieve compliance with the new regulations. In a one-stop shop, we devise a risk management strategy according to the ISO 14971 standard, perform biological evaluation of the medical device as part of the risk management process, and offer relevant in-vitro and in-vivo tests from the ISO 10993 series of standards. Clinical assessment is performed primarily based on scientific literature and, if required, can be complemented by clinical testing. We can provide optimal support to medical device manufacturers, as we pool our expertise in medical devices with our long-term experience in chemical risk assessment, nanomaterials, and biocompatibility.

Within the High-Performance Center, Fraunhofer ITEM also engages in the development and manufacturing of biomedical engineering products. What is your focus?

One focus in our team is on neural implants. Personalized medicine or rather personalized biomedical engineering is aimed at producing individualized prostheses and implants for each patient. This is where the development of a 3D printing process for medical-grade silicones is coming into play. In the High-Performance Center, we are further developing a 3D printing technology developed by the Hannover Medical School, to make it suitable for industrial use – and not only that: We are enhancing it into a manufacturing chain with integrated sensors, actuators and electronics. With this approach, the High-Performance Center is in a top position worldwide.

As a partner in the Cluster of Excellence Hearing4all, we are proud that this cluster has been selected for funding for the second time. Hearing4all is one of the world's leading centers in medical technology, hearing research, audiology, medical diagnostics, and therapy. Every cochlear implant in use around the world is somehow based on research conducted in Hannover and, to a certain extent, also on research by Fraunhofer ITEM.

The focus at Fraunhofer ITEM is on airway research – is this focus also reflected in the development of medical devices at Fraunhofer ITEM?

Inhaled aerosol therapies are getting more and more important in the medical area. At Fraunhofer ITEM, we are developing technologies for the administration of medical aerosols. An example is the development of an inhalation system for preterm infants whose lungs are not yet fully developed. They need a substance called surfactant, which allows the alveoli to expand with inspiration. It is not sufficient in this case to administer surfactant in the form of nebulized droplets, it has to be administered as dry powder via the breathing air. To avoid particle deposition in the upper airways, the dry substance needs to be humidified. Exact timing of this humidification is crucial, namely during inspiration. If you consider that the tidal volume of a preterm infant is less than half a shotglass, you can see the special challenge we are facing. The new technology will shorten therapy duration, thereby easing the strain on these little infants.

The way the system is currently designed, it can basically be used for inhaled drug administration to preterm infants, children, and also to adults. A first clinical prototype is available for use in clinical trials with adults. I guess it will take another three to five years before the system is ready for serial production.

We see great potential in this technology, because the system allows drugs to be delivered very specifically and efficiently to certain areas of the lung and exactly during the period of inhalation.

Our developments can give patients a better quality of life and improve their health.

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PROJECTS

Inhaled administration of surfactant in preclinical efficacy tests in ex-vivo lungs

Idiopathic pulmonary fibrosis (IPF) is a rapidly progressing fibrotic disease of the lung that has very limited treatment options and a high mortality, with a life expectancy comparably poor as lung cancer. The disease is characterized by a progressive decline of lung function due to scarring and growth of replacement tissue. The tissue damage in IPF is irreversible and cannot be cured – the only curative option at present is lung transplantation. A therapeutic option to attenuate the course of disease might be inhaled administration of lung surfactant. A functioning lung surfactant reduces the lung's surface tension to near zero, thus facilitating the work of breathing, preventing lung collapse at the end of expiration and enhancing mucociliary clearance. Administration of surfactant to IPF patients is expected to attenuate acute exacerbations in the course of disease and improve patients' quality of life. In the present project, Fraunhofer ITEM scientists collaborated with colleagues from the Hannover Medical School to develop a system for aerosolization of artificial surfactant for use in preclinical efficacy tests in ex-vivo lungs. Given that ex-vivo lungs pose a potential risk of infection, a special focus here was on safety aspects for user protection.

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Online measurement of inhaler dose rate and liquid water content

Numerous lung diseases are treated with inhalation therapies. When testing newly developed inhalation systems, effective release of the aerosolized drug directly at the patient interface is an important test parameter. The measurements in general and in particular those of breath-triggered aerosol release have to be performed in a setting with simulated breathing. Determination of the aerosol release according to the standard test protocol (DIN EN 13544-1) is very time-consuming, due to the required chemical analyses and frequently necessary changes of the collection filters. For the development of inhalation systems for preterm infants this test method is not applicable. The reason why is that preterm infants have a very high breathing rate and at the same time a very small tidal volume. Fraunhofer ITEM scientists have developed a new test method allowing the aerosol release and, if necessary, the liquid water content of the aerosol to be determined in real time in inhalation systems for preterm infants, newborns, and adults. The method is based on a combination of gravimetric and optical particle detection, with the optical measuring system being calibrated via an initial gravimetric measurement series. No further gravimetric measurements are necessary. Particle concentration and liquid water content are optically determined in real time without sampling, directly at the patient interface. In the future, this practicable method can be used for the development and rapid optimization of inhalation systems.

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Fraunhofer ITEM scientists have developed a new test method allowing the aerosol release to be determined in real time in inhalation systems for preterm infants and newborns. The current standard test methods are not applicable here.

Digitization and data sharing to simplify conformity assessment

Medical device manufacturers are obligated to perform conformity assessment of their products – a prerequisite for achieving CE labeling and marketing authorization for the European market. Depending on risk category and complexity, the assessment requires comprehensive functional and safety testing, e.g. to guarantee biocompatibility. Although numerous medical devices consist of similar components and materials, the individual products are tested almost exclusively by their respective manufacturers. Consequently, the same materials or components are tested again and again. This redundancy unnecessarily increases the costs of medical device manufacturing. Moreover, some tests require animal experiments, which in the present situation are performed several times. In the project "Medical Device Obligations Taskforce", Fraunhofer ITEM scientists are collaborating in a European network of partners to develop a platform aimed at simplifying conformity assessment, at providing access to state-of-the-art test methods, and at enabling joint performance of tests and data sharing between manufacturers in a safe and economically attractive manner. Parts of the assessment procedure will be translated into automated, digital processes, testing facilities and manufacturers will be linked in a network, and the overall costs of the assessments will be reduced. At the same time, the high level of patient safety stipulated by the European Medical Device Regulation will be guaranteed.

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Individualized implants for precision medicine

Precision medicine means that patients undergo differentiated examinations and receive customized therapies and biomedical engineering solutions. With regard to implants, it means that these are tailored to the patient's individual anatomy. With today's 3D printers, this should be perfectly feasible. It turns out, however, that the regulatory requirements are immense and the materials approved for use in medical devices have their pitfalls. Medical-grade silicone used in the production of cardiac pacemakers or cochlear implants, for example, appeared to be unprintable. At the High-Performance Center Translational Biomedical Engineering, which pools the expertise of the Lower Saxony Center for Biomedical Engineering, Implant Research and Development and of Fraunhofer ITEM, a printer for this material has been developed since 2014. Meanwhile, the High-Performance Center has become the world leader in this technology. Accordingly, the first presentation of this printer to the public at the trade fair MEDICA/COMPAMED 2018 was met with great interest. The next ambitious goals the developers are now going for are to further refine the resolution of the printer and to embed it into a system environment that allows electrode, conductor, and electronic components to be integrated in one go. This would help to finally overcome the still predominant manual production workflows in this medical device sector and allow individualized patient supply to be realized without cost increases.

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PERSONALIZED TUMOR THERAPY

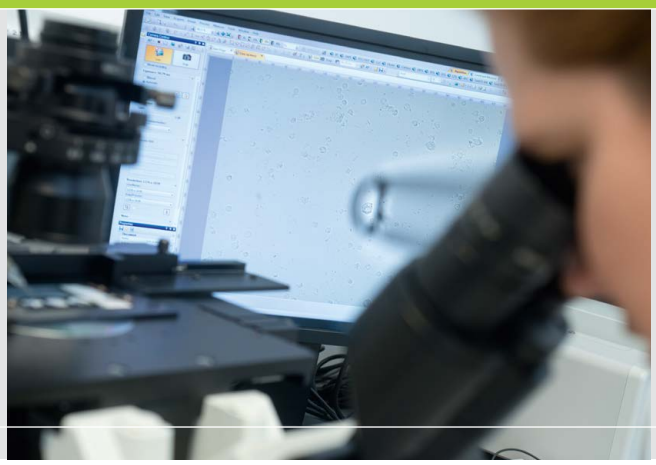
OUR SERVICES: FROM MOLECULAR ANALYSIS TO PERSONALIZED THERAPY

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.



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.

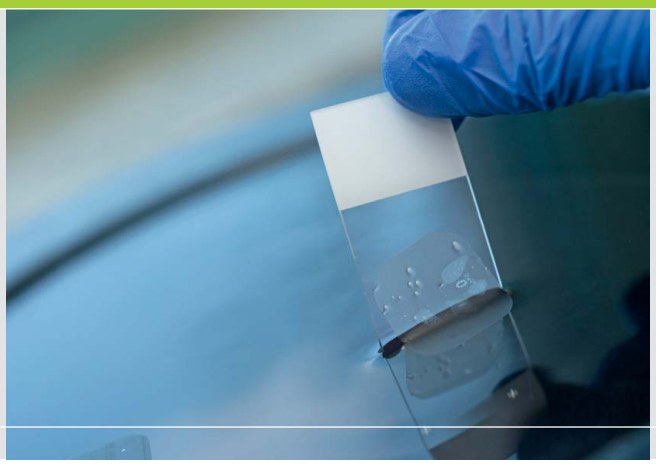
Decoding of single cells

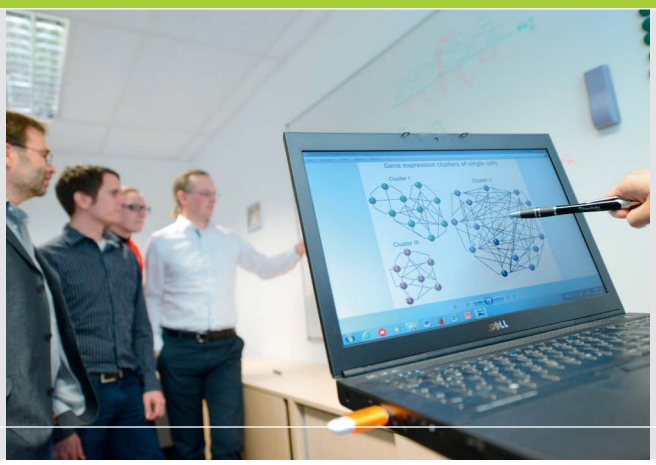
For the development of tailored solutions for single-cell or rare-cell analysis, we offer expert knowledge in next-generation sequencing (NGS) and microarray technologies, in particular at the single-cell DNA and RNA levels. Our in-house developed workflows are optimized for the analysis of clinical 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

Cerebrospinal fluid as a source of biomarkers for monitoring of pediatric brain tumors

Tumors of the central nervous system are among the most prevalent oncological entities in children, afflicted with a persistently dismal curing rate. There is great hope that insights into the molecular mechanisms of these tumors will allow the design of targeted treatment approaches. For several malignancies analysis of circulating tumor cells (CTCs) and cell-free tumor DNA (ctDNA) isolated from blood or of disseminated cancer cells (DCCs) from bone marrow or lymph nodes facilitated a timely diagnosis and enabled assessment of the therapy response. Identification, isolation, and molecular characterization of DCCs or ctDNA from the cerebrospinal fluid (CSF) provide fundamental insights into the clonal evolution of the cancer genome and, even more important, into treatment options for brain tumors. Fraunhofer researchers, therefore, established a workflow for the isolation of single tumor cells or tumor DNA from CSF samples collected from pediatric patients with brain tumors. Subsequent genomic and transcriptomic analyses provide a precious resource for studying the biology of rare childhood tumors, improving diagnostic monitoring assays, and laying the grounds to the understanding of existing targeted therapies as well as novel approaches. The aim is to provide a quick and less invasive assay than stereotactic biopsy to obtain important diagnostic information needed for the treatment of childhood brain tumors.

