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ITEM

FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM

ANNUAL REPORT 2019

FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM

PERFORMANCE AND RESULTS

ANNUAL REPORT 2019

Contents

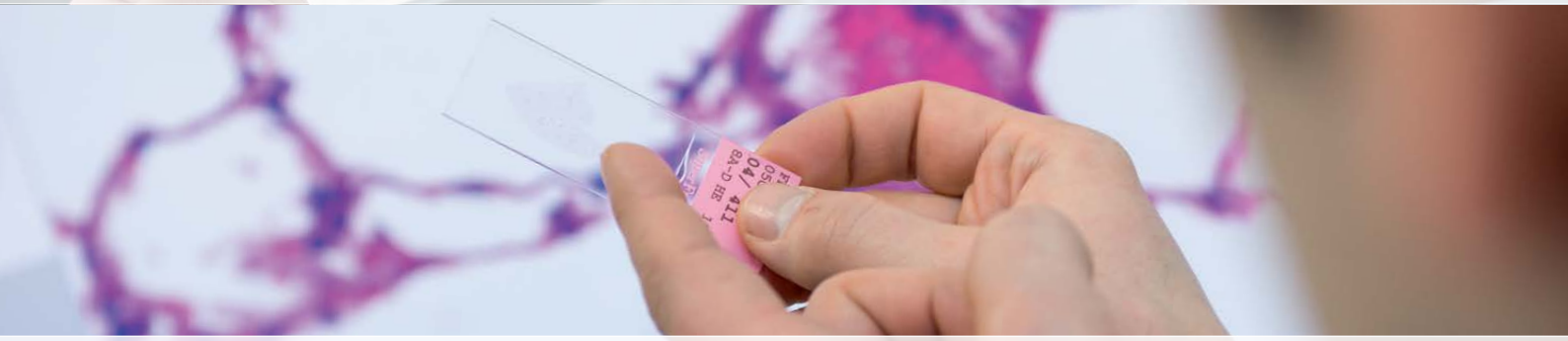
TRANSLATIONAL BIOMEDICAL ENGINEERING

PERSONALIZED TUMOR THERAPY

OUR MISSION – WHAT DRIVES US

We do research to improve health, to protect against hazards, and to generate safety.

We assess and develop tomorrow's materials, medicines, and medical devices.



We combine basic research and industrial application in the regulatory environment.

FOREWORD

Dear Reader,

We are living in an increasingly dynamic world. Technological cycles are getting ever shorter and our lifestyle and needs are changing rapidly. These developments entail questions and challenges – challenges in particular that affect people's sustainable health. Fraunhofer ITEM creatively develops solutions to address these needs.

In order to keep up with these dynamics and be well positioned for the future, we have recently formulated new guiding principles for our institute as a result of a participatory development process. These guiding principles, consisting of our mission, vision, and values for our collaboration, aim to provide both orientation and motivation and also a reference framework for our collaboration. They define what we stand for, what we are striving for, and what are the values and principles that guide us in jointly coping with current and future challenges. With our guiding principles, we have created a basis for successful applied and innovative research.

What drives us is our determination to improve people's health and protect it from hazardous effects. To this end, we develop or support the development of materials, therapeutics, and medical devices. Our basic research is geared to the health requirements and needs of society, while we also keep an eye on current market trends to allow the results of our research to be successfully translated into applications.

In this context, some of the projects we worked on in 2019 deserve special mention, such as the German-Australian project iCAIR®, aimed at exploring novel anti-infective therapies from the identification of potential target structures to the clinical proof of concept, and research projects on bacteriophages, addressing the problem of increasing resistance to antibiotic treatment. In addition, we collaborate with other Fraunhofer Institutes in the field of immune-mediated diseases: the research cluster Fraunhofer CIMD aims to translate innovative ideas into individualized therapies for such diseases. In the toxicological area, a paradigm shift is taking place in chemical risk assessment. Fraunhofer ITEM researchers are involved in the EU project ToxRisk, the European "flagship" program driving mechanism-based, animal-free toxicity testing and risk assessment for the 21st century. Our lighthouse projects furthermore include the High-Performance Center Translational Biomedical Engineering: its research and development activities are aimed at enabling a smooth translation of medical devices from the lab into clinical trials. Medical devices are also at the focus of the EU project MDOT, where we contribute to the development of an open-innovation test bed aimed at supporting small and medium-sized manufacturers of medical devices to get their products certified. And last but not least – to address the increasing role of digitalization in science – we have placed a new focus on bioinformatics. A project group dedicated to this subject area was set up at our institute in fall 2019.

Our vision at Fraunhofer ITEM is to be pioneers for sustainable health. Let me invite you, dear reader, to share a part of our way by reading this Annual Report.

Yours,

Norbert Krug
Executive Director

PROFILE OF THE INSTITUTE

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

Health protection

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

Reliable 21st-century assessment of chemical safety

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

Preclinical testing of candidate drugs

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

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

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Clinical trials for efficacy and tolerability testing of novel drugs

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

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

Biopharmaceutical manufacturing from cell line to investigational medicinal product

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

Bringing medical devices from the laboratory into clinical trials

In the field of translational biomedical engineering, we aim to bring medical devices from the lab into phase I of clinical development and to support clients in particular with the implementation of the 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 is collaborating with the Lower Saxony Center for Biomedical Engineering, Implant Research and Development (NIFE for short).

Personalized tumor diagnosis

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

Bioinformatics for better health and chemical safety

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

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

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

GXP – quality assurance according to international standards

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

Lighthouse projects

Our lighthouse projects are dedicated to topics that are of particular relevance for the health of individuals and society at large – topics that are, therefore, important to us.

www.item.fraunhofer.de/en/lighthouse-projects

EU-ToxRisk: toxicological risk assessment
European "flagship" program driving mechanism-based, animal-free risk assessment for the 21st century.

German-Australian project iCAIR®
Research consortium aiming to develop new anti-infective treatment options – from the identification of potential target structures to the preclinical proof of concept.

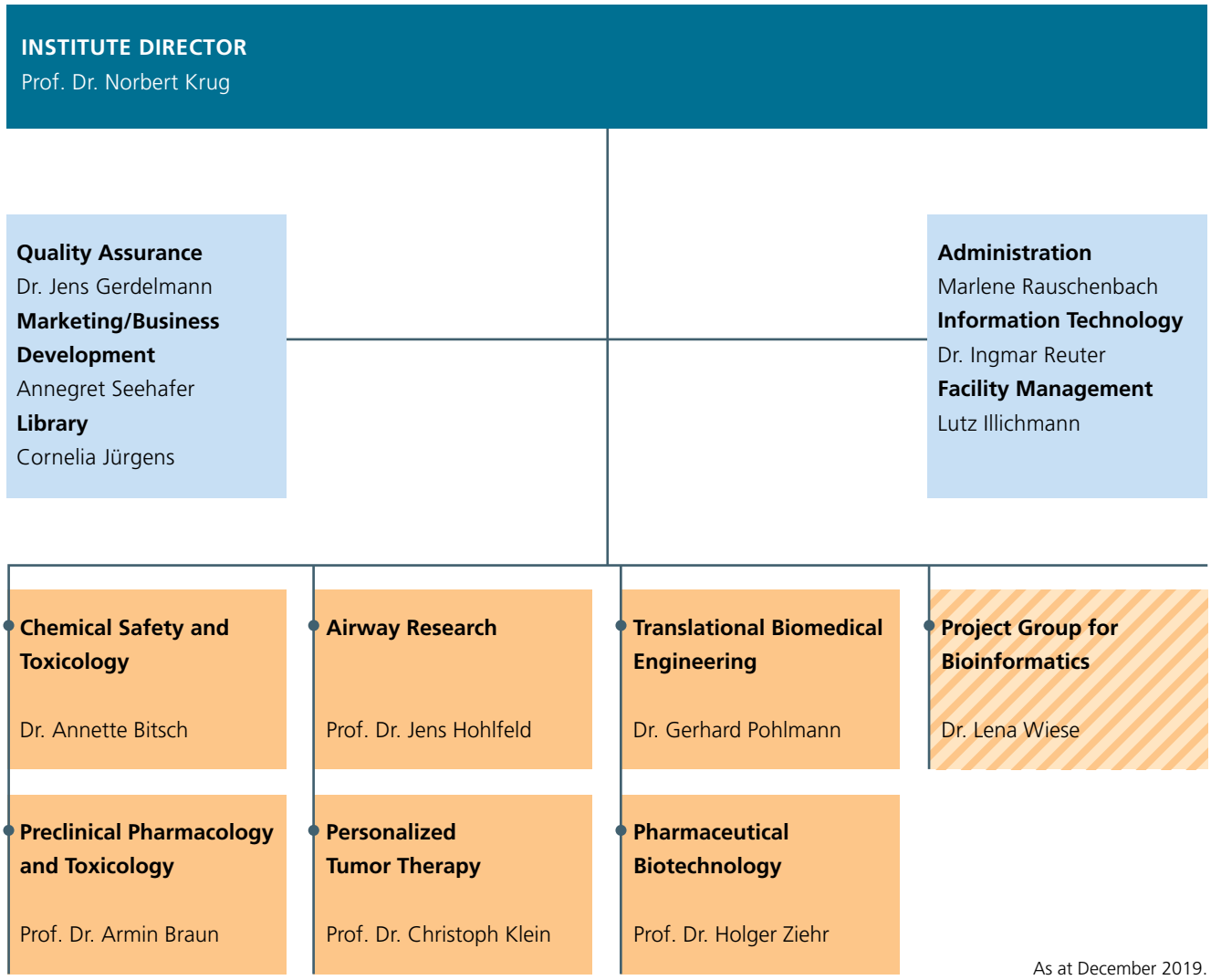
Bacteriophages as an approved drug
Developing bacteriophage therapies and getting phages approved as therapeutics to address the problem of increasing resistance to antibiotic treatment.

High-Performance Center Translational Biomedical Engineering
The aim of the High-Performance Center is to bring medical devices from the lab into clinical trials by successfully clearing scientific and economic hurdles.

EU-MDOT: supporting medical device manufacturers
Development of an open-innovation test bed aimed at supporting small and medium-sized manufacturers of medical devices to get their products certified.

Research cluster for immune-mediated diseases
Fraunhofer CIMD – pooled expertise of three Fraunhofer Institutes to efficiently translate innovative ideas into individualized therapies for immune-mediated diseases.

ORGANIZATIONAL STRUCTURE



As at December 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. Special expertise that is relevant for all business units, namely in bioinformatics, comes from the corresponding project group.

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

CONTACT PERSONS

On the following pages, 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.

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.

Institute Directors

Prof. Dr. Norbert Krug
Executive Director
Medical Director
Phone +49 511 5350-8100
norbert.krug@item.fraunhofer.de

Prof. Dr. Jens Hohlfeld
Deputy Director
Division Director of Airway Research
Phone +49 511 5350-8101
jens.hohlfeld@item.fraunhofer.de

Chemical Safety and Toxicology

Dr. Annette Bitsch
Division Director of Chemical Safety and Toxicology
Phone +49 511 5350-302
annette.bitsch@item.fraunhofer.de

Dr. Sylvia Escher
Head of Department of In-silico Toxicology
Phone +49 511 5350-330
sylvia.escher@item.fraunhofer.de

Ariane Zwintscher
Head of Department of Regulatory Affairs
Phone +49 511 5350-312
ariane.zwintscher@item.fraunhofer.de

Dr. Otto Creutzenberg
Head of Department of Inhalation Toxicology
Phone +49 511 5350-461
otto.creutzenberg@item.fraunhofer.de

Dr.-Ing. Katharina Schwarz
Head of Department of Aerosol Technology and Biophysics
Phone +49 511 5350-139
katharina.schwarz@item.fraunhofer.de

Dr. Sven Schuchardt
Head of Department of Bio- and Environmental Analytics
Phone +49 511 5350-218
sven.schuchardt@item.fraunhofer.de

Dr. Rupert Kellner
Manager of the Working Group on Databases and Information Systems
Phone +49 511 5350-106
rupert.kellner@item.fraunhofer.de

Petra Wiedemeier
Manager of the Working Group on Documentation
Phone +49 511 5350-327
petra.wiedemeier@item.fraunhofer.de

Preclinical Pharmacology and Toxicology

Prof. Dr. Armin Braun
Division Director of Preclinical Pharmacology and Toxicology
Phone +49 511 5350-263
armin.braun@item.fraunhofer.de

Dr. Katherina Sewald
Head of Department of Preclinical Pharmacology and In-vitro Toxicology
Phone +49 511 5350-323
katherina.sewald@item.fraunhofer.de

