Fraunhofer
ITEM

FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM

PRE-CLINICAL PHARMACOLOGY >

< TOXICOLOGY TESTING

< MANUFACTURING OF BIOPHARMA-
CEUTICALS FOR CLINICAL TRIALS

< EARLY-PHASE CLINICAL TRIALS

ENVIRONMENTAL, OCCUPATIONAL
AND CONSUMER PROTECTION >

REGISTRATION AND RISK ASSESSMENT >

ANNUAL REPORT 2014

This Annual Report 2014 of the Fraunhofer ITEM gives an insight into the activities and service profiles of the institute's six business units and provides examples of typical contract and pre-competitive research projects performed in each of these areas. The title page and also the opening pages of the different business units in this Annual Report show the business unit spokespersons, who represent, coordinate, and further develop the individual business units to meet market requirements.

Business units of the Fraunhofer ITEM

Pre-clinical Pharmacology

Toxicology Testing

Manufacturing of Biopharmaceuticals for Clinical Trials

Early-Phase Clinical Trials

Environmental, Occupational and Consumer Protection

Registration and Risk Assessment

FRAUNHOFER INSTITUTE FOR TOXICOLOGY AND EXPERIMENTAL MEDICINE ITEM

PERFORMANCE AND RESULTS

ANNUAL REPORT 2014

Contents

FOREWORD TO READERS

Dear Reader,

Like no other publicly funded research institution, the Fraunhofer-Gesellschaft and its research institutes have committed themselves to translational research, i.e. the translation of research results and early prototypes into economically successful and socio-politically accepted innovations.

For the past 15 years, the Fraunhofer ITEM has been very intensely and consistently engaged in the application and further development of a translational platform for the pharmaceutical and chemical products sectors; for medical products and implants, corresponding activities so far have been part of the institute's research and service portfolio only to a minor degree, but in response to increasing need and demand these are now being considerably expanded.

The translational platform of the Fraunhofer ITEM for pharmaceuticals, medical products and implants and for chemicals and chemical products on the one hand is characterized by performance of the clearly defined guideline studies that are required for certification, registration, and marketing authorization; on the other hand, this platform also strives to develop novel cost-effective, time-saving, and optimally predictive test methods and validated models for bringing product candidates to market and to apply these in contract research and cooperation projects.

The challenges are indeed huge, whether in the area of innovative therapies with recombinant human antibodies, in the field of cell and even stem-cell therapy in regenerative medicine, or in gene therapy as ultimate therapeutic approach tackling not only the symptoms, but the very cause of a particular disease at its site of origin, namely the genes. This holds also true for new implant materials and for the testing of active implants and medical products with an active pharmacological principle. With regard to chemical industry products, the challenges consist in developing more validated in-vitro and ex-vivo methods to assess hazards and risks to human health during manufacturing, processing, application, disposal and recycling processes and in reducing animal experiments to a minimum.

In the context of pharmaceuticals and medical products in particular, research institutions often tend to underestimate the extensive set of laws and regulations these products and related processes have to comply with to receive regulatory approval for use in man, and the vast amount of time and money that needs to be spent until a new product candidate can even be tested in a clinical proof-of-concept study. The aim here is to reduce time and cost to the first-in-man trial – enabling at the same time a high probability of success in the clinical proof-of-concept study.

The Fraunhofer ITEM has set up a large variety of technical, chemical analytical, biomedical, biotechnological, and clinical laboratories, staffed with highly qualified scientists and clinicians and supported by an internationally recognized quality assurance team to help clients, in particular also publicly funded research institutions, spin-offs, biotechnological companies and pharmaceutical start-ups develop their product candidates to market maturity.

Development and validation of product-specific biological and clinical test systems are focuses of research and activity at the Fraunhofer ITEM, as is the performance of studies required for registration in compliance with the GXP quality standards.

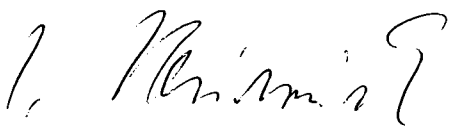
A very important part of the planning process for a drug development project, besides a pharmacoeconomic evaluation, is communication with the competent authorities at an early stage (scientific advice). The Fraunhofer ITEM experts continuously enhance their regulatory research expertise required to support this process.

With its translational research in the field of the life sciences, including also performance of early-phase clinical trials in the facilities of the research institution, the Fraunhofer ITEM is unrivaled in the publicly funded German and also European research landscape.

A facility deserving special mention is the Clinical Research Center Hannover with its imaging center, biobank, and a broad range of clinical diagnostic laboratories, through which the Fraunhofer ITEM has substantially enhanced its clinical research and its possibilities to perform proof-of-concept studies in cooperation with the Hannover Medical School and the Helmholtz Center for Infection Research under the same roof.

I am very pleased that we have been able to set up this translational platform, which we will continue to develop further. Let me take this opportunity to thank the institute's staff, whose commitment has allowed this progress to be made.

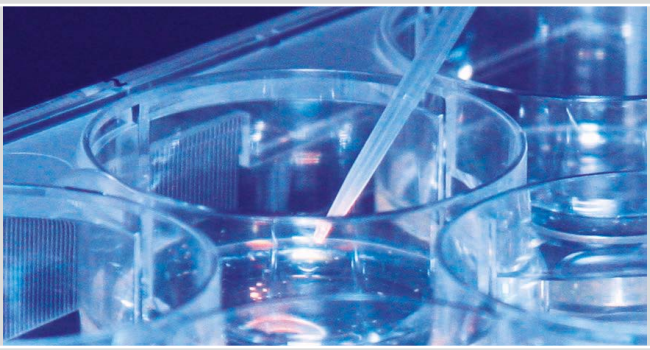
In particular, I would like to express my gratitude to our clients and cooperation partners – we will be happy to continue supporting them in their market-relevant research and development projects.



Prof. Dr. Dr. Uwe Heinrich
Executive Director

PROFILE OF THE INSTITUTE

Research at the Fraunhofer ITEM is focused on human health. The emphasis is on two aspects: firstly, on protecting health from potentially harmful, in particular airborne substances, be they gases, aerosols, particles, fibers, or nanomaterials, and secondly, on investigating and developing diagnostic and therapeutic approaches in the field of inflammatory and allergic respiratory conditions. For over 30 years already, the Fraunhofer ITEM has been building up and further enhancing its expertise in the areas of inhalation toxicology and pre-clinical airway research, and for over 10 years, the institute's clinical division has furthermore performed clinical proof-of-concept studies. Airway diseases, inhalation toxicology, and inhalable substances are thus at the focus of research at the Fraunhofer ITEM, even though the institute's research and services are not limited to these subject areas.



Protecting human health

Health protection includes environmental, occupational, and consumer protection. The Fraunhofer ITEM supports industry and public authorities in the early identification and prevention of health hazards from new products and processes and thereby also promotes sustainable development of Germany as a business location.

In this context, Fraunhofer scientists investigate novel products and processes whose potential hazards are as yet unknown, such as different nanomaterials. They evaluate the human exposure situation and develop suggestions on how to reduce or eliminate these potential hazards. For the experimental part of risk assessment, the Fraunhofer ITEM has at its disposal the necessary know-how and toxicological test methods, in particular in the field of inhalation toxicology. For the required tests, complex atmospheres and test aerosols can be generated at laboratory scale and exposure scenarios can be reproduced for in-vitro or in-vivo studies. Special computerized mathematical exposure models are also developed and used for this purpose.

The scientists perform exposure and risk assessment on behalf of clients, based on their own experimental studies, literature searches, and data provided by the client. They prepare reports on test substances and support clients in the registration of chemicals and complex mixtures and in the assessment of substances falling under the European chemicals regulation REACH.

Pre-clinical research and development

With regard to inflammatory and allergic diseases of the respiratory tract the Fraunhofer ITEM offers research and development services: from the molecular level to clinical trials. Methods of cell biology and molecular biology are used to validate novel target structures for diagnosis and therapy and optimize these during early development stages. Once possible drug candidates have been identified, efficacy and safety tests are performed. Toxicological and safety pharmacological testing for drug registration is performed in compliance with GLP.

The institute offers a broad range of efficacy and drug safety studies and makes use of a variety of in-vitro test systems and models of inflammation, asthma, and lung infection. Using a tiered approach, the scientists first perform studies in cell culture models and subsequently gain further insights in complex tissue cultures and eventually in animal models. The use of human tissue in particular allows them to obtain human data at an early stage already, data of pivotal importance above all in the testing of biopharmaceuticals.

Throughout this process, the Fraunhofer ITEM follows the 3-Rs concept ("reduce, refine, replace"), consistently trying to reduce the number of laboratory animals needed, to refine research methods, and to replace animal experiments by alternative methods.

Biopharmaceutical manufacturing: from the cell line to the investigational medicinal product

A team of scientists, engineers and technicians in the institute's facilities in Braunschweig advises and assists clients and co-operation partners in the development of novel biopharmaceutical agents – from the development of recombinant production cell lines via the manufacturing of master and working cell banks, bioprocess development and scale-up, to the manufacturing of pilot batches of the novel biopharmaceutical agent 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).

Therapies for respiratory diseases: clinical studies

For the registration of pharmaceuticals for the indications allergy, asthma, and COPD, the Fraunhofer ITEM conducts clinical studies managed by highly qualified physicians, mainly proof-of-concept studies, in compliance with GCP guidelines. Whenever needed, the required investigational medicinal products can be manufactured on site in compliance with GMP guidelines.

With the Fraunhofer Environmental Challenge Chambers (Fraunhofer ECC in short), the institute has its disposal special challenge chambers that are among very few of this kind worldwide. In these chambers, pollen, house dust mite and other allergens can be dispersed in the air in a precisely controlled manner. The efficacy of novel medications, for example, to treat seasonal allergic rhinitis can be tested there under controlled allergen challenge conditions. And in challenge studies with LPS or ozone, the clinical efficacy of new anti-inflammatory drugs can be verified. The temporary inflammation of the airways in healthy study participants induced by short-term controlled ozone inhalation challenge resembles the inflammatory condition seen in COPD patients.

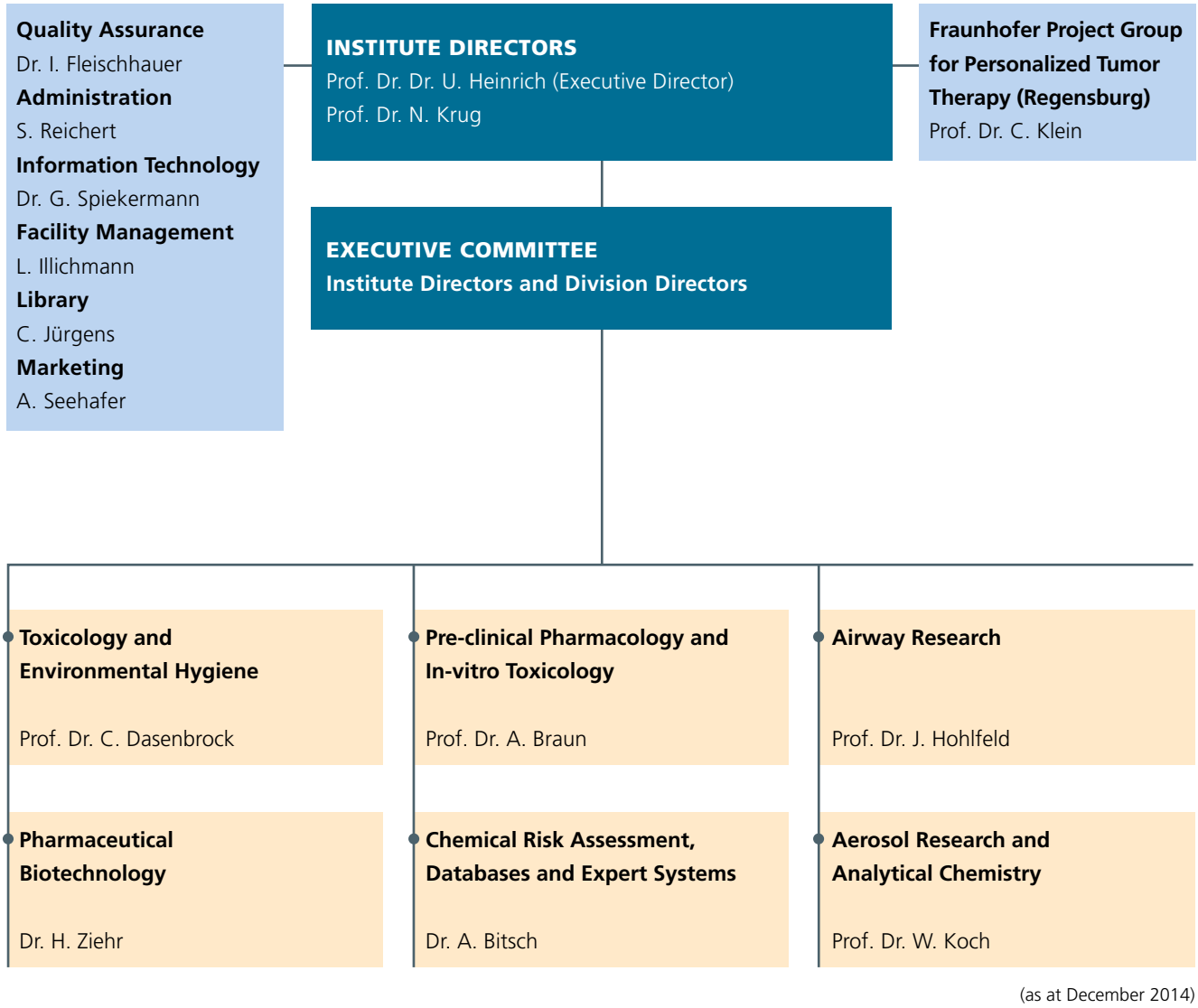
Aerosol technology in medicine

An essential prerequisite for the setup, further development, and operation of the Fraunhofer ECC is the comprehensive expertise and many years of experience of the institute's aerosol technologists. Their know-how on the aerosolization of substances and on the deposition and kinetics of inhaled materials is also important in the development of medicinal aerosols and their formulations and in the development of new technologies for medical application of aerosols.

Early-phase clinical trials in the Clinical Research Center Hannover

A new clinical study center, the "Clinical Research Center Hannover" (CRC Hannover), has been set up as a joint venture of the Fraunhofer ITEM, the Hannover Medical School, and the Braunschweig-based Helmholtz Center for Infection Research. The CRC Hannover offers an optimal infrastructure for conducting early-phase clinical trials (phases I and II) and has thus set the stage for performing the critical step in medical translational research, which is efficacy and tolerability testing of new drug candidates in human test subjects. The new proof-of-concept center was formally opened in September 2014 and first clinical trials have been performed.

ORGANIZATIONAL STRUCTURE



(as at December 2014)

Headed by the Institute Directors and the Executive Committee, the Fraunhofer ITEM is organized in six divisions. The institute's headquarters are in Hannover (Germany), except for the Division of Pharmaceutical Biotechnology, which has its facilities in Braunschweig on the campus of the Helmholtz Center for Infection Research.

The Fraunhofer Project Group for Personalized Tumor Therapy is based in Regensburg's BioPark and was set up as a joint initiative of the Fraunhofer ITEM, the Fraunhofer-Gesellschaft, and the University of Regensburg.

COMPETENCIES

The Fraunhofer ITEM has pooled the competencies from its various divisions in business units. This chart gives you the contact persons for the individual competencies, working groups, and departments at a glance (as at December 2014).

Toxicology and Environmental Hygiene

Inhalation Toxicology
Dr. O. Creutzenberg
Prof. Dr. C. Dasenbrock

General and Regulatory Toxicology
Dr. R. Fuhst

Reproductive Toxicology
Dr. J. Buschmann

Pathology
Priv.-Doz. Dr. S. Rittinghausen

Transgenic Technologies
Dr. R. Halter

Animal Laboratories
Dr. T. Tillmann

Pre-clinical Pharmacology and In-vitro Toxicology

Airway Pharmacology
Dr. H.-G. Hoymann

Immunopharmacology and Immunotoxicology
Dr. K. Sewald

Experimental Immunology
Prof. Dr. A. Braun

Microbiology and Infection
Dr. S. Wronski

Genetic Toxicology and Epigenetics
Dr. C. Ziemann

Pre-clinical Biomarkers and ADME
Dr. T. Hansen

In-vitro Inhalation Toxicology
Dr. J. Knebel

Molecular Toxicology and Pharmacology
Dr. M. Niehof

Primate Research
S. Knauf, D. V. M., Ph. D.

Airway Research

Clinical Airway Research
Prof. Dr. J. Hohlfeld
Dr. P. Badorrek

Clinical Method Development
Dr. O. Holz

Clinical Pharmacology
Prof. Dr. J. Frölich
Dr. P. Badorrek

Biomarker Analysis and Development
Dr. M. Müller

Pharmaceutical Biotechnology

Quality Control
Dr. L. Baydoun
Dr. U. Pägelow

Cell Culturing Techniques
Dr. S . Duvar
Dr. V. Hecht

Microbial Cultivation
Dr. A. Roß
Dr. C. Seitz

Downstream Processing
Dr. J. Paulsen
Dr. C. Lüer

Aseptic Fill and Finish
Dr. J. Paulsen
Dr. L. Baydoun

Chemical Risk Assessment, Databases and Expert Systems

Chemicals/REACH
Dr. G. Könnecker
Dr. O. Licht

Biocides
Dr. A. Bitsch
A. Zwintscher

Veterinary Medicinal Products
Dr. G. Könnecker
Dr. A. Wibbertmann

Exposure Assessment
Dr. S. Hahn

Testing Strategies and Structure-Activity Relationships
Dr. S. Escher
Dr. M. Batke

Databases and Information Systems
Dr. R. Kellner

Risk Assessment of Nanomaterials
Dr. K. Schröder

Aerosol Research and Analytical Chemistry

Aerosol Technology
Prof. Dr. W. Koch
Dr. K. Schwarz

Medical Inhalation Technology
Dr. G. Pohlmann

Bio- and Environmental Analytics
Dr. S. Schuchardt
Dr. K. Blümlein

Structure Analytics
Dr. S. Schuchardt

GXP – QUALITY ASSURANCE ACCORDING TO INTERNATIONAL STANDARDS

The Fraunhofer ITEM is striving to meet high quality standards with the services and products offered and to ensure maximum safety for trial subjects in clinical studies performed at the institute. Not only are the relevant legal regulations strictly complied with, but state of the art regulatory requirements are invariably taken into consideration. To guarantee that the work performed at the Fraunhofer ITEM satisfies internationally accepted quality standards, the Fraunhofer ITEM has implemented the GXP quality assurance systems. These include Good Laboratory Practice (GLP), Good Clinical Practice (GCP), and Good Manufacturing Practice (GMP). With their respective scopes of application, these quality assurance systems cover the translational approach in the institute's spectrum of activities. The central service unit "Quality Assurance" is responsible for putting into practice the relevant quality assurance programs.

GLP conformity of non-clinical safety studies

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

By means of study-based and facility-based inspections, the service unit "Quality Assurance" continuously monitors compliance with these principles in the institute's departments of toxicology, safety pharmacology, and analytics. During the past two decades, the competent authorities have performed regular inspections and certified the institute's GLP conformity for a broad range of studies. On the occasion of the most recent inspection in December 2014, the integrity of the GLP studies performed was once again confirmed. The established quality assurance system thus guarantees to all sponsors a recognized quality standard in the institute's non-clinical departments.

GCP standard of clinical trials

The ethical principles for biomedical research laid down in the Declaration of Helsinki form the basis of the GCP principles describing the quality standards to be met in clinical trials. At the Fraunhofer ITEM, a broad range of measures ensures that these requirements can be met both in trials falling under the German Drug Act and performed on behalf of international sponsors and also in clinical research projects. The service unit "Quality Assurance" assists the clinical investigators in fulfilling their responsibilities by closely monitoring implementation of the quality-relevant processes under aspects of GCP and by routinely checking the relevant documentation. Both the monitoring authority and the institute's sponsors have assessed the quality level reached to be GCP-compliant.

During setup of the Clinical Research Center Hannover (CRC Hannover), co-operated as a Fraunhofer research institution by the Fraunhofer ITEM, the Hannover Medical School (MHH) and the Helmholtz Center for Infection Research (HZI), the service unit "Quality Assurance" assumed lead responsibility in the establishment of a joint quality assurance system for the facilities used by the cooperation partners performing clinical trials according to GCP. During routine operation of the CRC Hannover, the service unit "Quality Assurance" is performing

Now that the semi-automatic filling machine at the institute's Braunschweig site is operable, the services which the Fraunhofer ITEM is able to offer cover the complete process chain from the very idea to the biopharmaceutical investigational product. The corresponding manufacturing authorization was granted by the competent authorities in January 2015.

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

GMP facilities at the institute's Hannover site

All manufacturing and quality control steps for investigational medicinal products to be used in clinical trials – including challenge agents – are subject to stringent GMP requirements. To enable patient-specific dilution and aseptic fill and finish of investigational medicinal products (liquid dosage forms) in spatial proximity to the clinical departments, an appropriate GMP facility was successfully established at the Fraunhofer ITEM in Hannover a few years ago. Furthermore, the possibility to manufacture ozone according to GMP for use as a challenge substance in clinical inhalation trials has been established and confirmed by the competent authorities. A corresponding GMP manufacturing authorization was granted by the competent authorities, but is dormant for the time being. The service unit "Quality Assurance" ensures that the regulatory conditions for resuming manufacturing operations, whenever needed, are met.

GMP facilities at the institute's Braunschweig site

The institute's Division of Pharmaceutical Biotechnology in Braunschweig develops GMP manufacturing processes for active biopharmaceutical ingredients and investigational medicinal products. The Division has many years of experience and comprehensive expertise in a broad range of products, including naturally occurring and recombinant proteins, DNA, virus-like particles, and allergens. In addition, it produces cell banks according to Annex 2 of the EU GMP Guide. For aseptic fill and finish of small-volume liquid dosage forms, an automated filling machine for vials and ampoules was set up in a joint project with the Packaging Technology Group of Robert Bosch GmbH. In 2014, aseptic fill and finish of vials was established and successfully validated by media fill studies. The Braunschweig facilities received their first manufacturing authorization in 1998, which has since been extended several times. The last inspection by the competent authorities took place in January 2015. The manufacturing authorization includes now also aseptic fill and finish.

CONTACT
Dr. Ilona Fleischhauer
Head of Quality Assurance at the
Hannover site
Phone +49 511 5350-304
ilona.fleischhauer@item.fraunhofer.de

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

STAFF AND INSTITUTE BUDGET PERFORMANCE

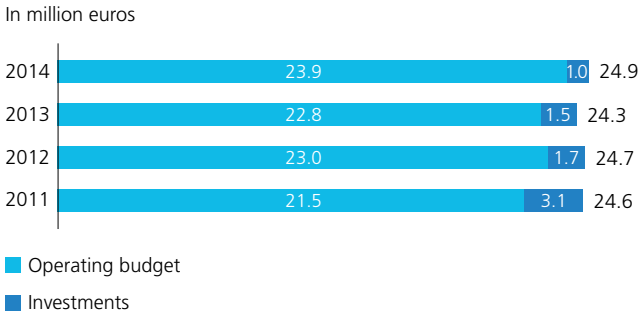
At the end of 2014, 299 people were employed at the Fraunhofer ITEM. The following list gives the numbers of employees by occupational groups:

87 scientists
106 graduates
53 technical staff
10 Ph. D. students
22 laboratory assistants
12 other assistants
9 apprentices

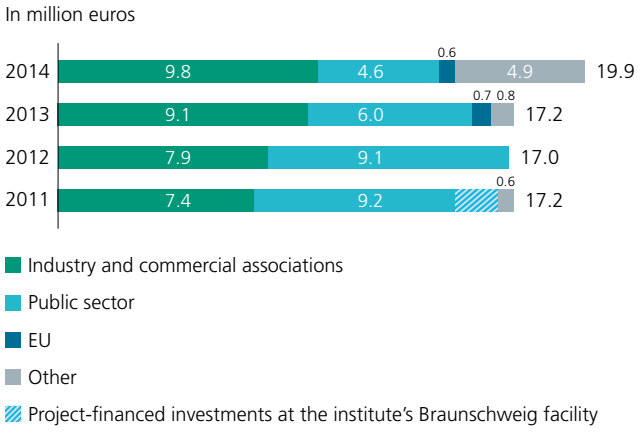
In 2014, the institute's budget reached a level of 23.9 million euros. Financing by acquired funding amounted to 83.3 percent. The share of industrial income in the institute's budget was 41 percent – with regard to the Fraunhofer ITEM in Hannover it was 64.2 percent. Investments of the Fraunhofer ITEM amounted to approximately 1 million euros.