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Small-cell lung cancer: personalized drug screening in a preclinical model

Small-cell lung cancer (SCLC) is a highly malignant form of bronchial carcinoma for which effective therapies are lacking to date. Applying the "liquid biopsy" concept, scientists at Fraunhofer ITEM in Regensburg successfully isolated rare circulating tumor cells (CTCs) from peripheral blood of a metastatic SCLC patient. CTCs were subsequently expanded in vitro under optimized culture conditions. The cells expressed SCLC-specific tumor markers and displayed patient-specific genetic aberrations, representing the actual target cells of systemic therapy. This SCLC patient-derived in-vitro model was subsequently screened against a drug library comprising 133 FDA-approved anticancer agents at five different doses. Twenty-eight of these drugs were identified to induce cell death or inhibit proliferation in the SCLC model. In addition to the chemotherapies (including the current standards of care), several classes of targeted therapies were identified, e.g. HDAC inhibitors, proteasome inhibitors, receptor tyrosine kinase and EGFR inhibitors. In personalized tumor therapy, such patient-derived CTC models enable novel drug discovery and also drug repurposing.

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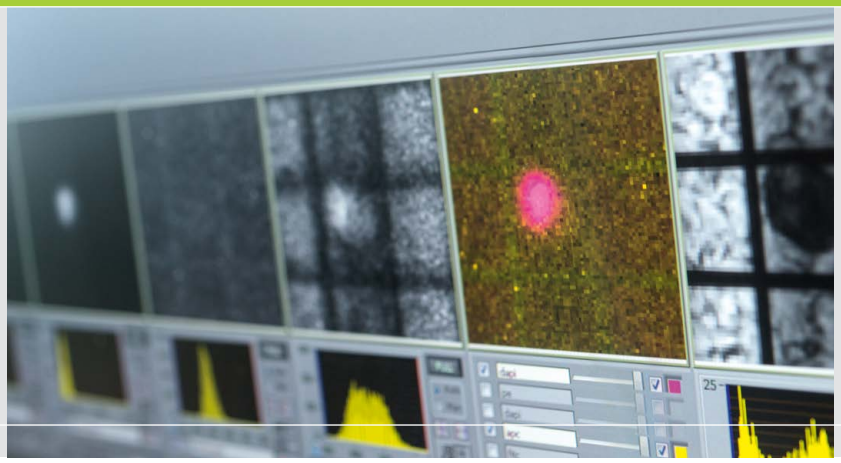
In the analysis of rare cells such as circulating tumor cells or disseminated cancer cells, the identification, isolation, and molecular characterization of these cells are essential.



Novel diagnostic approach to improve personalized treatment of cancer

In the course of cancer, single tumor cells detach from the primary tumor and spread in the body via the bloodstream and lymphatic system, sometimes resulting in metastasis. During surgical removal of the primary tumor, the adjacent lymph node is removed as well to investigate it for the presence of tumor cells. In certain cancer types (e.g. melanoma, bronchial carcinoma, and breast cancer) this is the most important indicator of the stage of disease and provides the basis for decisions on further treatment.

Today's routine lymph node diagnosis represents the starting point of a collaborative research project in which three Fraunhofer Institutes have teamed up. Their aim is to optimize and automate the standard method. At present, the resected tissue is frozen, cut into thin slices, and then analyzed by microscopy. This method, however, allows only a small fraction of the whole tissue to be examined and thus bears the risk of overlooking cancer cells. To minimize this risk, an innovative procedure has been developed at Fraunhofer ITEM in Regensburg: the lymph node tissue is first dissociated into single cells; in a second step, cancer cells are labeled by tumor-specific staining and isolated. In addition to the quantitative detection of tumor cells in the lymph node, the genome of these cells can be investigated (for example for therapeutically relevant mutations) using targeted molecular analyses.

Efficient implementation of this method in clinical diagnostic procedures is the focus of the collaborative project "High-throughput diagnostic system for tissue-based personalized tumor therapy using lymph nodes as an example" (LyDia HD in short). Within this project, scientists of Fraunhofer IPA are developing the "Tissue Grinder" as an improved and more efficient system for careful dissociation of lymph node tissue into single cells. In addition, laboratory software is being developed to support documentation of the whole process from preparation of the patient sample to the report on diagnostic findings. Fraunhofer IIS is working on a software algorithm for automated microscopic detection and digitization of stained tumor cells and on a cassette loading unit for the previously developed SCube® system. The aim is to enable analysis also of larger sample quantities independently of staff availability and time. Subsequent digital selection of the tumor cells to be examined is the only action that will have to be performed manually using a computer.

The combination of quantitative detection, individualized molecular analysis of tumor cells for diagnosis, and the high degree of automation make the LyDia HD diagnostic system a promising method which in the long run will be more accurate, faster, and more cost effective than the methods so far in use. This type of diagnostic is thus paving the way for personalized treatment approaches to be brought into clinical application.

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CONTACTS

Fraunhofer ITEM has pooled the competencies from its various divisions in three business units: Drug Development, Chemical Safety and Assessment, and Translational Biomedical Engineering. Another focus is on personalized tumor therapy, a subject area explored by the scientists of the corresponding Regensburg-based division of Fraunhofer ITEM. Below please find the contacts for the different thematic areas and services offered. Please do not hesitate to contact these persons directly, should you have any questions or want to make use of our services.

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Dr. Pohlmann and Prof. Doll are also your contacts for the following subject areas:

Device development and manufacturing processes

Testing and test methods

Regulatory support

Personalized Tumor Therapy

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FRAUNHOFER-GESELLSCHAFT

70 YEARS OF FRAUNHOFER **70 YEARS OF FUTURE** *#WHATSNEXT*

Research of practical utility lies at the heart of all activities pursued by the Fraunhofer-Gesellschaft. Founded in 1949, the research organization undertakes applied research that drives economic development and serves the wider benefit of society. Its services are solicited by customers and contractual partners in industry, the service sector and public administration.

At present, the Fraunhofer-Gesellschaft maintains 72 institutes and research units. The majority of the more than 26,600 staff are qualified scientists and engineers, who work with an annual research budget of more than 2.6 billion euros. Of this sum, more than 2.2 billion euros is generated through contract research. Around 70 percent of the Fraunhofer-Gesellschaft's contract research revenue is derived from contracts with industry and from publicly financed research projects. Around 30 percent is contributed by the German federal and state governments in the form of base funding, enabling the institutes to work ahead on solutions to problems that will not become acutely relevant to industry and society until five or ten years from now.

International collaborations with excellent research partners and innovative companies around the world ensure direct access to regions of the greatest importance to present and future scientific progress and economic development.

With its clearly defined mission of application-oriented research and its focus on key technologies of relevance to the future, the Fraunhofer-Gesellschaft plays a prominent role in the German and European innovation process. Applied research has a knock-on effect that extends beyond the direct benefits perceived by the customer: Through their research and development work, the Fraunhofer Institutes help to reinforce the competitive strength of the economy in their local region, and throughout Germany and Europe. They do so by promoting innovation, strengthening the technological base, improving the acceptance of new technologies, and helping to train the urgently needed future generation of scientists and engineers.

As an employer, the Fraunhofer-Gesellschaft offers its staff the opportunity to develop the professional and personal skills that will allow them to take up positions of responsibility within their institute, at universities, in industry and in society. Students who choose to work on projects at the Fraunhofer Institutes have excellent prospects of starting and developing a career in industry by virtue of the practical training and experience they have acquired.

The Fraunhofer-Gesellschaft is a recognized non-profit organization that takes its name from Joseph von Fraunhofer (1787–1826), the illustrious Munich researcher, inventor and entrepreneur.

www.fraunhofer.de/en.html

Figures are for January 2019.

FRAUNHOFER-INTERNAL NETWORK

Successful research requires scientific exchange – one of the reasons why Fraunhofer ITEM is well networked within the Fraunhofer-Gesellschaft. Fraunhofer Institutes working in related subject areas cooperate in Fraunhofer Groups and Alliances dedicated to specific topics to coordinate the development of appropriate solutions along the entire value chain. In addition, Fraunhofer Institutes cooperate in Fraunhofer research programs. In pre-competitive research projects, they work out a solid basis for contract research geared to practical applications.

Fraunhofer Group for Life Sciences

Six Fraunhofer Institutes and a Fraunhofer Research Institution, each having proven in-depth expertise in different areas within the life sciences, are involved in the Fraunhofer Group for Life Sciences: the Fraunhofer Institutes IBMT, IGB, IME, ITEM, IVV, and IZI, and the Fraunhofer Research Institution EMB. Their combined knowledge of biology, chemistry, biochemistry, biotechnology, medicine, pharmacology, ecology, and nutritional science is pooled and synergized within this Fraunhofer Group – to allow solutions to be provided even for clients with complex requirements.

https://www.lifesciences.fraunhofer.de/en.html

Fraunhofer Nanotechnology Alliance

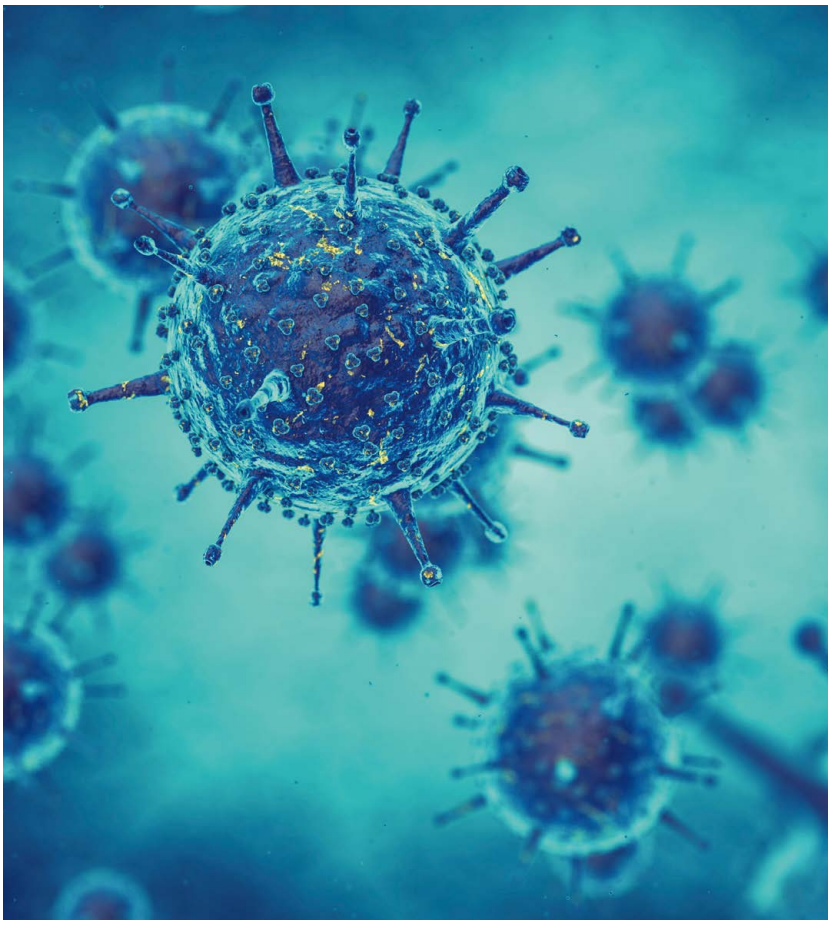
The Fraunhofer Nanotechnology Alliance covers the whole R&D value chain from applied research to industrial implementation. The focus is on nanomaterials, nanobiotechnology, nano-processing and handling, nano-optics and electronics, measuring methods and techniques, and technology transfer and consulting. Fraunhofer ITEM is bringing in its expertise in the fields of toxicology and safe handling of nanoparticles.