Dr. Sabine Wronski
Manager of the Working Group on Infection and Immunology
Phone +49 511 5350-444
sabine.wronski@item.fraunhofer.de

Dr. Christina Hesse
Manager of the Working Group on Respiratory Pharmacology
Phone +49 511 5350-421
christina.hesse@item.fraunhofer.de

Dr. Tanja Hansen
Manager of the Working Group on In-vitro Test Systems
Phone +49 511 5350-226
tanja.hansen@item.fraunhofer.de

Dr. Christina Ziemann
Manager of the Working Group on Genetic Toxicology and Tumor Research
Phone +49 511 5350-203
christina.ziemann@item.fraunhofer.de

Priv.-Doz. Dr. Susanne Rittinghausen
Head of Department of Pathology
Phone +49 511 5350-310
susanne.rittinghausen@item.fraunhofer.de

Airway Research

Prof. Dr. Jens Hohlfeld
Division Director of Airway Research
Phone +49 511 5350-8101
jens.hohlfeld@item.fraunhofer.de

Dr. Philipp Badorrek
Head of Department of Clinical Airway Research
Phone +49 511 5350-8130
philipp.badorrek@item.fraunhofer.de

Prof. Dr. Antje Prasse
Head of Department of Clinical and Translational Research on Pulmonary Fibrosis
Phone +49 511 5350-8151
antje.prasse@item.fraunhofer.de

Dr. Meike Müller
Head of Department of Biomarker Analysis and Development
Phone +49 511 5350-8144
meike.mueller@item.fraunhofer.de

Dr. Olaf Holz
Manager of the Working Group on Clinical Method Development
Phone +49 511 5350-8141
olaf.holz@item.fraunhofer.de

Personalized Tumor Therapy

Prof. Dr. Christoph Klein
Division Director of Personalized Tumor Therapy
Phone +49 941 298480-21
christoph.andreas.klein@item.fraunhofer.de

Dr. Stefan Kirsch
Manager of the Working Group on Innovative Molecular Technologies and Biomarker Discovery
Phone +49 941 298480-26
stefan.kirsch@item.fraunhofer.de

Dr. Bernhard Michael Polzer
Manager of the Working Group on Cellular and Molecular Diagnostics
Phone +49 941 298480-23
bernhard.michael.polzer@item.fraunhofer.de

Dr. Christian Werno
Manager of the Working Group on Preclinical Therapy Models
Phone +49 941 298480-51
christian.werno@item.fraunhofer.de

Dr. Kamran Honarnejad
Manager of the Working Group on High-Throughput Drug and Target Discovery
Phone +49 941 298480-54
kamran.honarnejad@item.fraunhofer.de

Dr. Jens Warfsmann
Manager of the Working Group on Bioinformatics and Data Management
Phone +49 941 298480-28
jens.warfsmann@item.fraunhofer.de

Translational Biomedical Engineering

Dr. Gerhard Pohlmann
Division Director of Translational Biomedical Engineering
Head of Department of Inhalation Therapy
Phone +49 511 5350-116
gerhard.pohlmann@item.fraunhofer.de

Prof. Dr. Theodor Doll
Head of Department of Implant Systems
Head of the High-Performance Center
Phone +49 511 5350-248
theodor.doll@item.fraunhofer.de

Pharmaceutical Biotechnology

Prof. Dr. Holger Ziehr
Division Director of Pharmaceutical Biotechnology
Phone +49 531 6181-6000
holger.ziehr@item.fraunhofer.de

Dr. Jens Paulsen
Manager of the Working Group on Downstream Processing
Phone +49 531 6181-6400
jens.paulsen@item.fraunhofer.de

Dr. Claudius Seitz
Manager of the Working Group on Microbial Cultivation
Phone +49 531 6181-6347
claudius.seitz@item.fraunhofer.de

Dr. Markus Heine
Manager of the Working Group on Cell Culturing Techniques
Phone +49 531 6181-6307
markus.heine@item.fraunhofer.de

Dr. Nico Langer
Manager of the Working Group on Quality Control
Phone +49 531 6181-6502
nico.langer@item.fraunhofer.de

Project Group for Bioinformatics

Dr. Lena Wiese
Manager of the Project Group for Bioinformatics
Phone +49 511 5350-303
lena.wiese@item.fraunhofer.de

Quality Assurance

Dr. Jens Gerdelmann
Head of Quality Assurance at the Hannover site
Phone +49 511 5350-349
jens.gerdelmann@item.fraunhofer.de

Dr. Neophytos Papamichael
Head of Quality Assurance at the Braunschweig site
Phone +49 531 6181-6200
neophytos.papamichael@item.fraunhofer.de

Marketing and Business Development

Annegret Seehafer
Head of Department of Marketing and Business Development
Phone +49 511 5350-402
annegret.seehafer@item.fraunhofer.de

Library

Cornelia Jürgens
Head of Library Department
Phone +49 511 5350-517
cornelia.juergens@item.fraunhofer.de

STAFF AND INSTITUTE BUDGET PERFORMANCE

At the end of 2019, Fraunhofer ITEM staff at all three sites – Hannover, Braunschweig and Regensburg – altogether amounted to 383 persons, with a female proportion of 62 percent. People from 15 countries work and do research together at Fraunhofer ITEM.

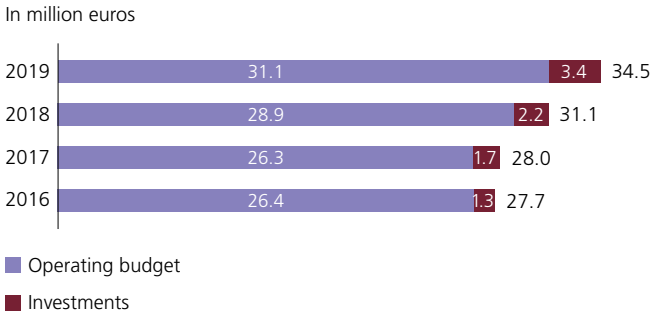
The institute's staff in 2019 included:
314 scientific, technical and administrative staff
17 Ph.D. students
38 students (bachelor's and master's programs)
11 apprentices
3 interns

In 2019, the institute's budget reached a level of approximately 31 million euros. Financing by acquired funding amounted to 69 percent. The share of industrial income in the institute's budget was 46 percent.

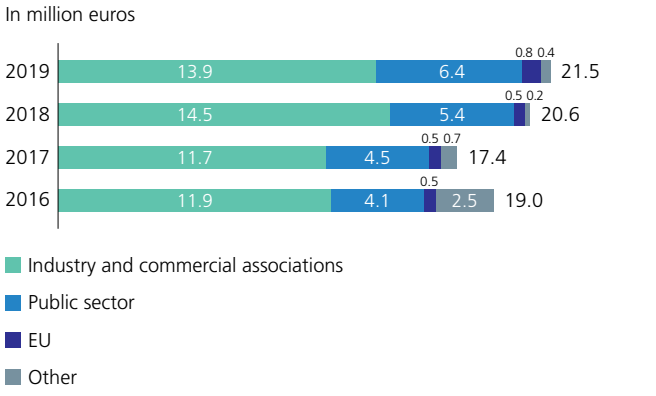
Investments of Fraunhofer ITEM amounted to approximately 3.4 million euros.

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 2019, the Fraunhofer ITEM board of trustees was made up of the following members:

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

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

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

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

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

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

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

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

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

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

Ministerialrätin Dr. Evelyn Obele
Head of Division 614 – Health Research, Medical Technology,
German Federal Ministry of Education and Research

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

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

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

NEWS IN 2019

Regensburg Oncology Award

Dr. Nataša Stojanović, researcher at Fraunhofer ITEM in Regensburg, has received the Regensburg Oncology Award for her paper "Microfluidic enrichment, isolation and characterization of disseminated melanoma cells from lymph node samples". The prize was awarded on July 3, 2019, during a German congress dedicated to the highlights of the American Cancer Congress. Major contributions to this research work also came from her Fraunhofer colleagues Dr. Kathrin Weidele and Dr. Bernhard Polzer. Their highly promising results were published in the International Journal of Cancer in January 2019.

www.item.fraunhofer.de/oncology-award

Founding of the first German Society for Metabolome Research

In May 2019, the first German Society for Metabolome Research (DGMet) was founded at the Braunschweig Integrated Centre of Systems Biology (BRICS) of Braunschweig University of Technology. DGMet is committed to investigating metabolism and the resulting compounds. Dr. Sven Schuchardt, Head of the Fraunhofer ITEM Department of Bio- and Environmental Analytics and one of the Society's founding members, was elected treasurer. Besides Sven Schuchardt (third from the left), members of the DGMet executive council are (from left to right) Jennifer Kirwan of Max Delbrück Center in Berlin, Karsten Hiller of Braunschweig University of Technology, Jerzy Adamski of

Helmholtz Zentrum München, Meina Neumann-Schaal of Leibniz Institute DSMZ, and Sabine Metzger of the University of Cologne. The aim of DGMet is to foster research in metabolism and to function as an interaction platform for scientists in the field, so as to promote joint research activities.

www.item.fraunhofer.de/dgmet-foundation

Rating the quality of sputum cell preparations in clinical trials for asthma and COPD treatment

The analysis of induced sputum is a non-invasive method to assess airway inflammation and is thus frequently used in clinical trials targeting asthma and COPD. The quality of sputum cell preparations depends on multiple factors. To avoid the unnecessary exclusion of samples from analysis and to define a better cut-off for the exclusion of samples, scientists of the German Center for Lung Research (DZL) and of Fraunhofer ITEM have collaborated to develop a novel quality score. The data have been published in the International Journal of COPD in the paper "Rating sputum cell quality in clinical trials for asthma and COPD treatment".

www.item.fraunhofer.de/sputum-center

Project partner in the EU project REMADYL

Fraunhofer ITEM is one of 15 European partners in the EU project REMADYL that will be funded under the Horizon 2020 Framework Program for the next four years. The aim of this collaborative project is to develop a breakthrough continuous process based on extractive extrusion technology. In combination with novel solvents and melt filtration, this process is aimed at allowing legacy substances regulated under REACH to be removed from polyvinyl chloride. "Old PVC" thus purified can then be recycled, providing a means for circular economy.

www.item.fraunhofer.de/project-remadyl

New Project Group for Bioinformatics

To address the increasing role of digitalization in science, a new Attract Project Group for Bioinformatics was set up at Fraunhofer ITEM in fall 2019. Headed by Dr. Lena Wiese, this Project Group aims to improve the analysis of data collected in health research by using novel intelligent methods and to provide special techniques that enable efficient and validated analyses. The grant program "Fraunhofer Attract" offers outstanding external scientists the opportunity to develop their ideas towards actual applications close to the market within an optimally equipped Fraunhofer Institute.

www.item.fraunhofer.de/bioinformatics

EU project MDOT to simplify testing and increase the safety of medical devices

Funded with 8.3 million euros over a period of five years, a platform shall be developed to support small and medium-sized manufacturers of medical devices in the conformity assessment of their products. This will include development of three demonstrator technologies in the fields of inhalers, neural implants, and coatings for hip replacements.

www.item.fraunhofer.de/project-mdot

Fraunhofer iCAIR® is breaking new ground in the development of antiviral drugs

In the Fraunhofer iCAIR® project, scientists from Griffith University in Australia, the Hannover Medical School and Fraunhofer ITEM are breaking new paths in the development of anti-infective therapies. For their research in this project, they also use precision-cut lung slices (PCLS), i.e. viable lung tissue slices. At the International Conference 2019 of the American Thoracic Society, they presented their finding that zanamivir, an already approved neuraminidase inhibitor developed by the Australian researchers, has the same antiviral effect in human PCLS infected with influenza viruses ex vivo as in the intact human organism. Human PCLS (see image) can thus be used for preclinical efficacy testing of novel antiviral drugs. The Fraunhofer scientists are currently testing new active agents developed by their Australian colleagues in the PCLS model.

www.item.fraunhofer.de/project-icair

Support with implementation of the guidance for the identification of endocrine disruptors

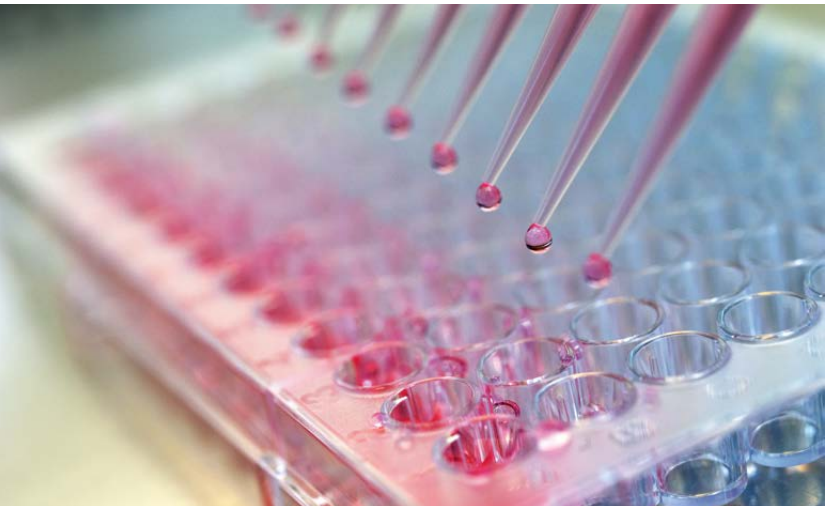
Endocrine disruptors are chemicals that may interfere with the body's hormonal system. In 2018, the guidance for the identification of endocrine disruptors (ED) came into force, laying down the implementation of ED criteria in the context of the Biocidal Products Regulation. With their specific toxicological expertise, Fraunhofer ITEM scientists can support clients in the evaluation of the endocrine potential of biocides and plant protection products.

www.item.fraunhofer.de/endocrine-disruptors

This is possible for pupils only on "Taster Day"!