Staff of the Fraunhofer ITEM

Total budget of the Fraunhofer ITEM



Sponsors and external income of the Fraunhofer ITEM



ADVISORY BOARD

The advisory boards 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 2014, the Board of the Fraunhofer ITEM was made up of the following members:

Dr. Eckhard von Keutz
Chairman of the Advisory Board
Senior Vice President, Global Head Early Development,
Bayer HealthCare AG

Professor Dr. Christopher Baum
President and member of the Presidential Council
responsible for the Division of Research and Teaching
of the Hannover Medical School

Professor Dr. Dieter Bitter-Suermann
Deputy Chairman of the Advisory Board (until June 30, 2014)
Former president and member of the Presidential Council
responsible for the Division of Research and Teaching of the
Hannover Medical School

Professor Dr. Helmut Blome
Director, Institute for Occupational Safety and Health
of the German Institutions for Statutory Accident Insurance
and Prevention (until June 30, 2014)

Professor Dr. Ulrich Deschl
Head of Nonclinical Drug Safety, Boehringer Ingelheim Pharma
GmbH & Co. KG

Professor Dr. Paul-Georg Germann
Head Preclinical Safety Germany, AbbVie Deutschland GmbH

Professor Dr. Thomas Jung
Chief Medical Officer, Delenex Therapeutics AG, Switzerland

Dr. Günther Karmann
Managing Director, Karmann Consulting GmbH

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

Dr. Edgar Leibold
Vice President Product Stewardship, BASF SE

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

Professor Dr. Klaus F. Rabe
Head of Pneumology, LungenClinic Grosshansdorf;
Endowed Professorship in Internal Medicine/Pneumology,
University of Kiel

Professor Dr. Gerhard Schlüter
Consultant in Toxicology, former Global Head Toxicology,
Bayer HealthCare AG

Ministerialrat Dr. Hans Schroeder
Head of Division for Science and Economy, EU Structural Funds,
Lower Saxony Ministry for Science and Culture
(until June 30, 2014)

Dr. Thor A. Voigt
Head of Global Clinical Operations, Biometrics &
Data Management, Boehringer Ingelheim Pharma
GmbH & Co. KG

CLINICAL RESEARCH CENTER HANNOVER – THE NEW PROOF-OF-CONCEPT CENTER IS PICKING UP SPEED

CRC HANNOVER

The Clinical Research Center Hannover (CRC Hannover) was formally opened on September 8, 2014 – a ceremony with high-ranking representatives of politics and science, during which Stephan Weil, Premier of Lower Saxony's state government, Stefan Schostok, Mayor of Hannover, Professor Alfred Gossner, Executive Vice President of the Fraunhofer-Gesellschaft, and Andreas Barner, Chairman of the Board of Managing Directors of Boehringer Ingelheim emphasized the importance of the CRC Hannover for the region and for Hannover's further development as a center of science and research. The CRC Hannover has since been establishing itself as a proof-of-concept center for early-phase clinical trials. Its focus is on

the development of novel medical methods, drugs, and diagnostics in an academic setting. The pooled expertise in the Hannover-Braunschweig area and the unique technical infrastructure of the research center enable new approaches in the development of study concepts and methods.

The CRC Hannover is operated by the Fraunhofer ITEM in cooperation with the Hannover Medical School (MHH) and the Braunschweig-based Helmholtz Center for Infection Research (HZI). It provides a platform for safety and efficacy testing of novel drugs and methods as part of the registration process. The close dovetailing of the involved partners yields a unique combination of the academic expertise of three well-established research institutions, each in its particular domain, and the infrastructure possibilities of the CRC Hannover. The CRC Hannover is thus perfectly predestined for conducting research-intensive studies. For the performance of phase-I studies, that is to say, first-in-man trials with novel drugs to test their safety in a small number of volunteers, and phase-II studies, required to provide the proof of concept of novel medications or therapeutic approaches in man, a total of 50 beds is available, 30 of which allow intensive monitoring of study participants. The technical equipment in the new center enables comprehensive diagnostics, complemented by additional infrastructure of the partners.

Relocation of the Fraunhofer ITEM Division of Airway Research to the CRC Hannover is complete – in July 2014, the first drug trial volunteers arrived to participate in a phase-I study in the new building. Eight further studies in the field of airway research have since been initiated. With a new Siemens magnetic resonance imaging (MRI) scanner, set up in April 2014 for use in research only, and a xenon polarizer, the scientists of the Fraunhofer ITEM and MHH in their studies have access to technological equipment that is unrivaled in Germany. This diagnostic method, which is not only highly accurate, but also has the advantage of placing no burden on test subjects, enables quantitative analysis of the inflammatory reactions in the lung that are typical of respiratory diseases. In combination with the possibility to detect cardiac alterations, this opens up new options for the development of innovative study concepts – an important step for further enhancement of study activities at the Fraunhofer ITEM. A first phase-IV study on the detection of alterations in the heart and lung by MRI has already been initiated.

Study activities of the other partners to the CRC Hannover have also rapidly evolved – and continue to do so. In 2014, the MHH performed first clinical phase-I trials, and in May 2014, the HZI study team began examining participants of the "National Cohort", Germany's largest epidemiological study, in the new study center.

CONTACT
Prof. Dr. med. Norbert Krug
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norbert.krug@item.fraunhofer.de

Infrastructure

- 30 intensive-monitoring beds (for clinical trials of phases I and IIa)
- 20 beds for study participants who do not require intensive monitoring
- Outpatient section for screening visits
- Infrastructure for study participants incl. cinema, gym, and cafeteria
- 15 rooms for special diagnostics
- Imaging technology (MRI)
- Biomarker laboratory
- Biobank

PROJECT GROUP IN REGENSBURG

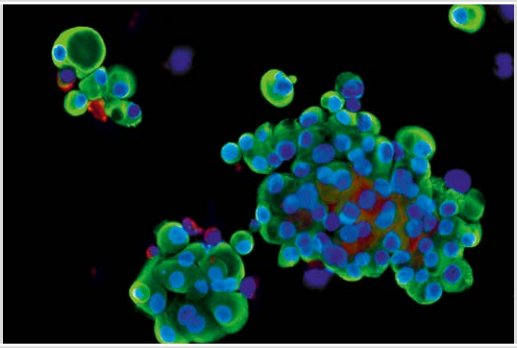
The Project Group for Personalized Tumor Therapy in Regensburg has been a part of the Fraunhofer ITEM since 2011. Its focus is on tumor diagnosis, in particular on detection of single disseminated und circulating tumor cells, and on the development of novel tumor therapies. The group, which meanwhile has reached a size of twelve scientists and seven technical assistants, is headed by Professor Christoph Klein, who is also holding the Chair of Experimental Medicine and Therapy Research of the University of Regensburg. In February 2014, Professor Klein was awarded the renowned German Cancer Prize for his outstanding experimental research into metastatic dissemination of cancer cells. Research activities of the Project Group in the year 2014 were focused on the development of new technologies for single-cell analysis, on molecular characterization of disseminated cancer cells, and on the development of novel pre-clinical models for adjuvant cancer therapy.

Combined high-resolution analysis of genome and transcriptome of single tumor cells

During the past years, numerous technologies allowing detection and even isolation of single cells have been developed and have even been incorporated into clinical diagnostic settings for the detection of circulating tumor cells (CTCs) and disseminated cancer cells (DCCs) in cancer patients. For a deeper understanding of their biological properties, however, reliable molecular methods for single-cell analysis are indispensable, especially as recent studies suggest the clinical utility of CTCs as "liquid biopsy" to replace tissue biopsies of metastatic tumors.

A team of scientists of the Fraunhofer Project Group for Personalized Tumor Therapy has developed workflows for combined high-resolution molecular analysis of DCCs following parallel whole-genome (WGA) and whole-transcriptome amplification (WTA) of the same single cell. This approach for the first time provides the possibility to carry out multiple analyses in parallel on mRNA and DNA from a single cell. The complex landscape of somatic alterations in DCCs can thus be cross-validated using independent nucleic acid amplification methods, thereby minimizing the risk of misinterpreting technical errors as true aberrations. Parallel RNA-Seq analyses of single cells of a prostate cancer cell line presenting markedly different gene expression levels of the prostate cancer fusion transcript marker TMPRSS:ERG were performed using the Roche 454 GS FLX+ and Illumina HiSeq 1000 platforms. Additionally, a protocol for experimental normalization of single-cell cDNA libraries to increase the sequence depth of the Roche 454 GS FLX+ system was developed. This made it possible to detect TMPRSS:ERG fusion transcripts even at very low levels of gene expression. Furthermore, by using high-resolution aCGH analysis (comparative genomic hybridization on microarrays), it was demonstrated that high-throughput analysis of both transcriptome and genome of the same single cell is feasible. Single cells of the analyzed prostate cancer cell line presented high-level amplification in a subregion of the human chromosome 11 combined with high expression levels of the genes located therein.

The established protocols were applied to comprehensively analyze the genome and transcriptome of disseminated cancer cells from bone marrow of metastatic prostate cancer patients. Overall, we obtained sequences for about 8000 mRNA transcripts and detected high levels of expression of the genes located in the subregion of chromosome 11 shown to be amplified in the prostate cancer cell line. Besides detection of prostate cancer-characteristic somatic alterations we noted no high-level amplification on chromosome 11. By bioinformatic evaluation and further validation experiments, we identified a novel fusion transcript in the DCCs of a prostate cancer patient.



For functional analysis of disseminated cancer cells, these are cultured in vitro under stem cell conditions. The image shows the resulting spheres stained with tumor cell markers.

In conclusion, the developed assays provide powerful molecular tools to analyze tumor cells on a single-cell level and therefore will help to characterize the full molecular profile and heterogeneity of systemic cancer.

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Development of novel pre-clinical models for adjuvant cancer therapy

Tumor cell heterogeneity has been recognized as a major driving force for the evolution of an individual cancer. Molecular diversity is especially high in early cancer, so that early dissemination even of few melanoma cells is a quantitative risk factor for patients. Identification, isolation, and characterization of disseminated cancer cells (DCC) might, therefore, provide important information for targeting precursor cells of metastases. Analysis of DCC, however, is limited by their extremely low numbers, and in-vitro/in-vivo models for functional analysis and consequently for screening of drugs to treat early systemic tumor spread are missing.

Scientists of the Project Group for Personalized Tumor Therapy, therefore, have developed protocols for expanding single DCC from melanoma patients and have established novel pre-clinical models for systemic melanoma therapies. To this end, they disaggregated parts of the lymph nodes of melanoma patients who had no signs of distant metastases and analyzed them for the presence of melanoma DCC. Single DCC were then propagated in vitro under specific sphere-forming conditions (see figure), expanded by transplantation in immunodeficient mice, and the resulting tumors were used to establish adherent cell lines. Establishment of this workflow to date has enabled successful engraftment of DCC from 20 percent of the melanoma patients included in this study. The origin of the expanded DCC could be confirmed by genomic fingerprint, and the stability of the genome during different steps of propagation was evaluated by genomic characterization. In addition, the scientists developed a novel pre-clinical mouse model based on expanded melanoma DCC. They first generated a human immune system in immunodeficient mice expressing human leukocyte antigen-A2 (HLA-A2) by transfer of HLA-A2-positive hematopoietic stem cells. In addition, they induced melanoma in such mice with a human immune system by transplantation of DCC-derived cell lines. Interestingly, the presence of an HLA-A2-restricted human immune system significantly induced tumor formation as well as minimal residual disease of melanoma cells in lungs and bone marrow of double-humanized mice compared to mice without a humanized immune system. These data indicate a prominent impact of human immune cells on tumor development and metastasis formation.

The development of DCC-based pre-clinical in-vitro/in-vivo models for the first time now enables functional characterization and drug testing in the actual target cells of adjuvant therapy settings. The presence of an HLA-A2-restricted human immune system additionally provides novel opportunities to understand the role of human immune cells during metastasis formation and their influence on the development of drug resistance. These models will help to identify new adjuvant therapies targeting minimal residual disease and to understand mechanisms of drug resistance of currently applied targeted therapies.

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BUSINESS UNITS OF THE FRAUNHOFER ITEM

Expertise pooled in six business units

The Fraunhofer ITEM has pooled its wide spectrum of expertise (see pages 10/11) in six business units and is thus able to investigate issues of human health on behalf of clients from industry, industry associations, occupational safety and health organizations, and public authorities. If desired, full-package solutions can also be offered, whenever necessary in cooperation with partners.

This Annual Report gives you an insight into the scope of services and selected projects performed in the different business units.

Pre-clinical Pharmacology

Toxicology Testing

Manufacturing of Biopharmaceuticals for Clinical Trials

Early-Phase Clinical Trials

Environmental, Occupational and Consumer Protection

Registration and Risk Assessment

BUSINESS UNIT
PRE-CLINICAL PHARMACOLOGY

The Business Unit "Pre-clinical Pharmacology" pools the institute's competencies in the field of efficacy testing of pharmaceuticals, including biopharmaceuticals in particular. Biopharmaceuticals are evaluated in compliance with the relevant regulations, such as EMA S6. We support our research partners and clients from the development of the study design to the analysis and interpretation of the obtained results.

To comply with legal and public demands on animal protection and also to increase model predictiveness, we use a tiered approach: Starting with in-vitro experiments, we characterize pharmaceutical agents and then develop them further in ex-vivo and in-vivo tests of increasing complexity, up to the proof of concept in man. This approach allows us to obtain human data at an early stage already and compare these with data from other species.

Different in-vitro and in-vivo models of inflammation, asthma, and lung infection, and ex-vivo models such as the standardized precision-cut lung slices (PCLS) are available in this business unit. PCLS enable efficacy testing in living tissue from mice, rats, monkeys, and humans. Using the Fraunhofer-patented P.R.I.T.®-ALI culturing and exposure system, PCLS can also be exposed to air-

Focus of activities in 2014

Alternative test methods are increasingly gaining importance in pre-clinical pharmacology and toxicology, given the objective to generally reduce, refine or even replace animal experiments as far as possible. For such studies, in particular in the field of inhalation toxicology and pharmacology, an ex-vivo model has proven highly useful: precision-cut lung slices. This model and some of its applications will be presented in the below report.

Precision-cut lung slices as a model of respiratory diseases and toxicity

Organotypic tissue models of the lung are widely used both in basic and applied research. Precision-cut lung slices are such an organotypic tissue model. For wide implementation in research and development, however, application of such tissue models requires high standards and quality. At the Fraunhofer ITEM, we have acquired expertise in the use of such biologically complex models over many years. In our laboratories, precision-cut lung slices (PCLS) are mainly used as models of lung diseases and lung injury.

PCLS are viable, three-dimensional sections of lung tissue. They are prepared, for example, from mouse, rat, guinea pig,

borne substances such as gases and aerosols. To meet the client's specific requirements, our models for efficacy testing can be customized and, if need be, developed further.

Numerous new developments are human-specific biopharmaceuticals whose efficacy and safety cannot be sufficiently tested in the classical rodent models. Because of their pronounced homology to humans with regard to anatomy and immunology, pre-clinical disease models in non-human primates, therefore, are often the only possibility to test such novel active pharmaceutical ingredients. In cooperation with the German Primate Center in Göttingen, Fraunhofer ITEM scientists have set up a working group for the development of novel translational animal models in common marmoset monkeys. The aim is to offer translational non-human primate models for pre-clinical testing of human-specific biopharmaceuticals for COPD and asthma treatment. The developed animal models make use of a tiered approach to keep animal numbers to a minimum. In-vitro and ex-vivo experiments must first be successfully completed, before in-vivo experiments are designed and performed based on the obtained data.

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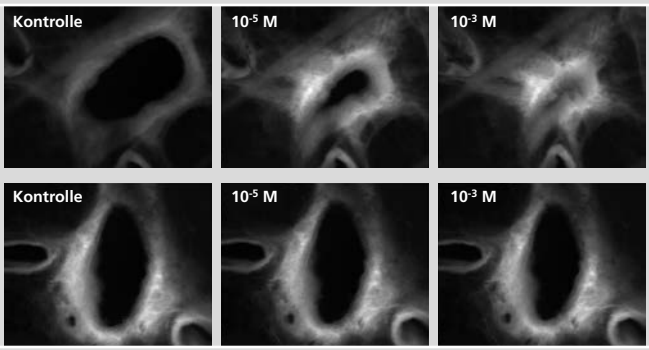
non-human primate, and human lung lobes. The lung lobes are cut by a microtome into about 250-µm-thick tissue sections. The tissue sections thus contain nearly all cells that are normally present in the lung. This means that they are composed, for example, of epithelial cells, endothelial cells, smooth muscle cells, fibroblasts, mast cells, and nerve fibers. After preparation the lung tissue slices can be cultured at normal cell culture conditions for several days. During this time, they are incubated with harmful chemicals, new drugs, mitogens (substances that stimulate the innate immune system), and proteins such as antibodies.

Using PCLS to display bronchoconstriction

There are several applications that are well-established at the Fraunhofer ITEM. One of the major applications is the use of PCLS to study the microscopic anatomy of cells in their natural environment. This means that the three-dimensional structure of the tissue allows the localization of cells in proximity to other cell types to be studied by confocal microscopy. This makes it possible to discover rare events that are difficult to detect in the very thin sections of the lung which are normally used.

Another very interesting application is the use of PCLS to display bronchoconstriction. To this end, lung slices are prepared with airways in the middle. They can be observed under a microscope to study changes in the size of the airways. Contraction of the airway can then be induced by addition of constricting agents (e.g. methacholine or allergens) or by stimulation of nerve fibers. The use of allergens in particular is very important for asthma research. For this purpose, the



Acetylcholine-induced bronchoconstriction in PCLS. Increasing concentrations of acetylcholine lead to bronchoconstriction (top images). Tiotropium – a bronchodilator – prevents contraction at the same acetylcholine concentrations (bottom images).

tissue is sensitized with IgE-containing serum of allergic donors. This leads to binding of IgE to mast cells present in lung tissue. Subsequent exposure to the appropriate allergen leads to activation and degranulation of mast cells. The mast cells release histamine, thereby inducing contraction of the airways. This process is also known as early airway response. The induced airway contraction can then be watched by video-microscopy as described above (see figure). The tissue slices thus allow investigation of the effects of new drugs that prevent contraction of the airways as induced, for example, by allergens.

PCLS as an ex-vivo model of asthma

PCLS can furthermore be used to model immune responses in lung tissue. A very simple example is activation of PCLS by molecules that are only present on pathogens. Such pathogen-associated molecules are, for example, endotoxins. They are recognized by cells of the immune system such as macrophages. Thus, in PCLS endotoxins induce activation of macrophages, indicated by release of pro-inflammatory cytokines – proteins that are able to induce fever, cell migration, and defense mechanisms. But also other molecules such as IL-13 (which is a key cytokine in asthma) have been shown to induce acute release of pro-inflammatory cytokines and increased sensitivity of the airways to normal stimuli (also referred to as airway hyperresponsiveness). This enables a model displaying features of asthma, although the donor was non-asthmatic.

13th Workshop "Models of Asthma and COPD"

The 13th workshop of this series attracted about 90 international participants from academia and industry. They appreciated a well-diversified program with top-notch speakers giving comprehensive overviews and presenting new exciting data. Key topics included: biomarkers of inflammatory lung disease; in-vitro and ex-vivo methods to model pulmonary disease; holistic tools to understand respiratory diseases; new therapeutic targets and technologies; and a special lecture entitled "Look back in anger – what clinical studies tell us about pre-clinical research". The workshop was organized by the Fraunhofer ITEM in cooperation with the German Center for Lung Research (DZL).

PCLS to reduce numbers of experimental animals

Another interesting application of PCLS is their use for assessment of harmful chemicals. In acute inhalation toxicity studies, animals inhale substances at given concentrations. Without additional information, the appropriate starting concentration for in-vivo inhalation studies is difficult to estimate. The Fraunhofer ITEM was involved in the standardization and prevalidation of PCLS as an alternative ex-vivo method to reduce the number of experimental animals in inhalation toxicology. To this end, lung tissue was exposed to 20 industrial chemicals. These chemicals were classified with regard to their ability to induce cell death and inflammation in lung tissue ex vivo. The effects of chemicals were shown to correlate very well with those of in-vivo inhalation toxicity studies.

Dr. Thomas Hartung from the Johns Hopkins University in Baltimore, USA, held the interesting and entertaining special lecture entitled "Look back in anger – what clinical studies tell us about pre-clinical research".

For a detailed report about this two-day workshop, please refer to the Web page:
http://www.item.fraunhofer.de/lungws2014

PCLS can be used as translational model

In summary, PCLS can be used as translational model to study several features of lung injury, COPD, and asthma ex vivo. The different tissue responses enable prediction of organ injury, respiratory sensitization, airway responses, and inflammation. With this method, we help to bridge the gaps that sometimes exist between basic research in experimental animals and applied science in humans.

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Equipment highlights

– Facilities for drug administration by inhalation in combination with lung function measurement and feedback dose control system (in animal models)

– Measurement unit for repetitive lung function measurement (in mice, rats, and primates)

– S2 laboratories with integrated animal facility for bacterial, fungal, and viral lung infection models (mouse and rat)

– P.R.I.T.® Air/Liquid Interface culturing and exposure system for in-vitro testing of airborne substances

– Equipment for multiplex measurement of biomarkers

– Confocal laser scanning microscope and 2-photon microscope for immunohistochemical and immunocytochemical analyses

– Equipment for genome-wide transcriptome analyses, pathway-specific arrays, and real-time PCR (for analyzing CYPs, proinflammatory genes, cytokines, oxidative stress, proliferation, apoptosis, and transcription factors)

PROJECTS

Biofilms for testing of antibiotics

Biofilms are aggregates of microorganisms, such as bacterial pathogens, embedded within a self-produced extracellular matrix. The biofilm matrix acts as a protective cover against attacks by the host's immune system or antibiotic treatment. *Pseudomonas aeruginosa* is one of the most frequent causative agents of chronic lung infection in patients with cystic fibrosis and very difficult to treat, due to its ability to form biofilms and thereby develop resistance towards antibiotic treatment. Consequently, there is an urgent need for therapeutics that not only exhibit an antibacterial effect, but moreover are able to disrupt biofilm structures.

To address this problem, the Working Group on Microbiology and Infection is developing biofilm models for pre-clinical testing of novel therapeutic strategies. *P. aeruginosa* biofilms can successfully be grown in vitro and exhibit substantially higher resistance to antibiotics such as tobramycin than the planktonic form of *P. aeruginosa*. In cooperation with the Department of Medical Inhalation Technology, a setup for biofilm exposure to aerosolized antibiotics has furthermore been developed. These new models enable pre-clinical in-vitro testing of novel therapeutics, in particular for inhaled administration. To test their efficacy against highly resistant biofilms, these new models, compared with traditional antimicrobial testing, provide enhanced predictivity for the in-vivo situation in chronic infections driven by biofilms.

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Pre-clinical efficacy testing in models of pulmonary fibrosis

Bleomycin-induced pulmonary fibrosis in rodents is the standard model for efficacy testing of new drugs for treating idiopathic pulmonary fibrosis (IPF). At the Fraunhofer ITEM, bleomycin models have been established in three species. Wistar rats or Golden Syrian hamsters were treated with two doses of bleomycin aerosol contralaterally administered by means of a MicroSprayer®. C57Bl/6 mice were subjected to bleomycin treatment by oropharyngeal aspiration. Starting on day 7, animals were treated intraperitoneally or orally with test substances versus placebo. On day 21, invasive but repeatable lung function measurements were performed in anesthetized yet spontaneously breathing rats and mice. These measurements included the parameters dynamic lung compliance and lung resistance. Immediately thereafter, in the hamster model on day 28, lung lavage was performed, followed by preservation of the lung tissue. Histological analyses demonstrated pronounced alveolar/interstitial fibrosis with increased collagen content (histomorphometric analysis), elevated hydroxyproline levels in tissue and lavage fluid, and increased macrophage, neutrophil, and lymphocyte counts in the bleomycin groups. The lung function measurements indicated reduced lung distensibility and elevated tissue and/or airway resistance. The three bleomycin models with their combination of lung function measurements and different pathological and biochemical analyses have proven useful in pre-clinical efficacy testing during development of new drugs for IPF treatment.

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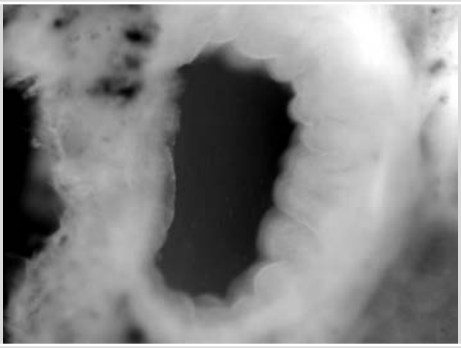

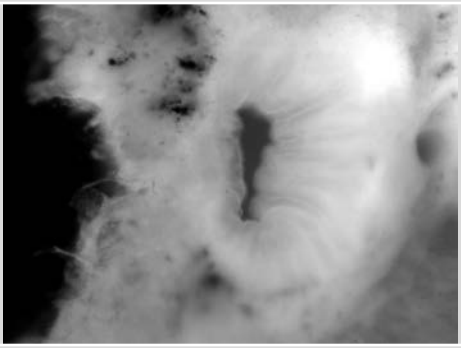

Contraction of peripheral airways (from left to right) upon administration of capsaicin as a sensory nerve stimulus in human sensitized precision-cut lung slices (PCLS).