https://www.nano.fraunhofer.de/en.html

Fraunhofer Cluster of Excellence for 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. In the medium term, the collaborating institutes want to bridge the existing gap from research on novel medications to what is actually available to patients. Three Fraunhofer Institutes dedicated to the life sciences – IME, IZI, and ITEM – have pooled their expertise for this purpose.

https://www.cimd.fraunhofer.de/en.html



Research project RIBOLUTION

In the project RIBOLUTION, five Fraunhofer Institutes are taking an innovative approach to identifying new biomarkers for modern diagnostic solutions. Their aim is to identify novel biomarkers based on ribonucleic acids that can serve as diagnostic indicators or enable prediction of disease progression or future therapy response, and develop these to the point of clinical proof of concept. In this project, Fraunhofer ITEM is screening for COPD biomarkers.

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. The 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. In this project, the collaborating Fraunhofer Institutes IME, IZI, IFAM, and ITEM are investigating synergistic combinations of active agents.

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.

Research project LyDia HD

Whether or not a tumor has already spread in the organism to form metastases can be determined by lymph node diagnosis. A cross-disciplinary team of scientists from the Fraunhofer Institutes IPA, IIS, and ITEM is developing a new "High-throughput diagnostic system for tissue-based personalized tumor therapy using lymph nodes as an example," LyDia HD in short. This system enables detection of all tumor cells in a lymph node tissue sample. This is not possible with the method that is normally used at present. Due to the automation, the new LyDia HD diagnosis is not only more accurate, but also faster and more cost effective than the methods so far in use. In addition, it provides important information about the types of cells.

NAMES, DATES, EVENTS

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Theses

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Lüer, Katrin
Sicherheit, Wirksamkeit und Reproduzierbarkeit einer neuen Provokationstechnik mit Hausstaubmilben im Fraunhofer-Allergenprovokationsraum.
Hannover Medical School, 2018

Schwotzer, Daniela
Investigations on the toxicity of CeO_2 nanoparticles after subchronic inhalation of low doses.
University of Veterinary Medicine Hannover, Foundation, 2018

Master's theses

Abt, Felix
Entwicklung einer Logistikkonzeption für eine dezentrale Fertigung von medizinischen Prüfprodukten.
Furtwangen University, 2018

Beneke, Valerie
Investigation of the role of flagellin in the interaction of *Pseudomonas aeruginosa* with the host immune response in an ex vivo model of lung infection.
Hannover Medical School, 2018

Borrmann, Fabian
Untersuchung für einen durchstimmbaren Soft-Ionization-Sensor für Umweltgase: Materialien und Messtechnik.
Leibniz Universität Hannover, 2018

Clement, Alexander
Entwicklung eines Verneblerkopfes für die inhalative Einnahme von pharmakologisch aktiven Substanzen.
Leibniz Universität Hannover, 2018

Danho, Madleen
Parameteranalyse zur Untersuchung des Degradationsverhaltens von Polymerimplantaten.
University of Bremen, 2018

Elenschneider, Leroy
Charakterisierung von humanen Präzisionsleberschnitten und In-vitro-Überprüfung von potenziellen Markergenen zur Prädiktion idiosynkratischer Arzneimittelinduzierter Hepatotoxizität.
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Gripp, Tatjana
Untersuchungen zum zytotoxischen, gentoxischen und pro-inflammatorischen Potenzial von Graphen-Nanoplättchen in Rattenalveolarmakrophagen.
Bielefeld University, 2018

Löhers, Katharina
Idiosynkratische Hepatotoxizität durch Troglitazon: Untersuchungen an humanen Präzisionsleberschnitten und HepG2-Zellen.
University of Düsseldorf, 2018

Martin, Gael
Characterization of influenza and parainfluenza infection and pharmacological intervention in human lung tissue.
Université de Poitiers (France), 2018

Nowak, Norman
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Leibniz Universität Hannover, 2018

Seegers, Carla
Studies towards development of drugs targeting *Aspergillus fumigatus*.
Hannover Medical School, 2018

Weber, Elena
Evaluierung der ökotoxikologischen Risikobewertung für genmodifizierte Arzneimittel.
University of Applied Sciences Emden/Leer, 2018

Wehr, Mathias
Modellierung eines Vorhersagemodells für respiratorisch irritierende Chemikalien.
University of Applied Sciences Emden/Leer, 2018

Wiedemeier, Petra
Der Umgang mit Forschungsdaten, im Kontext der Open Research Anforderungen, an außeruniversitären Forschungseinrichtungen – am Beispiel des Fraunhofer-Instituts für Toxikologie und Experimentelle Medizin (ITEM) als Teil der Fraunhofer-Gesellschaft.
Humbold-Universität zu Berlin, 2018

Wiegrebe, Alexander
Humane Präzisionsleberschnitte als Modell für die Untersuchung der entzündungsvermittelten Hepatotoxizität.
Hannover Medical School, 2018

Winkler, Sandro
Physiologisch basierte toxikokinetische (PBTK) Modellierung zur Aufnahme von Chemikalien/Aerosolen über die Lunge.
Leibniz Universität Hannover, 2018

Yilmaz-Bayraktar, Suheda
Design, Herstellung und Validierung von nanoporös mikrofluidischen Zellkammern als Führungsstrukturen für Dendritenwachstum.
Leibniz Universität Hannover 2018

Bachelor's theses

Jansky, Sandrine
Wirksamkeitsbewertung von Anti-Parainfluenza-Inhibitor in humanem Ex-vivo-Lungengewebe.
Fresenius University of Applied Sciences, 2018

Invited lectures

Dr. Philipp Badorrek
Cross table investigator & sponsor: Expectation management in feasibility & recruitment.
The Operational Excellence in Clinical Trials Summit (OECT)
Berlin (Germany), March 8, 2018

Dr. Annette Bitsch
Gesunder Arbeitsplatz der Zukunft.
Fachforum Life Sciences – Gegenwart und Zukunft II
Berlin (Germany), October 9, 2018

Praktische Erfahrungen mit den Datenanforderungen für das Produktdossier.
Biozidprodukte und behandelte Waren – BPR (EU) Nr. 528/2012-Update 2018
Leipzig (Germany), April 19, 2018

Dr. Sylvia Escher
EXITOX-II: Development of an animal-free testing strategy for the risk assessment of inhalable compounds.
3rd German Pharm-Tox Summit/84th Annual Meeting of the German Society for Experimental and Clinical Pharmacology and Toxicology (DGPT)
Göttingen (Germany), February 26 – March 1, 2018

Development of an animal-free testing strategy for risk assessment of inhalable compounds – EXITOX II.
R2N symosium "Alternative methods to replace or reduce animal models in biomedical research", Hannover Medical School
Hannover (Germany), November 6-7, 2018

AIMT8 – Prediction of systemic toxicity after repeated exposure by new approach methodologies (NAMs) – is a prediction of STOT-RE classification possible?
20th Annual Cefic-LRI Workshop
Brussels (Belgium), November 15, 2018

Dr. Ulrich Froriep
Neural implants in the valley of death.
Bernstein Center Freiburg
Freiburg (Germany), October 2, 2018

Dr. Stefan Hahn
Risikominderungsmaßnahmen: Effizienz und Weiterentwicklung.
Fachforum Life Sciences – Gegenwart und Zukunft II
Berlin (Germany), October 9, 2018

Prof. Dr. Jens Hohlfeld
Effect of lung deflation with indacaterol plus glycopyrronium on ventricular filling in patients with hyperinflation and COPD.
14th Pneumology Update 2018, Session "Science and Pneumology: Best of D-A-CH"
Igls (Austria), June 14-16, 2018

Dr. Benedikt Jäger
Role of NLRP3 inflammasome in sarcoidosis.
7th Annual Meeting of the German Center for Lung Research (DZL)
Bad Nauheim (Germany), February 8-9, 2018

Potential role of NLRP3 inflammasome and IL-1β pathway in granuloma generation of sarcoidosis.
59th Congress of the German Respiratory Society (DGP)
Dresden (Germany), March 15, 2018

Dr. Rupert Kellner
Update of new images and categorization in the *Dev*Tox database.
9th Berlin Workshop on Developmental Toxicology (as a satellite event to the 46th Annual Meeting of the European Teratology Society)
Berlin (Germany), September 13, 2018

Prof. Dr. Christoph Klein
Die Metastasierungskaskade – von der Einzelzelle zur dissimilierten Erkrankung.
33rd German Cancer Congress 2018
Berlin (Germany), February 24, 2018

Mechanisms of early dissemination and metastasis formation.
Gordon Research Conference on Mammary Gland Biology
Lucca (Italy), May 29, 2018

From early dissemination to metastatic colonization: What happens during dormancy?
AACR Special Conference on Cancer Dormancy and Residual Disease
Montréal, Québec (Canada), June 20, 2018

Studying the nature of the seed: unexpected findings and future challenges.
17th Biennial Congress of the Metastasis Research Society
Princeton, New Jersey (USA), August 2, 2018

The dynamics of metastatic spread.
3rd EACR Conference – Making it Personal – Cancer Precision Medicine
Bergamo (Italy), November 5, 2018

Detection, characterization and monitoring of early and advanced systemic cancer.
FORUM Translational Medicine, Session C: Enabling New Technologies for Therapies & Diagnostics
Würzburg (Germany), November 29, 2018

Liquid biopsy in melanoma.
34th Erlangen Minisymposium
Erlangen (Germany), December 8, 2018

Prof. Dr. Norbert Krug
Exacerbations of COPD and treatment.
ERS International Congress 2018, Postgraduate course PG1: Asthma and chronic obstructive pulmonary disease
Paris (France), September 15, 2018

Dr. Gerhard Pohlmann
From the idea to the safe pediatric medical device.
2nd international symposium "Pediatric Medical Devices, Safety & Protection by Innovation & Development" (PedMedDev) at University Medical Center-UKSH
Lübeck (Germany), November 16, 2018

Dr. Bernhard Polzer
Analytik von zirkulierenden Tumorzellen und Liquid Biopsy.
PathoLecT 2018
Berlin (Germany), April 20, 2018