Experimenting with cells, investigating extremely thin lung slices under a microscope – and learning about a real biobank ... on "Taster Day" 2019, 23 pupils took the opportunity to get insights into the working environment at Fraunhofer ITEM.

www.item.fraunhofer.de/tasterday2019



Making novel therapeutics safer: Fraunhofer ITEM is participating in the EU project imSAVAR

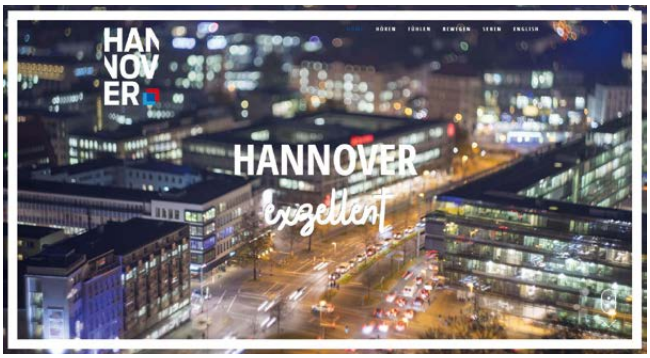
Cancer medicine is not the only area where cell and gene therapies are increasingly taking hold as alternatives or complements to classic, low-molecular drugs and biologicals. A significant challenge in the development of new therapies, however, continues to be their preclinical evaluation for efficacy and safety. While preclinical tests have so far mainly looked at the basic toxicity of a new therapeutic agent for the (healthy) immune system, there is a lack of nonclinical models that accurately capture the individual interactions of the human immune system in the pathogenic state. The EU consortium imSAVAR is addressing this shortfall by coming up with new ways of examining immunomodulatory therapies.

www.item.fraunhofer.de/project-imsavar

Open-innovation test bed for medical devices

Aiming to support European med-tech companies in the global competition, the EU has initiated the project TBMED – An Open-Innovation Test Bed for the Development of High-Risk Medical Devices. Together with 12 project partners from Spain, France, Ireland and Germany, Fraunhofer ITEM is actively participating in the development of a test bed for medical devices of risk classifications IIb and higher. The project will receive 8.5 million euros funding under the European Union's Horizon 2020 Framework Program and will run until the end of February 2023.

www.item.fraunhofer.de/project-tbmed



Excellent stage for excellent research!

The success of the state capital of Lower Saxony in the Excellence Strategy of the German federal and state governments prompted the city to launch the campaign "Hannover – city of excellence" to present itself on the national stage. As a representative of excellent research in Hannover and partner in the cluster of excellence Hearing4all, Fraunhofer ITEM is one of the protagonists in this campaign.

www.item.fraunhofer.de/hannover-excellence

DRUG DEVELOPMENT

FROM DRUG CANDIDATE TO PROOF OF CONCEPT

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

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

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

www.item.fraunhofer.de/drug-development

Development and manufacturing of active biopharmaceutical ingredients

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

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

PROJECTS

Fighting respiratory tract infections with joint expertise

There is an urgent need for novel therapeutics to fight the increasing global threat from infectious diseases, from resistant bacteria and viruses in particular. In the International Consortium for Anti-Infective Research – iCAIR® – Fraunhofer ITEM scientists and their colleagues from the Hannover Medical School and the Institute for Glycomics at Griffith University in Australia have established a proof-of-concept platform for the development of new anti-infective therapies. At present, the team is developing novel antiviral drugs for treating influenza and parainfluenza infections. The scientists are also studying the immune response triggered by an infection in the lung and how this response can be affected by risk factors such as smoking. To this end, they use viable lung tissue slices cultured ex vivo to mimic the impaired barrier function of airway epithelial cells upon cigarette smoke exposure and the resulting reduction of the antiviral immune response. Interaction with the host is an important aspect in bacterial infections as well. Bacteria such as Pseudomonas aeruginosa quickly adapt to the host environment and are thus able to escape the immune response, leading to chronic infections that are difficult to treat. In collaborations with partners from TWINCORE in Hannover and the Hannover Medical School, Fraunhofer ITEM scientists are investigating how risk factors of the host, such as age, can affect the infection and whether bacterial virulence factors influence the host's immune response and could thus be potential targets for novel therapeutics.

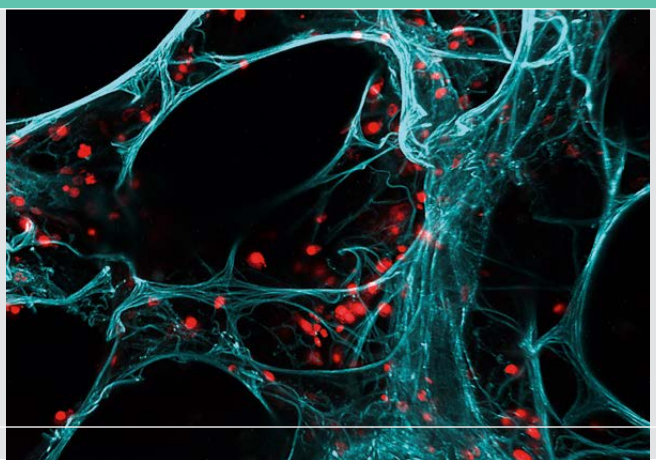
CONTACT
Dr. Sabine Wronski
Phone +49 511 5350-444
sabine.wronski@item.fraunhofer.de

Innovative approaches to tumor treatment: electron beam-inactivated NK cells

Among the most innovative and most promising oncological treatment approaches at present is the administration of genetically modified natural killer cells (NK cells). Due to their chimeric antigen receptors (CAR), these cells are able to specifically recognize tumor cells by their specific surface markers and destroy them without affecting healthy tissue. The cell products, however, must be inactivated before being administered to patients, to prevent tumor formation. To this end, electron irradiation of NK cells is now being developed as a method to inactivate NK cell proliferation. In the Fraunhofer-funded market-driven pre-competitive research project "Electron beam-based cell inactivation for the production of antitumor-efficient natural killer cells" (Elite NK Cells), involving also the Fraunhofer Institutes IZI, FEP, and IPA, Fraunhofer ITEM is developing a GLP-compliant battery of in-vivo and in-vitro studies aimed at ruling out tumorigenicity and toxicity of the novel cell products after their exposure to irradiation with electrons. Models for the detection of accumulated tumor cells in blood, lymph nodes, and lung material have been established for this purpose. The initial focus was on evaluating DNA damage by (CAR123)NK-92 cell products exposed to electron-beam irradiation. Potential negative responses in the body to the cell therapy and immunorelevant adverse effects of the CAR123-NK-92 cell products have been investigated in co-cultures with blood cells.

CONTACT
Dr. Susann Dehmel
Phone +49 511 5350-235
susann.dehmel@item.fraunhofer.de

In the iCAIR® project, scientists are breaking new paths in the development of anti-infective therapies. To prove the efficacy of a novel drug, they use for example precision-cut lung slices (PCLS). The image shows PCLS (displayed in green) that have been infected with the influenza virus H1N1 (displayed in red).



Development of novel treatment strategies for immune-mediated diseases

About eight percent of the population worldwide suffer from immunological diseases, such as rheumatoid arthritis, multiple sclerosis or chronic respiratory diseases. The central common feature of these diseases is a defective regulation of the immune system. Since there is a lack of preventive medications, treatment of such immune-mediated diseases is usually symptomatic, by targeted yet non-specific immunosuppression. The primary goal of the Fraunhofer Cluster of Excellence for Immune-Mediated Diseases CIMD is the translation of innovative ideas and identified targets into individualized therapies for immune-mediated diseases. To this end, the three Fraunhofer life sciences institutes IME, IZI and ITEM have pooled their competencies as core institutes in the Cluster, complemented by other Fraunhofer Institutes (including IGB, IPA, and FEP) as partners. In this context, researchers from the Fraunhofer ITEM Department of Preclinical Pharmacology and In-vitro Toxicology are investigating the restoration of immune tolerance by targeted neutralization of certain intestinal bacteria as a novel therapeutic concept for entire disease groups. Furthermore, based on their long-term experience, they are supporting a project aimed at mucosal application of RSV antigens to prevent juvenile bronchial asthma. In a third project, the scientists are investigating a possibility to prevent viral infections by inhalation of interferon nanocapsules in patients with chronic lung diseases.

CONTACT
Dr. Christina Hesse
Phone +49 511 5350-421
christina.hesse@item.fraunhofer.de

Immune chip to predict immunological responses to drugs and chemicals

In the market-driven pre-competitive research project MyCellFight, having a budget of over three million euros, six Fraunhofer Institutes – IGB, IMW, IOSB, IPA, IZI, and ITEM – are developing an automated immune chip that will enable prediction of unwanted immunological responses to protein-based drugs (e.g. antibodies) and chemicals. The underlying idea is not new: allow the close interactions between antigen-presenting cells and T lymphocytes to take place and study the impact of exogenous substances, such as drugs or chemicals, on these interactions. What is new here is the combination with a functional gene signature that reflects early events of cell activation and differentiation. The cells are incubated in a microfluidic multi-chamber chip with integrated micro-valves enabling realization of automated events. Using a video imaging system, the behavior of the antigen-presenting cells and T lymphocytes is simultaneously monitored by confocal microscopy. Cell motility is analyzed based on this visualization. The combined results provide clues to an unwanted activation of T lymphocytes and thus about the safety of new drugs and chemicals. As an integrated immune chip module, the system will be available for screening processes in traditional and fully automated laboratories and will be ready for immediate integration.

CONTACT
Dr. Katherina Sewald
Phone +49 511 5350-323
katherina.sewald@item.fraunhofer.de

Comparative pharmacokinetics in different compartments of the human lung

After inhaled or oral drug administration, only drug levels in blood are usually available, but these do not enable a detailed understanding of drug levels in the lung. This is why the usual pharmacokinetics in peripheral blood and drug levels in different compartments of the lung were comparatively investigated in humans in a clinical study. The study included 18 healthy volunteers who received certain drugs either orally or by inhalation. At different time points after drug administration, samples of blood, bronchoalveolar lavage, bronchial mucosa, and bronchial fluid were obtained and analyzed in the laboratory. Each study participant underwent two bronchoscopies to allow samples to be collected at different time points over a period of 24 hours after drug administration. Due to the detailed information that is now available about drug levels in different compartments of the lung over time, it is now possible to model drug uptake as a function of substance properties of the model drugs. This will enable a better understanding of pulmonary pharmacokinetics after inhaled and oral drug administration.

CONTACT
Prof. Dr. Jens Hohlfeld
Phone +49 511 5350-8101
jens.hohlfeld@item.fraunhofer.de

Exhaled breath particles as a novel tool to study lung lipid composition

Alterations of surfactant phospholipid composition in the epithelial lining fluid play a role in acute and chronic lung diseases. The investigation of disease mechanisms and the assessment of phospholipid composition and turnover currently require invasive sampling by bronchoalveolar lavage (BAL). The collection of exhaled breath particles (PEx), which are formed when collapsed small airways re-open during inhalation, is a non-invasive way to sample small airway respiratory tract lining fluid (RTLF). To test PEx analysis for its ability to detect inflammation-related changes in the lung, we compared a common set of 15 lipids in BAL, PEx, and induced-sputum samples from 10 healthy volunteers before and after segmental or inhaled endotoxin challenge. Our data demonstrates that the lipid composition of PEx is closely related to BAL, confirming that PEx samples originate from the peripheral lung. Repeated baseline PEx measurements within five weeks suggest that the method is reproducible. Some lipids change in concentration after endotoxin challenge, showing that peripheral lung inflammatory processes can be detected with this method. PEx analysis, therefore, appears to be suitable to study lipid composition in RTLF from small airways. The non-invasive nature of the method will not only allow multiple repeated assessments, important for lipid research in clinical trials, but also its use for diagnostics in patients where an invasive bronchoscopy is contraindicated.