Sensory nervous system affects asthmatic airway constriction

The human lung is equipped with a dense network of nerve fibers. To what extent these nerves communicate with mast cells that are also present there and in what way this affects contraction of the peripheral airways is being investigated in the DFG priority program "Mast cells". Scientists of the Fraunhofer ITEM were able to show in precision-cut lung slices (PCLS) that activation of sensory C fibers induces contraction of the peripheral airways (see figure). Passive sensitization of human lung tissue leads to enhanced contraction of the airways. To elucidate the mechanism of action of neuronally induced bronchoconstriction the scientists used different inhibitors. In their study, they found human IgE and receptors for both histamine and the neuropeptide substance P (SP) to be involved in this process. Evidence for a functional contact between nerves and mast cells was thus provided. Confocal immunofluorescence analyses demonstrated that anatomically, there is close contact between mast cells and nerve fibers and that activation of nearby sensory nerves triggers release of mediators from mast cells. These results provide deep insights into the process of potential allergic sensitization and clearly show that neuroimmunological processes have to be taken into account as well in the complex picture of allergic asthma.

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Carbon nanotubes as anticancer drug carriers

Scientists at the Fraunhofer ITEM are aiming to use multi-walled carbon nanotubes as a multifunctional system allowing active pharmacological agents to be transported through the human organism – which means, they want to develop a multi-functional drug delivery carrier system. Drug delivery systems serve the purpose of mobilizing poorly soluble substances and enabling their transport to the intended site of action. The resulting increased level of the active pharmacological agent in the target tissue reduces unspecific reactions between the drug and tissue and thus helps minimize unwanted side effects. Fraunhofer ITEM scientists are exploring the possibility of using modified multi-walled carbon nanotubes (MWCNT) as carriers for "safe" transport of cytostatic agents (or other anticancer drugs) through a biological system to the target, namely the tumor. The MWCNT were produced by the Leibniz Institute for Solid State and Materials Research (IFW) in Dresden, Germany. Synthesis of these nanotubes requires an iron catalyst, which subsequently remains inside the nanotubes. This iron core can then be used to produce heat inside the tumor (hyperthermia) by means of an external stimulus such as magnetic field generation, so as to induce further damage to the tumor tissue. By coupling the nanotubes to tumor-specific antibodies, the scientists intend to additionally increase the presence of carrier molecules at the site of action.

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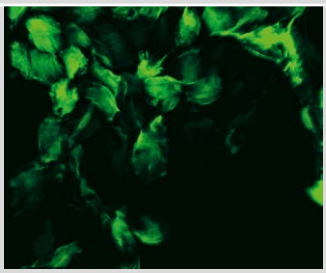
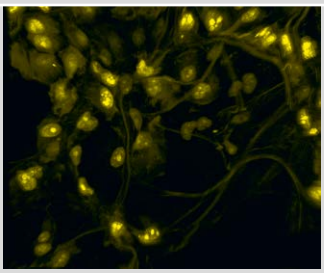
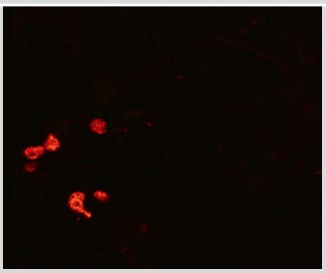


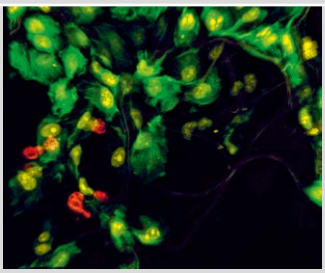
Cancer cells



Proliferation



CD68 immune cells



Merge

Development of a novel 3D human tumor model

The scientific community is facing the challenge of developing translational models involving no animal experiments to study the molecular basis of cancer development. In addition, such models are also required to enable testing of novel pharmaceuticals. Scientists at the Fraunhofer ITEM are now developing a human ex-vivo tumor model of the lung. To this end, they let GFP fluorescence-labeled cancer cells attach to human precision-cut lung slices, PCLS in short. Due to the GFP labeling, the cancer cells specifically differ from all other cells in the lung tissue slices. Growth behavior, proliferation, and dynamics of the tumor cells can thus be studied in an environment that is very close to the natural situation. The scientists analyzed the composition of occurring micrometastases by confocal fluorescence microscopy (see figure). In addition, they measured the release of signaling molecules (cytokines), allowing them to draw conclusions on the release of tumor markers and immune responses in lung tissue. Such analyses provide deeper insights into the initial events of tumor growth and serve the purpose of facilitating the development of targeted therapeutic approaches. The new model is being developed both for basic research and for testing of novel anti-cancer drugs.

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Transcriptome analyses in a PCLS-based viral infection model

The aim of the EU project U-BIOPRED is to investigate the mechanisms by which viral infections, for example with human rhinovirus (HRV), can cause exacerbations of asthma. Since this condition cannot be mimicked in mouse models (Rochlitzer et al., 2014), the focus is on development of novel translational models. The model of precision-cut lung slices (PCLS), established at the Fraunhofer ITEM, is now being further developed to investigate viral infections. In first experiments, human and murine PCLS were infected in vitro with HRV and the immune response was analyzed. Transcriptome analyses are intended to enable detailed comparison with clinical samples from HRV-infected patients. To this end, the Department of In vitro and Mechanistic Toxicology under guidance of Dr. Monika Niehof has established RNA isolation from PCLS from different species. As a result, sufficient RNA of adequate quality for the subsequent analyses can now be obtained. First transcriptome analyses performed by a project partner have shown HRV to specifically induce key signaling pathways of the antiviral immune response in human PCLS. The applicability of PCLS for molecular biological investigations such as transcriptomics, which can also be performed in-house, will henceforth allow more detailed comparison of the immune regulation between man and test species, not only for viral infections, but also for immune modulation by test items and other issues of interest.

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Micrometastasis in human lung tissue: In the first image, growing cancer cells are displayed in green. The second image shows their proliferation in yellow. The cancer cells form a network with locally resident immune cells in the human tissue (cell surface molecule CD68 displayed in red). The merge of all three images represents a complete image of the micrometastasis.

Establishment of a translational model of asthma

Non-human primates exhibit a close genetic relationship to humans, making them suitable animals for modeling human immunological diseases in cases where rodent models are of limited significance. Asthma is characterized by an excessive immune response accompanied by strong impairment of physical performance and thus requiring long-term treatment. Within an EU-funded project, the Fraunhofer ITEM has developed a model in the common marmoset that enables mimicking of human asthma. Asthma was induced in the animals by exposing them to house dust mite extract (HDM) during a sensitization phase and a challenge phase. Subsequent therapeutic intervention consisted in administration of either a glucocorticoid or a vehicle as control. After the sensitization phase, an increase in interleukin-13 could be demonstrated in HDM-stimulated peripheral lymphocytes. The therapeutic intervention was characterized by a specific increase in eosinophils in control animals. Furthermore, pulmonary function parameters were monitored with a device specifically designed for this purpose, complemented by analysis of bronchoconstriction in precision-cut lung slices. The results reveal that the common marmoset is a suitable model for asthma research. There are plans to complement this model with a model in the cynomolgus monkey, in order to improve development of human-specific asthma therapeutics.

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Stem cells in regenerative medicine

Introduction of a new technology enabling in-vitro reprogramming of adult maturated cells back into their immature stem cell state revolutionized the field of regenerative science and medicine. Such reprogrammed cells, also known as induced pluripotent stem cells (iPSC), have the potential to differentiate into any cell type of the three germ layers. Even though iPSC resemble embryonic stem cells regarding morphology and growth properties, they are not associated with the ethical concerns linked to embryonic stem cell research. Therefore, iPSC present an alternative source of stem cells for cell therapies. Within the REBIRTH excellence cluster ("From Regenerative Biology to Reconstructive Therapy") the Fraunhofer ITEM, in cooperation with the Institute of Experimental Hematology and the Institute for Laboratory Animal Science of the Hannover Medical School, is exploring the possibilities offered by iPSC in regenerative medicine. The focus of this project is on the characterization of complex hematopoietic differentiation and the development of transplantable human hematopoietic stem cells of iPSC origin in a murine xenograft teratoma model. In this context, human iPSC were used to induce teratomas, whose cellular composition was then characterized. By characterizing the different cell types and factors involved, the Fraunhofer ITEM scientists are aiming to elucidate underlying mechanisms and to improve in-vitro differentiation protocols for transplantable hematopoietic stem cells

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BUSINESS UNIT
TOXICOLOGY TESTING

The Business Unit "Toxicology Testing" offers a broad range of toxicological tests enabling assessment of potential risks to human health. Substances we investigate include pharmaceuticals, biopharmaceuticals, chemicals, particles, complex mixtures, and also nanomaterials. The focus is on characterizing inhalable substances. Our expertise ranges from the development of tests to accompanying companies in the registration process. A solid basis is provided by the institute's core competencies "Inhalation, Fiber and Particle Toxicology" and "Aerosol Research and Chemical Analyses".

For risk assessment and registration, we offer toxicological, toxicokinetic, pharmacokinetic, and safety pharmacological studies, in addition to in-vitro studies. In compliance with international registration guidelines, these studies are performed under GLP conditions. We furthermore support our clients in the registration of pharmaceuticals, biopharmaceuticals, and phytopharmaceuticals by completing what has been demanded by the competent authorities and preparing the necessary documentation. Clients benefit in particular from the close dovetailing of basic research and applied research. This allows guideline studies to be complemented, whenever necessary, by further investigations using novel toxicological and molecular toxicological methods.

For over 20 years, we have conducted inhalation studies in rodents and thus are experienced also in complex studies. Thanks to our cutting-edge equip-

Focuses of activity in 2014

In 2014, the focus of numerous projects performed in the Business Unit "Toxicology Testing" was on the one hand on the toxicology of nanomaterials, and on the other hand on in-vitro and ex-vivo tests as important methods in toxicological research. In the following, we will present a project dealing with an issue of everyday relevance, namely investigation of the mycotoxin alternariol. The aim of this study was to close existing data gaps to enable risk assessment of this toxic compound.

Toxicokinetics and genotoxicity of alternariol

Alternariol is a mycotoxin produced by molds belonging to the genus *Alternaria* and occurring ubiquitously in many foods. It is suspected to have mutagenic and perhaps even carcinogenic effects. The experimental data supporting this suspicion so far had been collected exclusively in in-vitro tests with bacteria and cell cultures. In 2011, the Panel on Contaminants in the Food Chain (CONTAM) of the European Food Safety Authority (EFSA) published an expert report on the risks from *Alternaria* toxins. It included a recommendation to further investigate the

ment, not only standard fiber and (nano-)particle aerosols can be generated, but also sophisticated exposure atmospheres, such as occupationally relevant bitumen aerosols. Over the past years, the focus of interest in toxicology has expanded and is no longer on fine particulate matter only, but because of their wide range of applications now also includes engineered nanoparticles (< 0.1 µm). This is why cross-departmental pilot projects have been initiated at the institute, aimed at establishing robust, validated screening assays that allow the toxic potential of this type of particles to be evaluated. Substance categories currently under investigation are carbon nanotubes (CNT) and graphene, a two-dimensional carbon modification with a regular hexagonal pattern.

Our offer furthermore includes a broad range of in-vitro test methods for preclinical testing of active pharmaceutical ingredients and for assessing the cytotoxic and genotoxic potentials of environmentally and occupationally relevant substances. This also includes alternative test methods in line with the current European chemicals policy (REACH). Selection of the appropriate cellular test systems and development of the study design is performed in consultation with the sponsor, governed by a variety of criteria such as relevance of the species, organ, and target site, endpoints to be analyzed, compliance with OECD guidelines, and any additional requirements.

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toxicokinetics and genotoxicity of these substances in vivo in order to close existing data gaps. Whether or not alternariol has mutagenic effects in vivo as well was still unknown at the time. Nor were there any data available to determine whether alternariol is absorbed from the gastrointestinal tract after oral intake. These questions were to be elucidated at the Fraunhofer ITEM.

Production of sufficient quantities of alternariol

The first great challenge was the supply of alternariol in sufficient quantities for animal experiments, as alternariol is not commercially available in gram quantities. Chemical synthesis was performed by Professor Joachim Podlech at Karlsruhe Institute of Technology. At the Fraunhofer ITEM, this material was then further purified by preparative HPLC to over 98 percent purity.

To investigate absorption and distribution of alternariol in the organism, mice were treated orally with ^{14}C-labeled alternariol. Radioactivity was then analyzed in blood, organs and tissues. In addition, excretion of ^{14}C alternariol was monitored in urine and feces for one week. The results of this study provide evidence that only small quantities of alternariol are absorbed from the gastrointestinal tract and that 90 percent of the administered dose are excreted in the feces. Further-

Molds are ubiquitous and occur on many foods, for example on ears of wheat. Some mycotoxins, including alternariol, are suspected to have mutagenic and perhaps even carcinogenic effects.

more, measurements of radioactivity in tissues and organs demonstrated very low absorption of alternariol after oral intake: 24 hours after treatment, overall less than 1 percent of the administered dose was found in the organism, the highest radioactivity values being measured in the gastrointestinal tract. After 7 days, only less than 0.01 percent of the total dose could be detected in organs and tissues.

Measurement of metabolites

The parent compound alternariol is metabolized in the organism, for example by insertion of hydroxyl groups at different positions. At the Fraunhofer ITEM, different analytical methods were established to enable measurement of such degradation products (metabolites) as well. Alternariol and its metabolites in blood were measured by LC-MS/MS, while urine analyses were performed with a GC-MS method. Alternariol metabolites for use as analytical standards were produced by incubation with rat microsomes. Overall, four hydroxylized metabolites of alternariol were found in blood and urine, and the positions of their OH-groups could be clearly ascertained by ^{1}H-NMR spectroscopy and mass spectrometry. Alternariol blood levels in the first three to six hours after treatment were in the double-digit ng/ml range.

Alternariol showed no toxic or genotoxic effects

In order to determine the genotoxic potential of alternariol, a micronucleus assay according to OECD Guideline 474 in combination with an alkaline comet assay in stomach, intestine and liver was performed as the next step. To this end, mice were treated three times each with 2000 mg/kg alternariol. The animals tolerated the treatment with alternariol at this dose without any symptoms of impaired well-being. The micronucleus assay did not suggest any toxic or genotoxic effect of alternariol in bone marrow. The result of the alkaline comet assays was negative as well, so that there was no indication of a genotoxic potential in the investigated tissues.

Summary

The in-vivo experiments performed in the present study did not confirm the genotoxic potential of alternariol described in the literature in connection with in-vitro experiments. In addition, the results of the present study suggest very low bioavailability of alternariol (< 0.1 %) after oral intake, so that its systemic toxicity can be considered low.

Registration of biopharmaceuticals: Fraunhofer ITEM can provide scientific advice

Registration of biopharmaceuticals is subject to less stringent regulation than that of chemicals. Rather than on strict rules, it is based on a guideline system that defines the focuses of testing, but allows for flexible approaches which may differ from case to case. The Fraunhofer ITEM is able to provide competent support in this complex process.

The most important guidelines for pre-clinical testing are laid down by the European Medicines Agency (EMA). These guidelines are valid in particular for substances such as cytokines, plasminogen activators, recombinant plasma factors, growth factors, fusion proteins, enzymes, receptors, hormones, monoclonal antibodies, recombinant DNA-

protein vaccines, synthetic peptides, plasma-derived products, endogenous proteins from human tissue, and oligonucleotides. According to the guidelines, the testing strategy should be scientifically grounded and selected with a view to the requirements of the particular case. Within the guideline system, different parameters such as selection of the relevant animal species, age, physiological state, the manner of delivery including dose, route of administration, and treatment regimen, stability of the test material, and the general GLP guidelines are to be taken into account for pre-clinical studies. This process poses a challenge both for companies developing biopharmaceuticals and for testing facilities, which in a joint effort have to set the stage for first clinical trials in man. The necessary testing strategy can be discussed and agreed with the competent authorities via a scientific recommendation, a procedure referred to as "scientific advice", giving companies the certainty that the intended testing is in line with the strategy accepted by the authorities.

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Equipment highlights

- Scanning electron microscope with energy-dispersive X-ray analysis system
- Transmission electron microscope with energy-dispersive X-ray analysis system
- High-resolution dark field microscope with hyperspectral microscopy
- Multi-headed transmitted light microscope for 21 observers, with digital camera and projection unit
- Slide scanner with image analysis software
- Zetasizer® for particle measurement in the submicrometer range by dynamic light scattering
- Electron spin resonance spectrometer

PROJECTS

Risks from inhaled graphene

Under the EU-funded research program ERA-NET, Fraunhofer ITEM scientists are investigating the potential risks from inhaled graphene in cooperation with other partners. Graphene can be described as a virtually two-dimensional, atomic-scale honeycomb lattice made of carbon atoms, where each carbon atom is surrounded by three others at an angle of 120 degrees. Graphene nano-platelets are nanoscaled in one dimension, while the other two dimensions are in the microscale range. Due to its thickness in the nanometer range, graphene exhibits special aerodynamic properties: Despite their relatively large size (up to 20 µm), graphene particles can penetrate deep into the lung as far as the alveoli, thus posing a disproportional lung hazard. The toxicological characterization of graphene is, as yet, incomplete. In the present project, therefore, different types of graphene (graphene, graphene oxide, graphite oxide, carboxyl graphene) are being compared using a toxicity screening protocol. In a first step, a selection of commercially available graphenes is being subjected to in-vitro screening with endpoints of cellular toxicity and genotoxicity, to identify the materials displaying the highest and the lowest toxicity. To validate the in-vitro results and complement the available in-vivo data on graphene, a 28-day inhalation study including analysis of inflammatory, genotoxic, and histopathological endpoints will be conducted. Based on the data thus obtained, graphene-specific risk assessment will eventually be performed.

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Engineered carbon black nanoparticles: prediction of human toxicity

The International Agency for Research on Cancer (IARC) of the World Health Organization has classified carbon black as possibly carcinogenic to humans (Group 2B). It is not clear, however, to what extent the hazard potential depends on the surface chemistry of the particles. The joint research project "CarbonBlack" was aimed at establishing a test system composed of test models of increasing complexity to evaluate the toxic effects of modified and well characterized carbon black nanoparticles (CBNP) on the airways and lungs. Subproject 2, conducted by the Fraunhofer ITEM, was focused in particular on detecting correlations between the properties of engineered CBNP and their toxic effects observed in human lung cell lines and precision-cut lung slices (PCLS) and on verifying the results from these in-vitro systems in a nose-only inhalation study in rats according to OECD Test Guideline 412. All in all, the results of this subproject have shown CBNP to be of low acute toxicity. The inhalation study was performed using Printex 90® as reference particles and acetylene soot and benzo[a]pyrene-coated Printex 90® as test items. Acetylene soot displayed higher toxicity than Printex 90® and benzo[a]pyrene-coated Printex 90®, both in vitro and in vivo. This result suggests surface chemistry, absorption of polycyclic aromatic hydrocarbons in particular, to have an impact on the acute toxicity of CBNP.

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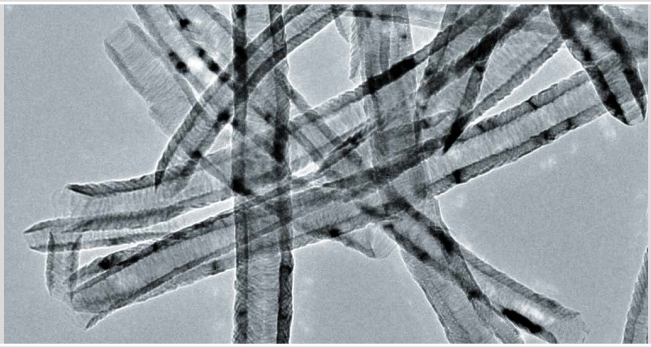

Carbon nanotubes visualized by electron microscopy. Copyright: Leonhardt, Leibniz Institute Dresden.

Carcinogenicity study with multi-walled carbon nanotubes

A focus in the joint project "CarboTox" was on investigating the carcinogenic potential of multi-walled carbon nanotubes (MWCNT) of different lengths and diameters[1] in a two-year carcinogenicity study. Amosite (10^8 WHO fibers with a length of 13.95 µm and a diameter of 0.394 µm) was used as positive control. A total of 500 male rats (50 per group) were treated by single intraperitoneal injection of MWCNT suspended in artificial lung medium (negative control) in two different dose groups (1 x 10^9 and 5 x 10^9 WHO fibers). Moribund animals were examined by histopathology and immunohistochemistry. All MWCNT used in this study induced tumors in all dose groups, and in most cases these were classified as mesothelioma. The highest tumor incidence and earliest tumor development were observed with needle-shaped MWCNT (8.57 µm length/ 0.085 µm diameter and 9.30 µm length/0.062 µm diameter). Only a little later, mesotheliomas appeared in the group treated with MWCNT with a length of 10.24 µm and a diameter of 0.04 µm, and in the course of the study also in the group treated with strongly coiled MWCNT (7.91 µm length/0.037 µm diameter). Overall, induction of malignant mesotheliomas was found with all MWCNT tested in this study. Besides the length-to-diameter ratio of the fibers, their morphology seems to have a decisive impact on the carcinogenic potential (Rittinghausen et al., 2014). These results could not yet be taken into account in the most recent evaluation of carbon nanotubes by the International Agency for Research on Cancer (IARC).

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[1] All indicated lengths and diameters refer to the WHO fiber fraction (length > 5 µm, diameter < 3 µm, length/diameter ratio > 3/1).

Improved safety for workers in the ceramics industry

The aim of the EU project SILICOAT was to minimize the hazardous potential of quartz-containing materials in the ceramics industry (tiles, tableware, sanitary ware) by surface modification, using technologies that would not interfere with ceramics manufacturing processes and would not affect product quality. Workers in the ceramics industry are theoretically at risk of developing respiratory diseases as a result of continued quartz exposure, including lung inflammation, silicosis, and even tumors. Certain respirable crystalline silica particles were therefore classified as human carcinogens by the IARC in 1997. In the EU project SILICOAT, researchers successfully developed cost-effective, tailor-made quartz coating technologies, based on stable, covalent saturation of reactive chemical groups on the surface of quartz particles. As one of the project partners, the Fraunhofer ITEM developed a conclusive in-vitro and in-vivo test battery allowing reliable screening for and quantitative comparison of quartz-dependent biological effects. Selected endpoints were cytotoxicity, genotoxicity, and the pro-inflammatory potential of quartz. Using the proposed test battery, the scientists initially screened raw materials to identify particularly active quartz species and subsequently assessed the effectiveness and stability of promising coatings. The toxicological data obtained were essential and provided decisive clues in the development of appropriate coating methods.

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Using in-vitro models to predict drug-mediated CYP induction

To clarify whether a new drug is capable of inducing CYP enzymes by activating nuclear receptors, CYP induction studies are required prior to drug registration. According to the guideline of the European Medicines Agency (EMA), such studies should first be performed in vitro, before testing a new drug in vivo in experimental animals. For the in-vitro studies, the use of human primary hepatocytes is recommended, while data from studies with cell lines should be included only as supporting data. Because of substantial inter-individual differences between human primary hepatocytes from different donors and limited availability of such cells, there is a great demand for alternative cell models. In a study performed at the Fraunhofer ITEM, therefore, three hepatocyte-like cell systems, HepaRG™, Upcyte® and HepG2, were tested to evaluate their suitability for use as induction systems as an alternative to human primary hepatocytes. The cells were treated with prototypical inducers and induction of the most important CYP450 enzymes (CYP1A2, CYP2B6, and CYP3A4) was analyzed by qPCR. In the hepatoma-derived cell line HepaRG™, all CYP450 genes analyzed showed induction levels comparable to those of human primary hepatocytes. The results show that all necessary nuclear receptors are expressed in these cells. HepaRG™ cells thus seem to be a promising alternative cell model for predicting drug-mediated cell induction.

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Alternative ex-vivo method to determine the activity of lung surfactant

The rat lung lavage model (RLL) is frequently used to determine the in-vivo activity of lung surfactant formulations, which are a treatment option for respiratory distress syndrome (RDS) in premature infants. In this model, restoration of lung function is tested by administering artificial surfactant after the lung function was impaired by performing lavages. Disadvantages of this model are high fluctuation in the measured parameters. In this context, Fraunhofer ITEM scientists are testing the isolated perfused rat lung (IPL) as an alternative ex-vivo model to assess the impact of surface-active compounds. By performing lavages, they bring the isolated lung into an RDS-like state with reduced breathability, before eventually administering artificial surfactant. This leads to improved lung compliance and an increase in partial oxygen pressure. Macroscopically, the result is an opening of the lung lobes. The short duration of organ removal is a refinement in animal experimentation in line with the internationally accepted 3-Rs guidelines to reduce experimental animal numbers and minimize animal distress. The constant data acquisition throughout the whole experiment adds a high gain in knowledge about the effects of lavages and the effectiveness of surfactant formulations or other surface-active compounds in the lung.

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The P.R.I.T.® ExpoCube® developed at the Fraunhofer ITEM enables testing of airborne and inhalable substances in cells and tissues at the air-liquid interface.