Clinical applications of single-cell analysis.
BACR Conference – Response and Resistance in Cancer Therapy
Canterbury (UK), September 10, 2018

Prof. Antje Prasse
Tumoröse Prozesse als treibende Kraft für die Lungenfibrose.
59th Annual Congress of the German Respiratory Society (DGP)
Dresden (Germany), March 14-17, 2018

Therapie der Sarkoidose.
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Use of biomarkers in idiopathic pulmonary fibrosis.
Annual Meeting of the American Thoracic Society (ATS) 2018, postgraduate course
San Diego, California (USA), May 18-23, 2018

New strategies tackling granuloma formation in sarcoidosis.
International Conference on Sarcoidosis and Interstitial Lung Diseases (WASOG 2018)
Heraklion (Greece), June 7-9, 2018

Lungenbeteiligung bei rheumatologischen Erkrankungen.
15th advanced rheumatology training at Wilhelmshaven hospital
Wilhelmshaven (Germany), August 22, 2018

A new humanized mouse model for IPF and effects of nintedanib treatment.
ERS International Congress 2018
Paris (France), September 15-19, 2018

BAL cell transcriptome predicts survival in IPF and can be used to gauge and model treatment effects interfering with the TGF-β pathway.
ERS International Congress 2018
Paris (France), September 15-19, 2018

Pulmonary fibrosis: recent advances and future perspectives.
Belgian Pneumology Days – 2018
Brussels (Belgium), November 30 – December 1, 2018

Dr. Franziska Schramm
Minimizing toxicity and enhanced safety – for a successful biocidal product authorization. Part II: Critical issues to consider for new/complex formulations.
4th Conference of Applied Hygiene, Microbiology and Virology – Dr. Brill Academy
Hamburg (Germany), November 22-23, 2018

Dr. Sven Schuchardt
Ergebnisse EASA CAQ-Projekt.
SAE (Society of Automotive Engineers) face-to-face AC-9M committee meeting
Frankfurt/Main (Germany), November 29, 2018

Dr. Florian Schulz
Sicherer Umgang mit chemischen Stoffen am Arbeitsplatz.
Fachforum Life Sciences – Gegenwart und Zukunft II
Berlin (Germany), October 9, 2018

Dr. Sabine Wronski
Bronchobini®-Wirksamkeitsstudie in lebenden Lungenschnitten.
Lunch symposium "Influenza, grippaler Infekt und Husten…" during the 8th "Berliner Kongress für Kinder- und Jugendmedizin"
Berlin (Germany), December 1, 2018

Dr. Christina Ziemann
GUM AG Statistics, an interdisciplinary working group to bridge the gap between genetic toxicology and statistics.
(Joint oral presentation by Dr. Christina Ziemann, Fraunhofer ITEM, and Wolfgang Igl, Bayer AG)
46th EEMGS and 30th GUM Meeting
Potsdam (Germany), March 19, 2018

In-vitro and in-vivo (geno)toxicity screening of diverse quartz species, surface-modified to reduce biological activity.
Workshop "Silica: are we bridging the gaps between surface states and toxicity?"
Torino (Italy), September 28, 2018

Ariane Zwintscher
Minimizing toxicity and enhanced safety – for a successful biocidal product authorization. Part I: General overview of data requirements.
4th Conference of Applied Hygiene, Microbiology and Virology – Dr. Brill Academy
Hamburg (Germany), November 22-23, 2018

Contributions to congresses and conferences

Ackermann, M.; Hashtchin, A. R.; Kempf, H.; Hetzel, M.; Hesse, C.; Figueiredo, C.; Viemann, D.; Schambach, A.; Wronski, S.; Moritz, T.; Zweigerdt, R.; Munder, A.; Lachmann, N.
iPSC-derived phagocytes as a cellular therapeutic to treat bacterial infections.
Herrenhausen Symposium "Individualized Infection Medicine – The future is now"
Hannover (Germany), June 21-23, 2018

Ackermann, M.; Kempf, H.; Hetzel, M.; Hesse, C.; Rafiei Hashtchin, A.; Glage, S.; Figueiredo, C.; Schambach, A.; Wronski, S.; Moritz, T.; Zweigerdt, R.; Munder, A.; Lachmann, N.
Human iPSC-derived phagocytes as a cellular therapeutic to treat bacterial infections.
24th Annual Meeting DG-GT – German Society for Gene Therapy
Freiburg (Germany), September 26-28, 2018

Boei, J.; Knebel, J.; Ritter, D.; Vrieling, H.; Sewald, K.; Obernolte, H.; Hansen, T.
Pilot studies with diacetyl leading to an adequate exposure strategy for diketones.
EU-ToxRisk General Assembly
Egmond aan Zee (The Netherlands), February 20-23, 2018

Botteron, C.
Development and characterization of pre-clinical in vitro/in vivo models from disseminated tumor cells of melanoma patients.
2nd EurOPDX Workshop
Weggis (Switzerland), October 1-3, 2018

Carstensen, S.
Validation of cell analysis by chip cytometry in induced sputum cells.
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Carstensen, S.; Müller, M.; Weigt, H.; Hohlfeld, J. M.
Usage of EBV-transformed B cell line PCL-12 optimizes the IgE FAB assay for clinical trial purposes.
17th Fraunhofer Seminar "Models of Lung Disease"
Hannover (Germany), January 18-19, 2018

Creutzenberg, O.
In vitro and in vivo investigations to characterize the respiratory toxicity of graphene nanoplatelets – PLATOX project.
45th Annual Meeting of the Japanese Society of Toxicology (JSOT)
Osaka (Japan), July 18-20, 2018

Creutzenberg, O.
PLATOX – In vitro and in vivo investigations to generate valid toxicity data for risk assessment of carbon-based nanoplatelets
NanoTox – 9th International Conference on Nanotoxicology
Neuss (Germany), September 18-21, 2018

Danov, O.
Rhinovirus-induced immune response in human lung.
17th Fraunhofer Seminar "Models of Lung Disease"
Hannover (Germany), January 18-19, 2018

Danov, O.
Rupintrivir reduced host immune response to RV1B infection ex vivo in HDM-sensitized lung tissue.
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Danov, O.
Inflammatory exacerbation and inadequate interferon response to RV1B infection in HDM-sensitized lung tissue.
ERS International Congress 2018
Paris (France), September 15-19, 2018

Danov, O.; Herr, C.; Röhrig, T.; Sewald, K.; Braun, A.; Empting, M.; Hesterkamp, T.; Hartmann, R. W.; Bals, R.; Wronski, S.
Establishment of a biotic biofilm model as well as a sub-chronic murine infection model for the evaluation of QS inhibitors as an adjunctive treatment against *P. aeruginosa* infections.
Herrenhausen Symposium "Individualized Infection Medicine – The future is now"
Hannover (Germany), June 21-23, 2018

Ehrmann, M.; Holz, O.
Measurement of volatile organic compounds (VOCs) in exhaled air of children of the DZL ALL Age Asthma Cohort (ALLIANCE).
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Ehrmann, M.; Mutius, E. V.; Hansen, G.; Kopp, M.; Hohlfeld, J.; Holz, O.; Fuchs, O.
Measurement of volatile organic compounds in exhaled breath of children of the ALL Age Asthma Cohort.
ERS International Congress 2018
Paris (France), September 15-19, 2018

Escher, S.; Gräpel, R.; White, A.; Quedraogo, G.; Limonciel, A.; Maclennan, R.; Norinder, U.; Pardo, L. T.; Exner, T.; Vugt, B. v.; Fisher, C.; Bois, F.; Long, T.; Schimming, J. P.
Microvesicular liver stetaosis: a case study with (un)branched carboxylic acids.
EU-ToxRisk General Assembly
Egmond aan Zee (The Netherlands), February 20-23, 2018

Escher, S.; Tluczkiewicz, I.; Vrijenhoek, N. G.; Gräpel, R.; Vugt, B. v.; Brotzmann, K.; Zdrazil, B.; Bois, F.; Maclennan, R.; Pardo, L. T.
Redox cycling versus general liver toxicity: read-across case study with hydro-quinones and alkylated phenols.
EU-ToxRisk General Assembly
Egmond aan Zee (The Netherlands), February 20-23, 2018

Ghosh, M. S.; Greiff, A.; Walter, V.; Hoffmann, M.; Schneider, E.; Hecht, E. M.; Czyz, Z. T.; Rack, B.; Raz, O.; Shapiro, E.; Hartkopf, A.; Klein, C. A.
Longitudinal tracking of breast cancer patients over systemic disease progression.
AACR Special Conference on Cancer Dormancy and Residual Disease
Montréal, Québec (Canada), June 19-22, 2018

Greindl-Junghans, J.; Markiewicz, A.; Scheitler, S.; Raz, O.; Czyz, Z.; Ulmer, A.; Werner-Klein, M.; Shapiro, E.; Klein, C. A.
Cellular lineage of early disseminated melanoma cells.
AACR Special Conference on Cancer Dormancy and Residual Disease
Montréal, Québec (Canada), June 19-22, 2018

Grujovic, A.; Lu, X.; Haunchild, G.; Obradovic, M.; Werner-Klein, M.; Heine, N.; Botteron, C.; Klein, C. A.
Identification and molecular profiling of dormant disseminated breast tumor cells.
AACR Special Conference on Cancer Dormancy and Residual Disease
Montréal, Québec (Canada), June 19-22, 2018

Hahn, S.; Blümlein, K.; Feddersen, B.; Simetska, N.; Gillies, A.; Woolley, A.
Efficiency of exposure control measures – developing a user database and communication tools.
BOHS Annual Conference – OH2018
Stratford-upon-Avon (UK), April 16-19, 2018

Hahn, S.; Blümlein, K.; Feddersen, B.; Simetska, N.; Gillies, A.; Woolley, A.
Efficiency of exposure control measures – developing a user database and communication tool.
ISES-Europe 2018 – European Exposure Science Strategy Workshop
Dortmund (Germany), June 19-20, 2018

Hahn, S.; Tischer, M.; Roitzsch, M.; Koch, W.
SprayExpo – a deterministic indoor air model for spray applications.
ISES-Europe 2018 – European Exposure Science Strategy Workshop
Dortmund (Germany), June 19-20, 2018

Hesse, C.
Specific induction of pro-fibrotic biomarker in human ex vivo lung tissue slices.
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Hesse, C.
Unravelling specific mechanisms of wound healing and pulmonary fibrosis in human ex vivo lung tissue slices.
ERS International Congress 2018
Paris (France), September 15-19, 2018

Hesse, S.; Hahn, S.; Oltmanns, J.; Kaiser, E.; Heine, K.; Schneider, K.; Tischer, M.; Roitzsch, M.; Krause, M.
Quantifying the effectiveness of personal protective equipment against dermal exposure.
ISES-Europe 2018 – European Exposure Science Strategy Workshop
Dortmund (Germany), June 19-20, 2018

Hoffmann, M.; Galle, J.
Stochastic system identification without an a priori chosen kinetic model – exploring feasible cell regulation with piecewise linear functions.
CIRM – Centre International de Rencontres Mathématiques, "Mathematical perspectives in the biology and therapeutics of cancer"
Marseille (France), July 9-13, 2018