CONTACT
Dr. Olaf Holz
Phone +49 511 5350-8141
olaf.holz@item.fraunhofer.de

With its Fraunhofer Sputum Core Facility, Fraunhofer ITEM offers optimal conditions for sputum collection and analysis, for multicenter clinical trials in particular. Clients are offered study-specific training, supervision of quality during study conduct, and analysis of a broad spectrum of biomarkers.

Sputum Core Facility – optimal sputum analyses for multicenter clinical trials

Fraunhofer ITEM scientists examine induced sputum both for basic research and in clinical trials. Based on this experience, the institute has set up its Sputum Core Facility, offering optimal conditions to pharmaceutical industry clients for sputum collection and analysis in multicenter clinical trials. The services offered include scientific consultancy on the study design, preparation of the required documentation, and use of the sophisticated infrastructure of Fraunhofer ITEM. In addition, the Sputum Core Facility offers methodological trainings to harmonize operating procedures, providing both central and online training in all aspects of sputum induction and processing to prepare for clinical trials. Services include the central evaluation at Fraunhofer ITEM of all cell preparations generated, quickly providing the client with cellular analysis data in a formalized process. This can be very helpful in the screening of test subjects to quickly determine whether they meet the requirements for inclusion in a study. The Sputum Core Facility continuously monitors the quality of all preparations received and extensively supports the study centers in maintaining the high quality level. At present, the services of the Sputum Core Facility are being used in two clinical trials, each involving more than 15 participating sites in Europe and the USA.

CONTACT
Dr. Meike Müller
Phone +49 511 5350-8144
meike.mueller@item.fraunhofer.de

Clinical testing of a class-I medical device in the Fraunhofer Allergen Challenge Chamber

Topical nasal gels that build a physical barrier on the nasal mucosa are considered medical devices. They offer a drug-free option to reduce symptoms of allergic rhinitis. Fraunhofer ITEM researchers tested the effects of a nasal gel (M et P Pharma AG, Switzerland) in an open-label, cross-over, sequence-randomized, monocentric trial. The study was performed in compliance with the amended Act on Medical Devices (MPG). Eighteen patients with allergic rhinitis and grass pollen allergy were challenged with grass pollen in the Fraunhofer Allergen Challenge Chamber in two 4-hour sessions three weeks apart. Half the patients were treated with a single dose of the nasal gel before the first pollen challenge, the other half before the second challenge, while they all underwent the other exposure without treatment. Clinical symptoms were assessed every 20 minutes using the Total Nasal Symptom Score (TNSS). In addition, the amount of nasal secretion was determined on an hourly basis. To evaluate local biomarkers and immune cells, nasal filter eluate samples and nasal lavage fluid were collected 2 and 18 hours post challenge. The nasal gel significantly reduced nasal symptoms and nasal secretions. In contrast, there was no significant effect on local inflammatory biomarkers and immune cells. The gel was well tolerated and safe. It may thus be an alternative for patients seeking non-pharmacological treatment to reduce allergic rhinitis symptoms.

CONTACT
Dr. Philipp Badorrek
Phone +49 511-8130
philipp.badorrek@item.fraunhofer.de

Preparation of precision-cut lung slices (PCLS). This ex-vivo model can be used to study the mode of action of antiviral therapeutics.

Natural medicines to treat viral infections

Every year, millions of people contract respiratory tract infections such as common colds or flu-like diseases, mostly caused by rhinoviruses. Traditional and proven therapeutics for their treatment are natural plant-based medicines. But how do these plant-based medicines act on the infection and the patient's immune defense? By state-of-the-art gene expression analysis, Fraunhofer ITEM scientists have investigated the mode of action of Bronchobini®, a natural medicine for use in children, on behalf of the German pharmaceutical company Biologische Heilmittel Heel GmbH. The medicine includes active ingredients from belladonna, bryony, Iceland moss, sundew, and ipecac, which are supposed to alleviate acute inflammation of the airways and support the host's defense against the infection. Its mode of action has now been investigated at Fraunhofer ITEM in precision-cut lung slices (PCLS for short), which are viable lung tissue slices cultured ex vivo. PCLS were infected with rhinovirus and treated with a solution of Bronchobini®'s active ingredients, and the immune response was subsequently analyzed in detail. PCLS treated with the Bronchobini® solution showed a dose-dependent decrease in the release of inflammatory mediators. Comprehensive gene expression analyses revealed that this was due to modulation of several important signaling pathways, such as the anti-viral interferon pathway (Reamon-Buettner et al., 2019). Bronchobini® reduced the viral-induced airway inflammation, thereby leading to a balanced host immune response.

CONTACT
Dr. Sabine Wronski
Phone +49 511 5350-444
sabine.wronski@item.fraunhofer.de

Testing the effects of drugs on airway basal cells in a new 3D organoid model

Airway basal cells are the progenitor cells of the airway epithelium and are key to proper regeneration of the airways and direct wound healing after injury. Airway basal cells are attached to the basement membrane and, through cell division and further differentiation, give rise to any type of airway epithelial cell including ciliated and secretory cells. In many chronic lung diseases, such as asthma, COPD, cystic fibrosis and pulmonary fibrosis, airway basal cells are altered and lose part of their function and stem cell capabilities. Moreover, in many diseases the cross talk between basal cells and other cell types like fibroblasts is misdirected and may lead to fibrosis and accumulation of extracellular matrix. Airway basal cells also lose part of their capacities during aging. Fraunhofer ITEM researchers have developed an in-vitro cell culture model allowing the stemness capacities of airway basal cells to be analyzed. The cells are cultured in a hydrogel consisting of extracellular matrix proteins of the basement membrane, where they can grow in all directions (3D). Within several weeks, they form organoid structures resembling bronchi, lined with bronchial epithelium. Other cell types can be added and the interaction of fibroblasts and airway basal cells can be quantified in detail. This 3D organoid model is perfectly suited to test the mode of action of drugs in airway basal cells and fibroblasts.

CONTACT
Prof. Dr. Antje Prasse
Phone +49 511 5350-8151
antje.prasse@item.fraunhofer.de

Development of a manufacturing process for oncolytic viruses

Over the past years, oncolytic viruses have evolved to be promising therapeutics for cancer treatment. In 2015, the first oncolytic virus based on herpes simplex virus 1 received regulatory approval. Many other oncolytic viruses have reached the stage of clinical development. In the research project TheraVision, started in April 2017, Fraunhofer ITEM scientists have been working on the development of a robust and scalable biopharmaceutical manufacturing process for an oncolytic virus based on herpes simplex. Vero cells, which can be cultivated on micro-carriers in a bioreactor, are used as host cells for the virus. To obtain a high virus yield, parameters such as cell density, medium exchange, and multiplicity of infection need to be optimized. Besides a high virus yield, another aspect to be considered is product quality, which depends on the pH value, temperature, and the day of virus harvest. Due to the small size of viruses, downstream processing with particle-based chromatography materials leads to low process yields, which is why the scientists are using a monolithic column developed for purification of viruses and a multimodal column in flow-through mode. This results in a very good overall process yield. Up to the present stage of this process development, first critical parameters with relevance for the GMP process and critical quality attributes for oncolytic viruses have been identified. Furthermore, the titer reached so far and the overall process yield are comparable to literature data.

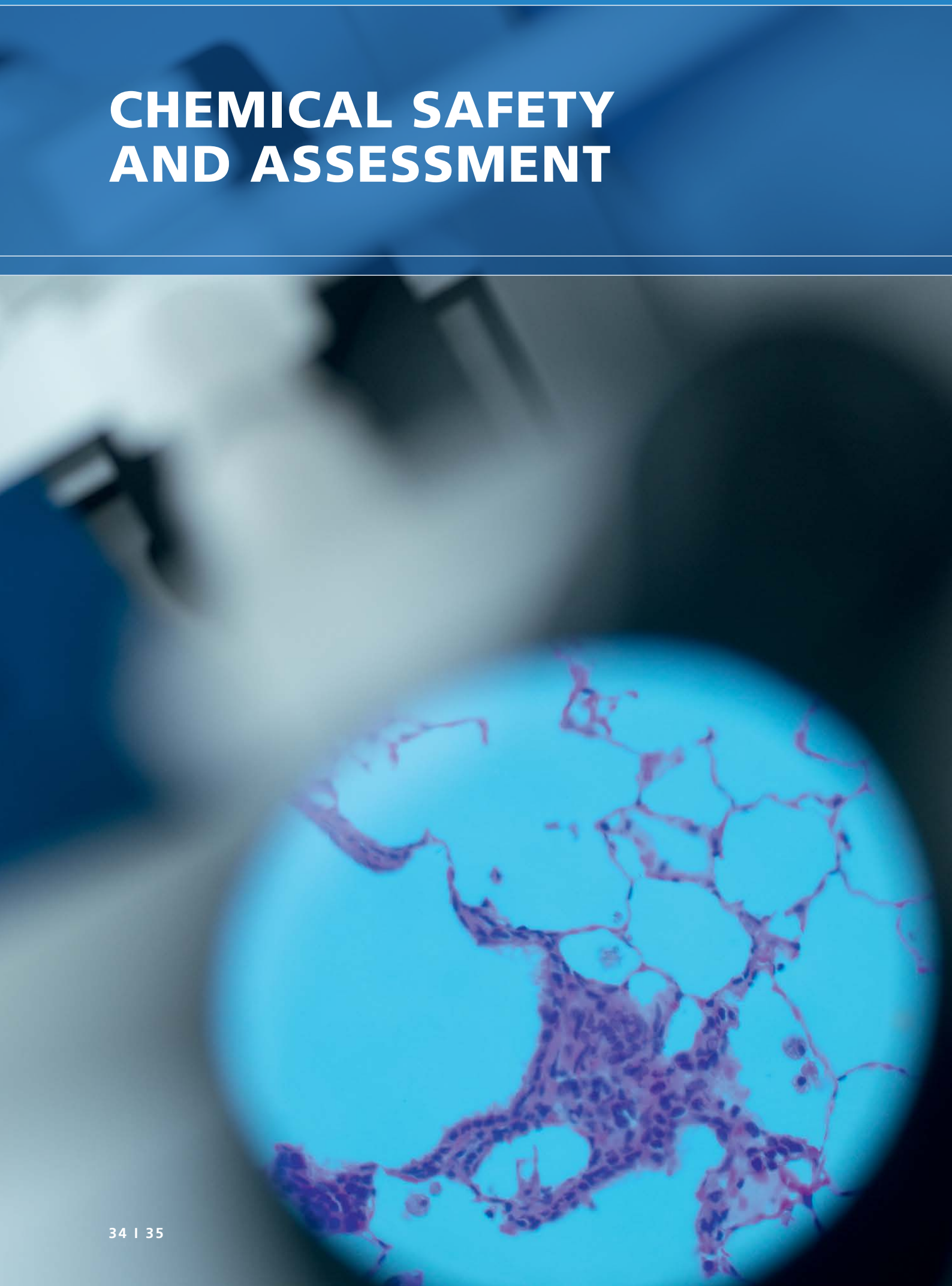
CONTACT
Melanie Spahn
Phone +49 531 6181-6312
melanie.spahn@item.fraunhofer.de

Suitable signal peptides increase the yield of recombinant therapeutics

CHO cell lines are the preferred expression systems to produce recombinant proteins for therapeutic use in humans. Inside these cells, the proteins undergo post-translational modification and human-compatible folding. Production of recombinant biotherapeutics in large quantities requires stable, high-producing CHO cells. Different methods are available to optimize protein production. An important production step inside the cell is translocation of the translated protein into the lumen of the endoplasmic reticulum (ER), where the protein is correctly folded and stabilized. Thereafter, it is glycosylated in the Golgi apparatus and packed for secretion. The protein secretion quantity depends on correct translocation of the protein into the ER, which is mediated by signal peptides. These short sequences, located at the beginning of the protein sequence, are recognized by the signal recognition particle (SRP). The SRP transports the protein to the correct location in the ER lumen. Using a suitable signal peptide allows the subsequent secretion of recombinant protein to be substantially increased. The appropriate choice of the signal peptide depends on the type of protein. For the future, Fraunhofer ITEM is planning to have a suitable signal peptide available for each molecule produced by CHO cells. Using the right signal peptide will enable maximum yields of full-size antibodies, antibody fragments and other proteins.