Standardized in-vitro testing of aerosols using the P.R.I.T.® ExpoCube®

In-vitro and ex-vivo test systems are getting increasingly important for toxicology testing of airborne substances from consumer products, medicinal products, or environmental sources, not least as a result of the ever more stringent legislation on animal experiments. Compared with common substance testing in a liquid system, the testing of airborne substances (gases, aerosols, particles) in an air-liquid system is much more complex and thus places more sophisticated requirements on the whole test method. In particular, standardized generation of the test atmosphere and adjustment of the test system for exposure at the air-liquid interface are imperative. With the P.R.I.T.® ExpoCube® (see figure) that has been developed at the Fraunhofer ITEM, a device-controlled method for this kind of in-vitro tests is already available. It enables exposure of target cell systems such as cell lines and primary cell cultures, but also of tissue-based systems (e.g. precision-cut lung slices) on traditional 12-well-plate systems with compatible membranes to a previously generated test atmosphere in an uninterrupted process. The system has a compact size and can be connected without problems to commercially available aerosol generation systems such as Aeroneb®. In a study, Fraunhofer ITEM scientists have developed a standardized setup that can be implemented in any laboratory and have demonstrated its suitability for aerosol toxicity testing.

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Cigarette smoke induces cytotoxicity and inflammatory signals in precision-cut lung slices

Chronic obstructive pulmonary disease (COPD) is a severe lung condition with high morbidity and mortality rates worldwide. Characteristics of COPD include chronic bronchitis, inflammation and pulmonary emphysema, developed mainly as a result of cigarette smoking. The goal of this study was to evaluate whether cigarette smoke condensate (Csc) induces features of COPD in precision-cut lung slices of different species, including human. Precision-cut lung slices are viable, three-dimensional sections of lung tissue. They contain a number of relevant cell types such as epithelial cells, endothelial cells, smooth muscle cells, fibroblasts, and macrophages.

Precision-cut lung slices were prepared and exposed to Csc. Subsequently, Csc-induced toxicity and inflammation were assessed. Csc induced tissue injury in all species. The half maximal effective concentrations (EC_{50}) ranged from 85 µg/ml in murine precision-cut lung slices to 194 µg/ml in rat precision-cut lung slices. In human precision-cut lung slices, the observed EC_{50} was at 121 µg/ml. Furthermore, cigarette smoke induced markers of inflammation in murine precision-cut lung slices, whereas human and rat tissue were less sensitive to Csc. In summary, PCLS from different species represent a promising model to reflect the toxic and inflammatory aspects of cigarette smoke induced by Csc. This model is thus available for use in drug development in the future.

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BUSINESS UNIT
MANUFACTURING OF BIOPHARMACEUTICALS FOR CLINICAL TRIALS

The Fraunhofer ITEM team in Braunschweig has 20 years of comprehensive experience and know-how in process development and GMP manufacturing of investigational biopharmaceuticals. Partners from the pharmaceutical and biotech industries and academic institutions much appreciate this expertise, which has enabled successful completion of many of their projects. A cross-disciplinary team of scientists, engineers and technicians stands for quality and experience, supporting and assisting clients in projects from the development of a suitable cell line to manufacturing of the investigational medicinal product.

The first and foremost requirement for a biopharmaceutical process development project is a high-yielding production cell line based on a recombinant microbial or animal cell system. This cell system must feature a well-documented history, robustness, and stability. Once a suitable cell line is available, the next step is the manufacturing of a GMP cell bank that is the starting point for any batch created with the future biotechnological production process. The Fraunhofer ITEM Division of Pharmaceutical Biotechnology manufactures master and working cell banks based on bacteria, yeasts, fungi, and mammalian cells up to safety level S2 in compliance with GMP.

Focuses of activity in 2014

In 2014, key topics in the Business Unit "Manufacturing of Biopharmaceuticals for Clinical Trials" included the production of GMP cell banks, development of cell lines for manufacturing of recombinant proteins, and the use of a state-of-the-art robotic system to select clones, a process referred to as clone picking.

GMP production of cell banks: first milestone in the life cycle of a biopharmaceutical

Since February 2013, a manufacturing license has been required for the production of cell banks according to Annex 2 of the EU GMP Guide. The Braunschweig-based Division of Pharmaceutical Biotechnology has more than 15 years of experience in GMP-compliant manufacturing and storage of cell banks and, as early as in summer 2013, was one of the first institutions to receive regulatory approval for GMP cell banking according to the new legislation.

For more than 20 years already, process development for a wide range of biopharmaceutical active ingredients has been the core business of the Division of Pharmaceutical Biotechnology: antibodies, antibody fragments, virus-like particles, bacteriophages, glycoproteins, and nucleic acids, in particular plasmids. The process first has to be thoroughly understood across all phases of process development. GMP elements are successively integrated already during the development phases, resulting in a transferrable GMP process including process analytics that will comply with regulatory requirements. Especially for antibodies and plasmids, manufacturing platforms based on largely pre-developed and pre-validated basic process sequences and process analytics have been developed, which then only have to be adapted to the special requirements of a particular active ingredient.

For GMP manufacture of pilot batches of biopharmaceutical active ingredients and their further processing to investigational medicinal products for use in clinical trials in compliance with regulatory requirements, a GMP facility with grade-C and grade-D clean rooms is available, comprising both USP and DSP suites. Downstream aseptic fill and finish of final dosage forms in ampoules and vials is performed in a grade-B clean room within a class-A RABS (restricted-access barrier system) including an automated filling machine.

BUSINESS UNIT SPOKESPERSONS

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Cell bank production is the first milestone in the life cycle of a biopharmaceutical. It constitutes an essential prerequisite for consistent production of biopharmaceutical active ingredients. Given that repeated subcultures and multiple generation cycles can result in unwanted changes in properties and integrity, production of any biopharmaceutical active ingredient should be based on cells from a cell bank prepared with low numbers of generation doublings. A two-tiered cell banking system, consisting of a master cell bank (MCB) and a working cell bank (WCB), guarantees a steady supply of starter cultures throughout the life cycle of a biopharmaceutical. A MCB usually consists of 200 to 300 vials with reference samples manufactured from a suitable cell clone. Like any other pharmaceutical raw material, it has to be tested for purity, identity, content, and viability prior to use. In case of animal cells, special emphasis is placed on virus safety testing. A vial from the MCB is expanded in growth medium and aliquoted as working cell bank into over 300 vials, which are then cryo-conserved in the gas phase of liquid nitrogen, under similar conditions as the MCB. Like the MCB, the WCB is character-ized and tested with regard to purity, identity, content, and viability. Cell bank production is performed in clean rooms. For GMP-compliant cell bank storage, a safe, controlled, and monitored cell bank system with temperatures below minus 150 °C is used.

In cell banks, cells are stored at temperatures below minus 150 °C in the gas phase above liquid nitrogen.

Development of suitable production cell lines

Industrial-scale production of recombinant proteins requires high-yield and robust production cell lines that grow to high cell densities and reproducibly express the gene of interest at high levels. The Fraunhofer ITEM biotechnologists have many years of experience in the development of suitable production cell lines. To establish CHO cell lines for heterologous gene expression, they make use of the proven CHO-DHFR expression system that enables fast and robust generation of production clones. This long-established system is accepted by the authorities and features high yields of the target product, in particular for monoclonal antibodies and bispecific antibody fragments, but also for other recombinant glycoproteins. The selection process to identify a CHO clone with high and stable protein expression from heterogeneous transfection cell pools requires comprehensive screening of a large number of clones. Furthermore, the history of the established cell line must be documented: the host cell line, the laboratory where the host cell line was originally isolated, or the collection of cultures from where the cell line was obtained. Documentation of passages, media, and media components – material certificates in particular – is also necessary. In addition, the sources of the recombinant gene, of the expression system, and cloning must be well documented. At the end of the cell line development process, robustness of the recombinant cell clones with regard to expression level, expression stability, and molecular quality (glycosylation) of the expressed target genes is evaluated.

Performance of RMCE-based cell lines

In parallel with traditional methods for the development of production cell lines, Fraunhofer ITEM scientists are studying the performance of production cell lines manufactured by means of recombinase-mediated cassette exchange (RMCE). Traditional methods for the manufacture of production cell lines, such as the CHO-DHFR expression system, are based on random integration of numerous copies of the transgene into the host genome. Benefits include the comprehensive experience gained with this established system and its high productivity. Drawbacks are the very time-consuming and labor-intensive selection process for identification of a CHO clone with high and stable expression levels and the fact that a cultivation strategy has to be developed for every new clone.

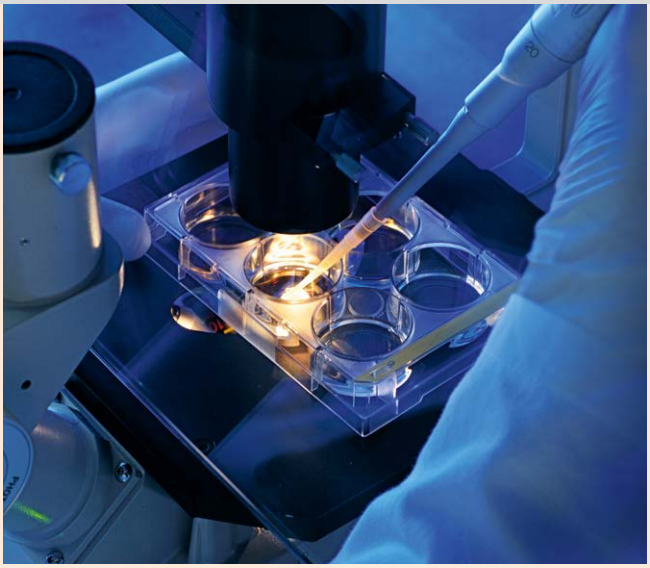
The individual clones generated so far in projects performed on behalf of clients displayed stable expression of the target gene – product concentrations of up to 3.5 g/l were achieved in fed-batch manufacturing processes.

Robotic system for clone picking

To enable screening of large groups of clones, the Fraunhofer ITEM possesses state-of-the-art technology and equipment. For fast and effective identification of suitable clones, a robotic system is used to screen cell clones for use in biopharmaceutical manufacturing. This system combines high-precision robotic technology with sophisticated image processing software and an integrated inverted microscope for direct image processing, specific selection, and complete documentation thanks to the use of bright-field and fluorescent illumination. The high-throughput system allows picking of over 1000 clones

In contrast to the traditional methods, RMCE-based cell line development relies on targeted integration of the transgene into a precisely identified and characterized locus. Comparative experiments with different factors influencing the cultivation process showed that clones produced according to the traditional method were affected to varying degrees within a defined range of different parameters. In contrast, clones produced with the RMCE-based method exhibited comparable growth and expression properties.

The Fraunhofer ITEM scientists thus successfully demonstrated for the first time that RMCE-based cell lines display predictable and homogeneous growth and expression properties in a cultivation process, thereby providing an advantage over traditionally developed cell lines.



within a very short time and ensures complete documentation for a reproducible history of the individual clones, which is a sine qua non for subsequent registration of the biopharmaceutical drug product.

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Equipment highlights

– 2000 m² of laboratory space for biopharmaceutical process development
– 600 m² of clean rooms (classes A, B, C, and D) for GMP manufacturing
– Manufacturing authorization since 1997

USP:
– Stainless steel: 50-l STR (batch, fed batch, and perfusion) and 400-l STR (batch and fed batch)
– Single use: 20-l WAVE bioreactor

DSP:
– Chromatography systems (GE Healthcare) with up to 180 l/h
– Preparative HPLC with up to 150 ml/min
– Crossflow filtration system (Sartorius) with up to 6 m²

Filling machine ARF 1010 (by Bosch):
– Semi-automated filling machine for ampoules (1-30 ml) and vials (2-50 ml)
– Nitrogen gassing
– Batch sizes of up to approx. 3500 units

PROJECTS

International cooperation for GMP manufacturing of a biosimilar

The biotechnological expertise of the Fraunhofer ITEM scientists in Braunschweig is highly rated not only in Germany, but also internationally. A special benefit according to a new project partner in Egypt is the new sterile filling plant of the Fraunhofer ITEM in Braunschweig, enabling sterile fill and finish of clinical investigational medicinal products immediately after they have been manufactured. The project partner has already developed part of the manufacturing process for a biosimilar – a copy of an already approved biopharmaceutical – and the Braunschweig-based team is currently working to adapt the manufacturing process to the given technical conditions, validate this process and thereby make it "fit for GMP manufacturing". Further plans within this project are to manufacture purified bulk in compliance with GMP, perform stability studies for the active ingredient and the final dosage form, eventually manufacture the investigational medicinal product (IMP) in compliance with GMP guidelines, label it for dedicated clinical trials (GCP labeling), and release it for final use in such trials.

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Custom filling processes: aseptic fill and finish of small volumes

In 1997 already, the Fraunhofer ITEM received regulatory approval according to § 13 of the German Drug Act (AMG) for GMP manufacturing of biopharmaceutical active ingredients. Meanwhile, this authorization has been extended several times to include manufacturing of a variety of novel active ingredients and investigational medicinal products (IMPs) and also aseptic fill and finish of liquid dosage forms (infusion bags). To enable also the hitherto missing aseptic fill and finish of small-volume IMPs, the company Bosch Packaging Technology (Crailsheim, Germany) has developed a semi-automatic filling machine for quantities of up to 3000 vials and ampoules. In 2011, this machine was enclosed in a restricted-access barrier system (RABS) and set up and qualified in a newly established class-B clean room. In 2014, the aseptic fill and finish process was successfully validated by means of media fills. Both the plant and the process have meanwhile passed inspection by the competent authorities. Regulatory approval is expected to be received in March 2015.

With this step, the Fraunhofer ITEM has closed the last gap in the process chain from the very idea to a new biopharmaceutical IMP, now covering development and validation of a cell line, process, and analytical methods, manufacturing of the active ingredient, formulation, and sterile fill and finish including release of IMPs for clinical trials. The steadily increasing demand of academic research institutions and industry for small-volume sterile IMPs can thus now be met by the Fraunhofer ITEM. Interested visitors can take a look at the plant from a footbridge installed especially for this purpose.

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Highly productive cell lines are developed for recombinantly produced veterinary medicinal products.

Cell line development for recombinantly produced veterinary medicinal products

In the field of veterinary medicine, there has been an increasing interest in recombinantly produced biopharmaceuticals over the past few years. Recombinantly produced veterinary medicinal products display several benefits over those obtained directly from biological raw materials: limited availability of raw materials is not an issue, constant quality is easier to ensure and, if development of a highly productive cell line can be successfully accomplished, production costs can be saved. On behalf of an industry partner, scientists of the Braunschweig-based Division of Pharmaceutical Biotechnology at present are working on the development of such a highly productive cell line. Their starting point for cell line development was the gene sequence of the protein, which previously had been optimized for the production organism. They subsequently developed different strategies for best possible production of the protein, cloned the required vectors, and performed cell transfection. After successful development of a highly productive cell line, further steps foreseen by the project plan include development of the corresponding cultivation and purification processes and GMP manufacturing of purified bulk of the new biopharmaceutical.

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Customized protein expression

There is an ever increasing diversity in the properties of protein-based biopharmaceutical therapeutics. This diversity requires flexible expression systems that can be combined according to a modular principle, enabling customized solutions for specific protein expression requirements. The idea which scientists of the Fraunhofer ITEM Pharmaceutical Biotechnology Division are currently exploring in cooperation with Professor Fleißner from the Institute of Genetics of Technische Universität Braunschweig aims to develop a fungal expression system that offers this potential. The red bread mold *Neurospora crassa* has been used as a eukaryotic model organism in basic research for several decades already. Over the past two years, a broad spectrum of potential production strains has been generated, including different combinations of promoters, additional deletions and products. After selection of promising target strains, it became possible for the first time to study the growth and production behavior of *N. crassa* in laboratory reactors. The key challenge in the current project phase is to adapt numerous cultivation parameters from laboratory to pilot scale and thus translate the knowledge gained in basic research into application-oriented solutions.

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BUSINESS UNIT
EARLY-PHASE CLINICAL TRIALS

In our Business Unit "Early-Phase Clinical Trials", scientists conduct clinical studies to test new pharmaceuticals, develop novel biomarkers, and assess the potential hazards of airborne pollutants. In this subject area, the Fraunhofer ITEM closely cooperates with the Hannover Medical School, with industry, and with different research institutions.

The core activity is the conduct of clinical pharmacological trials in volunteers and patients – trials of phases I and II in particular – to evaluate the efficacy and safety of new anti-inflammatory, anti-obstructive, and anti-allergic medicinal products. These trials are performed to the quality standards of Good Clinical Practice (GCP).

A major focus is on designing and performing proof-of-concept studies for the indications asthma, allergic rhinitis, COPD, and pulmonary fibrosis. The efficacy of new anti-allergic drugs in patients with allergic rhinitis (hay fever) can be tested in the Fraunhofer Environmental Challenge Chamber (Fraunhofer ECC), a grass pollen exposure room that provides controlled allergen challenge conditions and is operated in cooperation with the Department of Aerosol Technology. To test the efficacy of a specific immunotherapy, the Fraunhofer ECC is also used to expose test subjects to birch pollen and house dust mite allergens. Due to the universal patented aerosol generation technology, tests with other allergens, such as cat dander or other types of pollen, will also be possible in the future.

Focuses of activity in 2014

In 2014, the Business Unit "Early-Phase Clinical Trials" had its focus on getting started in the new proof-of-concept center for early-phase clinical trials, the CRC Hannover. Already prior to the formal opening of the CRC Hannover, the first phase-I study was initiated in the new building. The aim of this study was to test nasal administration of an active pharmaceutical ingredient to treat depression. Read more about this study in the below report.

Successful first phase-I study in the new Clinical Research Center Hannover

After completion of the Clinical Research Center Hannover (CRC Hannover) in 2014, the partners to this new study center now have at their disposal innovative infrastructure for conducting clinical trials. In particular the additional overnight capacities in two research wards for performance of phase-I trials have significantly enhanced the possibilities of the Fraunhofer ITEM. In addition to performing traditional

Our clinical research activities furthermore include bronchoscopic examinations after inhalation or instillation of allergens, endotoxin, or medicinal products. A state-of-the-art immunology laboratory enables comprehensive biomarker analyses in a variety of patient samples, for example in blood, sputum, broncho-alveolar or nasal lavage fluid.

Only few institutions worldwide have at their disposal comparable expertise and technical facilities. The existing infrastructure has been further enhanced with the new Clinical Research Center Hannover. More beds and recreation facilities allow more phase-I trials to be conducted. In addition, numerous rooms for special examinations, a biobank, and cutting-edge imaging technology for use in clinical studies are now available.

As a partner in the German Center for Lung Research, we are conducting clinical research projects to investigate the pathomechanisms of the allergic inflammation in the lung and to develop novel biomarkers.

A high quality standard, leading-edge technology, and professional expertise with an academic background are the hallmarks of this business unit, whose current core competencies are "Respiratory Proof-of-Concept Studies", "Aerosol Research and Analytical Chemistry", and "Process Development and GMP Manufacturing of Biopharmaceuticals".

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phase-I trials, namely first-in-human trials in which an investigational new drug is administered to healthy volunteers, it is now also possible to develop innovative study designs by combining established challenge models with an overnight stay of the test subjects in the early stages of drug development, thus allowing drug level monitoring over time. Such a study was already performed in the CRC Hannover in July 2014, shortly after the Fraunhofer ITEM staff had moved into the new building and even prior to its formal opening.

Intensive supervision and monitoring of test subjects

In this study, nasal administration of an active pharmaceutical ingredient to treat depression was tested. Following the traditional phase-I study design, the first part of this study was performed with healthy volunteers and not with patients. The focus here was on investigating absorption, distribution, and excretion of the active ingredient and on the occurrence of any unwanted side effects. To this end, the 24 study participants each received a single nasal spray dose of the drug under investigation, followed by several blood samplings at

The trial investigators explain in detail to each test subject the tests and examinations to be performed during the study.

regular intervals over the next 30 hours in order to determine blood levels of the active ingredient. In view of possible side effects, the test subjects were intensively monitored and supervised after administration of the nasal spray.

Evaluation of the impact of allergic rhinitis on nasal uptake

Another aim of this study was to evaluate if there are any differences in the uptake of the active ingredient via the nasal mucosa, if the person using the nasal spray suffers from (allergic) rhinitis. During allergic rhinitis, the nasal mucosa is usually swollen, so that the possibility of a modified uptake of administered drugs via the swollen nasal mucosa had to be taken into consideration. For this part of the study, the Fraunhofer Environmental Challenge Chamber (Fraunhofer ECC) was used, allowing generation of a grass pollen load in the ambient air like on a summer meadow. Twenty-four study participants with grass pollen allergy were exposed in small groups of four people each in the Fraunhofer ECC, so as to induce symptoms of allergic rhinitis with a swelling of the nasal mucosa. One hour after they had entered the Fraunhofer ECC, already presenting clear symptoms of allergic rhinitis, the test subjects received the nasal spray. Another hour later, they were allowed

"Fraunhofer Attract": Clinical and translational research on pulmonary fibrosis

In 2014, a "Fraunhofer Attract" research group headed by Professor Dr. Antje Prasse was set up at the Fraunhofer ITEM to explore new treatment options for pulmonary fibrosis. 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.

Professor Prasse's team is focused on clinical and translational research in the field of fibrotic lung diseases, opening up at the Fraunhofer ITEM a new indication and research area into which the pharmaceutical industry worldwide is currently investing. Pulmonary fibrosis is predominantly a disease of the elderly. Recent data suggest a prevalence of 2 percent in the normal population over 50 years of age and about 100,000 deaths per year in Germany. Patients with pulmonary fibrosis suffer from progressive scarring and destruction of lung tissue.

One of the aims of this project is to develop in-vitro and in-vivo assays for testing new anti-fibrotic compounds in collaboration with pharmaceutical industry. Several in-vitro assays based on human primary cells from patients with pulmonary fibrosis have already been established by the group and are available at the Fraunhofer ITEM. Another focus is on the development of biomarkers and cell-based read-out systems for use in early-phase clinical trials addressing pulmonary fibrosis, as well as on planning and performance of such trials at the CRC Hannover. Furthermore, in collaboration with the imaging facility at the CRC Hannover the group offers the development of imaging-based read-out systems for use in clinical trials.

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New therapeutic principle for asthma successfully tested

A new therapeutic principle developed by the company sterna biologicals GmbH & Co. KG consists in inhibiting the transcription factor GATA-3 by a so-called DNAzyme. It was recently tested for general efficacy in a four-week proof-of-concept study in patients with bronchial asthma. The test subjects showed significant improvement of lung function after standardized inhaled allergen challenge. The clinical study was performed as a multicenter study under the scientific direction of the Fraunhofer ITEM, where centralized analyses of biomarkers and pharmacokinetics were performed in addition. The results of this clinical trial will be presented during the annual conference of the American Thoracic Society and in parallel will be published in the "New England Journal of Medicine".

to leave the challenge chamber. Here again, several blood samples were collected at regular intervals over a period of 30 hours after administration of the experimental drug. The results of this clinical trial are not yet available, because the test results are still being analyzed.

The CRC Hannover has proven its worth

This first study has impressively demonstrated the possibilities of the CRC Hannover and the functionality of the available infrastructure. Test subjects and study staff alike much enjoyed the new facilities. What has essentially contributed to this success was the competent cooperation and great commitment of Fraunhofer ITEM staff from numerous departments, including Facility Management, Information Technology, Quality Assurance, and Administration, and, last but not least, the extraordinary flexibility and motivation of every single employee.

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Equipment highlights

- Challenge chambers (allergens, ozone)
- Phase-I unit with 25 beds
- GMP unit
- Imaging technology (MRI, PET, CT)
- Multicenter network for inhaled allergen challenge
- Segmental challenge during bronchoscopy
- Exercise testing (spiroergometry)
- Biomarker analysis and biobank
- Patient/volunteer database

PROJECTS

Allergen challenge in the Fraunhofer ECC: central examination method in multicenter studies

Due to its high level of standardization, allergen challenge in the Fraunhofer Environmental Challenge Chamber (Fraunhofer ECC) is frequently used for dose finding during clinical development of specific immunotherapy (SIT). An additional need for dose finding studies results from the therapy allergen ordinance issued by the Paul Ehrlich Institute. This ordinance stipulates that SIT preparations which have been authorized already but lack dose-finding data have to be subject to retrospective dose finding studies to keep their authorization. Given that patients who have undergone specific immunotherapy are no longer available for subsequent SIT studies, the Fraunhofer ITEM cannot perform the required investigations as a monocenter study, but is reliant on patient assignments from other study centers where patients are examined and treated as test subjects as well. In such multicenter studies, allergen challenge in the Fraunhofer ECC is used as a central examination method to determine dose-effect relationships. Patients under investigation in study centers all over Germany travel to Hannover especially for tests in the Fraunhofer ECC. After two studies were performed in cooperation with other study centers in Germany in 2014, the concept of centralized examination in the Fraunhofer ECC and the catchment area for such multicenter studies will be enhanced in 2015 to include also other European countries.