Hoffmann, M.; Scheitler, S.; Hodak, I.; Ulmer, A.; Klein, C. A.
Genetic alterations driving metastatic colony formation are acquired outside the primary tumor in patients with melanoma.
CIRM – Centre International de Rencontres Mathématiques, "Mathematical perspectives in the biology and therapeutics of cancer"
Marseille (France), July 9-13, 2018

Hohlfeld, J. M.
Lungenentblähung durch Indacaterol/Glycopyrronium verbessert die kardiale Funktion von COPD-Patienten: die CLAIM-Studie.
Annual Congress 2018 of the German Cardiology Society (DGK)
Mannheim (Germany), April 4-7, 2018

Hohlfeld, J. M.; Vogel-Claussen, J.; Biller, H.; Berliner, D.; Berschneider, K.; Tillmann, H.-C.; Hiltl, S.; Bauersachs, J.; Welte, T.
Lungenentblähung mit Indacaterol/Glycopyrronium verbessert die kardiale Funktion bei COPD-Patienten: Die CLAIM-Studie.
59th Annual Congress of the German Respiratory Society (DGP)
Dresden (Germany), March 14-16, 2018

Holz, O.
Breath VOC patterns in adult asthma patients of the ALLIANCE cohort.
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Holz, O.
Evidence for metabolic syndrome and insulin resistance in smokers with COPD from serum metabolite analysis at rest and during exercise.
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Huber, S.; Raz, O.; Shapiro, E.; Czyz, Z.; Haferkamp, S.; Renner, P.; Klein, C. A.; Werner-Klein, M.
Assessing the phylogenetic relationship of early cancer spread in melanoma as basis for neo-antigen identification for adjuvant immunotherapy.
AACR Special Conference on Cancer Dormancy and Residual Disease
Montréal, Québec (Canada), June 19-22, 2018

Hücker, S. M.; Kunze, J.; Klein, C. A.; Kirsch, S.
Flexible resolution CNV profiling in single cells.
Single Cell Europe Conference
Prague (Czech Republic), September 20-21, 2018

Irlbeck, C.; Patwary, N.; Durst, F.; Haunschild, G.; Lu, X.; Lahrmann, U.; Blochberger, I.; Schneider, E.; Rack, B.; Blankenstein, T.; Buchholz, S.; Lattrich, C.; Sotlar, K.; Winkler, S.; Nerlich, M.; Klein, C. A.
Differential gene expression profiles of disseminated cancer cells derived from bone marrow of luminal A and B breast cancer patients at minimal residual disease.
AACR Special Conference on Cancer Dormancy and Residual Disease
Montréal, Québec (Canada), June 19-22, 2018

Jäger, B.
3D organoid model for in vitro testing of medical compounds.
17th Fraunhofer Seminar "Models of Lung Disease"
Hannover (Germany), January 18-19, 2018

Jäger, B.
CXCR4 inhibition by the antibody AD114 blocks bronchosphere formation in a 3D organoid model.
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Jäger, B.
Nintedanib treatment attenuates pulmonary fibrosis in a new humanized mouse model for IPF.
ATS 2018 – International conference of the American Thoracic Society
San Diego, California (USA), May 18-23, 2018

Jäger, B.
Potential role of NLRP3 inflammasome and IL-1β pathway in granuloma generation of sarcoidosis.
EMBO Workshop "The inflammasomes" 2018
Martinsried (Germany), September 25-28, 2018

Jäger, B.
Role of HDAC6 in bronchosphere formation in IPF.
Fall Congress of the German Respiratory Society (DGP), Cell Biology Section
Essen (Germany), November 9-10, 2018

Kern, A. L.; Hohlfeld, J.
Hyperpolarized ^{129}Xe functional MR imaging to monitor the response of human lungs after segmental lipopolysaccharide challenge.
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Kirsch, S.
High-resolution single-cell genome and transcriptome analysis for clinical samples (liquid biopsy platform).
Frontiers of Predictive Oncology and Computing III, Intel Headquarters
Santa Clara, California (USA), August 14-16, 2018

Kirsch, S.
High-resolution single-cell genome and transcriptome analysis for clinical samples (liquid biopsy platform).
Single Cell Omics Germany Network Meeting
Saarbrücken (Germany), November 22-23, 2018

Klein, C. A.
Models of metastasis formation: new challenges ahead.
17th Fraunhofer Seminar "Models of Lung Disease"
Hannover (Germany), January 18-19, 2018

Koch, W.; Kock, H.; Blümlein, K.
Exposure to SO_2 during unloading of freight containers shipping holding goods – a model-based approach.
BOHS Annual Conference – OH2018
Stratford-upon-Avon (UK), April 16-19, 2018

König, C.; Markiewicz, A.; Guttenberger, L.; Scheitler, S.; Lu, X.; Greindl-Junghans, J.; Lahrmann, U.; Friedmann, M.; Werner-Klein, M.; Haferkamp, S.; Berneburg, M.; Klein, C. A.
The earliest precursor cell of melanoma metastasis: identification and molecular characterization of candidate metastasis founders.
AACR Special Conference on Cancer Dormancy and Residual Disease
Montréal, Québec (Canada), June 19-22, 2018

Konzok, S.
Tumor-microenvironmental factors and their intervention in co-cultures of fresh human lung tissue and patient-derived, disseminated cancer cells.
17th Fraunhofer Seminar "Models of Lung Disease"
Hannover (Germany), January 18-19, 2018

Konzok, S.
Modulation of cancer cell growth and tumor-microenvironmental factors in ex vivo co-cultures of fresh human lung tissue and patient-derived, disseminated cancer cells.
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Krug, N.
Rhinovirus challenge in asthmatics and healthy volunteers to evaluate the safety and appropriate dose of a GMP human rhinovirus 16 preparation for challenge studies in mild to moderate asthmatics taking ICS.
ERS International Congress 2018
Paris (France), September 15-19, 2018

Müller, L.; Krämer, N.; Müller, M.; Jonigk, D.; Braubach, P.; Fieguth, H. G.; Warnecke, G.; Krüger, M.; Knebel, J.; Ritter, D.; Braun, A.; Sewald, K.; Wronski, S.
Novel approaches to mimic persistent, biofilm-associated *Pseudomonas aeruginosa* respiratory infection in vitro and ex vivo.
11th Berlin Conference on Life Sciences
Berlin (Germany), March 2, 2018

Müller, L.; Murgia, X.; Siebenbürger, L.; Boerger, C.; Sewald, K.; Häußler, S.; Schwarzkopf, K.; Braun, A.; Lehr, C.-M.; Hittinger, M.; Wronski, S.
Human mucus environment differentially affects *Pseudomonas aeruginosa* susceptibility towards antibiotic treatment.
Herrenhausen Symposium "Individualized Infection Medicine – The future is now"
Hannover (Germany), June 21-23, 2018

Müller, M.
Slide-based cytometry.
17th Fraunhofer Seminar "Models of Lung Disease"
Hannover (Germany), January 18-19, 2018

Obernolte, H.; Braubach, P.; Jonigk, D.; Beinke, S.; Belyaev, N. N.; Lennon, M.; Warnecke, G.; Fieguth, H.; Hessel, E. M.; Braun, A.; Sewald, K.; Wronski, S.
Transcriptomic analyses reveal anti-viral responses of epithelial cells and multiple immune cell types in HRV infected human lung tissue.
EAACI 2018 – Annual Congress of the European Academy of Allergy and Clinical Immunology
Munich (Germany), May 26-30, 2018

Obernolte, H.; Braubach, P.; Jonigk, D.; Beinke, S.; Belyaev, N. N.; Lennon, M.; Warnecke, G.; Fieguth, H.-G.; Hessel, E. M.; Braun, A.; Sewald, K.; Wronski, S.; Twisterling, E. S.
Transcriptomic analyses reveal anti-viral responses of epithelial cells and multiple immune cell types in HRV infected human lung tissue.
Herrenhausen Symposium "Individualized Infection Medicine – The future is now"
Hannover (Germany), June 21-23, 2018

Obernolte, H.; Braubach, P.; Jonigk, D.; Krüger, M.; Warnecke, G.; Pfennig, O.; Fieguth, H.-G.; Braun, A.; Wronski, S.; Cunoosamy, D.; Sewald, K.
Polarization of alveolar macrophages in human viable lung tissue.
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Obernolte, H.; Braubach, P.; Jonigk, D.; Krüger, M.; Warnecke, G.; Zardo, P.; Pfennig, O.; Fieguth, H.-G.; Braun, A.; Wronski, S.; Sewald, K.
A novel demonstration of macrophage plasticity in an integrated human viable lung slice system.
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Obernolte, H.; Ritter, D.; Knebel, J.; Braubach, P.; Jonigk, D.; Warnecke, G.; Zardo, P.; Fieguth, H. G.; Pfennig, O.; Braun, A.; Sewald, K.
Early biomarkers indicating COPD can be induced by whole cigarette smoke in fresh human lung tissue.
17th Fraunhofer Seminar "Models of Lung Disease"
Hannover (Germany), January 18-19, 2018

Pabst, R.; Prenzler, F.; Tschernig, T.; Rittinghausen, S.; Hohlfeld, J.; Braun, A.
Lymphoid tissue in the bronchial wall in asthma patients. Is it bronchus-associated lymphoid tissue?
17th Fraunhofer Seminar "Models of Lung Disease"
Hannover (Germany), January 18-19, 2018

Pedersen, F.; Holz, O.
A comprehensive way to rate sputum quality in clinical trials.
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Plappert, L.
A new humanized mouse model for idiopathic pulmonary fibrosis (IPF).
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Prasse, A.
Sarcoidosis state of the art.
Van der Bosch Symposium
Utrecht (The Netherlands), January 11, 2018

Prasse, A.
New humanized in vivo and in vitro models of idiopathic pulmonary fibrosis (IPF).
17th Fraunhofer Seminar "Models of Lung Disease"
Hannover (Germany), January 18-19, 2018

Prasse A.
IPF und Lungenkrebs.
5th Congress of the Working Group for the Therapy of Lung Diseases (WATL)
Berlin (Germany), January 26-27, 2018

Prasse, A.
ERN-lung ILD-group update.
ERN Annual Meeting
Frankfurt/Main (Germany), March 8-9, 2018

Prasse, A.
European Reference Networks – ERN-lung.
COPD and beyond: Management of rare & orphan diseases in pulmonology
Barcelona (Spain), April 12-14, 2018

Prasse, A.
Sarcoidosis.
Summit Rare Diseases
Copenhagen (Denmark), April 29, 2018

Prasse, A.
BAL-based readouts for TGF-β signaling in IPF.
German Center for Lung Research, DPLD Annual Meeting
Heidelberg (Germany), June 14-15, 2018

Prasse, A.
Update Lungenfibrose.
4th Experts' Forum on Lung Fibrosis
Hannover (Germany), August 15, 2018

Prasse, A.
Rheumatoide Arthritis mit interstitieller Lungenerkrankung.
DZL/BREATH advanced training: "Rheumatology and Pneumology. Wenn Lunge und Gelenke erkranken …"
Hannover (Germany), October 30, 2018

Prasse, A.
Unloading mechanotransduction in pulmonary fibrosis.
International symposium of the DFG Clinical Research Unit KFO311
Hannover (Germany), November 23-24, 2018