CONTACT
Laura Rabsch
Phone +49 531 6181-6345
laura.rabsch@item.fraunhofer.de

CHEMICAL SAFETY AND ASSESSMENT



FROM RISK ANALYSIS TOWARDS SAFE PRODUCTS

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

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

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

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

www.item.fraunhofer.de/chemical-safety

Development of test methods and analytical procedures

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

Analytical chemistry

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

Aerosol research

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

Toxicology testing of chemical substances

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

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

Exposure characterization

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

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

Regulatory research and risk assessment of chemical substances

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

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

PROJECTS

Are non-genotoxic tumorigenic substances adequately covered by the current TTC approach?

The Cefic-LRI B18.2 project aims to identify the most sensitive dose descriptor after chronic oral exposure for non-genotoxic carcinogens. To this end, 137 organic substances were classified as non-genotoxic carcinogens after a detailed review of published experimental/predicted data. For these compounds, NOAELs (no observed adverse effect levels) were extracted from 689 long-term in-vivo studies with oral exposure. These studies originated from high-quality databases such as RepDose, ToxRef and COSMOS. NOAELs, either from the most sensitive adverse apical effect or (non)neoplastic lesion, were compared to the effective tumor dose (ETD_{10}[1]) or to the benchmark dose level ($BMDL_{10}$) calculated by model averaging (benchmark risk of 10%). Mainly bioaccumulating substances and steroids were below the 5th percentile of the NOAEL/EDT_{10}/$BMDL_{10}$ distributions. Exclusion of these compounds led to comparable 5th percentiles for chronic NOAELs/$BMDL_{10}$ values, whereas the 5th percentile EDT_{10} was about three times higher. These results were compared to the current threshold of toxicological concern (TTC), supporting the application of Cramer Class thresholds to non-genotoxic tumorigenic substances. Applicability of the resulting thresholds to non-genotoxic compounds will be evaluated with international stakeholders from academia, regulatory authorities and industry in a Cefic-LRI workshop in April 2020.

CONTACT
Dr. Sylvia Escher
Phone +49 511 5350-330
sylvia.escher@item.fraunhofer.de

[1] Calculated by a scientist from Molecular Networks based on tumor incidences in the CPDB (Cefic-LRI B18).

Endocrine disruptors – assessment of co-formulants

The identification of endocrine disruptors (ED) currently is an important aspect in the regulation of biocides and plant protection products (PPP). The criteria to be applied (to biocides since June 2018, to PPP since November 2018) have been laid down in the EU regulation 2018/605, developed by EFSA and ECHA. In addition to the active substances in a product, any co-formulants have to be assessed with regard to the defined ED criteria, for both humans and non-target organisms. For co-formulants in particular, a tiered approach is suggested: In a first step, it should be evaluated whether the co-formulant under consideration has already been identified as a potential endocrine disruptor within the EU or can be excluded as a food additive. In addition, other sources such as databases and literature should be checked for any clues to endocrine-disrupting properties. The final assessment has to be performed by the Member States and the EU Commission. They can finally request an extended toxicological assessment of co-formulants, including detailed evaluation of their estrogen, androgen, thyroid, and steroidogenic modalities (EATS). Fraunhofer ITEM with its specific expertise in toxicology supports its clients in all scientific and regulatory issues – including assessment of potential endocrine-disrupting properties of active substances and co-formulants.

CONTACT
Ariane Zwintscher
Phone +49 511 5350-312
ariane.zwintscher@item.fraunhofer.de

Fraunhofer ITEM scientists have developed an extended PBPK model that describes the uptake of gases, vapors, and aerosols. It enables evaluation of the efficacy or toxicity of airborne substances.

In-silico model of drug and pollutant uptake by inhalation

The lung is an important portal of entry for drugs and also for pollutants. Up to now, evaluation of the efficacy or toxicity of airborne substances requires bioavailability data from in-vivo studies, but these are often not available. Fraunhofer ITEM scientists have established a physiologically based pharmacokinetic (PBPK) model (based on existing PBPK models) for rats and humans and have extended it with a lung model specifically developed for this purpose. The lung model describes the uptake of gases, vapors, and (droplet) aerosols. While deposition on the lung surface is already well described by physical models, the transfer rate via lung tissue into the bloodstream is a substance-specific unknown which the Fraunhofer ITEM scientists determine by means of appropriate in-vitro and ex-vivo models. Using this PBPK model, they were able to make time-resolved predictions of venous blood levels for two low-molecular substances in good agreement with human data from literature. Within the Cefic-LRI project B21, the first version of the lung model is now being further developed by improving the description of particle solubility and of the lung-specific defense mechanisms (alveolar macrophages, mucociliary transport). To enable a better understanding of the so far insufficiently understood particle translocation the model will furthermore be extended with lung-associated lymph nodes.

CONTACT
Norman Nowak
Phone +49 511 5350-359
norman.nowak@item.fraunhofer.de

Case study on NAM integration into read-across approaches reviewed in the OECD IATA project

The EU-ToxRisk project developed a read-across concept[1] aimed at integrating mechanistic data from in-vitro assays into human risk assessment. The OECD Integrated Approaches to Testing and Assessment (IATA) Case Studies Project reviewed four RAX case studies. In one of these studies, the in-vivo data of two carboxylic acids showed microvesicular liver steatosis to be the most sensitive apical effect. An adverse outcome pathway (AOP) network was developed that illustrates the underlying molecular initiation (MIEs) and key events (KEs). Five MIEs and one KE (lipid accumulation) were used to characterize the mode of action of the 11 carboxylic acids of one group. In-vitro to in-vivo extrapolation was used to derive human equivalent oral doses, which might be used to define a threshold for risk assessment. The OECD group discussed mainly the uncertainty associated with AOPs that did not undergo review by the OECD. Nonetheless, it was noted that also non-endorsed AOPs might be used for hazard characterization, as long as clear reference is made to peer-reviewed publications. Further, the rationale for selecting certain MIEs and KE, while leaving out others, has to be made clear in the read-across strategy and its documentation. Testing of every single MIE and KE along the network was not considered necessary in a read-across context and the proposed targeted testing was approved. The case study was accepted for publication by OECD in 2020.

CONTACT
Dr. Sylvia Escher
Phone +49 511 5350-330
sylvia.escher@item.fraunhofer.de

[1] Escher & Kamp et al. 2019

Childhood leukemia: study on the impact of magnetic fields on the immune system

Several epidemiological studies have demonstrated a correlation between childhood leukemias and exposure to extremely low-frequency magnetic fields (ELF-MF), such as those resulting from the generation, transmission and use of electrical energy. The International Agency for Research on Cancer (IARC), therefore, classified ELF-MF as potentially carcinogenic in 2002. To date, however, experimental evidence and a postulated mechanism of action are still missing. Biophysically speaking, these low-energy magnetic fields are rather unlikely to be able to directly induce DNA damage and to be the immediate cause, for example, of B-cell acute lymphoblastic leukemia (B-ALL), the most common type of childhood leukemia. Three independent studies in mice, however, consistently showed a reduced number of cytotoxic T cells after ELF-MF exposure. Therefore, in a research project funded by the German Federal Office for Radiation Protection, Fraunhofer ITEM scientists are comparatively investigating the effects of magnetic field exposure on the phenotype and function of juvenile immune cells in a B-ALL mouse model. This study will enable comprehensive insights into key markers in the development of the lymphocyte compartment and corresponding cytokine patterns in the juvenile organism after ELF-MF exposure. Eventually, these may allow the possible mechanistic role of ELF-MF in B-ALL pathogenesis to be elucidated.

CONTACT
Dmitrij Sachno
Phone +49 511 5350-350
dmitrij.sachno@item.fraunhofer.de

Rejuvenating “old” PVC as an example of circular economy

To promote recycling and circular economy, the European Union is funding the project REMADYL[1], launched on June 1, 2019, under its Horizon 2020 research and innovation program. Over the time course of four years, a consortium of 15 multidisciplinary European partners will direct their work at developing a process to recycle “old” PVC and rejuvenating it into market-competitive high-purity PVC. The primary targets of REMADYL are legacy substances such as short-chain phthalates and lead- and cadmium-containing stabilizers and their removal from “old” PVC material such as window frames and waterproofing sheets. Among the 15 partners of the REMADYL consortium, there are also two Fraunhofer Institutes, namely the Fraunhofer Institute for Chemical Technology ICT and Fraunhofer ITEM. While Fraunhofer ICT is contributing to the process development (removal of phthalates), Fraunhofer ITEM will assess introduced and/or (partly) removed contaminants and establish guidelines for their safe handling and processing. Selected consortium partners have already undertaken first steps towards phthalate removal from PVC sheets in a batch process. Scientists at Fraunhofer ITEM are currently setting up analytical procedures including their validation for different legacy substances (short-chain phthalates). In addition, they have started contaminant assessment to address some toxicological and regulatory issues concerning safe handling.

CONTACT
Katharina Blümlein Ph.D.
Phone +49 511 5350-213
katharina.bluemlein@item.fraunhofer.de

[1] The REMADYL project is receiving funding from the European Union’s Horizon 2020 research and innovation program under Grant Agreement No. 821136.

Two LC-MS platforms allow up to 600 metabolites from a variety of biological matrices to be quantified.

Targeted metabolomics: forward-looking technology in systems medicine and toxicology

Metabolomics is one of the fast-growing research areas in the life sciences. In combination with bioinformatics methods, this technology can provide a snapshot of the metabolic status and also allows changes in biological systems to be analyzed. Fraunhofer ITEM scientists are currently developing mass spectrometry (MS)-based metabolomic analyses involving two LC-MS platforms for the usually kit-based analysis of the metabolome. In combination with other methods, over 600 metabolites can thus be quantified. In addition, the scientists are developing customized methods for specific applications. To complement this technology, automated NMR-based metabolomic methods are being further developed in cooperation with industry partners. In contrast to MS-based metabolomics, NMR spectroscopy in many biological matrices can be performed without sophisticated sample preparation and it stands out by its precise quantification results – making it ideally suited for clinical screenings. Metabolomics is becoming increasingly important not only in clinical research, but also in chemical risk assessment. Alterations in the composition of primary and secondary metabolites (amino acids, sugars, lipids, nucleosides, steroids, alcohols) often provide insights into the toxicology of compounds. For metabolomics research, the institute is pooling its expertise from different disciplines – toxicology, instrumental analytics, and bioinformatics/statistics – to enable interdisciplinary and well-founded responses to clients' problems.

CONTACT
Dr. Sven Schuchardt
Phone +49 511 5350-218
sven.schuchardt@item.fraunhofer.de

Inhibition of quartz toxicity due to material-adapted surface coatings

Occupational exposure to quartz-containing dusts is still a problem in industry sectors where quartz-based raw materials play a pivotal role. Inhalation of quartz can trigger pathological changes in the lung (silicosis) which, in addition, increase the workers' risk of lung cancer. In 1997, the IARC, therefore, classified respirable crystalline silica as Group-1 carcinogen. Given that reactive silanol groups on the surface of quartz particles are one decisive factor in the lung toxicity of respirable quartz, blocking of these groups represents a promising strategy to increase the safety of those working with quartz-containing raw materials. This approach was thoroughly explored in the EU project SILIFE (LIFE14 ENV/ES/00238; project duration: 2015-2019). The SILIFE consortium (12 partners from 3 countries; coordinator: ITC, Castellón, Spain) finally developed a dry surface-coating technology, suitable for use at an industrial level, to produce quartz-containing raw materials with significantly reduced lung toxicity. The technology is based on covalent masking of reactive silanol groups with suitable organosilanes. It has meanwhile been patented and can be applied to a broad spectrum of materials. Fraunhofer ITEM's responsibility in this project was the toxicity screening, which provided decisive clues in the development process. Using adapted in-vitro and in-vivo methods, the Fraunhofer ITEM scientists finally confirmed a very promising stability and effectiveness of the optimized surface coatings.

CONTACT
Dr. Christina Ziemann
Phone +49 511 5350-203
christina.ziemann@item.fraunhofer.de

TRANSLATIONAL BIOMEDICAL ENGINEERING

FROM IDEA TO SAFE MEDICAL DEVICE

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

www.item.fraunhofer.de/biomedical-engineering

Device development and manufacturing processes

Our services allow our clients to substantially reduce the obstacles encountered during development of innovative medical devices and the risk of technology transfer failure. We can perform device development as contract research or support the client's own device development in a targeted manner through simultaneous development of custom-fit test benches and test methods. At Fraunhofer ITEM, products and test benches are developed to the point of meeting the requirements for use in first clinical 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.