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Exhaled breath analysis in COPD patients

Human exhaled breath contains a large number of volatile organic compounds (VOCs), whose composition depends both on a person's metabolic processes and on environmental factors. The aim of an ongoing project funded by the German Center for Lung Research (DZL) is to identify a specific VOC signature that is characteristic of chronic obstructive pulmonary disease (COPD). To this end, exhaled breath was collected from 60 patients with COPD and 60 control subjects and was then analyzed in the Fraunhofer ITEM Department of Bio- and Environmental Analytics. To account for the influence of smoking, 50 percent of the test subjects in each group were active smokers, whose smoking status could be clearly distinguished from that of non- and ex- smokers by means of combustion products such as furans. The scientists furthermore identified VOCs that are found at elevated concentrations in healthy smokers and likewise in smokers and ex-smokers with COPD. Through cooperation within the DZL, an additional identical group of 120 test subjects could be recruited for this study in Marburg. The breath samples collected with a device developed at the Fraunhofer ITEM were sent to Hannover for GC/MS analysis. After completion of the tests, independent samples will be available for statistical evaluation, allowing verification of the study results obtained to date and investigation of local environmental factors. In addition, in a project cooperation with the Leibniz University of Hannover, the current dataset will be complemented by further analyses with highly sensitive technology.

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State-of-the-art imaging technology: Hyperpolarized xenon allows the air-filled airways to be visualized by MRI. To make use of this technology, a xenon polarizer has been set up in the CRC Hannover.

Contrast imaging of the airways with hyperpolarized xenon

Visualization of ventilated airways by magnetic resonance imaging (MRI) as a non-radiation imaging technique is not possible without contrast medium, because the actual resonance technology makes use of the properties of water molecules. Given that anatomical representation of the airways including function mapping provides valuable information, scientists are looking for a technical enhancement of the MRI technology to enable imaging of the airways. One possibility is inhalation of hyperpolarized ^{3}helium or ^{129}xenon as gaseous contrast medium. For reasons of expense, ^{3}helium is not available in sufficient quantities. Xenon, in contrast, can be obtained from natural sources. Funded through strategic investment funds, the Fraunhofer ITEM has purchased a xenon polarizer (Polarean, Inc., USA), set up in the imaging facility of the CRC Hannover in direct vicinity to the MRI scanner. As a result, there are now ideal conditions for further development of the MRI technology. First pilot experiments have already demonstrated the possibility of contrast imaging of the airways. Current preliminary studies are aimed at establishing and optimizing MRI sequences that will record not only the gaseous phase, but also the dissolved phase of xenon. This means that upon inhalation of xenon, part of the gas is absorbed by the airway mucosa and then into the blood, thereby enabling further conclusions, for example, about the degree of airway inflammation. In 2015, a clinical research project will be initiated, aimed at quantifying the degree of local inflammation in the lung by xenon-enhanced MRI technology.

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Birch pollen challenge established in the Fraunhofer ECC

Challenge with grass pollen in the Fraunhofer Environmental Challenge Chamber (Fraunhofer ECC) was established at the Fraunhofer ITEM already many years ago. During the past years, the Fraunhofer ECC has been used many times to test the efficacy of novel drugs for seasonal allergic rhinitis. Efficacy testing of a specific immunotherapy, however, requires generation of an allergen-specific atmosphere. This is why there was a need to establish a challenge with birch pollen in addition to grass pollen challenge.

In order to establish birch pollen challenge in the Fraunhofer ECC, 18 patients with seasonal allergic rhinitis and sensitization to birch pollen were exposed to increasing concentrations of natural birch pollen five times for four hours each. During the exposure, nasal symptoms, nasal flow, nasal secretion, and lung function were measured. Increasing concentrations of birch pollen led to a dose-dependent increase in symptoms. All exposures were safe, and reproducibility of a birch pollen concentration of 4000 pollen per cubic meter of air was verified in addition. With this study, the Fraunhofer ITEM scientists were able to demonstrate that besides grass pollen, birch pollen can equally be used safely and reproducibly to test the efficacy of a specific immunotherapy.

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BUSINESS UNIT
ENVIRONMENTAL, OCCUPATIONAL AND CONSUMER PROTECTION

The central topic in the business unit "Environmental, Occupational and Consumer Protection" is human exposure to potentially hazardous substances in workplaces, in the environment, and in consumer products. The focus is on inhalation exposure to chemicals, fibers, particles – nanoparticles in particular – and to complex mixtures. To our partners from industry, professional associations, and public authorities, we offer a broad spectrum of methods and services.

Taking into account the relevant regulations, our scientists develop tailored concepts for assessing potential risks to human health, design testing strategies whenever needed, and support clients with issues of product safety and product optimization. Furthermore, they develop customized methods for chemical analyses and aerosol measurement.

Potential inhalation toxicity of substances can be evaluated in different validated in-vitro and animal models. Comprehensive in-vitro test methods and in-silico models for risk estimates are established at the institute – helping to reduce animal experiments. A large variety of aerosols, gaseous atmospheres, and complex mixtures of substances can be generated for use in experimental studies. In addition, technologies for controlled exposure are available.

Focuses of activity in 2014

An increasing number of products in the market are applied in the form of aerosols. New tailored measurement and analysis methods have to be developed in order to characterize the relevant processes during aerosol application and to determine exposure levels.

In this context, a focus of activity in the Business Unit "Environmental, Occupational and Consumer Protection" was on infrared optical diagnosis of organic aerosols. Development work in this area was performed within an internal, pre-competitive research project involving several institutes and using quantum cascade lasers, and in an industry-funded project aimed at on-line characterization of the aerosols from e-cigarettes.

Another focus was on enhancing the service portfolio for exposure characterization of spray products, with regard to cosmetic applications in particular. This includes substance-

To characterize the exposure, the Fraunhofer ITEM provides standardized methods, test systems, and model rooms, allowing realistic simulation of pollutant release processes and quantification of the source strength. A focus is on the development of measurement technology for airborne substances, to the point of building prototypes of aerosol measurement devices. Physico-chemical models help determine harmful substances and their emission from building materials, furniture, interior decoration, and consumer products. In addition, Fraunhofer ITEM scientists design exposure scenarios and develop mathematical simulation models for exposure assessment (indoor, environment).

In close cooperation with the business units "Toxicology Testing" and "Registration and Risk Assessment" we are able to offer our clients a comprehensive package of services for the assessment and characterization of substances and products. The required studies are performed in compliance with national and international regulations and with the principles of Good Laboratory Practice (GLP).

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specific characterization of released inhalable aerosols and establishment of a method for determination of nanoparticle emission, for example during use of sunscreen sprays.

Important topics in this Business Unit were furthermore the validation of Tier-1 models for calculation of occupational exposure levels (e.g. ETEAM project) and the implementation of risk management measures in these models and calculations. The necessary measurement data were obtained both from external data sources and from measurements performed at the Fraunhofer ITEM.

Equipment highlights

- State-of-the-art analytical methods: LC-NMR, LC-MS, ICP-MS (non-target analyses, residue and trace-level analyses, bio-availability)
- Aerosol measurement technology, aerosol generation methods (nebulization, dry dispersion)
- Scanning electron microscope with energy-dispersive X-ray system for elementary analyses
- Determination of exposure from spray products
- Battery test rig for accident simulation and quantification of energy release and gas and particle emissions
- Model rooms for exposure characterization

PROJECTS

Verification of measures for safer use of solvents

For assessment of occupational exposure to chemicals and solvents under REACH, the ECETOC TRA (Targeted Risk Assessment) tool has been widely applied. The range of risk management measures (RMMs) available for selection by the TRA tool to deal with elevated exposures, however, is limited and may not be typical of the type of control measures applied in practice. The European Solvents Industry Group (ESIG) has, therefore, identified additional RMMs that are in line with common practice, such as the use of drum pumps for filling operations. Whether or not these non-standard-TRA controls are actually able to reduce workplace exposure as expected is being investigated at the Fraunhofer ITEM.

To implement the available RMMs into exposure calculations, information about their efficiency is required. Hence, scientists at the Fraunhofer ITEM started collecting data from literature and other sources such as contacts to industry. This data search, completed in 2014, showed that only insufficient data could be retrieved for most of the investigated RMMs. In a second part of this project, experimental simulations will thus be performed to investigate a set of model scenarios representing solvent filling and discharging operations with different levels of exposure control (e.g. local exhaust ventilation, use of drum pumps). The experimental studies are planned to be completed in 2015. The aim of this project is to contribute to an improvement of occupational exposure assessments and thus to occupational safety.

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Beryllium at European workplaces: comparison of two measurement methods

Inhalable beryllium (Be)-laden dust can pose a health hazard in the workplace. The majority of exposure data reported in epidemiological studies from which occupational exposure limits have been derived were determined based on the so-called "total dust" (TD) method that is commonly used in the US, but differs from the valid German and European standard of measuring the inhalable dust (ID) fraction. In a one-year field study conducted by the Fraunhofer ITEM, parallel measurements were performed to create a data set of Be concentrations, from which a conversion factor between both measurement methods was then derived. To this end, personal Be exposure measurements were performed using both the TD and the ID methods at a total of 40 industrial workplaces in Germany and other European countries characterized by different types of Be alloy processing. Taking the mean of all workplaces, the ID method yielded Be concentrations that were about three times higher than those measured with the TD method. The conversion factors determined for the individual workplaces ranged from 1 to 17. This is due to process-dependent differences, on the one hand in particle size distribution in the workplace-specific atmospheres and on the other hand in particle size dependence of the collection efficiency of the sampling method (TD, ID). The results of this project will feed directly into the ongoing debate about derivation of an occupational exposure limit for Be in Germany

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An optical sensor developed at the Fraunhofer ITEM enables online measurement of the vapor emitted during use of e-cigarettes.

E-cigarettes: online measurement of the emitted vapor

E-cigarettes are becoming more and more popular. Vapers, the users of e-cigs, inhale an aerosol of very fine droplets consisting mainly of glycerin and propylene glycol. Concentration and mean particle size of this aerosol are important parameters affecting product characterization and substance uptake via the lung. An optical sensor developed at the Fraunhofer ITEM enables measurement of these parameters with high time resolution, providing detailed information about the time-dependent course of mean droplet size and mass concentration during inhalation. The measurement principle is based on measurement of the light attenuation at three different wave lengths in the near and medium infrared frequency spectra. To measure the mass concentration, this technology makes use of the absorption band of the aerosol's two main chemical components at a wave length of 3.42 µm. Information about particle sizes is gained by measuring light attenuation at two smaller wave lengths, namely 2.0 and 1.65 µm beyond the absorption band, where light attenuation results only from droplet size-dependent light scattering by the aerosol particles. Development of a very small, cost-effective sensor was not possible until narrow-band light-emitting diodes with the above mentioned frequencies became available on the market. The sensor can generally be used in any processes involving generation of hydrocarbon vapors that require monitoring.

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Biomonitoring to capture occupational exposure of livestock workers to antibiotics

The use of antibiotics in livestock production can result in workers being exposed to these veterinary medicinal products via manure or during drug preparation and administration. This undesirable exposure to antibiotics can pose a health hazard due to the toxic or sensitizing properties of the drugs and can furthermore promote development of antibiotic-resistant microorganisms in man. On behalf of the German Federal Institute for Occupational Safety and Health ("Biomarkers" unit), the Fraunhofer ITEM Department of Bio- and Environmental Analytics is performing biomonitoring and corresponding workplace measurements. Whether or not biomonitoring is suitable for detecting and assessing occupational exposure is being evaluated by testing urine samples from livestock workers for veterinary antibiotics. Inhalation of stable dust, unintentional intake via the oral and dermal routes are three conceivable routes of exposure. Therefore, workplace measurements and analyses of stable dusts are performed in addition to the biomonitoring. The aims of this project are to help identify correlations between internal and external exposure and to detect and assess possible risks to livestock workers. In the first project phase, the analytical methods are adapted and validated to the special requirements of this task at the Fraunhofer ITEM. At the same time, first dust and human urine samples are collected on poultry farms. In cooperation with the University of Veterinary Medicine Hannover, the analytical limits of the intended biomonitoring are being explored.

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BUSINESS UNIT
REGISTRATION AND RISK ASSESSMENT

In our Business Unit "Registration and Risk Assessment", we offer the studies and services required to assess the potential risks of chemicals to human health and the environment and to register these substances for the intended use. This concerns primarily (industrial) chemicals, biocides, and veterinary medicinal products. Main activities in this business unit include the preparation of registration documents on behalf of industrial clients and contract research for regulatory authorities and associations. For different substances and application areas, we also prepare toxicological expert reports, for example to assess residues or contaminations.

The focus is on the legal requirements valid for the substance in question and its intended use, and on the information necessary to meet these requirements. This information is compiled in cooperation with the client. Our broad range of services includes literature searches, identification of data gaps, and development of a testing strategy, including commissioning and monitoring of the required experimental studies. Furthermore, we determine human and environmental exposure data and compare them with the applicable limit values. All these steps are documented in the required registration and substance dossiers.

Focuses of activity in 2014

In 2014, a focus of activity in the Business Unit "Registration and Risk Assessment" was on improving chemical risk assessment, for example by means of integrated testing strategies (ITS). As an example, we are presenting in the below report two research projects conducted on read-across – a method consisting in extrapolating the toxicity of one or more source substances to the so far unknown toxicity of one or several target substances.

Read across – further development of grouping concepts and their use in risk assessment

In risk assessment, grouping approaches such as read across (RAX) are used to fill data gaps. This method consists in extrapolating the toxicity of one or more source substances to the so far unknown toxicity of a target substance, enabling both qualitative and quantitative predictions. RAX is used primarily for complex endpoints such as repeated-dose systemic and reproductive toxicity. For these endpoints, alternative methods such as in-vitro test systems or in-silico methods

By enhancing the above portfolio in close cooperation with our business units "Toxicology Testing" and "Environmental, Occupational and Consumer Protection", we offer our clients a service tailored to their individual needs. The required studies can be performed at the Fraunhofer ITEM in compliance with international testing guidelines and with the principles of Good Laboratory Practice (GLP). Whenever necessary, we cooperate with other Fraunhofer institutes and also with external contract research institutions that have been our partners for many years.

In the future, alternative methods and tests without animal experiments and also integrated testing strategies shall be used increasingly in chemical risk assessment, so as to keep experimental studies to a minimum. To support this aim, we elaborate scientific basic principles in publicly funded projects and test their applicability in the regulatory context. In addition, our comprehensive activities in risk assessment frequently also spawn ideas for new scientific approaches that may help improve chemical risk assessment methodology in the future. For projects aimed at the development of alternative assessment concepts, such as the TTC concept, we have at our disposal comprehensive databases for toxicological endpoints from studies in rodents, which have been set up and further enhanced in this business unit over the past few years.

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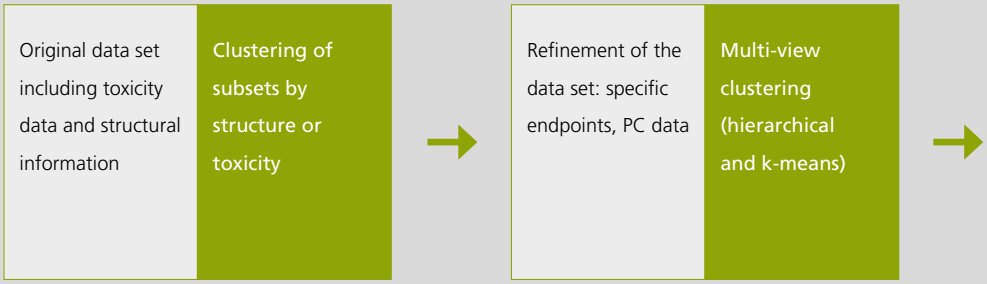
hardly exist to date[1]. In addition, RAX is an interesting option for cosmetic ingredients in particular, for which toxicity testing in animals is no longer permitted, since the new cosmetics directive has come into force.

A great challenge of the RAX approach is demonstration not only of chemical but also biological similarity of the source and target substances. Biological similarity can be based on identical mechanisms of action, for example on an adverse-outcome pathway (AOP), or on similar degradation pathways involving the same critical metabolites and their kinetics. The comprehensive mechanistic data on toxicodynamics and substance metabolization (ADME) that are required for the evaluation of biological similarity, however, are in most cases not available for all substances of the RAX group.

Within different national and international projects and in close cooperation with partners, Fraunhofer ITEM scientists are currently developing new concepts for a better definition of "similarity" of the RAX compounds. The aim is to improve regulatory acceptance of the extrapolation by RAX and thus to contribute to a direct reduction of animal experiments. Two

[1] http://echa.europa.eu/documents/10162/13639/alternatives_test_animals_2014_summary_en.pdf

Iterative process of data set refinement and identification of the best clustering method for grouping of the structural and toxicological data.



of these projects – one funded by the German Federal Ministry of Education and Research (BMBF) and one by the EU – will be described in the following.

Example: BMBF project

In the BMBF-funded joint research project "Entwicklung einer Strategie zur Bildung von Kategorien und Definitionen neuer Kategorien für die Endpunkte subakute, subchronische und chronische Toxizität zur Minimierung von Tierversuchen unter REACH" (development of a strategy for category building and definition of new categories for the endpoints sub-acute, sub-chronic and chronic toxicity to minimize animal experiments under REACH), a grouping concept was developed taking into account chemical similarity and toxicological profiles. The final data set, based on the RepDose and ELINCS databases, includes 1022 compounds, whose toxicity had been documented in in-vivo repeated-dose toxicity (RDT) studies. To achieve the best possible grouping of compounds, the following selection based on content and method was made:

- Toxicological endpoints: 28 organ-specific effects, grouped by thematic cohesion and chronology in repeated-dose studies with rats
- Toxicological potency: categorization of effect levels (LOELs) per endpoint by means of equal-frequency quantification
- Best method to deal with zeros: statistical imputation
- Structural information: SMILES codes for fragments and reactive groups
- Physicochemical parameters: selection of a few parameters with substantial contribution to the clustering
- Clustering method: predictive clustering tree (PCT)

Result of this project: A toxicologically meaningful grouping concept was achieved based on a data set refined by means of toxicological expertise and accompanied by manual verification of clusters during development of the model.

Fraunhofer scientists appointed to committees

Together with experts from federal and *Länder* authorities, universities, and other research institutions, experts of the Fraunhofer ITEM act as external, independent consultants to the German Federal Institute for Risk Assessment (BfR).

For the period 2014 to 2017, Dr. Annette Bitsch of the Fraunhofer ITEM has been reappointed to the BfR Committee for Food Additives, Flavorings and Processing Aids, and Dr. Katrin Schröder to the BfR Committee for Exposure Assessment and Exposure Standardization. A new appointment is that of Dr. Oliver Licht, who is now a member the BfR Committee for Contaminants and other Undesirable Substances in the Food Chain.

"Ensemble of Classifier Chains" turned out to be the best method for model development (www.mlc-reach.informatik.uni-mainz.de).

Example: EU project DETECTIVE

The aim of the EU-funded project DETECTIVE of the SEURAT research cluster is to enhance the existing knowledge about mechanistic processes associated with toxic events in man. Predictive biomarkers are being developed to this end, e.g. by combining different "omics" technologies. Before they can be used in risk assessment, these biomarkers, representing key or intermediate steps in such mechanisms, have to be validated. A concept for this approach is currently being developed by means of a RAX case study with valproic acid (VPA).

– Enlargement of the data set – Development of methods for handling missing values – Endpoints: specific organ-effect relationships	Prediction models: – Tests for predictivity of endpoints – Methods for handling potency: equal-frequency distribution of toxicity data	– Final data set based on RepDose and ELINCS DB – Toxicity profile based on predictable endpoints – Structural data, $logP_{ow}$ and molecular weight	Predictive clustering tree, correlations and prediction models

In 2014, Dr. Kathrin Schröder, Dr. Annette Bitsch and Dr. Oliver Licht were appointed as independent consultants to different committees of the German Federal Institute for Risk Assessment.

First of all, candidate biomarkers were identified in the TG-Gates database, based on transcriptome alterations associated with lipid and energy metabolism. According to this database, VPA is a potent inducer of such transcriptomic alterations. In addition, a causal relationship with effects observed in RDT studies could be established. VPA induced effects such as fatty liver, lipidosis, and vacuolization of hepatocytes after oral exposure.

To evaluate predictivity of the biomarker candidates, ten substances with similar structures, consisting in (un-)branched carboxylic acids for which RDT studies were also available, were identified. In-vivo data were obtained from the databases RepDose, IMI eTOX, ECHA CHEM, Cosmos, Leadscope and Nedo, and also from literature. Based on the effects observed in these studies, four VPA analogues were classified as "in vivo positive" and five as "in vivo negative". One analogue was defined as "borderline case", because the observed effects did not allow an unambiguous conclusion about deregulation of the lipid metabolism. At present, the biomarkers are being evaluated in vitro in different cells by quantitative RT-PCR: in human primary and rat hepatocytes and in HepG2 cells. The aim of this RAX case study is to develop an integration concept for the resulting biomarkers – qualitative markers to be used in a RAX approach and quantitative markers for use in chemical risk assessment without taking into account structurally related compounds.

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Equipment highlights

Databases
– RepDose (containing data on repeated-dose toxicity of chemicals)
– FeDTex (containing data on developmental and reproductive toxicity of chemicals)
– PaFtox (containing data on repeated-dose toxicity of nanoparticles)

Models
– Modeling software for human and environmental exposure assessment

Documentation
– Literature management with over 100,000 entries in 500 subject areas, with searching possibilities and access to 150 journals

PROJECTS

From draft decision to final decision with Fraunhofer expertise

The European Chemicals Agency (ECHA) routinely examines a random selection of at least five percent of registration dossiers and verifies their compliance with legal requirements. During this compliance check, dossiers are evaluated primarily with regard to consistency and sufficient quality of the underlying data, testing proposals, and justifications for the use of alternative methods (QSAR, waiving, or read-across). In addition, Member States select certain dossiers in a targeted way, usually in case of a specified concern, in order to perform detailed substance evaluation. ECHA will generally respond to registrants with a draft decision, asking for a dossier update and frequently requesting additional experimental studies. Registrants can return their written comments within a one-month deadline and, in favorable cases, discuss these directly with the European authority. After optional revision by ECHA and consent of the EU Member State authorities, any additional data requests (final decision) have to be met and the dossier must be updated accordingly.

The Fraunhofer ITEM Department of Chemical Risk Assessment so far has been involved in three ECHA compliance checks, during which it thoroughly discussed the additional requests with ECHA in the client's interest. The long-standing expertise of the Fraunhofer scientists, demonstrated already during numerous successful registrations, proved extremely helpful in proposing to the authorities solutions to improve dossier quality, while keeping costs at an acceptable level.

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Refinement of the environmental emission scenario for metalworking fluids

On behalf of the TEGEWA working group on "Metal Working Additives", the Fraunhofer ITEM investigated the handling and disposal of used metalworking fluids (cooling lubricants, PT13). In the course of this project, different aspects of environmental exposure to biocides due to waste treatment of metalworking fluids were evaluated, including relevant regulatory information and best available techniques as laid down in publicly available documents and guidelines. Moreover, applicability of current emission scenario documents was evaluated. Information collected from European metalworking industries and from waste management companies engaged in the handling and treatment of used metalworking fluids was also taken into account. After presentation of first project results at the second Biocides Technical Meeting in 2013, a working group including industry members and representatives of the competent authorities was formed. This working group collected further data from industry representatives and other sources of information and summarized it in an updated exposure algorithm that is currently being discussed with the authorities. The results of this project are intended to be used to replace the old emission scenario documents for biocide release from water-miscible metalworking fluids into the environment.

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Zebrafish is used for chemical risk assessment in ecotoxicology studies such as the FELS test.

Sensitivity comparison of acute ecotoxicity data under REACH

The fish early-life stage (FELS) toxicity test is used in ecotoxicology as a long-term study in fish for risk assessment of chemicals (see figure). In the EU, this test is considered to be an animal experiment and thus falls under the requirement to limit the use of vertebrates for regulatory testing to the necessary minimum. The benefit of a study for hazard evaluation and risk assessment, therefore, must be weighed against aspects of animal protection. In a research project on behalf of the German Federal Environment Agency, Fraunhofer ITEM scientists analyzed fish and *Daphnia* acute and chronic toxicity data of 240 substances with different chemical structures to determine under what conditions the chronic fish test might be avoidable. The result shows that for many chemicals it is possible to derive predicted no-effect values based on *Daphnia* chronic data, even without a FELS test. On the other hand, it became evident that under certain conditions the FELS test cannot be waived, for example in those cases where fish, compared with *Daphnia*, exhibit increased sensitivity to a substance already in acute tests. In this study, a classification scheme for comparing the sensitivity of both species in acute testing was developed to predict chronic data requirements. The method is proposed to complement the integrated testing strategy laid down in the REACH guidance document on ecotoxicology to enable a better assessment of the need for chronic fish tests.