Renne, J.; Biller, H.; Gutberlet, M.; Czerner, C.; Schiweck, M.; Hohl, K.; Risse, F.; Sarno, M.; Gupta, A.; Hohlfeld, J.; Vogel-Claussen, J.
Regional detection of edema following segmental LPS challenge using functional MR imaging.
ERS International Congress 2018
Paris (France), September 15-19, 2018

Ritter, D.; Knebel, J.; Niehof, M.; Hansen, T.; Strandh, M.; Falciani, C.; Flores, M.; te Welscher, Y.; van Nostrum, C. F.; Gracia, R.; Marradi, M.
In vitro cytotoxicity testing of therapeutic nanosystems for pulmonary infection.
17th Fraunhofer Seminar "Models of Lung Disease"
Hannover (Germany), January 18-19, 2018

Rittinghausen, S.; Keenan, C. M.; Bradley, A. V.; Goodman, D. G.; Harada, T.; Hayashi, S.-M.; Herbert, R.; Iwata, H.; Jacobsen, M.; Kellner, R.; Mahler, B.; Meseck, E.; Nolte, T.; Rühl-Fehlert, C.; Vahle, J. L.; Yoshizawa, K.
INHAND: International Harmonization of Nomenclature and Diagnostic Criteria for Lesions – An Update – 2018.
ESTP 2018 – 16th European Congress of Toxicologic Pathology
Copenhagen (Denmark), September 11-14, 2018

Tluczkiewicz, I.; Escher, S.; Hansen, T.; Obernolte, H.; Boei, J.; Vrieling, H.; Schimming, J.; Klima, S.; Farcal, L.; Fisher, C.
Overview on CS8: the popcorn lung – read-across on diketones.
EU-ToxRisk General Assembly
Egmond aan Zee (The Netherlands), February 20-23, 2018

Treitschke, S.
Development and characterization of preclinical in vitro/in vivo models from disseminated tumor cells of melanoma patients.
25th Biennial Congress of the European Association for Cancer Research
Amsterdam (The Netherlands), June 30 – July 3, 2018

Twisterling, E. S.
Ex-vivo RSV infection and inflammatory response in human and non-human primate precision-cut lung slices (PCLS).
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Twisterling, E. S.; Dahlmann, F.; Dehmel, S.; Wronski, S.; Braubach, P.; Jonigk, D.; Warnecke, G.; Krüger, M.; Zardo, P.; Sewald, K.; Braun, A.
Comparison of IP-10 production induced by ex-vivo stimulation with respiratory syncytial virus (RSV) and the TLR3 agonist Poly I:C in human and non-human primate lung tissues.
EAACI 2018 – Annual Congress of the European Academy of Allergy and Clinical Immunology
Munich (Germany), May 26-30, 2018

Twisterling, E. S.; Dahlmann, F.; Dehmel, S.; Wronski, S.; Braubach, P.; Krüger, M.; Zardo, P.; Jonigk, D.; Warnecke, G.; Sewald, K.; Braun, A.
Ex vivo respiratory syncytial virus (RSV) infection induces release of the antiviral interferon gamma-induced protein 10 (IP-10) in human and non-human primate lung tissue slices.
17th Fraunhofer Seminar "Models of Lung Disease"
Hannover (Germany), January 18-19, 2018

Twisterling, E. S.; Dehmel, S.; Wronski, S.; Dahlmann, F.; Braubach, P.; Jonigk, D.; Krüger, M.; Warnecke, G.; Zardo, P.; Sewald, K.; Braun, A.
Antiviral chemokine interferon gamma-induced protein 10 (IP-10) response induced by Respiratory Syncytial Virus (RSV) and the TLR3 agonist poly I:C in precision-cut lung slices.
Herrenhausen Symposium "Individualized Infection Medicine – The future is now"
Hannover (Germany), June 21-23, 2018

Voskrebenzev, A.; Hohlfeld, J.
Imaging-based spirometry in chronic obstructive pulmonary disease (COPD) patients using phase resolved functional lung imaging (PREFUL).
Joint Annual Meeting ISMRM-ESMRMB
Paris (France), June 16-21, 2018

Walter, D.
Reduced oxygenation capacity of RDS can be achieved by repetitive saline lavages ex vivo.
DZL Annual Meeting
Bad Nauheim (Germany), February 8-9, 2018

Werno, C.
Characterization of in vitro and in vivo models generated from disseminated tumor cells of patients without manifest metastasis.
AACR 2018 – Annual Meeting of the American Association for Cancer Research
Chicago, Illinois (USA), April 14-18, 2018

Wronski, S.
Impact of human mucus environment on antibiotic treatment efficacy of *Pseudomonas aeruginosa* biofilms.
European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)
Madrid (Spain), April 21-24, 2018

Ziemann, C.
ICONS – Integrated testing strategy for mechanistically assessing the respiratory toxicity of functionalized MWCNTs.
NanoTox – 9th International Conference on Nanotoxicology
Neuss (Germany), September 18-21, 2018

Ziemann, C.
PLATOX – Comparative in vitro investigations on the (geno)toxic and pro-inflammatory potential of carbon-based nanoplatelets in primary rat alveolar macrophages and NR8383 cells.
NanoTox – 9th International Conference on Nanotoxicology
Neuss (Germany), September 18-21, 2018

Active participation in committees

Dr. Annette Bitsch
German Federal Institute for Risk Assessment (BfR) Committee for Food Additives, Flavorings and Processing Aids

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
External assessor for international foundations

MD/Ph.D. commission "Molecular Medicine" of the Hannover Medical School

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

Member of the German Center for Lung Research (DZL)

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")

Dr. Franziska Dahlmann
Animal protection committee of Neu Encepharm GmbH

Prof. Dr. Clemens Dasenbrock
Scientific Council on Electromagnetic Fields of the Swedish Radiation Safety Authority (SSM)

Pool of experts of the German National Committee for the Protection of Laboratory Animals of the Federal Institute for Risk Assessment

Prof. Dr. 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. Sylvia Escher
Threshold of Toxicological Concern Task Force, ILSI Europe (co-chair)

Dr. Ilona Fleischhauer
Working groups on GLP quality assurance/monitoring "GLP: Qualitätssicherung/Überwachung" and GCP quality management "GCP-Qualitätsmanagement" of the German Quality Management Association (GQMA)

Head of the working committee on quality management "Qualitätsmanagement im VLS" in the Fraunhofer Group for Life Sciences

Dr. Stefan Hahn
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 (incl. "Annals of Work Exposures and Health")

Dr. Roman Halter
External expert in the quality control committee of the association for mineral wool quality "Gütegemeinschaft Mineralwolle e.V."

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

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)

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. "European Respiratory Journal", "PLOS ONE", "Respiratory Research", and "BMC Pulmonary Medicine")

Dr. Kamran Honarnejad
Reviewer for the international journal "SLAS Discovery"

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

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

Prof. Dr. Christoph Klein
External assessor for "Lichtenberg Professorships" of the Volkswagen Foundation

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, Dutch Cancer Society, Association for International Cancer Research, EU-FP7, MRC, Cancer Research UK, Kegg-Foundation

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

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

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

Dr. Gustav Könnecker
Working group on European chemicals policy "Europäische Chemikalienpolitik" of the 6th governmental commission "Energie- und Ressourceneffizienz" of the Land Lower Saxony.

Integrated REACH project team, German Federal Office of Bundeswehr Equipment, Information Technology and In-Service Support

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

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

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"

Deputy chairman of the Fraunhofer Group for Life Sciences

Working group "Fraunhofer-Gesellschaft and Deutsche Hochschulmedizin"

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

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

Dr. Oliver Licht
German Federal Institute for Risk Assessment (BfR) Committee for Contaminants in the Food Chain; chair of the 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. Norbert Lüthe
Working group on electronic data processing "EDV" of the German Quality Management Association (GQMA)

Fraunhofer quality management network

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 Medical Research Council (UK)

Reviewer for international journals in pathology and oncology ("British Journal of Cancer", "International Journal of Cancer", "Journal of Histochemistry and Cytochemistry", "Oncotarget", and "Thoracic Cancer")

Prof. 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.

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)

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

Deputy 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", "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", "Special Senses", and working group "Apoptosis"

Reviewer for the international journal "Toxicologic Pathology"

Dirk Schaudien Ph.D.
INHAND (International Harmonization of Nomenclature and Diagnostic Criteria) working group "Non-rodents: minipig" Minischwein)

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

Dr. Sven Schuchardt
Working group on air analyses "Luftanalysen" of the German Research Foundation (DFG)

GBM – Society for Biochemistry and Molecular Biology

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)

Reviewer for international journals in biochemistry and analytics (incl. "Journal of Proteome Research", "Proteomics", "Electrophoresis", and "Talanta")

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

Dr. Katherina Sewald
External assessor for international research grants

Steering group of the workshop "Respiratory Toxicity"

Member of the German Center for Lung Research (DZL)

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

Dr. Sabine Wronski
Reviewer for the international journal "European Respiratory Journal"

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

Working group on threshold mechanisms of genotoxins of the Geman Society for Environmental Mutation Research (GUM)

Working group on statistics of the Geman Society for Environmental Mutation Research (GUM)

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

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

Teaching activities

Dr. Annette Bitsch
Governmental Institute of Public Health of Lower Saxony (NLGA) in Hannover: lecture on the regulation of biocidal products within the DGPT course "Regulatory Toxicology"

Prof. Dr. Armin Braun
TRAIN Academy: professional education program "Translational Research & Medicine: From Idea to Product" (lecturer and person in charge of Module 6 "Preclinical development")

Hannover Medical School: lectures in the MD/Ph.D. program "Molecular Medicine"

Lower Saxony International Summer Academy in Immunology at the Hannover Medical School: lecture on neuroimmune interactions in allergic asthma in the session "Lung Inflammation, Asthma, Allergy"

Dr. Otto Creutzenberg
Governmental Institute of Public Health of Lower Saxony (NLGA) in Hannover: lecture on risk assessment and regulation of particulate matter within the DGPT course "Regulatory Toxicology"

University of Leipzig: lecture on inhalation toxicology in the postgraduate course "Toxicology and Environmental Protection"

Universities of Jena/Erfurt, Institute for Pharmacology and Toxicology: lecture on exposure methods/toxicokinetics within the DGPT course "Fundamentals of organ toxicology and organ pathology"

Dr. Zbigniew Czyz
University of Regensburg: course in pathology in the degree course "Molecular Medicine"

Prof. Dr. Theodor Doll
Leibniz University Hannover: lecture on polymers for implant production in the degree course "Biomedical Engineering"

Hannover Medical School: postgraduate training course in nanomedicine

Jade University of Applied Sciences Wilhelmshaven: lecture on biomechanics, breathing and neuro-rehabilitation in the degree course "Medical Technology"

TRAIN Academy: lectures on economic aspects in implant development

Dr. Sylvia Escher
European Food Safety Authority (EFSA), Parma (Italy): Training course and complementary webinar for members of EFSA's Scientific Committee/Panels, their working groups, members of the EFSA Networks, and EFSA staff on the topic "Computational toxicology tools"

Dr. Ilona Fleischhauer
German Primate Center, Göttingen: lecture introducing to the GLP principles within the "Laboratory Animal Science Course on Primates"

TRAIN Academy: lectures on quality management and Good Laboratory Practice (GLP) – Module 2