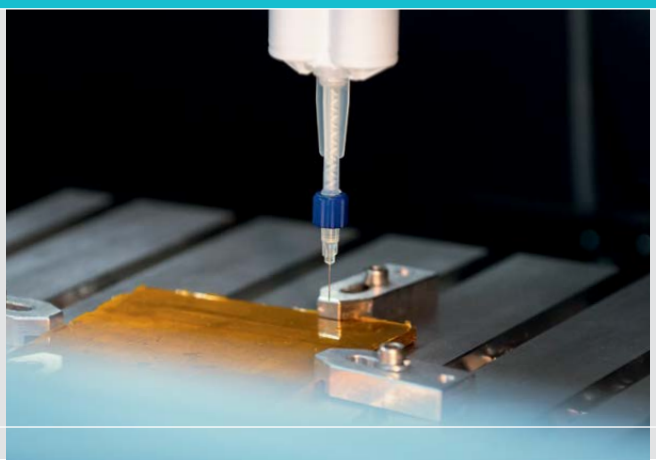
PROJECTS

EU project MDOT: open-innovation test bed to support regulatory processes for medical devices

Starting in January 2019, 13 partners from 7 European countries, including research institutes, universities and small and medium enterprises (SMEs), have been collaborating in the Horizon 2020 project MDOT (Medical Device Obligations Taskforce). This project is being coordinated by Fraunhofer ITEM, with a grant size of 8.3 million euros and 5 years overall duration. In contrast to the majority of Horizon 2020 EU projects, MDOT is planned to evolve into an established open-innovation test bed (OITB), a new European instrument that will allow the projects to be transferred into an association or company after the grant phase. MDOT is addressing medical device manufacturers' need for support with the obligatory conformity assessment, which has been exacerbated by the EU regulation 2017/745 (Medical Device Regulation, MDR for short). Under this regulation, coming into force at the end of May 2020 and replacing the Medical Device Directive (MDD), all existing medical devices need to undergo reassessment of their risk class, require more comprehensive documentation and increased clinical testing. To reduce the burden on medical device manufacturers, the consortium is developing a platform aimed at simplifying the process by establishing a database that will include data on regulatory affairs and testing up to clinical evaluation and clinical studies. To demonstrate usability of the platform, it is addressing three technologies as a starting point: inhalers for pre- and early-term neonates, 3D-printed neural implants, and coatings for orthopedic prostheses that reduce the wear of particles in the patient's tissue. Test beds for these technologies are being developed and upgraded to ensure safety and long-term stability of devices and materials – aspects particularly important for implants. Future extension of the platform towards other medical device sectors is planned. In addition to project coordination, Fraunhofer ITEM is involved in biocompatibility testing in accordance with ISO 10993 and database development.

Together with two affiliate projects, TBMED and Safe-N-MedTech, MDOT is part of the new EU cluster "Safety of Medical Devices". While the main focus of TBMED is on high-risk medical devices, Safe-N-MedTech is addressing devices involving nanoparticles. These efforts on the European level directly link to an ongoing certification in the Fraunhofer ITEM business unit Translational Biomedical Engineering, targeting the institute's support with regulatory processes and documentation under the ISO 13485 quality standard for medical devices. In this context, routines are being developed and processed that can be embedded into the platform development, enabling manufacturers to estimate their regulatory requirements and follow testing strategies and testing in accordance with the MDR. The initial certification audit by a notified body has already been successfully passed, the final certification is expected for April 2020.

CONTACT
Dr. Ulrich Froriep
Phone +49 511 5350-294
ulrich.froriep@item.fraunhofer.de



To demonstrate usability of the open-innovation test platform, three technologies will be addressed as a starting point: inhaler systems for pre- and early-term neonates, coatings for orthopedic prostheses, and 3D-printed neural implants. The image shows a part of the 3D printer at Fraunhofer ITEM.

Specific test bench for neonatal aerosol delivery

The absence of a test bed specific for aerosol delivery to infants, term and preterm neonates under standardized conditions poses a great challenge to health professionals. Age-specific test methods are necessary here, because drug delivery to the lungs of neonates is challenged by their small airways, small tidal volumes, high breathing rates, and unfavorable inhalation/exhalation ratios in the range of 1:3. These conditions are not adequately addressable by existing test beds. Fraunhofer ITEM scientists, therefore, have developed a test bed for inhalation systems tailored to the special requirements of infants, term and preterm neonates. In the EU project MDOT (see previous page), they are collaborating with the company DEMCON to further develop the existing lab prototype towards a standard test bed. In this development process, the scientists are taking into account the well-known engineering requirements and in particular newest insights gained from scientific data on neonatal breathing and pulmonary drug delivery. In parallel with the test bed development, the findings summarized above are fed into the development of a breath-triggered inhaler interface system[1] for pulmonary drug delivery to newborn infants and preterm neonates, which could be used, for example, with modern vibrating-mesh nebulizers or other novel inhaler systems.

CONTACT
Dr. Gerhard Pohlmann
Phone +49 511 5350-116
gerhard.pohlmann@item.fraunhofer.de

[1] Project FlexMax, BMBF Grant Number 16ES0779

Regulatory issues in biomedical engineering – postgraduate university program

Since 2017, the new European Medical Device Regulation has caused an estimated lack of 6000 additional specialists in Germany alone, who need to be qualified to perform the new procedures for (re)certification of medical devices. Even though the number of training programs offered in this subject area has substantially increased, a survey has shown that many companies are not satisfied with their quality. To respond to this demand, Fraunhofer ITEM, the Hannover Medical School and Leibniz Universität Hannover (LUH) have teamed up and developed the focus module "Regulatory issues and quality management in biomedical engineering", allowing for accreditation within the overall didactic concept of the university. The devised block modules (with a total of 35 ECTS points) are offered as a specialization in the university degree course Biomedical Engineering (Master of Science) at LUH and in addition as a training program for working professionals within the Fraunhofer Academy at Fraunhofer ITEM. Depending on the combination of modules, participants can be awarded the internationally recognized certificates "Regulatory Affairs Manager", "Manager Regulatory Affairs International", "Person Responsible for Regulatory Compliance (PRRC) (MDR 2017/745)", or "In-Vitro Diagnostics Expert". The degree course is planned to start in the summer semester of 2020. According to an interim evaluation, the preparatory lecture series held in the winter semester 2019/2020 with internationally renowned lecturers from industry and academia is already a great success.

CONTACT
Prof. Dr.-Ing. Theodor Doll
Phone +49 511 5350-248
theodor.doll@item.fraunhofer.de

PERSONALIZED TUMOR THERAPY

FROM MOLECULAR ANALYSIS TO PERSONALIZED THERAPY

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

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

With our expert knowledge in the fields of "Cellular and molecular diagnostics", "Innovative molecular technologies and biomarker discovery", "Preclinical therapy models", "Disease modeling", and "High-throughput drug and target discovery", we work on a broad variety of topics in the fields of liquid biopsy and rare cell populations. Our in-house data management and comprehensive bioinformatics enable custom-fit analyses of the generated data. The Division of Personalized Tumor Therapy has been certified by TÜV Süd according to DIN ISO 9001:2015 and thus complies with international standards.

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

www.item.fraunhofer.de/tumor-therapy

Single-cell analysis

Enrichment, isolation and molecular analysis of rare cells

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

Decoding of single cells

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

Innovative tumor models

In-vitro and in-vivo drug testing

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

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

Advanced preclinical PDX models

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

Mathematical modeling and bioinformatics

Multi-level disease modeling

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

Bioinformatics services

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

PROJECTS

High-throughput drug screening for discovery of novel therapies for bestrophinopathies

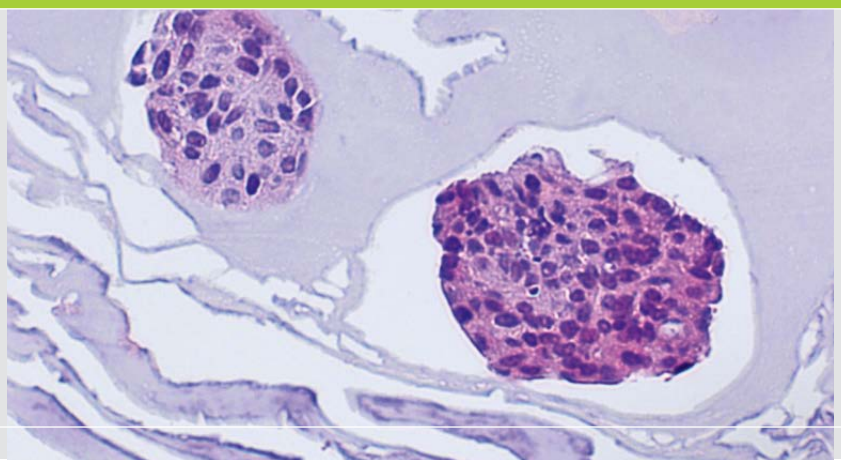
Bestrophinopathies belong to a group of clinically distinct inherited retinopathies. They are caused by mutations in the BEST1 gene, leading to an incorrect localization of the homo-pentameric bestrophin-1 protein complex (calcium-activated chloride channel) on the plasma membrane of retinal pigment epithelial cells. Until now, no therapy is available for bestrophinopathies. The aim of this project was to use a high-throughput approach to identify compounds, termed corrector molecules, that improve the localization of BEST1, so as to partly or even fully restore the BEST1 channel function. In collaboration with the Institute of Human Genetics of the University of Regensburg (Germany), an immunofluorescence localization high-content screening assay in 384-well format was established. To this end, MDCKII cells stably expressing BEST1 were treated with the compound libraries in a semi-automated fashion. The Operetta CLS High-Content Imaging System was used for automated imaging and image analysis. Screening of a library containing 2645 bioactive small molecules – including approximately 1500 FDA-approved drugs – led to the identification of over 70 active compounds and their respective targets. The team is now investigating the efficacy and specificity of the identified compounds to enable repurposing of existing drugs for bestrophinopathy treatment.

CONTACT
Silvia Materna-Reichelt
Phone +49 941 298480-54
silvia.materna-reichelt@item.fraunhofer.de

Cerebrospinal fluid analysis enables insights into meningeal carcinomatosis

In patients with an underlying tumor disease, additional colonization of the meninges with cancer cells leads to a condition referred to as meningeal carcinomatosis (MC). Patients affected with MC are often at an advanced stage of cancer and have a dismal prognosis. Fraunhofer ITEM scientists in Regensburg tried to apply the liquid biopsy analyses they established for blood samples to cerebrospinal fluid (CSF), in order to isolate circulating tumor cells (CTCs) and cell-free DNA (cfDNA) from cancer cells. CSF samples from patients with different primary cancer origins and suspected MC were analyzed with three different workflows in parallel. The scientists first enriched the available CTCs using an FDA-approved EpCAM ferrofluid-based technology and subsequently isolated single cells. After whole-genome amplification and molecular characterization, the cells could be confirmed as tumor cells derived from the primary cancer site. Isolation and amplification of cfDNA from the same sample led to subsidiary results. In addition, part of the CSF sample was cultivated under special conditions in an organoid model, which in the future may serve as a basis for further analyses and drug testing. Within the liquid biopsy concept, CSF thus represents a precious source for studying the biology of MC and for obtaining fundamental insights into treatment options for these patients.

CONTACT
Cäcilia Köstler
Phone +49 941 298480-27
caecilia.koestler@item.fraunhofer.de



Organoids are complex three-dimensional models used, among other things, to cultivate tumor cells. In the future, organoids may serve as a basis for further analyses and drug testing.

Sequencing of micro-RNAs at the single-cell level

Single cancer cells may be able to leave the primary tumor and subsequently might seed metastases in distant organs. These cells can be isolated from liquid biopsies, with little burden on the patient. Scientists of Fraunhofer ITEM in Regensburg have developed a method for parallel sequencing of the genome and transcriptome of such single disseminated cancer cells. They analyze the sequencing data for biomarker signatures, which enable prediction of how the disease will develop in a particular patient or what type of therapy should be preferred. For many cancer (sub)types, however, no reliable biomarker signature has, as yet, been discovered, neither at DNA nor at mRNA level. In these cases, other molecules such as micro-RNA (miRNA) might represent more accurate and better reproducible biomarkers. Mature miRNAs have a length of only 20-25 nt and act as important post-transcriptional regulators. They bind to partly complementary regions on mRNAs, usually leading to mRNA degradation. A miRNA can bind to several mRNAs and an mRNA can be targeted by several miRNAs, resulting in a complex regulatory network. In many diseases, including cancer, expression of miRNAs is deregulated and this has an impact on mRNA and protein abundance. Therefore, the Fraunhofer ITEM scientists in Regensburg are aiming to establish a single-cell miRNA sequencing protocol.