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Using QSAR methods to minimize animal testing under REACH

The use of alternative methods in risk assessment to minimize animal testing and optimize the use of existing knowledge is a requirement in different regulatory contexts, as for example in REACH Annex XI. The aim of this project, funded by the German Federal Environment Agency, is to support small and medium-sized enterprises in particular in the use of QSAR methods, so as achieve a broader use of these methods for substance registration, while ensuring compliance with regulatory requirements. To this end, special workshops with users, model developers, and representatives from regulatory agencies will be held on this topic in 2015 and 2016. The focus will be on QSAR models and their use under REACH. Strategies for an improved use of QSAR models will be developed, including evaluation of the quality and relevance of models, definition of criteria for validation of the generated data, and transparent and efficient documentation of models and of the predictions they yield. The aim is to improve the quality of registration dossiers that use QSAR under REACH, in order to achieve better acceptance of the computed data by the regulatory authorities. The overall results of this project will eventually be summarized in a clearly structured, practical guidance document tailored to support small and medium-sized enterprises.

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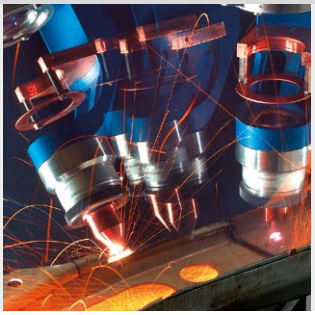
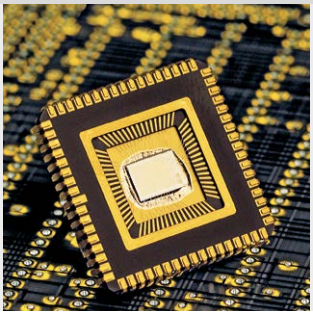
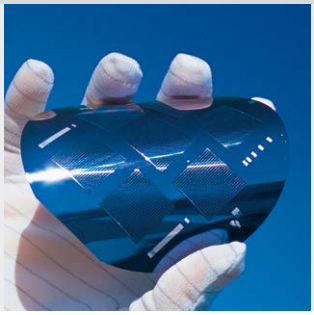
FRAUNHOFER-GESELLSCHAFT

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

At present, the Fraunhofer-Gesellschaft maintains 66 institutes and research units. The majority of the nearly 24,000 staff are qualified scientists and engineers, who work with an annual research budget of more than 2 billion euros. Of this sum, around 1.7 billion euros is generated through contract research. More than 70 percent of the Fraunhofer-Gesellschaft's contract research revenue is derived from contracts with industry and from publicly financed research projects. Almost 30 percent is contributed by the German federal and *Länder* governments in the form of base funding, enabling the institutes to work ahead on solutions to problems that will not become acutely relevant to industry and society until five or ten years from now.

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

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

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

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

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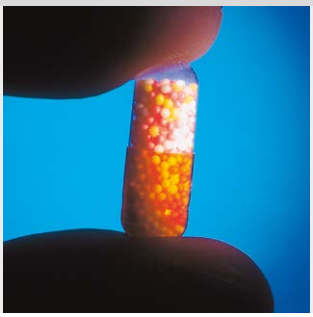
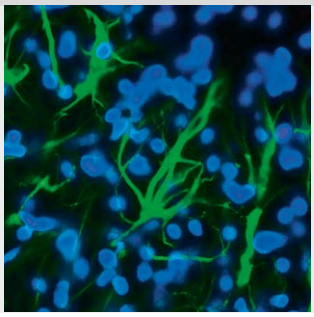
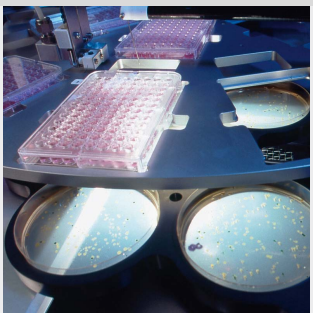
FRAUNHOFER GROUP FOR LIFE SCIENCES



Six Fraunhofer institutes and a Fraunhofer research institution have pooled their complementary areas of expertise in the life sciences and potentiate their capacities within the Fraunhofer Group for Life Sciences. With a staff of over 1700, the Group is an important R&D partner for the pharmaceutical and biotechnology sectors as well as for the chemicals industry and medical technology companies.

With their concentrated expertise and broad range of methods and equipment, the Fraunhofer Institutes for Biomedical Engineering IBMT, Interfacial Engineering and Biotechnology IGB, Molecular Biology and Applied Ecology IME, Toxicology and Experimental Medicine ITEM, Cell Therapy and Immunology IZI, and Process Engineering and Packaging IVV and the Fraunhofer Research Institution for Marine Biotechnology EMB are in a position to undertake even comprehensive projects for their clients. Research and development in the Fraunhofer Group for Life Sciences cover on the one hand the preventive areas of environmental and consumer protection, and on the other hand the regenerative areas of medical therapy and ecological recovery.

What characterizes the research performed in the Fraunhofer Group for Life Sciences is its closeness to industrial application, aiming to develop solutions that meet clients' actual requirements, always with a view to economic efficiency and sustainability. In addition, the institutes also undertake basic research to develop the basis for future applications in industry. The group has an international outlook that reflects the globalized nature of this scientific field and the related commercial market.

The business units of the Group include translational medicine research and biomedical technology, regenerative medicine, healthy foodstuffs, industrial biotechnology, and research aimed at the safety of processes, chemicals, and pesticides. The Group shows ways of preserving health and the environment in an industrialized world and develops new options for diagnosing and treating diseases in a setting of a more personalized healthcare and for remediating the environment.

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Wichmann, J.; Jimenez Delgado, S. M.; Curths, C.; Becker, T.; Eggel, A.; Kaup, F.; Braun, A.; Sewald, K.; Knauf, S.
Passively sensitized precision-cut lung slices from marmoset monkeys as a preclinical assay to test novel IgE inhibitors.
In: American Journal of Respiratory and Critical Care Medicine 189 (2014), Meeting Abstracts, 2 pp., Abstract A1063

Wichmann, J.; Jimenez Delgado, S. M.; Curths, C.; Becker, T.; Kaup, F. J.; Braun, A.; Sewald, K.; Knauf, S.
Frühe Phase der Allergen-induzierten Atemwegsreaktion beim Weißbüschelaffen nach passiver Sensibilisierung von Lungengewebe mit humanem Blutplasma.
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Winkler, C.; Bahlmann, O.; Viereck, J.; Knudsen, L.; Wedekind, D.; Hoymann, H. G.; Madsen, J.; Thum, T.; Hohlfeld, J. M.; Ochs, M.
Impact of a Met(11)Thr single nucleotide polymorphism of surfactant protein D on allergic airway inflammation in a murine asthma model.
In: Experimental Lung Research 40 (2014), No. 4, pp. 154-163.
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Winkler, C.; Witte, L.; Moraw, N.; Faulenbach, C.; Muller, M.; Holz, O.; Schaumann, F.; Hohlfeld, J. M.
Impact of endobronchial allergen provocation on macrophage phenotype in asthmatics.
In: BMC Immunology 15 (2014), No. 12, 11 pp.
doi: 10.1186/1471-2172-15-12

Zaripova, S.; Koch, W.
Numerical study of the RespiCon sampler performance in the calm air.
In: Aerosol Science and Technology 48 (2014), No. 1, pp. 74-80.
doi: 10.1080/02786826.2013.859653

Ziemann, C.; Harrison, P. T.; Bellmann, B.; Brown, R. C.; Zoitos, B. K.; Class, P.
Lack of marked cyto- and genotoxicity of cristobalite in devitrified (heated) alkaline earth silicate wools in short-term assays with cultured primary rat alveolar macrophages.
In: Inhalation Toxicology 26 (2014), No. 2, pp. 113-127.
doi: 10.3109/08958378.2013.863411

Ziemann, C.; Reamon-Buettner, S. M.; Tillmann, T.; Hansen, T.; Ibáñez, M. J.; Monfort, E.; Bonvicini, G.; Escrig, A.; Creutzenberg, O.
The SILICOAT project: In vitro and in vivo toxicity screening of quartz varieties from traditional ceramics industry and approaches for an effective quartz surface coating.
In: Naunyn-Schmiedeberg's Archives of Pharmacology 387 (2014), Suppl. 1, S104, Abstract 420.

Zwintscher, A.; Hahn, S.; Kühne, R.; Schüürmann, G.; Drost, W.; Ackermann, J.; Joehncke, U.; Schlechtriem, C.; Nendza, M.
Gastrointestinal absorption processes of substances: Do they have an impact on bioaccumulation?
In: SETAC Abstract book (2014), p. 314, Abstract WE194.

Doctorates

Bludau, Elisabeth
Untersuchungen zur Leistungsfähigkeit von Zelllinien mit Kassetten-austauschsystem.
Technische Universität Braunschweig, 2014

Neuhaus, Vanessa
New treatment strategies for respiratory diseases: ex vivo and in vivo evaluation of pharmacological immunomodulations using a nanoparticle-based drug delivery system.
Hannover Medical School; Hannover Biomedical Research School (HBRS), 2014

Tluczkiewicz, Inga
Improvement of the TTC concept for oral and inhalation exposure and its application in an integrated testing strategy (ITS) for the endpoint repeated-dose toxicity.
TU Bergakademie Freiberg, 2014

Master's theses

Baron, Lena
Kinetikanalysen des Aktivierungszustandes von ex vivo stimulierten dendritischen Zellen im murinen PCLS-Modell.
Hannover Medical School, 2014

Brandstetter, Ronja Lorena
Characterization of ex vivo immunostimulated dendritic cells in murine lung tissue.
Hannover Medical School, 2014

Drake, Helena
Characterization of IL-13- and allergen-induced airway hyperreactivity in precision-cut lung slices of different species.
University of Bonn, 2014

Gessner, Isabel
Inhalation toxicity of nanoparticle-based aerosols.
University of Cologne, 2014

Konzok, Sebastian
Invasion, proliferation and influence of cancer cell line MDA-MB-231 on organotypic tissue using precision-cut lung slices (PCLS).
Hannover Medical School, 2014

Requardt, Hendrik
Toxikologische Untersuchungen von Multiwalled Carbon Nanotubes, mit und ohne Eisenkatalysator, für den Einsatz in der targeted Drug Delivery, durchgeführt an humanen Lungenepithelzellen und Hepatozyten.
South Westphalia University of Applied Sciences, 2014

Romberg, Susanne
Entwicklung eines Rhinovirus-Infektionsmodells in Precision-Cut Lung Slices.
Bielefeld University, 2014

Sadlers, Sabine Jennifer
Einzelzell-Heterogenität von Melanomsphären, generiert aus disseminierten Tumorzellen.
Universität Regensburg, 2014

Schweiger, Julietta Ursula
1. Welche Auswirkung hat »Hungern« in Toxizitätsstudien mit wiederholter Verabreichung? 2. Prädiktivität von Organgewichten – Organgewicht als Biomarker in der Toxikologie?
Charité – Universitätsmedizin Berlin, 2014

Bachelor's theses

Arndt, Hendrik
Etablierung eines Modellsystems mit Aerosolen zur Charakterisierung von Expositionssystemen für die Untersuchung inhalierbarer Substanzen in vitro.
University of Applied Sciences Emden/Leer, 2014

Donath, Mandy
Etablierung eines *Pseudomonas aeruginosa*-Biofilmassays zur Antibiotikawirksamkeitstestung.
Brandenburg University of Technology Cottbus-Senftenberg, 2014

Ganser, Iris
Entwicklung eines Assays zu Qualitätskontrolle von Whole Transcriptome Amplifications.
Universität Regensburg, 2014

Heiermann, Steffen
Untersuchung der CYP450-Expression in primären humanen Hepatozyten und Hepatozyten-ähnlichen Zellsystemen.
University of Applied Sciences Emden/Leer, 2014

Leichtling, Karolina
Einfluss von Kultivierungsparametern auf die Produktion eines Antikörper-fusionsproteins in *Neurospora crassa*.
Technische Universität Braunschweig, 2014

Tautenhahn, Sven
Untersuchungen zum Wirkmechanismus von nanostrukturiertem Carbon Black mit unterschiedlicher Oberflächenbeschaffenheit.
University of Applied Sciences Emden/Leer, 2014

Invited lectures at congresses and conferences

Dr. Luma Baydoun
Verpackung von Prüfpräparaten: Case Study Kleinstchargen-Proteinarzneimittel. Verpackung von High Potent APIs, Proteinarzneimittel. Seminar "Verpackungstrends".
Frankfurt/Main (Germany)
December 4, 2014

Dr. Annette Bitsch
Dermal absorption data of chemicals. External speaker at the European Union Scientific Committee on Consumer Safety (SCCS), Working Group on Methodologies.
Luxembourg (Luxembourg)
July 8, 2014

Regulation von Bioziden. DGPT course "Regulatory Toxicology" at the Governmental Institute of Public Health of Lower Saxony (NLGA).
Hannover (Germany)
September 1-5, 2014

Biocides in the present EU-regulation: General aspects and scientific considerations. European Coatings Conference – novel biocide technology.
Düsseldorf (Germany)
September 29-30, 2014

Dr. Katharina Blümlein and Heiko Kock
Lung burden: Results of a 28-day study. Workshop on Biokinetics and Environmental Fate, German Federal Institute for Risk Assessment.
Berlin (Germany)
June 23-24, 2014

Prof. Dr. Armin Braun
In-vivo- und Semi-in-vivo-Methoden zur Analyse obstruktiver Atemwegs-erkrankungen in Tiermodellen. 80th Annual Congress of the German Society for Experimental and Clinical Pharmacology and Toxicology, Advanced Courses in Pharmacology: "Lungenpharmakologische Methoden".
Hannover (Germany)
March 31 – April 3, 2014

Ist die Zeit der Mäuse vorbei? Asthmamodelle der Gegenwart und Zukunft. DGAKI Workshop "Allergie im Focus: Asthma".
Berlin (Germany)
April 4-5, 2014

Strategies to develop new drugs against human airway diseases. Seminar at the Center for Comparative Respiratory Biology and Medicine (CCRBM) of UC Davis.
Davis, California (USA)
May 16, 2014

Neuro-immune mechanisms in lung infections. Gut-Brain-Axis, 2nd European Conference of Microbiology and Immunology.
Berlin (Germany)
June 6-7, 2014

Neuro-immune mechanisms in viral lung infections. Annual Congress 2014 of the European Academy of Allergy and Clinical Immunology (EAACI), Workshop 21: "Mechanisms of viral bronchiolitis".
Copenhagen (Denmark)
June 6-11, 2014

Neuroimmune interactions in allergic asthma. LISA Summer School, Session "Lung Inflammation, Asthma, Allergy".
Hannover (Germany)
September 4, 2014

Use of precision-cut lung slices to test physiological and pathophysiological lung response. IIVS Workshop "Assessment of in-vitro COPD Models for Tobacco Regulatory Science".
Bethesda, Maryland (USA)
December 8-10, 2014

Dr. Jochen Buschmann
News in Testing Effects on Fertility and Development, Status of OECD Tests and in vitro Alternatives. 80th Annual Congress of the German Society for Experimental and Clinical Pharmacology and Toxicology.
Hannover (Germany)
March 31 - April 3, 2014

Comparative atlas of external malformations in laboratory animals and humans. International Symposium on Developmental Toxicity including the 8th Berlin-Workshop on DevTox Terminology.
Berlin (Germany)
May 14-16, 2014

Materno-fetal anomalies: Introduction and overview. International Symposium on Developmental Toxicity including the 8th Berlin-Workshop on DevTox Terminology.
Berlin (Germany)
May 14-16, 2014

Developmental effects of glyphosate? Guideline studies in rat and rabbits. International Symposium on Developmental Toxicity including the 8th Berlin-Workshop on DevTox Terminology.
Berlin (Germany)
May 14-16 2014

Dr. Otto Creutzenberg
Biokinetics of CNT following acute inhalation in rats using ^{60}Co labeling. OECD Expert Meeting on Toxicokinetics of Nanomaterials.
Seoul (South Korea)
February 26-27, 2014

Biokinetics study to compare three TiO_2 (NM-103, NM-104, NM-105) in a 28-day inhalation test in rats. OECD Expert Meeting on Toxicokinetics of Nanomaterials.
Seoul (South Korea)
February 26-27, 2014

Biokinetics of nano-ZnO and nano-SiO_2 after inhalation in rats. OECD Expert Meeting on Toxicokinetics of Nanomaterials.
Seoul (South Korea)
February 26-27, 2014

Agglomeration status and solubility as determinants for the translocation potential of nanomaterials. Workshop on Biokinetics and Environmental Fate, German Federal Institute for Risk Assessment.
Berlin (Germany)
June 23-24, 2014

Dr. Sylvia Escher
Toxikologische Datenbanken in der Risikobewertung als Alternative zu Tierversuchen. 85th ZEBET Seminar, ZEBET – Alternative Methods to Animal Experiments. German Federal Institute for Risk Assessment.
Berlin (Germany)
September 17, 2014

Use of alternative methods to support read across – experiences from the Detective project. OpenTox InterAction Meeting: Industrial and Regulatory Application of Predictive Toxicology.
Athens (Greece)
September 22-24, 2014

Dr. Ilona Fleischhauer
Qualitätssicherung: Audits bei klinischen Studien. Lecture in the training course "Qualifikation zum Prüfarzt/Prüfärztin bzw. Assistenz in klinischen Studien" (GCP basic class) at the Hannover Medical School.
Hannover (Germany)
January 25, April 4, and December 19, 2014

Einführung in die Gute Laborpraxis. Training course for blood donation service "DRK-Blutspendedienst NSTOB GmbH".
Springe (Germany)
May 6, 2014

Introduction to the Principles of GLP. Workshop on Toxicology of Gene-Modified Hematopoietic Cells.
Hannover (Germany)
June 5, 2014

Introduction to GLP and GMP. Training course at the Hannover Biomedical Research School (HBRS).
Hannover (Germany)
December 10, 2014

Prof. Dr. Dr. Uwe Heinrich
Vom Blockbuster zur personalisierten Arzneimittelentwicklung.
10th Bioethics Symposium of the Braunschweig Scientific Society.
Braunschweig (Germany)
February 20, 2014

Dr. Susanne Hesse
Uncertainty analysis. The ETEAM Conference – Challenges and Perspectives of Tier 1 Exposure Assessment. German Federal Institute for Occupational Safety and Health (BAuA).
Dortmund (Germany)
March 25-26, 2014

Prof. Dr. Jens Hohlfeld
Gefahr vom Extrafeinen? 55th Congress of the German Respiratory Society.
Bremen (Germany)
March 26-27, 2014

Inhalative und bronchoskopische Provokationsverfahren beim Menschen.
80th Annual Congress of the German Society for Experimental and Clinical Pharmacology and Toxicology.
Hannover (Germany)
March 31 - April 3, 2014

Wirksamkeitsprüfung von Medikamenten im Allergenprovokationsraum.
Expertenforum Allergologie – Update 2014.
Hannover (Germany)
November 14-15, 2014

Inhalationstherapie. Update Pneumologie 2014.
Hannover (Germany)
November 29, 2014

Dr. Rupert Kellner
Survey of new terms in Version 2 nomenclatures. International Symposium on Developmental Toxicity including the 8th Berlin-Workshop on DevTox Terminology.
Berlin (Germany)
May 14-16, 2014

Dr. Stefan Kirsch
High-resolution analysis of genome and transcriptome of a single cell.
25th Annual Meeting of the German Society of Human Genetics.
Essen (Germany)
March 19, 2014

Next-generation sequencing – perspectives for precision medicine.
MEDICA EDUCATION 2014.
Düsseldorf (Germany)
November 13, 2014

Prof. Dr. Christoph Klein
Selection and adaptation during metastatic cancer progression. ISREC SYMPOSIUM 2014.
Crans-Montana (Switzerland)
January 22-25, 2014

Molecular profiling of single circulating tumor cells: Impact for therapy selection and the understanding of cancer evolution. Microgenomics 2014.
Paris (France)
May 14-15, 2014

The dynamics of systemic melanoma progression. From Omics to Novel Therapies in Cancer. Molecular Cancer Research Centre of the Charité (MKFZ).
Berlin (Germany)
May 23-24, 2014

Early dissemination and metastasis in breast cancer: insights from mouse models and patient-derived data. Mammary Gland Biology Gordon Research Conference (GRC) 2014.
Lucca/Barga (Italy)
June 8-13, 2014

Mutation and selection during metastatic cancer progression. 23rd Biennial Congress of the European Association for Cancer Research (EACR).
Munich (Germany)
July 5-8, 2014

Untersuchungen zur frühen Disseminierung von Melanomzellen.
24th German Skin Cancer Congress.
Frankfurt/Main (Germany)
September 11-13, 2014

Methoden zu Nachweis und Charakterisierung von MRD/Selektion und Adaptation bei der Metastasierung solider Tumore. 1st German Congress for Laboratory Medicine.
Mannheim (Germany)
September 24-27, 2014

Ectopic evolution of disseminated cancer cells. 2nd international symposium "Advances in Circulating Tumor Cells" (ACTC 2014).
Rethymnon, Crete (Greece)
October 8-11, 2014

Molecular profiling of single circulating tumor cells with diagnostic intention.
10th NCRI Cancer Conference 2014.
Liverpool (UK)
November 2-5, 2014

Molecular Profiling of single circulating tumor cells with diagnostics intention.
1st Annual DEPArray User Meeting.
Bologna (Italy)
December 2, 2014

The dynamics of systemic melanoma progression. 2nd international symposium "Trends in Melanoma Research".
Regensburg (Germany)
December 11-13, 2014

Sascha Knauf, Ph. D.
Translational non-human primate models for human airway diseases.
Seminar at the Center for Comparative Respiratory Biology and Medicine (CCRBM) of UC Davis.
Davis, California (USA)
May 16, 2014

Prof. Dr. Wolfgang Koch
Ultrafine and nanoparticles: health-related physical properties.
KFU Development Program. Kazan Federal University.
Kazan (Russia)
June 23, 2014

Modern principles of monitoring fine particles in the environment.
KFU Development Program. Kazan Federal University.
Kazan (Russia)
June 24, 2014

Interactions of aerosol particles with the human lung.
KFU Development Program. Kazan Federal University.
Kazan (Russia)
June 25, 2014

Dr. Gustav Könnecker
REACH-Erfahrungen aus der wissenschaftlichen Beratung: Probleme von KMU mit Registrierung, Zulassung, ECHA-Vorgaben. 5th meeting of the Working Committee on European Chemicals Policy of the Lower Saxony Government Commission.
Hannover (Germany)
October 27, 2014

REACH 2014 – Einschätzungen von (Markt-)Akteuren: Bewertung von Stoffen, Erstellung von Dossiers. REACH-Kongress 2014 – Dialog. Verantwortung. Perspektiven. German Federal Environment Agency.
Dessau (Germany)
December 1-2, 2014

Prof. Dr. Nobert Krug
Das Konzept des Clinical Research Center Hannover (CRC Hannover) als Teil des TRAIN-Verbundes. BVMed special event "Translation: Wissenschaft und Ökonomie – ein Widerspruch?"
Hannover (Germany)
May 27, 2014

The proof-of-concept center for early-phase clinical development and medical devices. Fraunhofer Life Science – Biopharmaceuticals and Biotechnology.
Istanbul (Turkey)
September 23, 2014

A rhinovirus challenge model in asthmatic patients to study asthma exacerbation and potential therapeutic interventions. 6th TWINCORE Symposium "Principles of pathogen control and implications for preventive and therapeutic strategies".
Hannover (Germany)
September 25-26, 2014

Dr. Oliver Licht
Stoffbewertung und Risikoabschätzung. DGPT course "Regulatory Toxicology" at the Governmental Institute of Public Health of Lower Saxony (NLGA).
Hannover (Germany)
September 1-5, 2014

Aktuelle Entwicklungen und Herausforderungen in der Toxikologie. National academy 2014 "Verantwortung in Forschung und Entwicklung", organized by the Working Group on Innovation and Environment of scholarship holders of the Friedrich Naumann Foundation for Freedom.
Hannover (Germany)
September 22, 2014

Dr. Bernhard Polzer
CTCs und liquid biopsies – Rolle im onkologischen Diagnostik- und Behandlungskonzept. German Cancer Congress 2014.
Berlin (Germany)
February 19, 2014

Moving molecular single cell analysis towards clinical diagnostics.
Tumor Immunology Symposium 2014.
Munich (Germany)
May 26, 2014

Molekulare Analyse einzelner zirkulierender Tumorzellen – Chancen für Forschung, Diagnostik und Therapie. MEDICA EDUCATION 2014.
Düsseldorf (Germany)
November 13, 2014

Molecular characterization of disseminated and circulating tumor cells – Insights into metastasis and diagnostic consequences. 12th Congress of the European Society for Diseases of the Esophagus.
Bologna (Italy)
November 21, 2014

Molecular profiling of single circulating tumor cells. 4th Munich Biomarker Conference.
Munich (Germany)
November 26, 2014

Priv.-Doz. Dr. Susanne Rittinghausen
INHAND Nomenclature: Non-proliferative and proliferative lesions of the pituitary gland and pineal gland in rodents. 12th European Congress of Toxicologic Pathology, Cutting Edge Pathology, Joint 32nd Meeting of the European Society of Veterinary Pathology.
Berlin (Germany)
August 27, 2014

Dr. Katrin Schröder
Conceptual evaluation. The ETEAM Conference – Challenges and Perspectives of Tier 1 Exposure Assessment. German Federal Institute for Occupational Safety and Health (BAuA).
Dortmund (Germany)
March 25-26, 2014