Hannover Medical School: binational study program "Master of Science in Infection Biology – Alemania-Argentina (AMIBA)", module "Translational Medicine": lecture on Good Laboratory Practice

Hannover Biomedical Research School (HBRS) at the Hannover Medical School: workshop "Introduction to GLP and GMP"

Prof. Dr. Jens Hohlfeld
Hannover Medical School: lectures on allergic respiratory diseases

Dr. Kamran Honarnejad
University of Regensburg: course in pathology in the degree course "Molecular Medicine"

Dr. Sarah Hücker
University of Regensburg: course in pathology in the degree course "Molecular Medicine"

Dr. Stefan Kirsch
University of Regensburg: lectures and hands-on training in molecular oncology in the degree course "Molecular Medicine"

Prof. Dr. Christoph Klein
University of Regensburg: lectures in pathology and molecular oncology in the degree course "Molecular Medicine"; course and hands-on training in molecular oncology; lectures on pathology in the degree course "Human Medicine"

Ostbayerische Technische Hochschule Regensburg: lecture "What is metastatic dissemination?" in the degree course "Medical Information Technology" (as part of the series of introductory lectures into the different subject matters of medicine)

Dr. Oliver Licht
RWTH Aachen: lectures in toxicology and risk assessment

Governmental Institute of Public Health of Lower Saxony (NLGA) in Hannover: lecture on substance assessment and risk assessment within the DGPT course "Regulatory Toxicology"

Dr. Gerhard Pohlmann
Jade University of Applied Sciences Wilhelmshaven: lecture on biomechanics, breathing and neuro-rehabilitation in the degree course "Medical Technology"

TRAIN Academy: lectures on economic aspects in implant development and in Module 6 "Preclinical Development of Medical Devices"

Dr. Bernhard Polzer
University of Regensburg: lectures on molecular oncology in the degree course "Molecular Medicine"; hands-on training in molecular oncology

Ostbayerische Technische Hochschule Regensburg: lecture "What is metastatic dissemination?" in the degree course "Medical Information Technology" (as part of the series of introductory lectures into the different subject matters of medicine)

Prof. Antje Prasse
Hannover Medical School: lectures on interstitial lung disease

Priv.-Doz. Dr. Susanne Rittinghausen
University of Veterinary Medicine Hannover, Foundation: courses in toxicological pathology

Dr. Anton Roß
Hamburg University of Applied Sciences: lectures in Good Manufacturing Practice (GMP)

Dirk Schaudien Ph.D.
University of Veterinary Medicine Hannover, Foundation: lectures and courses in special and toxicological pathology

Dr. Katherina Sewald
Hannover Medical School: lectures on allergy and asthma and on analgesics in the degree course "Biomedicine"; lectures on hypertension in the degree course "Biochemistry"; laboratory course in biomedicine; laboratory course in biochemistry: immunology

RWTH Aachen: lectures on immunotoxicology in the vocational training course "M. Sc. Laboratory Animal Science"

TRAIN Academy: lectures on immunotoxicology

Dr. Nataşa Stojanovic
University of Regensburg: course in pathology in the degree course "Molecular Medicine"

Dr. Henning Weigt
TRAIN Academy: lectures on "Principles of quality management – risk management, audits, deviation and change management" and "Preclinical development, phases, costs, and quality assurance"

Dr. Christian Werno
University of Regensburg: lectures on pathology and molecular oncology in the degree course "Molecular Medicine"; hands-on training in molecular oncology

Course in "Understanding animal experiments" on behalf of the secondary school St. Michaels-Gymnasium Metten

Dr. Holger Ziehr
RWTH Aachen: lectures on "Regulatory Affairs"

Technische Universität Braunschweig: lectures on applied and technical biochemistry

Dr. Christina Ziemann
European Food Safety Authority (EFSA), Parma (Italy): Training course and complementary webinar for members of EFSA's Scientific Committee/Panels, their working groups, members of the EFSA Networks, and EFSA staff on the topic "Principles of genotoxicity in scientific assessment"

Publicly funded research projects

National

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
From Regenerative Biology to Reconstructive Therapy (REBIRTH 2). Excellence cluster

Identification of tumor-specific peptides for adjuvant immunotherapy of melanoma patients without distant metastasis

(Pre)terminal heart and lung failure: mechanical unloading and repair. Clinical Research Unit 311

Systematic analysis of metastatic cancer: central mouse and in-vitro projects. FOR 2127, TP C1, project no. 242727105

Federal Environment Agency
Chronic toxicity/carcinogenicity assessment of selected nanomaterials. R&D project 3712 61 206

Support for the use of computerized calculations such as quantitative structure-activity relationships (QSAR methods) to reduce animal experiments under REACH. R&D project 3714 67 413 0

Animal-free assessment under REACH – further development and application of read-across. R&D project 3715 67 418 0

Relevance of physiological and anthropometric parameters for the standardization and assessment of human biomonitoring results. R&D project 3716 62 214 0

Consideration of disinfection by-products as part of the environmental risk assessment of biocidal products – Inventory & development of recommendations for evaluation. R&D project 3718 65 403 0

Expert report about health effects of phthalate exposure. Project number 00377 7205-1

Federal Institute for Occupational Safety and Health (BAuA)
Histopathological examination of samples from a long-term inhalation study. Research project F 2325

Comparison of inhalation and instillation as testing methods for characterization of granular biopersistent particles (GBP). Research project F 2364

Human exposure to biocidal products: Measurement of inhalation and dermal exposure during the application of biocide foams. Research project F 2366

Mode of toxic action of nanocarbons. Research project F 2376

Collection of toxicokinetic data for the assessment of different exposure routes using the example of the antibiotic enrofloxacin. Research project F 2430

Federal Institute for Risk Assessment (BfR)
Subacute in-vivo toxicity study in male rats with six structurally representative pyrrolizidine alkaloids

Subacute in-vivo toxicity study with pesticides in female rats as part of the EuroMix project

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

Establishment of processing and cultivation protocols for vital primary tissue slices and development of strategies to measure their contractility for validation of 3D-printed physiological tissue for preclinical substance testing

Scalable human 3D tissue models based on functionally immortalized smooth muscle cells for drug development

Collaborative project: Self-curling electrode carrier for cochlear implants with hydrogel/LCST (sketch)

Development of a technology for thick-film coating with hydrogel/silicone rubber composite materials for the manufacturing of individualized electrode carriers for cochlear implants, including testing of long-term functionality and biocompatibility of the materials used

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 CD19-positive lymphoblastic leukemia – subproject "Production of the anti-CD19 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: ANTI-TB
Antibiotic nanocarrier for inhalation treatment of tuberculosis

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

Federal Ministry of Education and Research (BMBF) funding program "Alternatives to Animal Testing"
Project: InhalAb
Alternative models for testing of inhalable antibiotics

Federal Ministry of Education and Research (BMBF) funding program "Ersatz und Ergänzungsmethoden zum Tierversuch" (alternatives and complements to animal experiments)
Project: ExITox2 – Explain Inhalation Toxicity 2
Animal-free mechanism-based toxicity testing – predict toxicity after repeated-dose inhalation exposure by using a read-across approach

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 NanoCare: "Auswirkungen synthetischer Nanomaterialien auf den Menschen" (impact of synthetic nanomaterials on human health)
Project: CaNTser
Investigation of the toxic potency of carbon nanotubes following long time inhalation

Project: InhalT90

90-day inhalation testing with CeO_2 in the rat and subsequent analysis of gene expression profiles for the early detection of toxic/carcinogenic effects

Project: NanoCOLT
Long-term effect of modified carbon black nanoparticles on healthy and damaged lungs

Federal Ministry of Education and Research (BMBF) project "Förderung von Forschungsstrukturen mit Argentinien, Brasilien, Chile, Kolumbien und Mexiko" (support of collaborative research structures with Argentina, Brazil, Chile, Colombia, and Mexico)
International Hearing Research
Establishment of a Chilean-German center of hearing medicine and research

Federal Office for Radiation Protection
Experimental analysis of emissions and radiological consequences after transportation accidents with surface-contaminated objects (SCO)

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

German Center for Lung Research (DZL)
Allergy and asthma

Chronic obstructive pulmonary disease (COPD)

Diffuse parenchymal lung diseases (DPLD)

Lower Saxony Ministry of Science and Culture
Collaborative project: TransPlaMed
Establishment of distributed multicenter medical device prototype manufacturing with joint quality and risk management

Statutory Accident Insurance (DGUV)
Evaluation of usability of the physical characteristics of endogenously generated exhaled aerosols in the diagnosis of occupational lung diseases

International

Cefic-LRI project: N5-FRAU
Histopathology of rats exposed to Barium sulfate nanoparticles by life-time inhalation exposure – Effects and Biokinetics

EFSA project: Applying a tested procedure for the identification of potential emerging chemical risks in the food chain to the substances registered under REACH – REACH 2

EU project: Approach for Evaluation of PBTs Subject to Authorisation and Restriction Procedures in Context of Socio-Economic Analysis

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

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

EU project: ICONS – Integrated Cooperation On Nanotube Safety
An integrated testing strategy for mechanistically assessing the respiratory toxicity of functionalized multi-walled carbon nanotubes

EU project: PLATOX
In-vitro and in-vivo investigations to generate validated toxicity data of graphene nanoplatelets vs. a carbon black reference

EU project: PneumoNP
Nanotherapeutics to treat antibiotic-resistant Gram-negative infections of the lung

EU project: SILIFE
Production of quartz powders with reduced crystalline silica toxicity

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

German Federal Ministry of Education and Research (BMBF) and Ministry of Research, Technology and Higher Education of the Republic of Indonesia (RISTEK): joint research program for the identification and use of natural substances from Indonesia for the development of new therapeutics
Collaborative research project: Triple-IN
Insect-derived anti-infectives from Indonesia

***i*CAIR**
Fraunhofer International Consortium for Anti-Infective Research

Cooperation partners

National

Advanced Bionics AG

Assay.Works, Regensburg

Augsburg University Hospital

BASF SE, Ludwigshafen

Bayer AG, Berlin

BioMedVet Research GmbH, Walsrode

Blackrock Microsystems Europe GmbH, Hannover

Boehringer Ingelheim Pharma GmbH & Co. KG

Cardior Pharmaceuticals GmbH, Hannover

Cellex Patient Treatment GmbH, Dresden and Cologne

Center of Allergy & Environment (ZAUM), Munich

Charité – Universitätsmedizin Berlin

Charité Research Organisation GmbH, Berlin

Cortec GmbH, Freiburg

Cytena GmbH, Freiburg

dysantect, Wiesbaden

Envigo CRS GmbH, Rossdorf

Epomedics GmbH, Göttingen

Essen University Hospital

EurA Consult AG, Hamburg Office

EURICE – European Research and Project Office GmbH, Saarbrücken

European Aviation Safety Agency (EASA), Cologne

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

FOBIG, Forschungs- u. Beratungsinstitut Gefahrstoffe GmbH, Freiburg

Forschungszentrum Jülich

Fraunhofer Center for International Management and Knowledge Economy IMW

Fraunhofer Institute for Cell Therapy and Immunology IZI, Leipzig

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

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 Molecular Biology and Applied Ecology IME, Schmallenberg