For bulk miRNA sequencing, there are several protocols and commercial kits available; however, at the single-cell level only one protocol has been published. To find out which protocol works best with very low-input samples, the scientists used single cells of a breast cancer cell line spiked with 950 different miRNAs in equimolar concentrations. Overall, they tested 19 protocols and variations thereof. It turned out that some samples predominantly consisted of adapter dimers instead of amplified miRNA. In contrast, eight different protocols showed only low amounts of adapter dimers and two-thirds of the spiked-in miRNAs could be detected. In the next step, these eight protocols with good performance were used for miRNA sequencing of single cells. One protocol performed superior, because the reproducibility between replicates was high, a low number of reads had to be removed during quality control, and more than 200 different miRNAs per single cell could be detected. In the future, the Fraunhofer ITEM scientists will use this protocol to sequence disseminated single cells of lung cancer patients. Furthermore, they are working on protocol improvements, are planning to automate the workflow to increase the throughput, and want to combine mRNA and miRNA sequencing of the same single cell.

CONTACT
Dr. Sarah Hücker
Phone +49 941 298480-25
sarah.huecker@item.fraunhofer.de

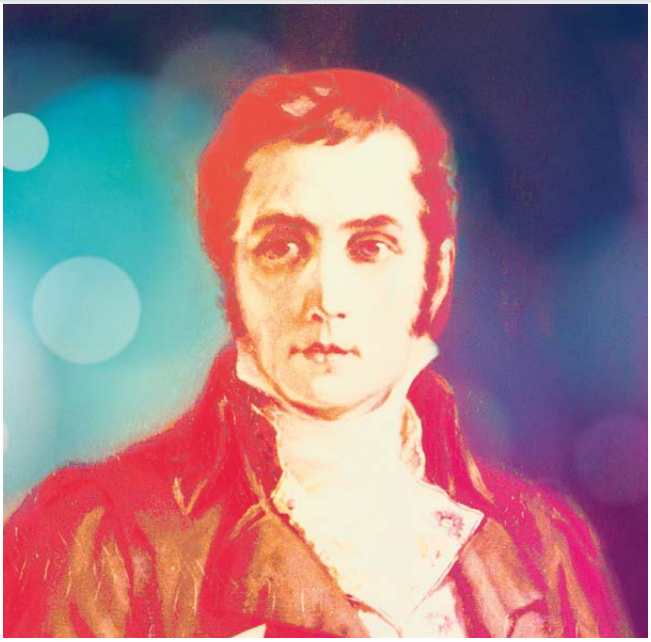
70 YEARS OF FRAUNHOFER – 70 YEARS OF FUTURE

The Fraunhofer-Gesellschaft zur Förderung der angewandten Forschung e. V. was founded in Munich on March 26, 1949, to help rebuild Germany's economy. It celebrated its 70th anniversary in 2019, like the Federal Republic of Germany and its constitution, the Basic Law. With its clear focus on new key technologies and markets, the Fraunhofer-Gesellschaft has become the German economy's innovation engine and Europe's leading organization for applied research. The anniversary year was an occasion for the Fraunhofer-Gesellschaft not only to look back, but also to look ahead to the future by preparing strategic initiatives for Germany and Europe. The anniversary year kicked off with a ceremony on the date of the founding, followed by a Bavarian state reception in Munich.

The Fraunhofer-Gesellschaft currently operates 74 institutes and research institutions. The majority of the 28,000 staff are qualified scientists and engineers, who work with an annual research budget of 2.8 billion euros. Of this sum, 2.3 billion euros is generated through contract research. Around 70 percent of Fraunhofer's contract research revenue is derived from contracts with industry and from publicly funded research projects. The remaining 30 percent comes from the German federal and state governments in the form of base funding. This enables the institutes to work ahead on solutions to problems that are likely to become crucial for industry and society within the not-too-distant future.

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

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.

www.fraunhofer.de/en.html

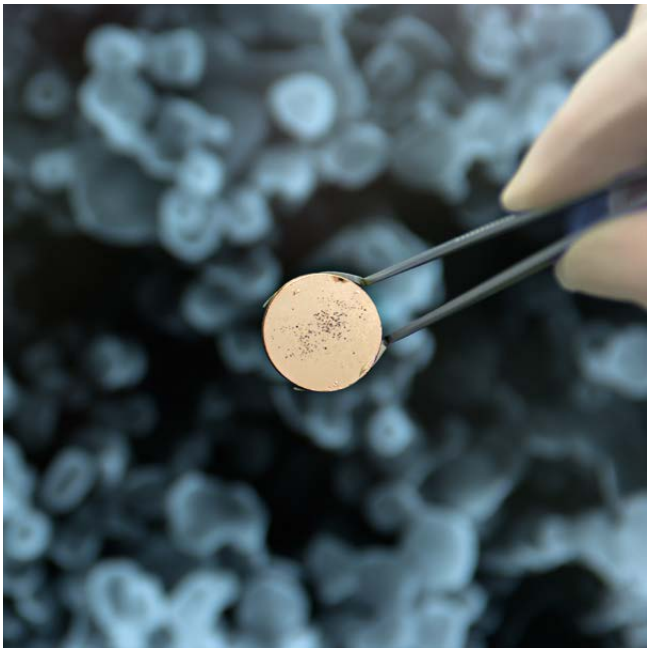
Figures are for February 2020.

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.



www.lifesciences.fraunhofer.de/en.html

Fraunhofer Nanotechnology Alliance

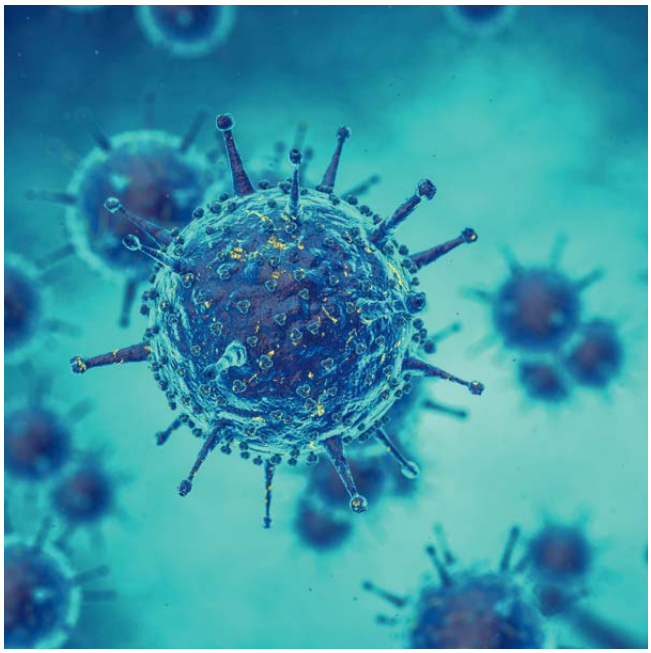
The Fraunhofer Nanotechnology Alliance covers the whole R&D value chain from applied research to industrial implementation. The focus is on nanomaterials, nanobiotechnology, nano-processing and handling, nano-optics and electronics, measuring methods and techniques, and technology transfer and consulting.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

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.

www.cimd.fraunhofer.de/en.html



Research project TheraVision

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

Research project MyCellFight

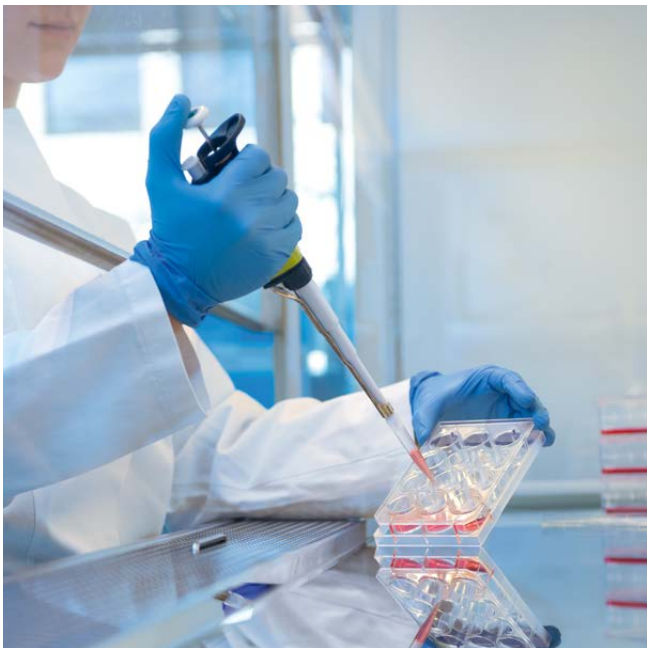
For this ambitious research project, the Fraunhofer Institutes IGB, IMW, IZI, IOSB, IPA, and ITEM have teamed up. The aim is to develop an automated immune chip enabling prediction of the specific immunological responses to a drug or chemical of up to 100 individuals at the same time.

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 has developed 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. This project was successfully completed in 2019.

NAMES, DATES, EVENTS

383 employees

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

17 Ph.D. students

31 published abstracts

62 publications

17 employees with activities for international journals

Cooperation partners in **21** countries on 6 continents

126 oral presentations

69 congresses and exhibitions

24 employees teaching at 12 universities in Germany

28 publicly funded projects

51 cooperation partners outside Germany

35 employees actively participating in committees

46 teaching activities at universities

6 completed theses

107 cooperation partners in Germany

13 EU projects

105 scientific posters

Figures are for December 31, 2019.

Up to date throughout the year

Being a research institution, our ambition is to find answers to questions and solutions for problems that are relevant to society and also to companies in the field of human health. In our research, we collaborate with national and international scientific organizations and actively participate in a broad range of panels. Unless precluded by the terms of the contract, we publish our results in renowned scientific journals and present them at congresses and meetings. The figures on the two preceding pages give a first impression of our activities. On the following pages, you will find details of our active participation in committees, an overview of the publicly funded projects in which our scientists were involved in 2019, of our cooperation partners, and of congresses and other events to which we actively contributed in 2019.

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

www.item.fraunhofer.de/annual-report

Active participation in committees

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

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

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

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

Prof. Dr. Armin Braun
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")

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. Ilona Fleischhauer
Working group on GLP quality assurance/monitoring "GLP: Qualitätssicherung/Überwachung" of the German Quality Management Association (GQMA)

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

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

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

Reviewer for international journals (incl. "Annals of Work Exposures and Health" and "Environmental Science & Technology")

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)

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

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

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

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

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

Reviewer for the journal "SLAS Discovery"

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

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

Prof. Dr. Christoph Klein
External assessor for numerous national and international organizations and foundations: German Research Foundation, German Federal Ministry of Education and Research, Wilhelm Sander Foundation for Cancer Research, ERC, Deutsche Krebshilfe, Christian Doppler Research Association, Dutch Cancer Society, Association for International Cancer Research, EU-FP7, MRC, Cancer Research UK, Kegg-Foundation
Deputy chairman of the scientific committee of Comprehensive Cancer Center Ostbayern (CCCO)

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

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

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

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

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

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

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

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

External assessor for the German Research Foundation (DFG)

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

Advisory board of the expertise network "Asthma und COPD"

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

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

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

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

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

Public relations delegate of the German Society of Toxicology

Dr. Norbert Lüthe
Working group on information technology "IT" and working subgroup on electronic archiving 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 for Aerosols in Medicine (ISAM)

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

External assessor for the Swiss Cancer League

External assessor for the Medical Research Council (UK)

External assessor for North West Cancer Research (UK)

Reviewer for international journals in pathology and oncology ("British Journal of Cancer", "Chemical Science", "International Journal of Cancer", "Journal of Histochemistry and Cytochemistry", "Journal of Visualized Experiments", "Oncotarget", "Scientific Reports", and "Thoracic Cancer")

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

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

Board member of Deutsche Atemwegsliga e. V.

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

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

Reviewer for the international journal "Toxicologic Pathology"

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

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

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

Organizational committee of the 17th European Congress of Toxicologic Pathology

Examination board of the European College of Veterinary Pathology

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

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

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

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

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

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

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

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

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

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

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

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

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

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

BioPharma-Translationsinstitut e. V.