Dr. Katharina Schwarz
Formation, characterization and diagnostic usability of exhaled aerosols endogenously generated in the human lung. BMT 2014 – 48th Annual Conference of the German Society for Biomedical Engineering within VDE (DGBMT).
Hannover (Germany)
October 8-10, 2014

Dr. Susanne Schwonbeck
Environmental risk assessments – strategies for a successful registration of veterinary medicinal products. CIR Informa.
Barcelona (Spain)
September 11, 2014

Umweltbewertung von Tierarzneimitteln. Forum Seminar "Generika-Zulassung von Tierarzneimitteln".
Hamburg (Germany)
October 23, 2014

Dr. Katherina Sewald
Basic concepts of respiratory sensitization by proteins and chemicals.
EU Technical Session, Workshop "Respiratory sensitization, asthma, and diisocyanates".
Rotterdam (The Netherlands)
July 15, 2014

Dr. Christian Werno
Mechanismen der Disseminierung beim Bronchialkarzinom. Training course 2014 of the University Hospital Regensburg Department of Internal Medicine II.
Regensburg (Germany)
May 5, 2014

Molekulare Charakterisierung disseminierter und zirkulierender Tumorzellen (DTC/CTC). "Treffpunkt In-vitro-Diagnostik" – Onkologie 2014.
Berlin (Germany)
November 27, 2014

Dr. Holger Ziehr
Bioprocess development and early-stage GMP manufacturing of biopharmaceutical and biosimilar APIs. Fraunhofer Life Science – Biopharmaceuticals and Biotechnology.
Istanbul (Turkey)
September 23, 2014

Contributions to congresses and conferences

Blazejewska, P.; Wichmann, J.; Curths, C.; Schmitt, A.; Knauf, S.; Bertram, S.; Zmora, P.; Nehlmeier, I.; Pöhlmann, S.
Activation of influenza virus by type II transmembrane serine proteases from non-human primates. 24th Annual Meeting of the Society for Virology.
Alpbach, Tyrol (Austria)
March 26-29, 2014

Bludau, E.; Hecht, V.; Ziehr, H.
RMCE-based cell line development – towards predictable and reproducible transgene expression? 14th Conference on Cell Culture Engineering (CCE XIV).
Quebec (Canada)
May 4-9, 2014

Calverley, P.; Könen-Bergmann, M.; Metzdorf, N.; Bell, S.; Hohlfeld, J. M.
Tiotropium respimat: Comparison of bronchodilator efficacy of 5 and 2.5 µg doses. 24th International Congress of the European Respiratory Society.
Munich (Germany)
September, 6-10, 2014

Creutzenberg, O.
Biodistribution of ^{60}Co-labeled carbon nanotubes (CNT) following acute inhalation in rats. Advances and Controversies in Fibre Toxicology.
Cranfield (UK)
June 3-4, 2014

Creutzenberg O., Kock, H; Blümlein, K.
The TiO_2 triple – Do crystal and surface modifications influence toxicokinetics and exhibited toxcitiy? BNASS/TraceSpec Tandem Conference.
Aberdeen (UK)
August 31 – September 4, 2014

Curths, C.; Wichmann, J.; Becker, T.; Kaup, F. J.; Hohlfeld, J. M.; Hoymann, H. G.; Windt, H.; Dunker, S.; Braun, A.; Knauf, S.
Measuring lung function in marmoset models of lung inflammation. 3rd Annual Meeting of the German Center for Lung Research (DZL).
Heidelberg (Germany)
January 21-22, 2014

Czyż, Z. T.; Hoffmann, M.; Schlimok, G.; Polzer, B.; Klein, C. A.
Reliable single cell array CGH for clinical samples. 25th Annual Meeting of the German Society of Human Genetics.
Essen (Germany)
March 19-23, 2014

Danov, O.; Jiménez Delgado, S.; Drake, H.; Pfennig, O.; Förster, C.; Braun, A.; Sewald, K.
Species comparison of interleukin-13-induced airway hyperreactivity in precision-cut lung slices. 3rd Annual Meeting of the German Center for Lung Research (DZL).
Heidelberg (Germany)
January 21-22, 2014

Danov, O.; Jiménez Delgado, S.; Drake, H.; Jonigk, D.; Braubach, P.; Pfennig, O.; Förster, C.; Braun, A.; Sewald, K.
Species comparison of interleukin-13-induced airway hyperreactivity as model for allergic asthma. 24th International Congress of the European Respiratory Society.
Munich (Germany)
September 6-10, 2014

Ernst, H.; Schaudien, D.; Rittinghausen, S.
Proliferative lesions of the endocrine system in 600 control Han:AURA Syrian hamsters from four 24-month toxicity/carcinogenicity studies conducted at Fraunhofer ITEM during the period 1988-2009.
Cutting Edge Pathology 2014, 2nd Joint European Congress of the ESVP, ESTP and ECVP.
Berlin (Germany)
August 27-30, 2014

Fenner, K.; Hahn, S.; Honti, M.; Junker, T.; Hennecke, D.
Developing improved strategies to assess chemical persistence at the water-sediment interface. CEFIC LRI-ECO18.16th Annual CEFIC-LRI Workshop.
Brussels (Belgium)
November 19-20, 2014

Gaida, A.; Holz, O.; Schuchardt, S.; Langejuergen, J.; Zimmermann, S.; Heusser, K.; Jordan, J.; Tank, J.; Schindler, C.; Hohlfeld, J. M.
Analysis of volatile organic compounds in exhaled breath of healthy volunteers exposed to ozone and ultrafine particles. Breath Analysis 2014 – 8th International Conference on Breath Research & Cancer Diagnosis.
Toruń (Poland)
July 6-9, 2014

Garn, H.; Krug, N.; Hohlfeld, J. M.; Kirsten, A. M.; Kornmann, O.; Beeh, K.; Kappeler, D.; Korn, S.; Ignatenko, S.; Rogon, C.; Bille, J.; Homburg, U.; Turowska, A.; Buhl, R.; Renz, J.; Renz, H.
Attenuation of allergen-induced asthmatic responses by inhaled GATA-3 specific DNAzyme. 24th International Congress of the European Respiratory Society.
Munich (Germany)
September 6-10, 2014

Gužvić, M.; Braun, B.; Ganzer, R.; Burger, M.; Nerlich, M.; Winkler, S.; Werner-Klein, M.; Czyż, Z. T.; Polzer, B.; Klein, C. A.
Targeted expression profiling of single disseminated cancer cells isolated from bone marrow of prostate cancer patients. 15th International Biennial Congress of the Metastasis Research Society.
Heidelberg (Germany)
June 28 – July 1, 2014

Hahn, S.; May, M.; Drost, W.; Germer, S.; Juffernholz, T.
Comparison of acute to chronic ratios for *daphnia* and fish. 6th Joint Congress of SETAC GLB and the German Society of Chemists (GDCh) Working Group on Environmental Chemistry and Ecotoxicology.
Gießen and Homberg/Ohm (Germany)
September 6-7, 2014

Haunschild, G.; Rack, B.; Polzer, B.; Appel, I.; Hoffmann, M.; Gužvić, M.; Blankenstein, T.; Maak, M.; Buchholz, S.; Schlimok, G.; Klein, C. A.
Comprehensive gene expression profiling of single EpCAM-positive cells isolated from bone marrow of breast cancer patients. Metastatic Colonization: Micro-environments, Mechanisms, and Therapeutic Targeting.
Crans-Montana (Switzerland)
January 22-25, 2014

Havlik, D.; Bohle, K.; Fleißner, A.
Engineering of *Neurospora crassa* for the production of heterologous proteins. ECFG12 – 12th European Conference on Fungal Genetics.
Sevilla (Spain)
March 23-27, 2014

Havlik, D.; Bohle, K.; Fleißner, A.
Engineering of *Neurospora crassa* for the production of heterologous proteins. European Neurospora Meeting (Satellite Meeting at the 12th European Conference on Fungal Genetics ECFG12).
Sevilla (Spain)
March 23, 2014

Heinrich, U.; Sewald, K.; Braun, A.
Ex vivo models for acute lung injury and inflammation in precision-cut lung slices. Translational Research Excellence (TRX) 2014.
Brisbane (Australia)
October 24, 2014

Hohlfeld, J. M.; Furtwaengler, A.; Könen-Bergmann, M.; Wallenstein, G.; Walter, B.; Bateman, E. D.
Evaluating cardiac safety of tiotropium in patients with COPD: combined analysis of Holter-ECG data from four trials. 24th International Congress of the European Respiratory Society.
Munich (Germany)
September 6-10, 2014

Holz, O.
Exhaled breath diagnostics. 13th Fraunhofer Seminar Translational Airway Research "Models of Asthma and COPD".
Hannover (Germany)
January 24-25, 2014

Holz, O.; Roepcke, S.; Watz, H.; Lahu, G.; Hohlfeld, J. M.
Effect of exercise challenge on systemic inflammatory markers in healthy smokers and smokers with COPD. 24th International Congress of the European Respiratory Society.
Munich (Germany)
September 6-10, 2014

Hoymann, H. G.; Ernst, H.; Creutzenberg, O.; Schaudien, D.; Müller, M.; Knudson, L.; Braun, A.
Invasive but repetitive lung function measurements in rodent models of pulmonary fibrosis. 13th Fraunhofer Seminar Translational Airway Research "Models of Asthma and COPD".
Hannover (Germany)
January 24-25, 2014

Jiménez Delgado, S. M.; Schindler, S.; Braun, A.; Sewald, K.
Airway hyperresponsiveness (AHR) is mediated by neuropeptide-induced degranulation of mast cells in passively sensitized human precision-cut lung slices. 44th Annual Meeting of the German Society for Immunology 2014.
Bonn (Germany)
September 17-20, 2014

Jiménez Delgado, S. M.; Schindler, S.; Sewald, K.; Braun, A.
Capsaicin-induced bronchoconstriction in passively sensitized human precision-cut lung slices is mast cell dependent. 24th International Congress of the European Respiratory Society.
Munich (Germany)
September 6-10, 2014

Kirsch, S.; Feliciello, G.; Gužvić, M.; Czyż, Z. T.; Lahrmann, U.; Polzer, B.; Klein, C. A.
High-resolution analysis of genome and transcriptome of a single cell.
6th Next-Generation Sequencing and 2nd Single-Cell Analysis Congress.
London (UK)
November 20-21, 2014

Knebel, J.; Ritter, D.
Echtzeitmessung der Toxizität inhalierbarer Noxen mit in-vitro zellbasierten Systemen. Angewandte Forschung für Verteidigung und Sicherheit in Deutschland.
Berlin (Germany)
February 3-5, 2014

Knebel, J.; Ritter, D.; Brodbeck, C.; Gessner, I.
Developments for a fundamental improvement of the prevalidated air-liquid interface technique for testing inhalable compounds in vitro. 18th International Congress on In vitro Toxicology, ESTIV 2014.
Egmond aan Zee (The Netherlands)
June 10-13, 2014

Knebel, J.; Ritter, D.; Gessner, I.
Optimization and standardization of the workflow for testing of airborne substances in vitro. 10th International Conference and Workshop on Biological Barriers.
Saarbrücken (Germany)
February 16-21, 2014

Koch, W.
Charakterisierung und Bewertung luftgetragener Gefahrstoffe. Angewandte Forschung für Verteidigung und Sicherheit in Deutschland.
Berlin (Germany)
February 3-5, 2014

Koch, W.; Lödding, H.; Lange, F.
Resuspension rates of particles from surfaces: A phenomenological study on the influencing parameters. Aerosol Technology 2014.
Karlsruhe (Germany)
June 15-17, 2014

Konzok, S.; Schindler, S.; Braun, A.; Sewald, K.
Interaction of MDA-MB-231 cells with tissue-resident macrophages in a human organotypic tumor invasion model. 44th Annual Meeting of the German Society for Immunology 2014.
Bonn (Germany)
September 17-20, 2014

Köstler, C.; Schamberger, T.; Fehm, T.; Janni, W.; Rack, B.; Klein, C. A.; Polzer, B.
Sample processing logistics, genome integrity index and targeted molecular characterization of single CTCs. 2nd International Symposium on Advances in Circulating Tumor Cells (ACTC 2014).
Rethymnon, Crete (Greece)
October 8-11, 2014

Krug, N.; Hohlfeld, J. M.; Kirsten, A. M.; Kornmann, O.; Beeh, K. M.; Kappeler, D.; Korn, S.; Ignatenko, S.; Timmer, W.; Rogon, C.; Bille, J.; Homburg, U.; Turowska, A.; Buhl, R.; Renz, J.; Garn, H.; Renz, H.
Attenuation of allergen induced asthmatic responses by inhaled GATA 3 specific DNAzyme. BPS James Black Meeting – British Pharmacological Society.
Cambridge (UK)
September 18, 2014

Kunz, S.; Rittinghausen, S.; Hoffmann, D.; Schambach, A.; Müller, T.; Glage, S.; Bleich, A.
Immunohistochemical characterization of teratomas induced by pluripotent stem cells. Lung regeneration and beyond, 3rd International Conference BREATH – DZL.
Hannover (Germany)
May 8-10, 2014

Lödding, H.; Pohlmann, G.; Schwarz, K.; Koch, W.
A traceable standard for the number concentration of submicron particles. Aerosol Technology 2014.
Karlsruhe (Germany)
June 15-17, 2014

Lüer, K.; Windt, H.; Schwarz, K.; Badorrek, P.; Sebastian, R.; Haefner, D.; Koch, W.; Krug, N.; Hohlfeld, J. M.
Dose-range finding of natural birch pollen exposure in patients with seasonal allergic rhinitis in the Fraunhofer Environmental Challenge Chamber.
European Academy of Allergy and Clinical Immunology (EAACI) Congress 2014.
Copenhagen (Denmark)
June 7-11, 2014

Müller, M.
Use of a human in-vitro allergy model based on dendritic cells to test anti-allergic drugs. 13th Fraunhofer Seminar Translational Airway Research "Models of Asthma and COPD".
Hannover (Germany)
January 24-25, 2014

Müller, M.; Donath, M.; Pankalla, J.; Braun, A.; Pohlmann, G.; Rochlitzer, S.
Development of an in-vitro test system for nebulized antimicrobial treatment efficacy using *Pseudomonas aeruginosa* biofilms. Microbiology & Infectious Diseases Congress.
London (UK)
September 29-30, 2014

Philipp, F.; Rittinghausen, S.; Daudert, J.; Hoffmann, D.; Glage, S.; Sewald, K.; Neuhaus, V.; Rothe, M.; Braun, A.; Schambach, A.
Immunohistochemical analysis of cell populations in teratomas generated by induced pluripotent stem cells in NSG mice. Lung regeneration and beyond, 3rd International Conference BREATH – DZL.
Hannover (Germany)
May 8-10, 2014

Philipp, F.; Rittinghausen, S.; Daudert, J.; Hoffmann, D.; Glage, S.; Sewald, K.; Neuhaus, V.; Rothe, M.; Braun, A.; Schambach, A.
Identification of hematopoietic cells in teratomas generated in mouse by human induced pluripotent stem cells. Fraunhofer Life Science Symposium.
Leipzig (Germany)
October 9-10, 2014

Philipp, F.; Rittinghausen, S.; Daudert, J.; Hoffmann, D.; Glage, S.; Sewald, K.; Neuhaus, V.; Rothe, M.; Braun, A.; Schambach, A.
Characterization of hematopoietic progenitor cells generated with human induced pluripotent stem cells in a teratoma-based model. 2nd International Annual Conference of the German Stem Cell Network (GSCN).
Heidelberg (Germany)
November 3-5, 2014

Polzer, B.; Gužvić, M.; Ganzer, R.; Weckermann, D.; Braun, B.; Appel, I.; Obradović, M.; Huppert, V.; Klein, C. A.
Identification and molecular characterization of different subpopulations of EpCAM-positive single disseminated cancer cells in prostate cancer.
15th International Biennial Congress of the Metastasis Research Society.
Heidelberg (Germany)
June 28 – July 1, 2014

Polzer, B.; Köstler, C.; Pütz, K.; Schamberger, T.; Patwary, N.; Czyż, Z.; Sandri, M. T.; Rack, B.; Fehm, T.; Janni, W.; Klein, C. A.
TP53 microheterogeneity in circulating tumor cells of breast cancer patients. 2nd International Symposium on Advances in Circulating Tumor Cells (ACTC 2014).
Rethymnon, Crete (Greece)
October 8-11, 2014

Ritter, D.
Current developments in the field of testing inhalable compounds in vitro based on the air-liquid interface (ALI) technique. Advancing Aerosol Dosimetry Research – Emerging Issues, Research Needs and Opportunities for Modeling Inhaled Particles, Gases and Vapors.
Irvine, California (USA)
October 24-25, 2014

Ritter, D.; Knebel, J.; Brodbeck C.
Biological monitoring of inhalable substances in vitro – development of an improved exposure process based on the air-liquid interface (ALI) cell culture technique. 8th International Symposium on Modern Principles of Air Monitoring and Biomonitoring (AIRMON 2014).
Marseille (France)
June 15-19, 2014

Rittinghausen, S.
Induction of malignant mesotheliomas by intraperitoneal injection of multi-walled carbon nanotubes in rats. Advances and Controversies in Fibre Toxicology.
Cranfield (UK)
June 3-4, 2014

Rittinghausen, S.; Hackbarth, A.; Ernst, H.; Heinrich, U.; Leonhardt, A.; Schaudien, D.
Immunohistochemical characterization of carbon nanotube-induced malignant mesotheliomas in rats. 33rd Annual Symposium of the Society of Toxicologic Pathology.
Washington, District of Columbia (USA)
June 22-26, 2014

Rittinghausen, S.; Hackbarth, A.; Ernst, H.; Heinrich, U.; Leonhardt, A.; Schaudien, D.
Induction of malignant mesotheliomas by intraperitoneal injection of carbon nanotubes in rats. Cutting Edge Pathology 2014, 2nd Joint European Congress of the ESVP, ESTP and ECVP.
Berlin (Germany)
August 27-30, 2014

Rochlitzer, S.; Danov, O.; Jiménez, S.; Pfennig, O.; Förster, C.; Müller, M.; Sewald, K.; Braun, A. on behalf of the U-BIOPRED consortium.
Rhinovirus infection in human and mouse precision-cut lung slices.
Keystone Symposium Innate Immunity to Viral Infections.
Keystone, Colorado (USA)
January 19-24, 2014

Rochlitzer, S.; Romberg, S.; Danov, O.; Jiménez, S.; Pfennig, O.; Förster, C.; Müller, M.; Sewald, K.; Braun, A. on behalf of the U-BIOPRED consortium.
Rhinovirus infection in human and mouse precision-cut lung slices.
Microbiology & Infectious Diseases Congress.
London (UK)
September 29-30, 2014

Schäfer, D.; Rath, N.-F.; Molderings, G. J.; Jensen, K.; Ziemann C.
Eicosanoid-Imbalance bei systemischer Mastozytose. Annual Meeting 2014 of the Working Group on Clinical Immunology, Allergology and Environmental Medicine of the German Society of Oto-Rhino-Laryngology.
Berlin (Germany)
October10-11, 2014

Schaudien, D.; Hackbarth, A.; Ernst, H.; Leonhardt, A.; Heinrich, U.; Rittinghausen, S.
Cell proliferation measurement as early detection method of carcinogenic potential of carbon nanotubes. Advances and Controversies in Fibre Toxicology.
Cranfield (UK)
June 3-4, 2014

Schaudien, D.; Hackbarth, A.; Ernst, H.; Leonhardt, A.; Heinrich, U.; Rittinghausen, S.
The value of cell proliferation measurement for early detection of carcinogenic potential of carbon nanotubes after intraperitoneal injection in rats. Cutting Edge Pathology 2014, 2nd Joint European Congress of the ESVP, ESTP and ECVP.
Berlin (Germany)
August 27-30, 2014

Schaudien, D.; Kellner, R.; Rinke, M.
The RITA database – The value of incidences of tumors in young animals.
33rd Annual Symposium of the Society of Toxicologic Pathology.
Washington, District of Columbia (USA)
June 22-26, 2014

Schaudien, D.; Kellner, R.; Rinke, M.
The RITA database – Incidences of preneoplastic and neoplastic lesions in young animals. Cutting Edge Pathology 2014, 2nd Joint European Congress of the ESVP, ESTP and ECVP.
Berlin (Germany)
August 27-30, 2014

Schindler, S.; Jiménez Delgado, S. M.; Braun, A.; Sewald, K.
A comparative study of peripheral C-fiber microanatomy, neuropeptide release and bronchoconstriction in response to the neuropeptide Substance P using precision-cut lung slices of monkeys and humans. 24th International Congress of the European Respiratory Society.
Munich (Germany)
September 6-10, 2014

Schindler, S.; Jiménez Delgado, S. M.; Sewald, K.; Braun, A.
A comparative study of mast cell and sensory nerve fiber interactions concerning histological anatomy, mast cell activation, neuropeptide release and broncho-constriction in response to capsaicin using precision-cut lung slices of monkeys and humans. EMBRN-COST International Mast Cell and Basophil Meeting 2014.
Munich (Germany)
December 11-12, 2014

Schindler, S.; Jiménez Delgado, S. M.; Sewald, K.; Braun, A.
The role of neuronal-induced mast cell degranulation in bronchoconstriction in a human organotypic lung tissue model of allergic asthma. EMBRN-COST International Mast Cell and Basophil Meeting 2014.
Munich (Germany)
December 11-12, 2014

Schmidt, O.; Doblinger, E.; Haunschild, G.; Pasch, S.; Polzer, B.; Rack, B.; Schamberger, T.; Treitschke, S.; Weidele, K.; Klein, C. A.
Detection of ERBB2-amplified DCC in non-metastatic breast cancer patients with ERBB2-negative primary tumors by single cell qPCR. 2nd International Symposium on Advances in Circulating Tumor Cells (ACTC 2014).
Rethymnon, Crete (Greece)
October 8-11, 2014

Schwarz, K.; Koch, W.
Universal method for exposure assessment of spray applications. Aerosol Technology 2014.
Karlsruhe (Germany)
June 15-17, 2014

Schwarz, K.; Koch, W.
Universal method for inhalation exposure assessment of foam and droplet spray applications. The ETEAM Conference – Challenges and Perspectives of Tier 1 Exposure Assessment. German Federal Institute for Occupational Safety and Health.
Dortmund (Germany)
March 25-26, 2014

Schwarz, K.; Bitsch, A.; Hahn, S.; Bissantz, K.; Koch, W.; Holthenrich, D.
Does foam application reduce aerosol formation? The ETEAM Conference – Challenges and Perspectives of Tier 1 Exposure Assessment. German Federal Institute for Occupational Safety and Health.
Dortmund (Germany)
March 25-26, 2014

Sewald, K.
Development of a translational model of the human precision-cut lung slice technique for testing biopharmaceuticals against asthma. 13th Fraunhofer Seminar Translational Airway Research "Models of Asthma and COPD".
Hannover (Germany)
January 24-25, 2014

Weidele, K.; Werno, C.; Treitschke, S.; Botteron, C.; Werner-Klein, M.; Klein, C. A.
Development of preclinical in-vitro/in-vivo models from rare patient-derived disseminated cancer cells. Fraunhofer Life Science Symposium.
Leipzig (Germany)
October 9-10, 2014

Wichmann, J.; Jiménez Delgado, S. M.; Curths, C.; Becker, T.; Kaup, F. J.; Braun, A.; Sewald, K.; Knauf, S.
Frühe Phase der Allergen-induzierten Atemwegsreaktion beim Weißbüschelaffen nach passiver Sensibilisierung von Lungengewebe mit humanem Blutplasma.
Fall Conference of the German Respiratory Society sections of Cell Biology and Infectiology & Tuberculosis.
Lübeck (Germany)
November 14-15, 2014

Wilson, S.; Ward, J.; Sousa, A.; Corfield, J.; Bansal, A.; Sterk, P.; Chung, F.; Djukanovic, R.; Dahlen, S. E.; Chanez, P.; Shaw, D.; Krug, N.; Sandström, T.; Howarth, P.
The U-BIOPRED severe asthma study: Immunopathological characterization.
24th International Congress of the European Respiratory Society.
Munich (Germany)
September 6-10, 2014

Ziemann, C.; Bellmann, B.; Hackbarth, A.; Leonhardt, A.; Niehof, M.; Rittinghausen, S.; Reamon-Buettner, S. M.
Multiwalled carbon nanotubes induce DNA damage and cellular senescence in human peritoneal mesothelial LP9 cells. Advances and Controversies in Fibre Toxicology.
Cranfield (UK)
June 3-4, 2014

Ziemann, C.; Dreßen, P.; Brettner, S.; Rath, N.-F.; Molderings, G. J.; Jensen, K.; Schäfer, D.
Prostaglandin D_2-supplemented "functional eicosanoid testing and typing" assay with peripheral blood leukocytes as a new tool in the diagnosis of systemic mast cell activation disease: an explorative diagnostic study. EMBRN-COST International Mast Cell and Basophil Meeting 2014.
Munich (Germany)
December 11-12, 2014