Fraunhofer Institute for Process Engineering and Packaging IVV

Fraunhofer Institute for Silicate Research ISC, Würzburg

Fraunhofer Institute for Surface Engineering and Thin Films IST

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

Friedrich Schiller University Jena

GEMoaB Monoclonals GmbH, Dresden

Genewiz Germany GmbH

GeneXplain GmbH, Wolfenbüttel

German Aerospace Center (DLR), Cologne

German Center for Infection Research (DZIF)

German Center for Lung Research (DZL)

German Primate Center, Göttingen

Hannover Clinical Trial Center (HCTC), Hannover

Hannover Medical School

Helmholtz Center for Infection Research, Braunschweig

Helmholtz Institute for Pharmaceutical Research Saarland (HIPS), Saarbrücken

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

Heraeus Medical GmbH, Wehrheim

HYpharm GmbH, Bernried

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

Karlsruhe Institute of Technology, Karlsruhe

Kiel University

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

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

Leibniz University Hannover

Ludwig-Maximilians-Universität München (LMU), Munich

LungenClinic Grosshansdorf GmbH

Martin Luther University Halle-Wittenberg

Max Planck Institute, Giessen

Merck KGaA, Darmstadt

Molecular Machines & Industries MMI GmbH, Eching

Ostbayerische Technische Hochschule Regensburg

Otto Bock HealthCare GmbH

Research Center Borstel

Rodos Biotarget GmbH

RWTH Aachen

Sanum Kehlbeck GmbH & Co. KG, Hoya

Technische Universität Braunschweig

Technische Universität München (TUM), Munich

Telexos GmbH, Weilheim

TRAIN – biomedical translation alliance in Lower Saxony, Hannover

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

Ulm University

Universitätsklinikum Erlangen

University Hospital Carl Gustav Carus, Dresden

University of Applied Sciences and Arts, Göttingen

University of Cologne

University of Düsseldorf

University of Freiburg

University of Giessen

University of Leipzig

University of Marburg

University of Regensburg

University of Tübingen

University of Veterinary Medicine Hannover, Foundation

Vakzine Projekt Management GmbH, Hannover

Wacker Silicones, Munich

International

ACMIT GmbH – Austrian Center for Medical Innovation and Technology (Austria)

AIT Austrian Institute of Technology GmbH (Austria)

Amgen, Thousand Oaks, California (USA)

Angle plc, Guildford (UK)

AstraZeneca (Sweden)

Biosafe SA, GE Life Sciences, Nyon (Switzerland)

BOHS – British Occupational Hygiene Society, Derby (UK)

Brains On-Line (The Netherlands)

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)

Erasmus Medical Center, Rotterdam (The Netherlands)

European Food Safety Authority (EFSA), Parma (Italy)

Fundación CIDETEC (CID), San Sebastián (Spain)

GlaxoSmithKline Research and Development Ltd., Brentford (UK)

Griffith University, Gold Coast (Australia)

Haisco Pharmaceutical Group (China)

HANSABIOMED Ltd., Tallinn (Estonia)

Harvard T.H. Chan School of Public Health, Boston, Massachusetts (USA)

HiberCell Therapeutics Inc., Chicago, Illinois (USA)

IBMCC (Instituto de Biología Molecular y Cellular del Cáncer), Salamanca (Spain)

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

Instituto de Tecnología Cerámica, Castellón (Spain)

International Agency for Research on Cancer (IARC), Lyon (France)

Izmir Biomedicine and Genome Center, Izmir (Turkey)

Johannes Kepler University Linz, Linz (Austria)

Loughborough University, Leicestershire (UK)

Maastricht University, Maastricht (The Netherlands)

Massachusetts Institute of Technology, Cambridge, Massachusetts (USA)

Mathys Ltd, Bettlach (Switzerland)

McMaster University Medical Center, Hamilton, Ontario (Canada)

Medical University of Graz, Graz (Austria)

Menarini Biomarkers (Singapore)

Menarini Silicon Biosystems, Bologna (Italy)

Nanoconsult, Meerssen (The Netherlands)

North Carolina State University (NCSU), Raleigh, North Carolina (USA)

Novartis (Switzerland)

Oregon Health & Science University, Portland, Oregon (USA)

PExA, Gothenburg (Sweden)

Poznan University of Medical Sciences, Poznan (Poland)

Sahlgrenska University Hospital, Gothenburg (Sweden)

Society for Laboratory Automation and Screening (SLAS), Chicago, Illinois (USA)

Université catholique de Louvain, Louvain (Belgium)

University of Alberta, Alberta (Canada)

University of Amsterdam, Amsterdam (The Netherlands)

University of Basel, Basel (Switzerland)

University of Bern, Bern (Switzerland)

University of Chile, Santiago de Chile (Chile)

University of Kent, Canterbury (UK)

University of Leeds, Leeds (UK)

University of Leiden, Leiden (The Netherlands)

University of Siena, Siena (Italy)

University of Southampton, Southampton (UK)

University of Utrecht, Utrecht (The Netherlands)

US Environmental Protection Agency (EPA), Chapel Hill, North Carolina (USA)

Weizmann Institute of Science, Rehovot (Israel)

World Health Organization (WHO), Geneva (Switzerland)

Yale University, New Haven, Connecticut (USA)

Exhibitions, congresses and workshops

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 2018, the institute hosted or played an active role in the following events:

January 18-19, 2018
17th Fraunhofer Seminar "Models of Lung Disease"
Hannover (Germany)

February 8-9, 2018
DZL Annual Meeting
7th Annual Meeting of the German Center for Lung Research
Bad Nauheim (Germany)

February 24, 2018
33rd German Cancer Congress
Berlin (Germany)

February 26 – March 1, 2018
DGPT Annual Conference 2018
84th Annual Conference of the German Society of Pharmacology and Toxicology
Göttingen (Germany)

March 2, 2018
Berlin Conference on Life Sciences
Novel Antimicrobials and AMR Diagnostics 2019
Berlin (Germany)

March 7-8, 2018
Operational Excellence in Clinical Trials Summit (OECT)
Berlin (Germany)

March 11-15, 2018
SOT 2018
57th Annual Meeting of the Society of Toxicology; including Fraunhofer ITEM Exhibitor-Hosted Sessions on "Risk assessments for cosmetics: new approaches and science behind the data" and "Optimized in-vitro models for the prediction of drug-induced liver injury"
San Antonio, Texas (USA)

March 14-16, 2018
DGP Congress 2018
59th Congress of the German Respiratory Society
Dresden (Germany)

March 18-21, 2018
EEMGS 2018
Annual Meeting of EEMGS (European Environmental Mutagenesis and Genomics Society) and GUM (Geman Society for Environmental Mutation Research)
Potsdam (Germany)

April 4-7, 2018
Annual Congress of the German Cardiology Society (DGK)
Mannheim (Germany)

April 14-18, 2018
AACR 2018
Annual Meeting of the American Association for Cancer Research
Chicago, Illinois (USA)

April 16-19, 2018
OH2018
Annual Meeting of the British Occupational Hygiene Society (BOHS)
Stratford-upon-Avon (UK)

April 20, 2018
PathoLecT 2018
Berlin (Germany)

April 21-24, 2018
European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)
Madrid (Spain)

May 13-17, 2018
SETAC Europe 2018
28th European Annual Meeting of the Society of Environmental Toxicology and Chemistry
Rome (Italy)

May 18-23, 2018
ATS International Conference 2018
International conference of the American Thoracic Society
San Diego, California (USA)

May 26-30, 2018
EAACI 2018
Annual Congress of the European Academy of Allergy and Clinical Immunology
Munich (Germany)

June 4-7, 2018
BIO International Convention 2018
Boston, Massachusetts (USA)

June 7-9, 2018
WASOG 2018
International Conference on Sarcoidosis and Interstitial Lung Diseases
Heraklion (Greece)

June 19-20, 2018
ISES-Europe 2018 – European Exposure Science Strategy Workshop
Dortmund (Germany)

June 19-22, 2018
Cancer Dormancy and Residual Disease
Conference of the American Association for Cancer Research
Montréal, Québec (Canada)

June 21-23, 2018
Herrenhausen Symposium "Individualized Infection Medicine – The future is now"
Hannover (Germany)

June 30 – July 3, 2018
EACR25
25th Congress of the European Association for Cancer Research
Amsterdam (The Netherlands)

July 9-13, 2018
Mathematical perspectives in the biology and therapeutics of cancer
CIRM – Centre International de Rencontres Mathématiques
Marseille (France)

July 18-20, 2018
45th Annual Meeting of the Japanese Society of Toxicology
Osaka (Japan)

September 2-5, 2018
EUROTOX 2018
54th Annual Congress of the European Societies of Toxicology
Brussels (Belgium)

September 6-7, 2018
11th International VPM Days
Hannover (Germany)

September 9, 2018
Umwelt 2018
Münster (Germany)

September 10, 2018
Response and Resistance in Cancer Therapy
Conference of the British Association for Cancer Research (BACR)
Canterbury (UK)

September 11, 2018
Mit der EU-Medizinprodukteverordnung (über)leben
Forum organized by the High-Performance Center Translational Biomedical Engineering on the current state of implementation and consequences of the European Medical Device Regulation (MDR)
Berlin (Germany)

September 11-14, 2018
ESTP 2018
16th European Congress of Toxicologic Pathology
Copenhagen (Denmark)

September 12, 2018
Biomedical Engineering Conference of the Fraunhofer Group for Life Sciences
Berlin (Germany)

September 13-14, 2018
9th Berlin Workshop on Developmental Toxicology
Berlin (Germany)

September 15-19, 2018
ERS Congress 2018
International Congress of the European Respiratory Society
Paris (France)

September 18-21, 2018
9th International Conference on Nanotoxicology
Neuss (Germany)

September 25-28, 2018
EMBO Workshop "The inflammasomes" 2018
Martinsried (Germany)

October 1-3, 2018
EurOPDX Workshop 2018
Weggis (Switzerland)

October 9, 2019
Fachforum Life Sciences – Gegenwart und Zukunft II
Berlin (Germany)

October 15-18, 2018
ESTIV2018
20th International Congress of the European Society of Toxicology In Vitro
Berlin (Germany)

November 3, 2018
Open house day
Fraunhofer ITEM opened its doors to interested visitors
Hannover (Germany)

November 5-7, 2018
BIO-Europe 2018
Copenhagen (Denmark)

November 6-7, 2018
R2N symosium "Alternative methods to replace or reduce animal models in biomedical research"
Hannover (Germany)

November 12-15, 2018
COMPAMED 2018
Düsseldorf (Germany)

November 12-15, 2018
MEDICA 2018
Düsseldorf (Germany)

November 16, 2018
2nd PedMedDev Conference
Pediatric Medical Devices: Safety & Protection by Innovation & Development
Lübeck (Germany)

November 22-23, 2018
4th Conference of Applied Hygiene, Microbiology and Virology
Hamburg (Germany)

November 29, 2018
FORUM Translational Medicine
Würzburg (Germany)

November 30 – December 1, 2018
Belgian Pneumology Days – 2018
Brussels (Belgium)

December 1, 2018
8. Berliner Kongress für Kinder- und Jugendmedizin
8th Berlin congress on pediatrics and adolescent medicine
Berlin (Germany)

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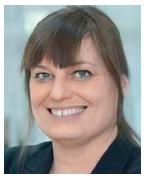

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