Dr. Christina Ziemann
Working group "Genotoxicity" of the DIN Standards Committee "Water Practice"

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

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

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

External assessor for applications submitted to the German Federal Environmental Foundation

German Pharm-Tox Summit program committee

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

Publicly funded research projects

National

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

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

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

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

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

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

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

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

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

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

Federal Ministry of Education and Research (BMBF) action plan for individualized medicine, funding area "Innovations for individualized medicine"
Collaborative project: TurbiCAR
UniCAR-based treatment of 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: 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 FlexMax: flexible active sensor matrix for medical applications
Use of sensor arrays in two different biomedical engineering systems:
sub-project "Sensorgesteuerte Atmungsüberwachung, Atmungstriggerung und Inhalation bei Frühgeborenen" (sensor-controlled breath monitoring, breath triggering, and inhalation in preterm infants)

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

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

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

Federal Ministry of Education and Research (BMBF) funding program "NanoCare4.0 – application-safe material innovations"
Project: MetalSafety
Development of evaluation concepts for fibrous and granular metal compounds: bioavailability, toxicological efficacy profiles and comparative in vitro, ex vivo and in vivo studies

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

Federal Ministry of Education and Research (BMBF) funding program "Sicherer Umgang mit synthetischen Nanomaterialien – Erforschung der Auswirkungen synthetischer Nanomaterialien auf den Menschen – NanoCare" (safe handling of synthetic nanomaterials – research on the impact of synthetic nanomaterials on human health – NanoCare)
Project: CaNTser
Investigation of the toxic potency of carbon nanotubes following long time inhalation

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

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: fibromics
Translating Omics studies into clinically relevant insights for lung fibrosis patients

International

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: 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: IMI-eTranSafe
Enhancing translational safety assessment through integrative knowledge management

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

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

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

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

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

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

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

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

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

Cooperation partners

National

AC Aircontrols GmbH, Kempen

Activoris Medizintechnik GmbH, Gemünden (Wohra)

Adjutem GmbH, Oldenburg

Advanced Bionics AG

Aquarray GmbH, Eggenstein-Leopoldshafen

Assay.Works, Regensburg

Augsburg University Hospital

BASF SE, Ludwigshafen

Bayer AG, Berlin

Bielefeld University

BioMedVet Research GmbH, Walsrode

Blackrock Microsystems Europe GmbH, Hannover

Boehringer Ingelheim Pharma GmbH & Co. KG

Brain AG, Zwingenberg

Cardior Pharmaceuticals GmbH, Hannover

Cellex Patient Treatment GmbH, Dresden and Cologne

Center for Bioinformatics (CBI), Saarbrücken

Center of Allergy & Environment (ZAUM), Munich

Ceres GmbH, Lörrach

Charité – Universitätsmedizin Berlin

Charité Research Organisation GmbH, Berlin

Cilian AG, Münster

Cortec GmbH, Freiburg

Cytena GmbH, Freiburg

dysantect, Wiesbaden

Epomedics GmbH, Göttingen

Essen University Hospital

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

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

Leibniz University Hannover

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TRAIN – biomedical translation alliance in Lower Saxony, Hannover

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

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PExA, Gothenburg (Sweden)

Poznan University of Medical Sciences (Poland)

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University of Southampton, Southampton (UK)

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

Weizmann Institute of Science, Rehovot (Israel)

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 2019, the institute hosted or played an active role in the following events (among others):

January 24-25, 2019
18th Fraunhofer seminar "Models of Lung Disease"
Hannover (Germany)

February 4-5, 2019
1st German Cancer Research Congress (GCRC)
Heidelberg (Germany)

February 7-8, 2019
DZL Annual Meeting
8th Annual Meeting of the German Center for Lung Research
Mannheim (Germany)

February 21-22, 2019
Workshop "Biometrical Aspects of Genome Analysis XIII"
Lübeck (Germany)

February 25-28, 2019
DGPT Annual Conference 2019
85th Annual Conference of the German Society of Pharmacology and Toxicology and 4th German Pharm-Tox Summit
Stuttgart (Germany)

March 7-10, 2019
ERS Lung Science Conference (LSC)
Estoril (Portugal)

March 10-14, 2019
SOT 2019
58th Annual Meeting of the Society of Toxicology; including Fraunhofer ITEM Exhibitor-Hosted Sessions on "Animal-free testing strategies for risk assessment of inhalable compounds" and "Characterizing indoor air quality and human exposure"
Baltimore, Maryland (USA)

March 14-16, 2019
DGP Congress 2019
60th Annual Congress of the German Respiratory Society (DGP)
Munich (Germany)

March 19, 2019
European Coatings Show – Biocides
Nuremberg (Germany)

March 25-26, 2019
Revolutionizing Next-Generation Sequencing (3rd edition)
Antwerp (Belgium)

March 28-29, 2019
Symposium "Ersatz- und Ergänzungsmethoden zum Tierversuch" (alternatives and complements to animal experiments)
Hannover (Germany)

April 1-4, 2019
OH2019
Annual Conference of the British Occupational Hygiene Society (BOHS)
Brighton (UK)

April 9-10, 2019
3rd Joint Symposium on Nanotechnology
Stuttgart (Germany)

April 12-13, 2019
AASOG 2019
Annual conference of the Americas Association of Sarcoidosis and Other Granulomatous Disorders
Iowa City, Iowa (USA)

April 13-16, 2019
European Congress of Clinical Microbiology and Infectious Diseases (ECCMID)
Amsterdam (The Netherlands)

April 24-26, 2019
IHeaR 2019
Second International Hearing Research Symposium
Buenos Aires (Argentinia)

May 5-8, 2019
26th ESACT Meeting
Copenhagen (Denmark)

May 15-17, 2019
EACR-ESMO Joint Conference on Liquid Biopsies
Bergamo (Italy)

May 17-22, 2019
ATS International Conference 2019
International Conference of the American Thoracic Society
Dallas, Texas (USA)

May 19-23, 2019
EEMGS 2019
Annual Meeting of EEMGS (European Environmental Mutagenesis and Genomics Society) and GUM (Geman Society for Environmental Mutation Research)
Rennes (France)

May 26-30, 2019
SETAC Europe 2019
29th European Annual Meeting of the Society of Environmental Toxicology and Chemistry
Helsinki (Finland)

May 27-29, 2019
Himmelfahrtstagung 2019: Intensification and digitalisation for integral bioprocessing
DECHEMA (Society for Chemical Engineering and Biotechnology) conference
Hamburg (Germany)

June 3-6, 2019
BIO International Convention 2019
Philadelphia, Pennsylvania (USA)

June 5-7, 2019
Symposium FOR 2127: Selection and adaptation during metastatic cancer progression
Regensburg (Germany)

June 17-18, 2019
31st Pezcoller Symposium: cancer as a corrupted tissue
Trent (Italy)

June 22-27, 2019
STP 2019
38th Annual Meeting of The Society of Toxicologic Pathology (STP)
Raleigh, North Carolina (USA)

June 26-28, 2019
JSOT 2019
46th Annual Meeting of the Japanese Society of Toxicology
Tokushima City (Japan)

July 8, 2019
TBMED Open Session
Public event to provide stakeholders and medical device manufacturers with more information about the EU initiative TBMED – An Open-Innovation Test Bed for the Development of High-Risk Medical Devices
Paris (France)

July 21-25, 2019
ISMB/ECCB 2019
27th Conference on Intelligent Systems for Molecular Biology and 18th European Conference on Computational Biology
Basel (Switzerland)

September 1-4, 2019
31st GUM Meeting
Basel (Switzerland)

September 3-7, 2019
ESAO 2019: Smartificial Devices for our Future
Congress of the European Society for Artificial Organs
Hannover (Germany)

September 4-7, 2019
47th Congress of the German Society for Rheumatology
Dresden (Germany)

September 5-6, 2019
4th International Workshop on Clinical Tolerance
Pittsburgh, Pennsylvania (USA)

September 8-11, 2019
Breath Summit 2019
Loughborough (UK)

September 8-11, 2019
EUROTOX 2019
55th Annual Congress of the European Societies of Toxicology
Helsinki (Finland)

September 11-12, 2019
Clinical Innovation Partnerships 2019 Conference
Berlin (Germany)

September 11-13, 2019
IPTC 2019
12th International Particle Toxicology Conference
Salzburg (Austria)

September 13, 2019
7th ILD Colloquium: Sarcoidosis & Rare DPLDs
Essen (Germany)

September 13-14, 2019
21st Hannoverian Cochlear Implant Congress
Hannover (Germany)

September 15-18, 2019
ESOT Congress 2019
19th Congress of the European Society for Organ Transplantation (ESOT)
Copenhagen (Denmark)

September 17, 2019
RCS International Conference: Implications of Occupational Exposure to Respirable Crystalline Silica. Scientific and Legal Aspects.
Castellón (Spain)

September 17-20, 2019
ESTP 2019
17th European Congress of Toxicologic Pathology
Cologne (Germany)

September 24, 2019
Institute colloquium of the Institute for Plastics Technology and Recycling (IKTR)
Weissandt-Gölzau (Germany)

September 25-27, 2019
SPhERe 2019
3rd International Symposium on Pharmaceutical Engineering Research
Braunschweig (Germany)

September 26, 2019
Bio-based Economy Day
2nd Symposium within the series of events "Innovations in the Life Sciences" of the Fraunhofer Group for Life Sciences
Berlin (Germany)

September 27 – October 1, 2019
ESMO Congress 2019
Congress of the European Society for Medical Oncology
Barcelona (Spain)

September 28 – October 2, 2019
ERS International Congress 2019
International Congress of the European Respiratory Society
Madrid (Spain)

September 30 – October 1, 2019
1st Hannover Symposium on Infection Susceptibility
Hannover (Germany)

October 2-5, 2019
4th ACTC – Advances in Circulating Tumor Cells
"Liquid Biopsy: Latest Advances and Future Challenges"
Corfu (Greece)

October 7-9, 2019
2nd joint EACR-MRS Conference on Seed and Soil: Mechanisms of Metastasis
Joint conference of the European Association for Cancer Research (EACR) and the Metastasis Research Society (MRS)
Berlin (Germany)

October 10-11, 2019
Liquid Biopsies Congress
London (UK)

October 10-13, 2019
EUSAAT 2019
19th Annual Congress of the European Society for Alternatives to Animal Testing (EUSAAT)
Linz (Austria)

October 11-12, 2019
36th InterPneu
Nürnberg (Germany)

October 16-17, 2019
1st International DECIPHER Symposium on Hypoxia and the Lung
Iquique (Chile)

October 17-19, 2019
28th Annual Meeting of the German Transplantation Society
Hannover (Germany)

October 28-29, 2019
International Symposium 2019 of the Cluster of Excellence Hearing4all
Hannover (Germany)

November 4-5, 2019
Annual Congress of the French Society of Toxicology (SFT)
Paris (France)

November 4-6, 2019
SCOG workshop "Advances in Single Cell Epigenomics"
International conference of the network "Single Cell Omics Germany" (SCOG)
Überherrn (Germany)

November 7-8, 2019
5th Conference of Applied Hygiene, Microbiology and Virology
Hamburg (Germany)

November 7-9, 2019
PPF Summit 2019
5th biennial health care conference of the Pulmonary Fibrosis Foundation (PFF)
San Antonio, Texas (USA)

November 11-13, 2019
BIO-Europe® 2019
Hamburg (Germany)

November 13-14, 2019
Breath Biopsy Conference 2019
Cambridge (UK)

November 14-15, 2019
3rd Annual Inhalation & Respiratory Drug Products Summit
Vienna (Austria)

November 18-21, 2019
MEDICA/COMPAMED 2019
Düsseldorf (Germany)

November 20-21, 2019
21st Annual Cefic-LRI Workshop
Brussels (Belgium)

November 20-22, 2019
6th International Workshop on the Causes of Childhood Leukemia
Freising (Germany)

November 28-29, 2019
"From virus to vector to medicine"
Workshop of the Working Group on Virus Vectors and Gene Therapy of the German Society for Virology (GfV)
Witten/Herdecke (Germany)

November 29-30, 2019
Autumn Meeting of the Cell Biology Section of the German Respiratory Society (DGP)
Berlin (Germany)

December 4-5, 2019
Genomics LIVE 2019
Basel (Switzerland)

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Dr. Cathrin Nastevska

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CONTACT

Dr. Cathrin Nastevska
Public Relations
Phone +49 511 5350-225
cathrin.nastevska@item.fraunhofer.de

Fraunhofer ITEM
Headquarters
Nikolai-Fuchs-Strasse 1
(main entrance: Stadtfelddamm)
30625 Hannover
Germany
Phone +49 511 5350-0
Fax +49 511 5350-155

Fraunhofer ITEM
Pharmaceutical Biotechnology
Inhoffenstrasse 7
38124 Braunschweig
Germany
Phone +49 531 6181-6001
Fax +49 531 6181-6099

Fraunhofer ITEM
Personalized Tumor Therapy
Biopark 1
Am Biopark 9
93053 Regensburg
Germany
Phone +49 941 298480-0
Fax +49 941 298480-10

Further information: www.item.fraunhofer.de