Ziemann, C.; Harrison, P. T. C.; Bellmann, B.; Brown, R. C.; Zoitos, B. K.; Class, P.
Cristobalite in heated alkaline earth silicate wools does not cause increased cyto- and genotoxicity in short-term in-vitro assays. Advances and Controversies in Fibre Toxicology.
Cranfield (UK)
June 3-4, 2014

Zwintscher, A.
Gastrointestinal adsorption processes. Bioaccumulation Workshop, organized by the Fraunhofer ITEM and the German Environmental Agency.
Dessau (Germany)
June 27, 2014

Active participation in committees

Dr. Luma Baydoun
GMP discussion group "GMP-Gesprächskreis" of the Lower Saxony business inspectorate

Dr. Edith Berger-Preiß
Working group on analyses in biological materials "Analysen in biologischem Material" of the German Research Foundation (DFG)

Reviewer for international journals in analytics and biomonitoring

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

Expert panel on wood preservatives in timber construction of the German Federal Institute for Construction Technology (DIBt)

Working committee on probabilistic exposure and risk assessment "Probabilistische Expositions- und Risikoabschätzung"

Member of the GUM working group on threshold mechanisms of genotoxins

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

Prof. Dr. Armin Braun
Reviewer for international journals in respiratory medicine and immunology (incl. "American Journal of Respiratory and Critical Care Medicine" and "Journal of Allergy and Clinical Immunology")

Reviewer for international foundations (incl. Boehringer Ingelheim Foundation)

External expert for the German Research Foundation (DFG)

Ph. D. commission of the Hannover Medical School (MHH)

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

Member of the German Center for Lung Research (DZL)

Dr. Jochen Buschmann
Working committee on reproductive toxicity "AK Reproduktionstoxizität" of the toxicology advisory board of the German Committee on Hazardous Substances (AGS)

ECHA expert group on the Guidance on Information Requirements and Chemical Safety Assessment, Chapter R.7a, Section R.7.6 "Reproductive Toxicity"

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

Prof. Dr. Clemens Dasenbrock
Committee on Non-Ionizing Radiation, German Radiation Protection Board (SSK)

Scientific Council on Electromagnetic Fields of the Swedish Radiation Safety Authority (SSM)

Editorial board of the journal "Experimental and Toxicologic Pathology"

Scientific Expert Group (SEG) of the International Commission on Non-Ionizing Radiation Protection (ICNIRP)

Uta Dörfel
Working group on GLP analytics "GLP-Analytik" of the German Society for Good Research Practice (DGGF)

Dr. Heinrich Ernst
Editorial board of the journal "Experimental and Toxicologic Pathology"

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

INHAND (International Harmonization of Nomenclature and Diagnostic Criteria) organ working groups "Soft Tissue" and "Skeletal System"

Reviewer for the international journal "Toxicologic Pathology"

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

Dr. Ilona Fleischhauer
Working groups on GLP quality assurance/monitoring "GLP: Qualitätssicherung/Überwachung" and GCP quality management "GCP-Qualitätsmanagement" of the German Society for Good Research Practice (DGGF)

Dr. Stefan Hahn
Working committee on chemical risk assessment (deputy head) of the division of environmental chemistry and ecotoxicology "Umweltchemie und Ökotoxikologie" within the German Chemical Society (GDCh)

Prof. Dr. Dr. Uwe Heinrich
Research Committee of the Health Effects Institute (HEI), Boston, USA

Invited member of the IARC working groups on particles, fibers, diesel engine exhaust, polycyclic aromatic hydrocarbons, metals, irritant gases, and air pollution for the compilation of IARC Monographs on the Evaluation of Carcinogenic Risks to Humans

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; working group on the definition of occupational exposure limits; working group on the classification of carcinogens; ad-hoc working group on heavy metals

Committee on Hazardous Substances (AGS) under the German Federal Minister of Labor and Social Affairs; AGS Subcommittee III (UA III); Subcommittee III: working groups on metals (chairman) and on fibers/dust

Scientific advisory committee of the German Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte, BfArM)

Advisory committee of the Institute for Prevention and Occupational Medicine (IPA) of the German Social Accident Insurance (DGUV)

Committee supporting the public authorities responsible for the approval of animal experiments (Animal Protection Commission)

Editorial board of the journal "Umweltmedizin in Forschung und Praxis"

Editorial board of the "International Journal of Hygiene and Environmental Health"

Co-editor of the manual on hazard assessment of environmental pollutants "Gefährdungsabschätzung von Umweltschadstoffen"

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

External expert 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 e.V. (DZL)

Scientific advisory group of the European Medicines Agency (EMA)

Dr. Olaf Holz
Reviewer for international journals (incl. "European Respiratory Journal", "PLoS One", "Respiratory Research", and "BMC Pulmonary Medicine")

European Respiratory Society taskforce "Exhaled biomarkers in lung disease" (TF-2012-11)

Dr. Heinz-Gerd Hoymann
Working group of German safety pharmacologists

Michéla Kaisler
Working group on archiving "Archivierung" of the German Society for Good Research Practice (DGGF)

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)

Sascha Knauf, D.V.M., Ph.D.
Reviewer for international journals (incl. "Journal of Zoo and Wildlife Medicine", "PLoS One", "International Journal of Primatology", and "International Scholarly Research Notices")

Primate specialist group, Africa section of the Species Survival Commission (SSC) in the International Union for Conservation of Nature (IUCN)

Prof. Dr. Wolfgang Koch
Lecturer at Clausthal University of Technology on dissemination of pollutants in the atmosphere and on aerosols in the environment

ECETOC task force "Lung Overload"

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

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

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

Prof. Dr. Norbert Krug
Reviewer for international journals in respiratory medicine and allergy (incl. "American Journal of Respiratory and Critical Care Medicine", "Thorax", "European Respiratory Journal", "Journal of Allergy and Clinical Immunology", "Allergy", and "Clinical and Experimental Allergy")

External expert for the German Research Foundation (DFG)

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

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

Advisory board of the expertise network "Asthma und COPD"

Scientific board of the U-BIOPRED project under the Innovative Medicines Initiative (IMI)

Dr. Oliver Licht
German Federal Institute for Risk Assessment (BfR) Committee for Contaminants and other Undesirable Substances in the Food Chain

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 within the German Society of Clinical and Experimental Pharmacology and Toxicology (DGPT)

Lecturer at RWTH Aachen University on toxicology and risk assessment

Dr. Norbert Lüthe
Working group on electronic data processing "EDV" of the German Society for Good Research Practice (DGGF)

Fraunhofer quality management network

Priv.-Doz. Dr. Susanne Rittinghausen
Editorial board of the journal "Experimental and Toxicologic Pathology"

Co-optive member of the ESTP board: representative for nomenclature and RITA

"Guess What" Committee (chair) 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"

Reviewer for the international journal "Toxicologic Pathology"

Dr. Anton Roß
Member of the advisory committee for the DECHEMA/GVC division of bioprocess engineering

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

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

"Webinar" Committee of the International Federation of Societies of Toxicologic Pathology (IFSTP)

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

German Federal Institute for Risk Assessment (BfR) Committee for Exposure Assessment and Exposure Standardization

Dr. Sven Schuchardt
GBM – Society for Biochemistry and Molecular Biology

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

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

Dr. Katherina Sewald
Reviewer for the international journals "Toxicology Letters", "Toxicology in Vitro", "Nanotoxicology", and for international research grants

Steering Group of the Respiratory Toxicity Workshop

Dr. Holger Ziehr
Association of German Engineers (VDI) committee 6305 "Technical Good Manufacturing Practice"

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

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

BioPharma-Translationsinstitut e. V.

Dr. Christina Ziemann
Working group "Genotoxicity" of the DIN Water Practice Standards Committee (NA 119-01-03-07-03 AK)

Member of the GUM working group on threshold mechanisms of genotoxins

Member of the working group on carcinogenesis "Carcinogenese" of the German Society of Toxicology (GT)

Research projects

National

Chemie Wirtschaftsförderungs-GmbH
Collection of information for refinement of the environmental emission scenario for metalworking fluids (PT13) under the EU Biocide Regulation

DFG – German Research Foundation
Experimental exposure to air pollutants and sympathetic nerve activity in human subjects

Surfactant inactivation, alveolar collapsibility and their role in the progression to pulmonary fibrosis in animal models of lung injury and fibrosis

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

DFG priority program "Mast Cells – Promoters of Health and Modulators of Disease" (SPP 1394)
Characterization of mast cell anatomy and function in primate airways – interaction with the nervous system. DFG Br2126/3-1

Federal Environment Agency
Carcinogenicity and mutagenicity of nanoparticles – assessment of existing knowledge as a regulatory basis. R&D project 3709 61 220

Investigation of non-lipid-based bioaccumulation behavior of compounds. R&D project 3711 63 405/01

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

Time extrapolation of the effect of local irritants after inhalation exposure. R&D project 40191

Expert report: Human biomonitoring of "novel" hazardous substances – substance dossier for hexabromocyclododecane (HBCD), development of toxicological assessment values. Project number 27434

Integrated assessment of mercury based on the data collected by the German Environmental Specimen Bank (UPB). Project number 32 842

Federal Institute for Occupational Safety and Health (BAuA)
Evaluation of tier 1 exposure assessment models under REACH. Research project F 2303

Histopathological examination of samples from a long-term inhalation study. Research project F 2325

Method for the identification of granular biopersistent dusts at workplaces. Research project F 2336

Aerosol release during application of biocidal foam products

Exposure patterns during application of wood preservatives by deluging

Federal Institute for Risk Assessment (BfR)
Further scientific development of the DevTox project

Further development of the DevTox Web page and translation into Chinese

Federal *Länder* (Schleswig-Holstein and North-Rhine Westfalia)
Generation of NIS substance data sets (NIS-TOX, NIS-WIRK, and NIS-EXPO) on behalf of the Schleswig-Holstein Ministry for Social Affairs, Health and Family and of the North-Rhine Westfalian Agency for Nature, Environment and Consumer Protection

Federal Ministry of Education and Research (BMBF) funding program NanoCare: "Auswirkungen synthetischer Nanomaterialien auf den Menschen" (impact of synthetic nanomaterials on human health)

Project: CarbonBlack
Prediction of the human-toxicological effect of synthetic carbon black nanoparticles

Project: CarboTox
Development of screening methods to analyze cancerogenous potential of carbon nanotubes

Project: InhalT90
90-day inhalation testing with CeO_2 in the rat and subsequent analysis of gene expression profiles for the early detection of toxic/carcinogenic effects

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

Federal Ministry of Education and Research (BMBF) funding program "Ersatz und Ergänzungsmethoden zum Tierversuch" (alternatives and complements to animal experiments)
Development of a strategy for establishing categories and defining new categories for the endpoints subacute, subchronic, and chronic toxicity to minimize animal experiments under REACH

ExITox – Explain Inhalation Toxicity. Development of an integrated testing strategy for the prediction of toxicity after repeated-dose inhalation exposure: a proof of concept

Federal Ministry of Education and Research (BMBF) funding program "Vermeidung von Tierversuchen" (avoiding animal experiments)
Validation of the ex-vivo model PCLS for prediction of respiratory toxicological effects

Federal Ministry of Education and Research (BMBF) joint research project "IntegITEM"
Integration of bioprocess engineering into the ITEM (IBI)

Federal Office for Radiation Protection
Experimental development of simple methods to minimize dispersion of surface contamination after incidents with open resuspendable radioactive materials

German Center for Lung Research
Allergy and Asthma

Chronic Obstructive Pulmonary Disease (COPD)

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

International

CEFIC ERASM
Science-based derivation and refinement of safety factors (SF)

CEFIC-LRI project: LRI-ECO18
Identifying limitations of the OECD water-sediment test (OECD 308) and developing suitable alternatives to assess persistence

EFSA project: Combined toxicokinetic and in-vivo genotoxicity study on *Alternaria* toxins

EFSA project: Preparation of pre-evaluation documents, including toxicological and non-toxicological data, for the re-evaluation of food additives permitted in the European Union

EFSA project: Testing a procedure for the identification of emerging chemical risks in the food chain

ESIG (European Solvents Industry Group): Verifying the effectiveness of solvent risk management measures

EU program FP7: Primomed
Use of PRImate MOdels to support translational MEDicine and advance disease-modifying therapies for unmet medical needs

EU project: ACTICOSPACK
Development of antimicrobial packaging materials for cosmetic products

EU project: ARIMMORA
Advanced research on interaction mechanisms of electromagnetic exposures with organisms for risk assessment

EU project: CELL-PID
Advanced cell-based therapies for the treatment of primary immunodeficiency

EU project: Detective
Detection of endpoints and biomarkers for repeated-dose toxicity using in-vitro systems

EU project: Innovative Medicines Initiative (IMI) – eTOX
Integrating bioinformatics and chemoinformatics approaches for the development of expert systems allowing the in silico prediction of toxicities

EU project: Innovative Medicines Initiative (IMI) – "Understanding Severe Asthma"
Unbiased biomarkers for the prediction of respiratory disease outcomes (U-BIOPRED)
WP3 Cross-sectional and longitudinal cohort
WP4 Bronchoscopy studies
WP5 Clinical models
WP6 Pre-clinical laboratory models

EU project: NANODEVICE
Novel concepts, methods, and technologies for the production of portable, easy-to-use devices for the measurement and analysis of airborne engineered nanoparticles in workplace air

EU project: PHOENIX
Synergic combination of high-performance flame retardant nanolayered hybrid particles as real alternative to halogen-based flame retardant additives

EU project: PneumoNP
Nanotherapeutics to treat antibiotic-resistant Gram-negative respiratory infections

EU project: SILICOAT
Industrial implementation of processes to render RCS safer in manufacturing processes

European Commission Joint Research Centre (JRC), Institute for Health and Consumer Protection (IHCP)
Endocrine Active Substances Information System (EASIS) content provision. JRC/IPR/2013/I.05/0023/NC

Cooperation with institutions and universities

National

Augsburg University Hospital
– Medical Clinic II
– Urological Clinic

BioMedVet Research GmbH, Walsrode

Boehringer Ingelheim Pharma GmbH & Co. KG, Div. Research Germany

Bonn University, Institute of Human Genetics

Center of Allergy & Environment (ZAUM), Munich

Charité, Berlin
– Department of Internal Medicine/Infectious Diseases and Respiratory Medicine
– Institute of Clinical Pharmacology and Toxicology

Charité Research Organization, Berlin

Clausthal University of Technology, Institute of Particle Technology

Cologne University Hospital, Institute of Medical Microbiology, Immunology und Hygiene

Essen University Hospital, Clinic for Internal Medicine (Tumor Research)

European Research and Project Office GmbH, Saarbrücken

Federal Environment Agency, Berlin and Dessau

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

Federal Institute for Risk Assessment (BfR), Berlin

Federal Office for Radiation Protection (BfS), Salzgitter

FOBIG, Forschungs- u. Beratungsinstitut Gefahrstoffe GmbH, Freiburg

Freie Universität Berlin, Institute of Animal and Environmental Hygiene

GeneXplain GmbH, Wolfenbüttel

German Cancer Research Center (DKFZ), Heidelberg

German Center for Infection Research (DZIF)

German Center for Lung Research (DZL)
– Airway Research Center North (ARCN), Borstel/Lübeck/Kiel/Grosshansdorf
– Universities Giessen and Marburg Lung Center (UGMLC), Giessen and Marburg
– Translational Lung Research Center Heidelberg (TLRC-H), Heidelberg
– Comprehensive Pneumology Center (CPC-M), Munich

German Primate Center, Göttingen
– Cost Center Primate Facilities
– Infection Biology Unit/Virology
– Pathology Unit
– Primate Genetics Laboratory

Gesellschaft für Anlagen- und Reaktorsicherheit (GRS), Cologne

Hannover Clinical Trial Center (HCTC), Hannover

Hannover Medical School
– Biobank
– Center for Anatomy
– Clinic for Dermatology
– Clinic for Pediatric Pneumology and Neonatology
– Clinic for Pneumology
– Department of Conservative Dentistry, Periodontology and Preventive Dentistry
– Department of Experimental Pneumology
– Department of Mass Spectrometry/Proteomics
– Excellence Cluster REBIRTH
– Hannover Biomedical Research School
– Institute for Clinical Pharmacology
– Institute for Functional and Applied Anatomy
– Institute for Medical Microbiology and Hospital Epidemiology
– Institute for Radiology
– Institute of Experimental Hematology and Oncology
– Institute of Immunology
– Institute of Laboratory Animal Science, Experimental Pathology
– Institute of Pathology
– Institute of Pharmacology
– Quality Management in Clinical Research
– Research Core Unit Metabolomics

Heidelberg University Hospital, Medical Biometry and Informatics

Helmholtz Center for Environmental Research – UFZ, Leipzig

Helmholtz Center for Infection Research, Braunschweig
– Technology Platform "Flow Cytometry and Cell Sorting"
– Technology Platform "Recombinant Protein Expression"

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

Hospital Grosshansdorf – Center for Pneumology and Thoracic Surgery

IDT Biologika GmbH, Dessau-Rosslau

Institute of Pharmacology and Preclinical Drug Safety (IPAS), Nycomed: a Takeda company, Barsbüttel

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

Karlsruhe Institute of Technology, Division of Combustion Technology at the Engler-Bunte Institute, Karlsruhe

Kiel University
– Institute of Organic Chemistry
– Institute of Toxicology

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

Leibniz University Hannover
– Institute of Inorganic Chemistry
– Institute of Multiple-Phase Flows
– Institute of Organic Chemistry
– Institute of the Basics of Electrical Engineering, Sensor Technology Section

LungenClinic Grosshansdorf GmbH

QuoData, Gesellschaft für Qualitätsmanagement und Statistik mbH, Dresden

Research Center Borstel, Priority Area "Asthma and Allergies", Division of Experimental Pneumology

Robert Bosch GmbH – Packaging Technology, Crailsheim

Robert Koch Institute, Center for Biological Threats, Berlin

Technische Universität Braunschweig
– Center of Pharmaceutical Engineering (PVZ)
– Department of Biotechnology
– Institute for Drug Delivery Systems
– Institute of Biochemical Engineering
– Institute of Genetics
– Institute of Microbiology
– Institute of Pharmaceutical Chemistry

Technische Universität München (TUM), Munich, Chirurgische Klinik und Poliklinik (surgical and ambulant clinic)

Translation Center for Regenerative Medicine (TRM), Leipzig

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

Ulm University Hospital, Department of Gynecology and Obstetrics

Universitätsmedizin Göttingen
– Center for Pharmacology and Toxicology, Department of Pharmacology
– Department of Bioinformatics
– Department of Diagnostic and Interventional Radiology

University Hospital Düsseldorf
– Department of General, Visceral and Pediatric Surgery
– Department of Gynecology

University Hospital Erlangen, Department of Medicine 3

University Hospital of Munich (LMU)
– Gynecological and Maternity Hospital and Ambulant Clinic
– Institute and Outpatient Clinic for Occupational, Social and Environmental Medicine

University Hospital RWTH Aachen
– Institute and Out-patient Clinic of Occupational Medicine
– Institute for Molecular Cardiovascular Research
– Institute of Pharmacology and Toxicology

University of Cologne, Institute of Inorganic Chemistry

University of Freiburg, Institute of Physics

University of Giessen
– Institute of Anatomy and Cell Biology
– Veterinary Clinic, Department of Small-Animal Internal Medicine

University of Leipzig, Institute for Medical Physics and Biophysics

University of Lübeck, Institute of Anatomy

University of Mainz, University Medical Center, Institute of Toxicology

University of Marburg, Faculty of Medicine, Department of Pneumology, Working Group on Cell Biology of the Lung

University of Regensburg
– Chair of Dermatology and Venerology
– Chair of Experimental Medicine and Therapy Research
– Chair of Gynecology and Obstetrics
– Chair of Immunology
– Chair of Neurology
– Chair of Pathology
– Chair of Statistical Bioinformatics
– Chair of Surgery
– Chair of Thoracic Surgery
– Chair of Trauma Surgery
– Chair of Urology

University of Tübingen
– Department of Dermatology
– Institute for Clinical Epidemiology and Applied Biometry

University of Veterinary Medicine Hannover, Foundation
– Department of Pharmacology, Toxicology and Pharmacy
– Institute for Animal Welfare and Behavior
– Institute for Food Toxicology and Analytical Chemistry
– Institute for Pathology

Vetter Pharma International GmbH, Ravensburg

International

Adenium Biotech, Copenhagen (Denmark)

Asociación Centro de Investigación Cooperativa de Biomateriales – CIC Biomagune, San Sebastián (Spain)

Asociación de Investigación Cooperativa de Materiales Plásticos y Conexas, AIMPLAS, Valencia (Spanien)

Biomedical Primate Research Center, Department of Immunology, Rijswijk (The Netherlands)

Centro Ceramico – Bologna, Bologna (Italy)

École Nationale Supérieure de Chimie de Lille (ENSCL), Lille (France)

Erasmus Medical Centre, Rotterdam (The Netherlands)

Española de Nuevos Tratamientos S. A., Alicante (Spain)

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

Fraunhofer USA – Center for Molecular Biotechnology, Newark, Delaware (USA)

Fundación CIDETEC (CID), San Sebastián (Spain)

GEPACK – Empresa Transformadora de Plasticos, SA, Aveiras de Cima (Portugal)

GlaxoSmithKline Research and Development Ltd., Brentford (UK)

Imperial College of Science, Technology and Medicine, London (UK)

INDUPLAST S.P.A., Bolgare (Italy)

Ingeniatrics, Sevilla (Spain)

Institute of Occupational Medicine, Edinburgh (UK)

Instituto de Tecnología Cerámica, Castellón (Spain)

Instituto Tecnológico del Plástico, Valencia (Spain)

IT'IS Foundation for Research on Information Technologies in Society, Zurich (Switzerland)

ITENE Instituto Tecnológico del Embalaje, Transporte y Logística, Paterna/Valencia (Spain)

Janssen Labs (a Johnson&Johnson company), La Jolla – San Diego (USA)

Laboratorios Almirall S. A., Barcelona (Spain)

LAMEPLAST S.P.A., Novi di Modena (Italy)

Life Sciences Queensland, Brisbane (Australia)

McMaster University Medical Centre, Hamilton, Ontario (Canada)

National Institute of Occupational Health, Oslo (Norway)

Nuova Ompi, Padua (Italy)

OECD QSAR Expert Group (France)

PathoFinder, Maastricht (The Netherlands)

RIVM National Institute of Public Health and the Environment, Bilthoven (The Netherlands)

SetLance, Siena (Italy)

TNO Quality of Life, Zeist (The Netherlands)

UCB Pharma S. A., Brussels (Belgium)

Umaps Communication, Paris (France)

University of Amsterdam, Academic Medical Center (The Netherlands)

University of Basel, Institute of Biochemistry and Genetics, Basel (Switzerland)

University of Bern, Institute of Immunology, Bern (Switzerland)

University of Eastern Finland, Department of Environmental Science, Kuopio (Finland)

University of Kazan (Russia)

University of Southampton, Southampton (UK)

University of Virginia, Charlottesville, Virginia (USA)

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

Utrecht University, Utrecht (The Netherlands)

World Health Organization (WHO), Geneva (Switzerland)

Exhibitions, congresses and workshops

The Fraunhofer ITEM presents its research and the services it offers at national and international congresses and exhibitions. In addition, the institute organizes a variety of seminars and workshops. In 2014, the institute hosted or played an active role in the following events:

January 24-25, 2014
13th Workshop "Models of Asthma and COPD"
Fraunhofer ITEM
Hannover (Germany)

February 28 – March 4, 2014
AAAAI 2014
Annual Meeting of the American Academy of Allergy, Asthma and Immunology
San Diego, California (USA)

March 23-24, 2014
SOT 2014
Annual Meeting of the Society of Toxicology
Phoenix, Arizona (USA)

March 31 – April 3, 2014
80th Annual Conference of the German Society of Pharmacology and Toxicology (DGPT)
Hannover (Germany)

May 11-15, 2014
SETAC Europe
24th European Annual Meeting of the Society of Environmental Toxicology and Chemistry
Basel (Switzerland)

May 16-21, 2014
ATS 2014
International Conference of the American Thoracic Society
San Diego, California (USA)

June 7-11, 2014
EAACI 2014
European Academy of Allergy and Clinical Immunology Congress 2014
Copenhagen (Denmark)

June 22-26, 2014
STP 2014
33rd Annual Symposium of the Society of Toxicologic Pathology
Washington, District of Columbia (USA)

June 23-26, 2014
BIO International Convention 2014
San Diego, California (USA)

July 2-4, 2014
41st Annual Meeting of the Japanese Society of Toxicology
Kobe (Japan)

July 6-9, 2014
Breath Analysis 2014
Toruń (Poland)

August 24-28, 2014
9th World Congress on Alternatives and Animal Use in the Life Sciences
Prague (Czech Republic)

September 6-10, 2014
ERS International Congress 2014
24th International Congress of the European Respiratory Society
Munich (Germany)

October 29-31, 2014
AusBiotech
Australia's Life Sciences Conference
Brisbane, Queensland (Australia)

November 3-5, 2014
BIO-Europe 2014
Frankfurt/Main (Germany)

November 22, 2014
Open House at the Fraunhofer ITEM
Hannover (Germany)

EDITORIAL NOTES

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